FINAL

Report on Carcinogens Background Document for

Formaldehyde

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U.S. Department of Health and Human Services
Public Health Service
National Toxicology Program
Research Triangle Park, NC 27709

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FOREWORD

The Report on Carcinogens (RoC) is prepared in response to Section 301 of the Public Health Service Act as amended. The RoC contains a list of identified substances (i) that either are known to be human carcinogens or are reasonably be anticipated to be human carcinogens and (ii) to which a significant number of persons residing in the United States are exposed. The Secretary, Department of Health and Human Services (HHS), has delegated responsibility for preparation of the RoC to the National Toxicology Program (NTP), which prepares the report with assistance from other Federal health and regulatory agencies and nongovernmental institutions.

Nominations for (1) listing a new substance, (2) reclassifying the listing status for a substance already listed, or (3) removing a substance already listed in the RoC are reviewed in a multi-step, scientific review process with multiple opportunities for public comment. The scientific peer-review groups evaluate and make independent recommendations for each nomination according to specific RoC listing criteria. This background document was prepared to assist in the review of formaldehyde. The scientific information used to prepare Sections 3 through 5 of this document must come from publicly available, peer-reviewed sources. Information in Sections 1 and 2, including chemical and physical properties, analytical methods, production, use, and occurrence may come from published and/or unpublished sources. For each study cited in the background document from the peer-reviewed literature, information on funding sources (if available) and the authors' affiliations are provided in the reference section. The draft background document was peer reviewed in a public forum by an *ad hoc* expert panel of scientists from public and private sectors with relevant expertise and knowledge selected by the NTP in accordance with the Federal Advisory Committee Act and HHS guidelines and regulations. The document has been finalized based on the peer-review recommendations of the expert panel and public comments received on the draft document. The document also has been reviewed and revised for technical accuracy and clarity. Any interpretive conclusions, comments, or statistical calculations made by the authors or peer reviewers of this document that are not contained in the original citation are identified in brackets [ ].

A detailed description of the RoC nomination review process and a list of all substances under consideration for listing in or delisting from the RoC can be obtained by accessing the 12th RoC at http://ntp.niehs.nih.gov/go/9732. The most recent RoC, the 11th Edition (2004), is available at http://ntp.niehs.nih.gov/go/19914.

CONTRIBUTORS

Project Managers, Authors, and Principal Reviewers

National Toxicology Program (NTP) and National Institute of Environmental Health Sciences (NIEHS)

Ruth Lunn, Dr.P.H.	Director, Report on Carcinogens Center
Gloria Jahnke, D.V.M.	Health Scientist, Report on Carcinogens Center
Diane Spencer, M.S.	Health Scientist, Report on Carcinogens Center

SRA International, Inc. (Support provided through NIEHS Contract Number NO1-ES-35505)

Sanford Garner, Ph.D.	Principal Investigator
Stanley Atwood, M.S., D.A.B.T.	
Greg Carter, M.E.M.	
Andrew Ewens, Ph.D., D.A.B.T.	
Dana Greenwood, B.S.	
Jennifer Ratcliffe, Ph.D.	

Consultants

Tania Desrosiers, M.P.H.	University of North Carolina
Joe Haseman, Ph.D.	Independent Consultant
C.W. Jameson, Ph.D.	CWJ Consulting, LLC

Administrative Support

Ella Darden, B.S.	SRA International, Inc.
Tracy Saunders, B.S.	SRA International, Inc.
Jenayalynn Combs Riojas	Contractor, Preferred Staffing Group

Editorial Support

Susan Dakin, Ph.D.	Independent Consultant in Technical & Scientific Writing & Editing

PEER REVIEW

The Report on Carcinogens (RoC) expert panel for formaldehyde exposures met at the Hilton Raleigh-Durham Airport Hotel at Research Triangle Park, North Carolina on November 2-4, 2009, to peer review the draft background document on formaldehyde exposures and make a recommendation for listing status in the 12th Edition of the RoC.

Members of the expert panel are as follows:

Kenneth E. McMartin, Ph.D., Chair
Department of Pharmacology
Toxicology & Neuroscience
Louisiana State University
Health Sciences Center - Shreveport

Farhang Akbar-Khanzadeh, M.S.P.H., Ph.D., C.I.H.
Department of Health and Homeland Security
University of Toledo Health Sciences Campus

Gary A. Boorman, D.V.M., Ph.D.
Pathology Department
Covance, Inc.

Anneclaire DeRoos, M.P.H., Ph.D.
Department of Epidemiology
Fred Hutchinson Cancer Research Center
School of Public Health
University of Washington

Paul Demers, Ph.D.
School of Environmental Health
The University of British Columbia

Lisa Peterson, Ph.D.
Masonic Cancer Center
University of Minnesota

Stephen M. Rappaport, Ph.D.
School of Public Health
University of California, Berkeley

David Barrie Richardson, M.S.P.H., Ph.D.
Department of Epidemiology
School of Public Health
University of North Carolina-Chapel Hill

Wayne T. Sanderson, Ph.D., C.I.H.
Department of Occupational Health & Environmental Health
College of Public Health
University of Iowa

Martha S. Sandy, Ph.D.
Reproductive & Cancer Hazard Assessment Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

Technical experts to the panel: (Non-voting)

Laura Beane Freeman, Ph.D.
Division of Cancer Epidemiology and Genetics
National Cancer Institute

Michael DeVito, Ph.D.
National Toxicology Program, NIEHS

Susan A. Elmore, M.S., D.V.M., D.A.C.V.P.
National Toxicology Program, NIEHS

Luoping Zhang, Ph.D.
School of Public Health
University of California, Berkeley

Criteria for Listing Agents, Substances, or Mixtures in the Report on Carcinogens

U.S. Department of Health and Human Services

National Toxicology Program

The criteria for listing an agent, substance, mixture, or exposure circumstance in the RoC are as follows:

Known To Be Human Carcinogen:

There is sufficient evidence of carcinogenicity from studies in humans*, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.

Reasonably Anticipated To Be Human Carcinogen:

There is limited evidence of carcinogenicity from studies in humans*, which indicates that causal interpret`ation is credible, but that alternative explanations, such as chance, bias, or confounding factors, could not adequately be excluded,

or

there is sufficient evidence of carcinogenicity from studies in experimental animals, which indicates there is an increased incidence of malignant and/or a combination of malignant and benign tumors (1) in multiple species or at multiple tissue sites, or (2) by multiple routes of exposure, or (3) to an unusual degree with regard to incidence, site, or type of tumor, or age at onset,

or

there is less than sufficient evidence of carcinogenicity in humans or laboratory animals; however, the agent, substance, or mixture belongs to a well-defined, structurally related class of substances whose members are listed in a previous Report on Carcinogens as either known to be a human carcinogen or reasonably anticipated to be a human carcinogen, or there is convincing relevant information that the agent acts through mechanisms indicating it would likely cause cancer in humans.

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

*This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.

Executive Summary

Introduction

Formaldehyde is a high-production-volume chemical with a wide array of uses. The predominant use of formaldehyde in the United States is in the production of industrial resins (mainly urea-formaldehyde, phenol-formaldehyde, polyacetal, and melamine-formaldehyde resins) that are used to manufacture products such as adhesives and binders for wood products, pulp and paper products, plastics, and synthetic fibers, and in textile finishing. Formaldehyde is also used as a chemical intermediate. Resin production and use as a chemical intermediate together account for over 80% of its use. Other, smaller uses of formaldehyde that may be important for potential human exposure include use in agriculture, medical use as a disinfectant and preservative (for pathology, histology, and embalming), and use in numerous consumer products as a biocide and preservative.

Formaldehyde (gas) is listed in the *Eleventh Report on Carcinogens* (RoC) as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in laboratory animals (NTP 2005a); it was first listed in the 2nd RoC (NTP 1981). Formaldehyde (all physical forms) was nominated by NIEHS for possible reclassification in the 12th RoC based on the 2004 review by the International Agency for Research on Cancer (IARC 2006), which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans.

Human Exposure

Formaldehyde has numerous industrial and commercial uses and is produced in very large amounts (billions of pounds per year in the United States) by catalytic oxidation of methanol. Its predominant use, accounting for roughly 55% of consumption, is in the production of industrial resins, which are used in the production of numerous commercial products. Formaldehyde is used in industrial processes primarily as a solution (formalin) or solid (paraformaldehyde or trioxane), but exposure is frequently to formaldehyde gas, which is released during many of the processes. Formaldehyde gas is also created from the combustion of organic material and can be produced secondarily in air from photochemical reactions involving virtually all classes of hydrocarbon pollutants. In some instances, secondary production may exceed direct air emissions. Formaldehyde is also produced endogenously in humans and animals.

Formaldehyde is a simple, one-carbon molecule that is rapidly metabolized, is endogenously produced, and is also formed through the metabolism of many xenobiotic agents. Because of these issues, typical biological indices of exposure, such as levels of formaldehyde or its metabolites in blood or urine, have proven to be ineffective measures of exposure. Formaldehyde can bind covalently to single-stranded DNA and protein to form crosslinks, or with human serum albumin or the *N*-terminal valine of hemoglobin to form molecular adducts, and these reaction products of formaldehyde might serve as biomarkers for exposure to formaldehyde.

Occupational exposure to formaldehyde is highly variable and can occur in numerous industries, including the manufacture of formaldehyde and formaldehyde-based resins, wood-composite and furniture production, plastics production, histology and pathology, embalming and biology laboratories, foundries, fiberglass production, construction, agriculture, and firefighting, among others. In fact, because formaldehyde is ubiquitous, it has been suggested that occupational exposure to formaldehyde occurs in all work places.

Formaldehyde is also ubiquitous in the environment and has been detected in indoor and outdoor air; in treated drinking water, bottled drinking water, surface water, and groundwater; on land and in the soil; and in numerous types of food.

The primary source of exposure is from inhalation of formaldehyde gas in indoor settings (both residential and occupational); however, formaldehyde also may adsorb to respirable particles, providing a source of additional exposure. Major sources of formaldehyde exposure for the general public have included combustion sources (both indoor and outdoor sources including industrial and automobile emissions, home cooking and heating, and cigarette smoke), off-gassing from numerous construction and home furnishing products, and off-gassing from numerous consumer goods. Ingestion of food and water can also be a significant source of exposure to formaldehyde.

Numerous agencies, including the Department of Homeland Security, CPSC, DOT, EPA, FDA, HUD, the Mine Safety and Health Administration, OSHA, ACGIH, and NIOSH, have developed regulations and guidelines to reduce exposure to formaldehyde.

Human Cancer Studies

A large number of epidemiological studies have evaluated the relationship between formaldehyde exposure and carcinogenicity in humans. The studies fall into the following main groups: (1) historical cohort studies and nested case-control studies of workers in a variety of industries that manufacture or use formaldehyde, including the chemical, plastics, fiberglass, resins, and woodworking industries, as well as construction, garment, iron foundry, and tannery workers; (2) historical cohort studies and nested case-control studies of health professionals, including physicians, pathologists, anatomists, embalmers, and funeral directors; (3) population-based cohort or cancer registry studies; and (4) population-based or occupationally based case-control incidence or mortality studies of specific cancer endpoints. In addition, several studies have re-analyzed data from specific cohort or case-control studies or have conducted pooled analyses or meta-analyses for specific cancer endpoints.

The largest study available to date is the cohort mortality study of combined mixed industries conducted by the National Cancer Institute (NCI). This cohort includes 25,691 male and female workers, enrolled from 10 different formaldehyde-producing or -using plants, employed before 1966 and followed most recently to 1994 and 2004, most of whom were exposed to formaldehyde (Hauptmann *et al.* 2003, 2004 and Beane Freeman *et al.* 2009). Quantitative exposure data were used to construct job-exposure matrices for individual workers, some of whom experienced peak exposures to formaldehyde ≥ 4 ppm. This cohort is the only study in which exposure-response relationships between

peak, average, cumulative, and duration of exposure and mortality for multiple cancer sites were investigated. Two other large cohort studies are available: (1) a large multi-plant cohort study (N = 14,014) of workers in six chemical manufacturing plants in the United Kingdom (Coggon *et al.* 2003), which calculated SMRs among ever-exposed and highly exposed workers for formaldehyde, and (2) a NIOSH cohort of garment workers (N = 11,039) (Pinkerton *et al.* 2004) which evaluated mortality for duration of exposure, time since first exposure, and year of first exposure to formaldehyde for selected cancer sites. The other cohort studies (for both industrial and health professional workers) were smaller, and in general only reported mortality or incidence for ever-exposed workers in external (SMR or PMR) analyses, although some of the studies of health professional workers attempted indirect measures of exposure (such as length in a professional membership) as a proxy for exposure duration. Several of the nested case-control studies attempted to evaluate exposure-response relationships, but were limited by small numbers of exposed cases, and many of the population-based case-control studies lacked quantitative data or sufficient numbers of cases to evaluate exposure-response relationships. However, the nested case-control study of lymphohematopoietic, nasopharyngeal, and brain cancers among U.S. embalmers and funeral directors by Hauptmann *et al.* (2009) had large numbers of exposed cases of lymphohematopoietic cancer and used both questionnaire- and experimental model-based exposure metrics of exposure, including average, cumulative, peak, and duration of exposure, and number of embalmings. [Since most of the cohorts have relatively low statistical power to evaluate rare cancers such as sinonasal and nasopharyngeal cancers, case-control studies are generally more informative for these outcomes.] Findings across studies for cancer sites that have been the principal focus of investigation are summarized below.

Sinonasal cancers

In cohort studies, increased risks of sinonasal cancers were observed among male (SPIR = 2.3, 95% CI = 1.3 to 4.0, 13 exposed cases) and female (SPIR = 2.4, 95% CI = 0.6 to 6.0, 4 exposed cases) Danish workers exposed to formaldehyde (Hansen and Olsen 1995, 1996) and among formaldehyde-exposed workers in the NCI cohort (SMR = 1.19, 95% CI = 0.38 to 3.68, 3 deaths) (Hauptmann *et al.* 2004). One death from squamous-cell sinonasal cancer was reported in the study of tannery workers among formaldehyde-exposed workers by Stern *et al.* (1987). No increase in risk was found among formaldehyde-exposed workers in the other large cohort studies (Coggon *et al.* 2003, Pinkerton *et al.* 2004). The smaller cohort studies did not report findings or did not observe any deaths for this specific endpoint. [Sinonasal cancers are rare, and even the larger cohort studies have insufficient numbers of exposed workers and expected deaths (e.g., approximately three in the NCI cohort) to be very informative.]

Of the six case-control studies reviewed, four (Olsen *et al.* 1984 and Olsen and Asnaes 1986; Hayes *et al.* 1986; Roush *et al.* 1987; and Luce *et al.* 1993) reported an association between sinonasal cancers and formaldehyde exposure; statistically significant risks were found in three studies among individuals ever exposed to formaldehyde or with higher probabilities or levels of exposure (Olsen *et al.* 1994 and Olsen and Asnaes 1986; Hayes *et al.* 1986; and Luce *et al.* 1993). All of these studies found elevated risks among individuals with low or no exposure to wood dust or after adjusting for exposure to wood

dust. Stronger associations were found for adenocarcinoma, with higher risks for this endpoint observed among individuals with higher average and cumulative exposure, duration of exposure, and earlier dates of first exposure (Luce *et al.* 1993). A pooled analysis of 12 case-control studies of sinonasal cancer from seven countries (Luce *et al.* 2002) found statistically significant increases in adenocarcinoma among subjects in the highest exposure groups (OR = 3.0, 95% CI = 1.5 to 5.7, 91 exposed cases for men, adjusted for wood dust exposure; and OR = 6.2, 95% CI = 2.0 to 19.7, 5 exposed cases for women, unadjusted for wood dust exposure). For squamous-cell carcinoma, the corresponding ORs were 1.2 (95% CI = 0.8 to 1.8, 30 exposed cases) for men and 1.5 (95% CI = 0.6 to 3.8, 6 exposed cases) for women; neither OR was adjusted for wood dust exposure. A statistically significant increase in risk for sinonasal cancers (mRR = 1.8, 95% CI = 1.4 to 2.3, 933 deaths) was found in a meta-analysis of 11 case-control studies by Collins *et al.* (1997); however, no increase in risks was found in meta-analyses of three cohort studies by Collins *et al.* (1987) or in eight industrial cohort studies by Bosetti *et al.* (2008).

Nasopharyngeal cancers

Similar to sinonasal cancers, nasopharyngeal cancers are rare [and most of the risk estimates reported in the cohort studies are based on small numbers of expected cases or deaths]. Among cohort studies, a statistically significant increase in mortality from nasopharyngeal cancer was observed in the large NCI cohort (SMR = 2.10, 95% CI = 1.05 to 4.21, 8 deaths) (Hauptmann *et al.* 2004), and statistically nonsignificant elevated risks were observed among white embalmers from the United States (PMR = 1.89, 95% CI = 0.39 to 5.48, 3 deaths) (Hayes *et al.* 1990) and among male Danish workers exposed to formaldehyde (SPIR = 1.3, 95% CI = 0.3 to 3.2, 4 cases) (Hansen and Olsen 1995, 1996). One incident case of nasopharyngeal cancer was reported among Swedish workers in the abrasive materials industry (expected deaths not reported, but only 506 workers were potentially exposed) (Edling *et al.* 1987b). No associations between formaldehyde exposure and nasopharyngeal cancer were found in the other two large cohorts: one death was observed (vs. 2 expected) in the British chemical workers cohort (Coggon *et al.* 2003) and no deaths were observed (vs. 0.96 expected) in the NIOSH cohort (Pinkerton *et al*. 2004). The other, smaller, cohort studies did not report findings or did not observe any deaths for nasopharyngeal cancer.

Exposure-response relationships between formaldehyde exposure and nasopharyngeal cancer were evaluated in the large NCI cohort study. Among seven exposed and two unexposed deaths, relative risks of nasopharyngeal cancers increased with cumulative exposure (P_{trend} = 0.025 among exposed groups) and with peak and average exposure (P_{trend} = 0.044 and 0.126, respectively, across exposed and unexposed groups, using unexposed as the referent as no deaths were observed in the lowest exposed group). Adjustment for duration of exposure to a number of potentially confounding substances and plant type did not substantively alter the findings. Most of the deaths occurred at one factory (Plant 1), which appears to have had the largest numbers of highly exposed workers. In a nested case-control analysis of nasopharyngeal deaths in this plant, Marsh *et al.* (2007b) reported that several of the nasopharyngeal cancers occurred among workers with previous employment in metal-working occupations.

Six of the nine available case-control studies reported increases in nasopharyngeal cancers in association with probable exposure to formaldehyde or at higher levels or duration of estimated exposure (Olsen *et al.* 1984 [women only], Vaughan *et al.* 1986a, Roush *et al.* 1987, West *et al.* 1993, Vaughan *et al.* 2000, and Hildesheim *et al.* 2001). Risks of nasopharyngeal cancers increased with exposure duration and cumulative exposure in two population-based case-control studies (Vaughan *et al.* 2000, Hildesheim *et al.* 2001). In some studies, higher risks were found among individuals in the high-exposure groups (Vaughan *et al.* 1986a, Roush *et al* 1987), or with more years since first exposure (West *et al.* 1993), and some studies reported that risks were still elevated after taking into account smoking (Vaughan *et al.* 2000, Vaughan *et al.* 1986a, West *et al.* 1993) or exposure to wood dust (Hildesheim *et al.* 2001, Vaughan *et al.* 2000, West *et al.* 1993). No associations between nasopharyngeal cancer and formaldehyde exposure were found in population-based case-control studies in Denmark (Olsen *et al.* 1984 [men only]), and Malaysia (Armstrong *et al.* 2000), a case-cohort study among Chinese textile workers (Li *et al*. 2006), or in a nested case-control study among embalmers (Hauptmann *et al.* 2009).

Several meta-analyses were available. A statistically significant increase in risk (mRR = 1.3, 95% CI = 1.2 to 1.5, 455 deaths) was reported in a large meta-analysis of 12 case-control and cohort studies (Collins *et al.* 1997), and a nonsignificant increase in risk in a small meta-analysis of three other cohort mortality studies (SMR = 1.33, 95% CI = 0.69 to 2.56, 9 deaths) (Bosetti *et al.* 2008). Bachand *et al*. (2010) reported a borderline statistically significant risk in a meta-analysis of seven case-control studies (mRR = 1.22, 95% CI = 1.00 to 1.50) but did not find an increase in risk (mRR = 0.72, 95% CI = 0.4 to 1.29) in an analysis of data from six cohort studies, which excluded Plant 1 of the NCI cohort and used the re-analysis data from Marsh *et al.* (2005) for the other plants. [The Bachand meta-analysis used data for all pharyngeal cancer or buccal cavity cancer from some cohort studies and one case-control study, however.]

Other head and neck cancers, and respiratory cancer

Most of the cohort studies reported risk estimates for cancers of the buccal cavity, pharynx, larynx, and lung, or combinations of these cancers. Most of these studies, including two of the large cohorts (Pinkerton *et al.* 2004 and Coggon *et al.* 2003), three of the professional health worker studies (Hayes *et al.* 1990, Walrath and Fraumeni 1983 and 1984), and two of the smaller industrial cohorts (Andjelkovich *et al.* 1995 and Hansen and Olsen 1995, 1996) found elevated (between approximately 10% and 30%) but statistically nonsignificant risks for cancers of the buccal cavity or buccal cavity and pharynx combined; risk estimates were usually based on small numbers of deaths or cases. In the NCI cohort, increased risks for all upper respiratory cancers or buccal cavity cancer combined were generally found among workers in the highest categories of exposure (compared with the lowest category), but trends were not statistically significant (Hauptmann *et al*. 2004).

Most of the population-based or nested case-control studies that reported on head and neck cancers found small increases (usually statistically nonsignificant) in risks for formaldehyde exposure and cancers of the buccal cavity and pharynx (or parts of the

pharynx) (Vaughan *et al.* 1986a, Merletti *et al.* 1991, Gustavsson *et al.* 1998, Laforest *et al.* 2000, Marsh *et al.* 2002, Wilson *et al.* 2004, Berrino *et al.* 2003) or of the upper respiratory tract (Partanen *et al.* 1990). Exposure-response relationships were not clear in most of the available studies; however, positive exposure-response relationships between probability and duration of exposure and cancers of the hypopharynx and larynx combined were reported by Laforest *et al.* (2000) and between combined probability and intensity of exposure and salivary cancer by Wilson *et al.* (2004). No associations between formaldehyde exposure and pharyngeal cancers (subtypes or combinations) were observed in case-control studies by Shangina *et al.* (2006) and Tarvainen *et al.* (2008). Most of the cohort studies and two of the four available case-control studies found no association between formaldehyde exposure and laryngeal cancer. Two case-control studies (Wortley *et al.* 1992, Shangina *et al.* 2006) reported increased risk among subjects with the highest exposure to formaldehyde.

Small excesses of mortality or incidence of cancers of the lung or respiratory system among formaldehyde-exposed workers were observed in four cohort studies (Andjelkovich *et al.* 1995, Dell and Teta 1995, Hansen and Olsen 1996 [women only], and Coggon *et al.* 2003). A statistically significant increase in risk of lung cancer was observed in the large study of British chemical workers (SMR = 1.22, 95% CI = 1.12 to 1.32, 594 deaths, among all workers) (Coggon *et al.* 2003). In this study, risks increased with increasing exposure level ($P_{trend} < 0.001$) but not with duration of exposure. No association between formaldehyde exposure and lung cancer was observed in the other two large cohorts (Pinkerton *et al.* 2004, Hauptmann *et al.* 2004), in several of the smaller cohorts (Bertazzi *et al.* 1989, Hansen and Olsen 1995 [in men], Edling *et al.* 1987b, Stellman *et al.* 1998, Stern 2003), or in the six studies of health professional workers. Findings from the population-based or nested case-control studies were also mixed. Increases in risk were reported in several studies (De Stefani *et al.* 2005, Gérin *et al.* 1989, Andjelkovich *et al.* 1994, Chiazze *et al.* 1997), and were statistically significant in two studies (Marsh *et al.* 2001, Coggon *et al.* 1984). Risks did not increase with increasing exposure in most of the studies. An exception is the study by De Stefani *et al.* (2005), in which a statistically significant trend with duration of employment was observed. No association between lung cancer and formaldehyde exposure was reported in three other occupational case-control studies (Bond *et al.* 1986, Jensen and Andersen 1982, Partanen *et al.* 1990) and one population-based study (Brownson *et al.* 1993).

Lymphohematopoietic cancers

Among workers in the NCI cohort study, peak exposure to formaldehyde was associated with increased mortality for several types of lymphohematopoietic cancers (Beane Freeman *et al.* 2009). For all lymphohematopoietic cancers combined, for leukemias combined, and for myeloid leukemia, relative risks increased with increasing peak exposure: statistically significant increased risks were found among workers with the highest peak exposure (≥ 4 ppm) vs. the lowest exposed category for all lymphohematopoietic cancers (RR = 1.37, 95% CI = 1.03 to 1.81, 108 deaths, P_{trend} = 0.02), and statistically nonsignificant increases for all leukemias combined and peak exposure ≥ 4 ppm (RR = 1.42, 95% CI = 0.92 to 2.18, 48 deaths, P_{trend} = 0.12) and for myeloid leukemia and peak exposure ≥ 4 ppm (RR = 1.78, 95% CI = 0.87 to 3.64, 19

deaths, $P_{trend} = 0.13$; trends among exposed person-years). No associations were found with cumulative or average exposure.

An excess of leukemia, especially myeloid leukemia, was also found among garment workers in the large NIOSH cohort (Pinkerton *et al.* 2004), but not in the British chemical workers cohort (Coggon *et al.* 2003). In the NIOSH cohort, risks for leukemia, myeloid leukemia, and acute myeloid leukemia were higher among workers with longer duration of exposure (10+ yrs), longer time since first exposure (20+ years), and among those exposed prior to 1963 (when formaldehyde exposure was thought to be higher) (Pinkerton *et al*. 2004). In the smaller industrial cohort studies, some studies reported excesses for all lymphohematopoietic cancers combined among formaldehyde-exposed workers (Bertazzi *et al.* 1989, Stellman *et al.* 1998) or leukemia (Hansen and Olsen 1995, 1996), but others observed no association for all lymphohematopoietic cancers combined (Andjelkovich *et al.* 1995, Stern 2003, Pinkerton *et al.* 2004) or leukemia (Andjelkovich *et al.* 1995, Stellman *et al.* 1998, Stern 2003).

Each of the six cohort studies of health professionals, and the nested case-control study of embalmers from three of these studies, found elevated mortality for lymphohematopoietic cancers. Hall *et al.* (1991), Hayes *et al.* (1990), Stroup *et al.* (1986), Levine *et al.* (1984) and Walrath and Fraumeni (1983, 1984) reported increases in risk for all lymphohematopoietic cancers combined and for leukemia. Most estimates were statistically nonsignificant with the exception of the studies of Hayes *et al.* (1990) and Stroup *et al.* (1986), where statistically significant excess mortality was found for all leukemia combined or for myeloid leukemia in association with formaldehyde exposure. In the nested case-control study by Hauptmann *et al.* (2009), sufficient numbers of cases of lymphohematopoietic cancer deaths among embalmers and funeral directors were identified to enable evaluation of exposure-response relationships, using models of potential formaldehyde exposure. A significant increase in nonlymphoid lymphohematopoietic cancers was observed among ever-embalmers (OR = 3.0, 95% CI = 1.0 to 9.5, 44 exposed cases), and significant increases in risk were observed at the highest levels of cumulative, average, and peak exposure. Most of the increase was attributable to myeloid leukemia, which was significantly elevated among ever-embalmers (OR = 11.2, 95% CI = 1.3 to 95.6, 33 exposed cases) and showed significant trends with duration of exposure and peak exposure, and a more attenuated trend with 8-hour time-weighted average intensity of exposure. In further analyses of non-lymphoid lymphohematopoietic cancers using workers with < 500 lifetime embalmings as the reference group, statistically significant increases in relative risks were found among workers with the longest duration of working in jobs with embalming, the highest number of lifetime embalmings, and the highest cumulative exposure to formaldehyde.

With respect to other case-control studies, a population-based study found no clear association between leukemia and exposure to formaldehyde (Blair *et al.* 2001), and two nested case-control studies reported statistically nonsignificant increases in leukemia risk based on small numbers of exposed cases (Partanen *et al.* 1993, Ott *et al.* 1989).

Few cohort or case-control studies reported findings for subtypes of lymphohematopoietic cancers other than leukemia. Most of the cohort studies had

relatively low power to detect effects, and either did not report findings or did not evaluate exposure-response relationships. For Hodgkin's lymphoma, the NCI study was the only cohort or case-control study that reported an increase in risk. In an external analysis, an SMR of 1.42 (95% CI = 0.96 to 2.10, 25 deaths) was observed among formaldehyde-exposed workers and, in internal analyses, statistically significant exposure-response relationships were observed with peak (P_{trend} = 0.01 among the exposed group) and average exposure (P_{trend} = 0.05 among the exposed group), but not with cumulative exposure (Beane Freeman *et al.* 2009). For non-Hodgkin's lymphoma, statistically non-significant increases in risks were observed in one cohort study (Hayes *et al.* 1990), and in most of the population-based or nested case-control studies (Partanen *et al.* 1993, Ott *et al.* 1989, Richardson *et al.* 2008, Wang *et al.* 2009a, Tatham *et al.* 1997, Blair *et al.* 1993). The risk of non-Hodgkin's lymphoma (large B cell type) increased with increasing probability of exposure ($P_{trend} < 0.01$) in a large case-control incidence study of U.S. women (Wang *et al.* 2009a). No increase in non-Hodgkin's lymphoma was reported in the population-based case-control study by Gérin *et al.* (1989), or in the nested case-control study of embalmers by Hauptmann *et al.* (2009). For multiple myeloma, peak exposure of ≥ 4 ppm was associated with a statistically significant increase in risk in the NCI cohort (RR = 2.04, 95% CI = 1.01 to 4.12, 21 deaths, P_{trend} = 0.08 among the exposed group) (Beane Freeman *et al.* 2009), although an increase in risk was also seen among unexposed workers for this endpoint. Increased risks also were seen among British chemical workers (Coggon *et al.* 2003), abrasive materials workers (Edling *et al.* 1987b), and U.S. embalmers (Hayes *et al.* 1990). Other cohort studies did not find associations, based on small numbers of observed deaths or cases, or did not report findings. Among case-control studies, statistically nonsignificant increases in risks were observed by Boffetta *et al.* (1989), Pottern *et al.* (1992) (women only), and Hauptmann *et al.* (2009), but not by Heineman e*t al.* (1992) (men only).

Several meta-analyses were available. (Hauptmann et al. [2009] was not available for any of the analyses.) Statistically significant risks were reported for all lymphohematopoietic cancers and leukemia among cohort studies of health professionals by Bosetti *et al.* (2008) (RR = 1.31, 95% CI = 1.16 to 1.47, 263 deaths for all lymphohematopoietic cancers; and RR = 1.39, 95% CI = 1.15 to 1.68, 106 deaths for leukemia) and among studies of occupations with known high formaldehyde exposure by Zhang *et al.* (2009a), (mRR = 1.25, 95% CI = 1.09 to 1.43, 19 studies for all lymphohematopoietic cancers combined; mRR = 1.54, 95% CI = 1.18 to 2.00, $P < 0.001$, 15 studies for leukemia; and mRR = 1.90, 95% CI = 1.31 to 2.76, $P = 0.001$, 6 studies for myeloid leukemia. A statistically nonsignificant increase in leukemia risk was also estimated among the combined studies of health professional workers by Bachand *et al.* (2010). No increased risks for leukemia were found in the available meta-analyses of industrial cohorts (Bosetti *et al.* 2008, Bachand *et al.* 2010), or combined cohort and case-control studies (Collins and Lineker 2004).

Other cancer sites

With the exception of brain and central nervous system cancers, few of the cohort studies reported consistently elevated risks for cancers at other sites. Few case-control studies of other cancer endpoints have been conducted. Excess mortality from brain and central

nervous system cancers has been reported in each of the six cohort studies of health professionals, with statistically significant SMRs/PMRs (1.94 to 2.7) reported in three studies (Stroup *et al.* 1986, Walrath and Fraumeni 1983, 1984). However, in the nested case-control analysis of brain cancers among embalmers and funeral directors by Hauptmann *et al.* (2009), which used subjects from cohort studies of Hayes *et al.* (1990) and Walrath and Fraumeni (1983, 1984), a statistically nonsignificant increase in brain cancers was observed in association with ever-embalming (OR = 1.9, 95% CI = 0.7 to 5.3, 42 exposed cases). There were no clear exposure-response patterns with duration of employment in embalming jobs, or estimated cumulative, peak, or average exposure to formaldehyde, however. No increases in brain and central nervous system cancers have been observed in the industrial cohort studies that have reported findings. A meta-analysis by Bosetti *et al.* (2008) reported a statistically significant increase in the risk of brain cancer among health professional workers (RR = 1.56, 95% CI = 1.24 to 1.96, 74 deaths), but not among industrial workers.

Several industrial studies have reported increases in one or more of stomach, colon, rectal, and kidney cancers, and a case-control study of pancreatic cancer (Kernan *et al.* 1999) suggested an increase in this endpoint at higher levels of formaldehyde exposure. Two meta-analyses of pancreatic cancer (Ojajärvi *et al.* 2000, Collins *et al.* 2001) showed no consistent increase in risk across studies, however, with the exception of a borderline statistically significant increase among pathologists, anatomists and embalmers.

Studies in Experimental Animals

Formaldehyde has been tested for carcinogenicity in mice, rats, and hamsters. Studies reviewed include chronic and subchronic inhalation studies in mice, rats, and hamsters; chronic and subchronic drinking-water studies in rats; and one chronic skin-application study in mice. No chronic studies in primates were found, but one subchronic inhalation study and one acute/subacute inhalation study in monkeys was reviewed. [Several of these studies were limited by a small number of animals per group, short exposure duration, short study duration, incomplete pathology or data reporting, and/or incomplete statistical analysis.]

Formaldehyde exposure resulted in nasal tumors (primarily the extremely rare squamous-cell carcinoma) in several strains of rats when administered chronically by inhalation (Kerns *et al.* 1983a, Sellakumar *et al.* 1985, Appelman *et al.* 1988, Woutersen *et al.* 1989, Monticello *et al.* 1996, Kamala *et al.* 1997). Only two inhalation studies in mice or hamsters were found. No tumors were reported in C3H mice exposed to formaldehyde at 200 mg/m^3 [163 ppm] for 1 hour/day, 3 days/week, for 35 weeks (Horton *et al.* 1963), but squamous-cell carcinoma of the nasal cavity occurred in 2 of 17 B6C3F$_1$ male mice exposed at 14.3 ppm for 6 hours/day, 5 days/week, and sacrificed at 24 months (Kerns *et al.* 1983a). Although the increase was not statistically significant, the authors concluded that the tumors were exposure-related. [Biological significance is implied because these tumors are extremely rare in non-exposed mice and rats; no nasal squamous-cell carcinomas have been observed in more than 2,800 B6C3F$_1$ mice and 2,800 F344 rats used as controls in NTP inhalation studies.] No tumors were reported in Syrian golden

hamsters exposed at 10 ppm 5 hours/day, 5 days/week for life (Dalbey 1982) or at 2.95 ppm 22 hours/day, 7 days/week for 26 weeks (Rusch *et al.* 1983). No tumors occurred in male cynomolgus monkeys exposed at 2.95 ppm for 22 hours/day, 7 days/week for 26 weeks (Rusch *et al.* 1983) or in male rhesus monkeys exposed at 6 ppm for 6 hours/day, 5 days/week for 6 weeks (Monticello *et al.* 1989); however, squamous metaplasia and hyperplasia in the nasal passages and respiratory epithelia of the trachea and major bronchi occurred.

Male Wistar rats administered formaldehyde in drinking water at 5,000 ppm for 32 weeks developed forestomach tumors (squamous-cell papillomas) in one study (Takahashi *et al.* 1986); however, in two other drinking-water studies, no tumors were reported in either male or female Wistar rats administered formaldehyde at concentrations ranging from 20 to 5,000 ppm for two years (Til *et al.* 1989, Tobe *et al.* 1989). In another study, male and female Sprague-Dawley breeder rats administered formaldehyde at 2,500 ppm in drinking water. Offspring of these breeder rats exposed transplacentally beginning on gestation day 13 and postnatally via drinking water for life showed increased incidences of benign and malignant tumors of the gastrointestinal tract, particularly intestinal leiomyosarcoma (a very rare tumor). Male Sprague-Dawley rats administered formaldehyde at concentrations up to 1,500 ppm showed increased incidences (compared with control groups given tap water) of the number of animals bearing malignant tumors, hemolymphoreticular neoplasms (leukemia and lymphoma combined), and testicular tumors (interstitial-cell adenoma) (Soffritti *et al.* 2002a). Compared with the vehicle control group (tap water containing 15 mg/L methanol), the incidence of testicular tumors was significantly higher in the 1,000-ppm exposure group, and the incidence of hemolymphoreticular tumors was higher in the 1,500-ppm exposure group. Female rats in the 1,500-ppm exposure group showed higher incidences of malignant mammary-gland tumors and hemolymphoreticular neoplasms than the tap-water control group; however, the incidences were not significantly higher than in the vehicle control group. In addition, some rare stomach and intestinal tumors occurred in a few male and female rats in the exposed groups but not in the control groups.

Other studies examined the promoting effects of formaldehyde when administered after initiation with DBMA, DEN, MNU, or MNNG or cocarcinogenic effects when administered with coal tar, benzo[*a*]pyrene, wood dust, and hydrogen chloride. Some of these studies did not show an enhanced tumor response. However, a few studies, including a skin-painting study in mice (Iverson *et al.* 1986), a drinking-water study in rats (Takahashi *et al.* 1986), and inhalation studies in rats (Albert *et al.* 1982, Holmström *et al.* 1989a) and hamsters (Dalbey *et al.* 1986), indicated that formaldehyde could act as a tumor promoter or act as a co-carcinogen when administered with other substances.

Adsorption, distribution, metabolism, and excretion

Formaldehyde is a metabolic intermediate that is essential for the biosynthesis of purines, thymidine, and some amino acids. The metabolism of formaldehyde is similar in all mammalian species studied. Differences in distribution following inhalation exposure can be related to anatomical differences. For example, rats are obligate nose breathers while

monkeys and humans are oronasal breathers. Thus, in humans, some inhaled formaldehyde will bypass the nasal passages and deposit directly into the lower respiratory tract. The endogenous concentrations in the blood of humans, rats, and monkeys are about 2 to 3 μg/g and do not increase after ingestion or inhalation of formaldehyde from exogenous sources (Casanova *et al.* 1988, Heck *et al.* 1985, Heck and Casonova 2004). Although formaldehyde is rapidly and almost completely absorbed from the respiratory or gastrointestinal tracts, it is poorly absorbed from intact skin. When absorbed after inhalation or ingestion, very little formaldehyde reaches the systemic circulation because it is rapidly metabolized by glutathione-dependent formaldehyde dehydrogenase and *S*-formyl-glutathione hydrolase to formic acid, which is excreted in the urine or oxidized to carbon dioxide and exhaled (IARC 2006). Formaldehyde reaching the circulation is rapidly hydrated to methanediol, which is the predominant form in the circulation (Fox *et al.* 1985). Although the metabolic pathways are the same in all tissues, the data indicate that the route of absorption does affect the route of elimination. When inhaled, exhalation is the primary route of elimination; however, when ingested, urinary excretion as formate is more important. Unmetabolized formaldehyde reacts non-enzymatically with sulfhydryl groups or urea, binds to tetrahydrofolate and enters the single-carbon intermediary metabolic pool, reacts with macromolecules to form DNA and protein adducts, or forms crosslinks primarily between protein and single-stranded DNA (Bolt 1987).

Toxic effects

Formaldehyde is a highly reactive chemical that causes tissue irritation and damage on contact. Formaldehyde concentrations that have been associated with various toxic effects in humans show wide interindividual variation and are route dependent. Symptoms are rare at concentrations below 0.5 ppm; however, upper airway and eye irritation, changes in odor threshold, and neurophysiological effects (e.g., insomnia, memory loss, mood alterations, nausea, fatigue) have been reported at concentrations ≤ 0.1 ppm. The most commonly reported effects include eye, nose, throat, and skin irritation. Other effects include allergic contact dermatitis, histopathological abnormalities (e.g., hyperplasia, squamous metaplasia, and mild dysplasia) of the nasal mucosa, occupational asthma, reduced lung function, altered immune response, and hemotoxicity (IARC 2006). Some studies of Chinese workers suggest that long-term exposure to formaldehyde can cause leucopenia, and one study reported that a significantly higher percentage of formaldehyde-exposed workers had blood cell abnormalities (leucopenia, thrombocytopenia, and depressed serum hemoglobin levels) compared with unexposed controls (reviewed by Tang *et al.* 2009). Zhang *et al.* (2010) reported that Chinese factory workers exposed to high levels of formaldehyde had significantly lower counts of white blood cells, granulocytes, platelets, red blood cells and lymphocytes than unexposed controls. *In vitro* studies indicated that formaldehyde exposure caused a significant, dose-related decrease in colony forming progenitor cells (Zhang *et al*. 2010). Other studies have shown that formaldehyde exposure affects changes in the percentage of lymphocyte subsets (Ying *et al.* 1999, Ye *et al.* 2005). Higher rates of spontaneous abortion and low birth weights have been reported among women occupationally exposed to formaldehyde (IARC 2006, Saurel-Cubizolles *et al.* 1994). Oral exposure is rare, but there have been several apparent suicides and attempted

suicides in which individuals drank formaldehyde. These data indicate that the lethal dose is 60 to 90 mL (Bartone *et al.* 1968, Yanagawa *et al*. 2007). Formaldehyde ingestion results in severe corrosive damage to the gastrointestinal tract followed by CNS depression, myocardial depression, circulatory collapse, metabolic acidosis, and multiple organ failure.

The toxic effects of formaldehyde in experimental animals include irritation, cytotoxicity, and cell proliferation in the upper respiratory tract, ocular irritation, pulmonary hyperactivity, bronchoconstriction, gastrointestinal irritation, and skin sensitization. Other reported effects include oxidative stress, neurotoxicity, neurobehavioral effects, immunotoxicity, testicular toxicity, and decreased liver, thyroid gland, and testis weights (IARC 2006, Aslan *et al*. 2006, Sarsilmaz *et al*. 2007, Golalipour *et al*. 2008, Özen *et al.* 2005, Majumder and Kumar 1995).

In vitro studies have demonstrated that formaldehyde is directly cytotoxic and affects cell viability, cell differentiation and growth, cell proliferation, gene expression, membrane integrity, mucociliary action, apoptosis, and thiol and ion homeostasis (IARC 2006). Since metabolism of formaldehyde is glutathione-dependent, cells depleted of glutathione are more susceptible to formaldehyde toxicity (Ku and Killings 1984).

Carcinogenicity of metabolites and analogues

Formic acid (formate + H^+), the major metabolite of formaldehyde, has not been tested for carcinogenic effects. Acetaldehyde, an analogue of formaldehyde, is listed as *reasonably anticipated to be a human carcinogen* by the NTP (2004). Acetaldehyde induced respiratory tract tumors in rats (adenocarcinoma and squamous-cell carcinoma of the nasal mucosa) and laryngeal carcinoma in hamsters. In addition, epidemiological studies have reported increased risks of cancers of the upper digestive tract (esophagus, oral cavity, and pharynx) and upper respiratory tract (larynx and bronchi) in humans (Salaspuro 2009).

Glutaraldehyde and benzaldehyde have also been tested for carcinogenicity in 2-year bioassays by the NTP. Glutaraldehyde was not considered to be carcinogenic in rats or mice, and benzaldehyde was not considered to be carcinogenic in rats. The NTP concluded that there was some evidence of carcinogenicity for benzaldehyde in mice based on an increased incidence of squamous-cell papilloma and hyperplasia in the forestomachs of male and female mice (NTP 1999).

Genetic and related effects

Formaldehyde is a direct-acting genotoxic compound that affects multiple gene expression pathways, including those involved in DNA synthesis and repair and regulation of cell proliferation. Most studies in bacteria were positive for forward or reverse mutations without metabolic activation and for microsatellite induction (Mu and Harris 1988). Studies in non-mammalian eukaryotes and plants also were positive for forward and reverse mutations, dominant lethal and sex-linked recessive lethal mutations, and DNA single-strand breaks (Conaway *et al.* 1996, IARC 2006). *In vitro* studies with

mammalian and human cells were positive for DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, unscheduled DNA synthesis, single-strand breaks, mutations, and cytogenetic effects (chromosomal aberrations, sister chromatid exchange, and micronucleus induction).

In *in vivo* studies in rats, formaldehyde caused DNA-protein crosslinks (in the nasal mucosa and fetal liver but not bone marrow) (Casanova-Schmitz *et al.* 1994a, Wang and Liu 2006), DNA strand breaks (lymphocytes and liver) (Im *et al.* 2006, Wang and Liu 2006), dominant lethal mutations (Kitaeva *et al.* 1990, Odegiah 1997), chromosomal aberrations (pulmonary lavage cells and bone marrow in one of two studies) (Dallas *et al.* 1992, Kitaeva *et al.* 1990), and micronucleus induction in the gastrointestinal tract (Migliore *et al*. 1989). However, it did not induce sister chromatid exchange or chromosomal aberrations in lymphocytes or micronucleus formation in peripheral blood (Kilgerman *et al.* 1984, Speit *et al.* 2009). Mutations in the *p53* gene were detected in nasal squamous-cell carcinomas from rats (Recio *et al.* 1992). Inhalation exposure to formaldehyde also induced DNA-protein crosslinks in the nasal turbinates, nasopharynx, trachea, and bronchi of rhesus monkeys (Casanova *et al.* 1991). In mice, formaldehyde exposure did not cause dominant lethal mutations (Epstein *et al.* 1972, Epstein and Shafner 1968), micronucleus induction (Gocke *et al.* 1981), or chromosomal aberrations (Fontignie-Houbrechts 1981, Natarajan *et al.* 1983) when exposed by intraperitoneal injection or induce micronuclei by intravenous or oral exposure (Morita *et al.* 1997), but did induce heritable mutations when exposed by inhalation (Liu *et al.* 2009b).

In studies of lymphocytes from health professional workers exposed to formaldehyde, higher levels of formaldehyde-albumin adducts were found in workers exposed to relatively high concentrations compared with workers exposed to lower concentrations (Pala *et al.* 2008) and higher levels of DNA-protein crosslinks, strand breaks, and pantropic p53 protein levels were found in exposed workers compared with unexposed workers (Shaham *et al*. 2003). Wang *et al.* (2009) found higher levels of DNA adducts (N^6-hydroxymethyldeoxyadenosine [N^6-HOMe-dAdo]) among smokers compared with non-smokers; however, the source of formaldehyde is not clear (for example, it could be formaldehyde in tobacco or a metabolite of a tobacco-specific compound). Numerous studies have evaluated chromosomal aberrations and sister chromatid exchange in lymphocytes and micronucleus induction in lymphocytes, or nasal or oral epithelial cells from humans exposed to formaldehyde (primarily health professionals, but also industrial workers, volunteers and subjects exposed from environmental sources). Among formaldehyde-exposed subjects, statistically significant increased frequencies (compared with unexposed, low exposure or pre- exposure vs. post-exposure) of cytogenetic damage in lymphocytes were observed for chromosomal aberrations in 7 of 12 reviewed studies, sister chromatid exchanges in 6 of 12 studies and micronuclei induction in 5 of 7 studies reviewed. In addition to these studies, Zhang *et al.* (2010) reported that lymphocytes from workers exposed to high levels of formaldehyde had statistically increased frequency of monosomy of chromosome 7 and trisomy of chromosome 8. Statistically significant increased frequencies of micronuclei were also observed in the buccal cavity or oral epithelium in four of five reviewed studies and in the nasal epithelium in all five available studies (Note that findings from two studies, Suruda *et al.* [1993] and Tikenko-Holland *et al.* [1996], evaluating the same study participants are treated as one study in

this count). In addition to these studies, a review of cytogenetic studies in the Chinese literature on formaldehyde-exposed workers reported increased incidences of chromosomal aberrations in lymphocytes (one study) and micronuclei in lymphocytes and nasal epithelial cells (one study each); however, two studies did find increases in sister chromatid exchanges in lymphocytes.

Regulation of gene expression by formaldehyde was investigated in eight studies. Formaldehyde exposure increased expression of genes involved in intracellular adhesion, inflammation, xenobiotic metabolism, nucleic acid metabolism, cell-cycle regulation, apoptosis, and DNA repair. Thus, multiple biochemical pathways are affected by formaldehyde exposure.

Mechanistic considerations

Although the biological mechanisms associated with formaldehyde-induced cancer are not completely understood, it is important to recognize that chemicals can act through multiple toxicity pathways and mechanisms to induce cancer or other health effects (Guyton *et al.* 2009). Potential carcinogenic modes of actions for formaldehyde include DNA reactivity (covalent binding), gene mutation, chromosomal breakage, aneuploidy, and epigenetic effects.

Studies evaluating nasal tumors in rats have shown that regional dosimetry, genotoxicity, and cytotoxicity are believed to be important factors. Computational fluid dynamics models have been developed to predict and compare local flux values in the nasal passages of rats (Kimbrell *et al*. 1993, 1997), monkeys (Kepler *et al.* 1998), and humans (Subramaniam *et al.* 1998). Regions of the nasal passages with the highest flux values are the regions most likely affected by formaldehyde exposure. Similar flux values were predicted for rats and monkeys for regions of the nasal passages with elevated cell proliferation rates, thus providing support for the hypothesis that formaldehyde flux is a key factor for determining toxic response. Furthermore, DNA-protein crosslinks and cell-proliferation rates are correlated with the site specificity of tumors (Pala *et al.* 2008). Cell proliferation is stimulated by the cytotoxic effects of formaldehyde. Increased cell proliferation may contribute to carcinogenesis by increasing the probability of spontaneous or chemically induced mutations. The dose-response curves for DNA-protein crosslinks, cell proliferation, and tumor formation show similar patterns with sharp increases in slope at concentrations greater than 6 ppm. The observed sequence of nasal lesions is as follows: rhinitis, epithelial dysplasia, squamous metaplasia and hyperplasia, and squamous-cell carcinoma.

Biological mechanisms have been proposed for the possible association between lymphohematopoietic cancers and formaldehyde exposure. Proposed mechanisms for formaldehyde-induced leukemia are: (1) direct damage to stem cells in the bone marrow, (2) damage to circulating stem cells, and (3) damage to pluripotent stem cells present in the nasal turbinate or olfactory mucosa (Zhang *et al.* 2009a,b). Evidence in support of the potential for DNA damage to circulating hematopoietic stem cells is that DNA-protein crosslinks have been identified in the nasal passages of laboratory animals exposed to formaldehyde, and increased micronuclei have been identified in the nasal and oral

mucosa of formaldehyde-exposed humans. In addition, olfactory epithelial cells obtained from rat nasal passages contain hematopoietic stem cells, which have been shown to re-populate the hematopoietic tissue of irradiated rats (Murrell *et al.* 2005). However, some authors have questioned the biological plausibility of an association between formaldehyde exposure and leukemia, because formaldehyde is rapidly metabolized, and it would not be expected to enter the systemic circulation (Cole and Axten 2004, Golden *et al.* 2006, Heck and Casanova 2004, Pyatt *et al.* 2008). They stated that formaldehyde does not cause bone marrow toxicity or pancytopenia, which are common features of known leukemogens, and that the genotoxic and carcinogenic effects in animals and humans are limited to local effects. [The recent reports of adducts in leukocytes of smokers (Wang *et al.* 2009b), albumin adducts in medical research workers (Pala *et al.* 2008), DNA-protein crosslinks measured in peripheral blood cells of hospital workers (Shaham *et al.* 2003), and the hematologic changes measured by Zhang *et al.* (2010) suggest that formaldehyde might enter the systemic circulation of humans exposed to formaldehyde.]

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Abbreviations

ACGIH: American Conference of Governmental Industrial Hygienists

ADC: adenocarcinoma

ADH: alcohol dehydrogenase

AGT: O^6-alkylguanine DNA alkyltransferase (also known as MGMT)

AIPH: 2,2'-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride

ALDH: aldehyde dehydrogenase

AML: Acute myelogenous leukemia

ANOVA: analysis of variance

AOPC: all other pharyngeal cancers (except NPC)

ATSDR: Agency for Toxic Substances and Disease Registry

b.w.: body weight

BCF: bioconcentration factor

BEAM: Boston Exposure Assessment in Microenvironments

BEI: biological exposure indices

BLS: Bureau of Labor Statistics

BMCR: binucleated micronucleated cell rate

BrdU: 5-bromodeoxyuridine

C: control

CA: chromosomal aberrations

CAS: Chemical Abstracts Service

CDC: Centers for Disease Control and Prevention

CFD: computational fluid dynamics

CHO: Chinese hamster ovary

CLL: chronic lymphocytic leukemia

cm: centimeter

CMBN: cytokinesis-blocked micronucleus assay

CML: chronic myeloid leukemia

CNS: central nervous system

CPBI: cytokinesis proliferation block index

CR: creatinine

CYP: cytochrome P450

Cyt-B: cytochalasin B

Da: Dalton

DC: decarboxylase

DDX: DNA-DNA crosslinks

DNA: deoxyribonucleic acid

DNA-GSH: *S*-[1-(N^2-deoxyguanosinyl)methyl]glutathione

DOT: Department of Transportation

dpm: disintegrations per minute

DPX: DNA-protein crosslinks

E: exposed

EBV: Epstein-Barr virus

EPA: Environmental Protection Agency

EPHX: epoxide hydrase

ESTR: expanded simple tandem repeats

E.U.: European Union

F: female

FDA: Food and Drug Administration

FDH: formaldehyde dehydrogenase

FEMA: Federal Emergency Management Agency

FISH: fluorescence *in-situ* hybridization

FR: frequency ratios

g: gram

GGT: gamma-glutamyl transpeptidase

GI: gastrointestinal

GPA: glycophorin A

GSH: glutathione

h: hour

HA: hydroxylapatite

HazDat: Hazardous Substances Release and Health Effects Database

HCHO: formaldehyde

HE: human erythrocytes

HEL: human embryonic lung

HFC: high-frequency cells

Hg: mercury

HIC: highest ineffective concentration

HID: highest ineffective dose

HMMECs: human mucosal microvascular endothelial cells

HPLC: high performance liquid chromatography

HR: hazard ratio

HSA: human serum albumin

HSDB: Hazardous Substances Data Bank

Hz: Hertz

i.p.: intraperitoneal

IARC: International Agency for Research on Cancer

ICAM: intercellular adhesion molecule

ICD: International Classification of Diseases

IFN: interferon

IgG: immunoglobin G

IgM: immunoglobin M

IMIS: Integrated Management Information System

IRR: incidence rate ratio

IUPAC: The International Union of Pure and Applied Chemistry

JEM: job-exposure matrix

kBq: 1,000 becquerel (units of radioactivity)

kg: kilogram

K_{oc}: soil organic carbon-water partitioning coefficient

K_{ow}: octanol-water partition coefficient

L: liter

LC: liquid chromatography

LD_{50}: lethal dose for 50% of the population

LEC: lowest effective concentration

LED: lowest effective dose

LH: lymphohematopoietic

LHC: lymphohematopoietic cancer

LWAE: lifetime weighted average exposure

M: male or molar

m^3: cubic meter

MAK: maximum workplace concentration

MAPKs: mitogen-activated protein kinases

mCi: millicuries

MDF: medium-density fiberboard

MDS: myelodysplastic syndrome

mEH: microsomal epoxide hydrolase

MF: melamine-formaldehyde

mg: milligram, 10^{-3} gram

MGMT: O^6-methylguanine DNA methyltransferase (also known as AGT)

mL: milliliter

mm: millimeter

mM: millimolar

MN: micronuclei

mol wt: molecular weight

mRNA: messenger RNA

mRR: meta relative risk

MS: mass spectrometry

MTT: methylthiazole tetrazolium

MUF: melamine-urea-formaldehyde

N: sample size

NA: not available

NA-AAF: *N*-acetoxy-2-acetylaminofluorene

NAcT: *N*-acetyltransferase

NADPH: nicotinamide adenine dinucleotide phosphate, reduced form

NALT: nasal associated lymph tissue

NAP: not applicable

NCEs: micronucleated normochromatic erythrocytes

NCHS: National Center for Health Statistics

NCI: National Cancer Institute

ND: not detected

NDMA: *N*-nitrosodimethylamine

NDT: not determined

NF-κB: nuclear factor kappa B

ng: nanogram

NGF: nerve growth factor

NHANES: National Health and Nutrition Examination Survey

NHL: non-Hodgkin's lymphoma

NI: not identified

NIEHS: National Institute of Environmental Health Sciences

NIOSH: National Institute for Occupational Safety and Health

NLM: National Library of Medicine

NMR: nuclear magnetic resonance

NNK: 4-(*N*-nitrosomethylamino)-1-(3-pyridyl)-1-butanone

NOS: not otherwise specified

NPC: nasopharyngeal cancer

NQ: not quantified

NR: not reported

NRC: National Response Center

NS: not significant

NT: not tested

NTP: National Toxicology Program

OH: hydroxyl

OHPC: oro- or hypopharyngeal

OPC: oropharyngeal

OR: odds ratio

OSB: oriented strandboard

OSHA: Occupational Safety and Health Administration

OVA: ovalbumin

PAH: polycyclic aromatic hydrocarbon

PBL: peripheral blood lymphocytes

PCEs: micronucleated polychromatic erythrocytes

PCMR: proportionate cancer mortality ratio

PCR: polymerase chain reaction

PEL: permissible exposure limit

PET: polyethylene terephthalate

PF: phenol-formaldehyde

PGA: phenylglyoxylic acid

PHA: phytohemagglutinin

PHEMA: phenylhydroxyethyl mercapturic acids

PMR: proportionate mortality ratio

POTW: publicly owned treatement works

ppb: parts per billion

ppbv: parts per billion by volume

ppm: parts per million

r: correlation coefficient

Ref.: referent group

REL: recommended exposure limit

RLU: relative light units

RNA: ribonucleic acid

RoC: Report on Carcinogens

RR: relative risk

RRX: RNA-RNA crosslinks

RTECS: Registry of Toxic Effects of Chemical Substances

SB: DNA strand breaks

s.c.: subcutaneous

SCC: squamous-cell carcinoma

SCE: sister chromatid exchange

SD: standard deviation

SDH: sorbitol dehydrogenase

SE: standard error of the mean

SEER: Surveillance, Epidemiology and End Results program

SIR: standardized incidence ratio

SMR: standardized mortality ratio

SNC: sinonasal

SOC: Standard Occupational Classification

SOCMI: Synthetic Organic Chemical Manufacturing Industry

SPIR: standardized proportionate incidence ratio

SSB: single-strand breaks

STEL: short-term exposure limit

TLV: threshold-limit value

TRI: Toxics Release Inventory

TSH: thyroid stimulating hormone

TWA: time-weighted average

UDS: unscheduled DNA synthesis

UF: urea-formaldehyde

UFFI: urea-formaldehyde foam insulation

USITC: United States International Trade Commission

VCAM: vascular cell adhesion molecule

VOC: volatile organic chemical

WHO: World Health Organization

XRCC: X-ray repair cross-complementing group

yr: year

μg: microgram; 10^{-6} gram

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1 Introduction

Formaldehyde is a high-production-volume chemical with a wide array of uses. The predominant use of formaldehyde in the United States is in the production of industrial resins (mainly urea-formaldehyde [UF], phenol-formaldehyde [PF], polyacetal, and melamine-formaldehyde [MF] resins) that are used to manufacture products such as adhesives and binders for wood products, pulp and paper products, plastics, and synthetic fibers, and in textile finishing. Formaldehyde is also used as a chemical intermediate. Resin production and use as a chemical intermediate together account for over 80% of its use. Other, smaller uses of formaldehyde that may be important for potential human exposure include use in agriculture, medical use as a disinfectant and preservative (for pathology, histology, and embalming), and use in numerous consumer products as a biocide and preservative.

Formaldehyde is present in outdoor air as a result of its formation from the combustion of organic materials (e.g., in automobiles, forest fires, and power plants), its formation from the breakdown of hydrocarbons in the air, and releases from industrial facilities. In indoor air, it is present as a result of off-gassing from formaldehyde-containing materials such as wood products, carpets, fabrics, paint, and insulation, and it is formed from combustion sources such as wood stoves, gas stoves, kerosene heaters, open fireplaces, and furnaces, through cooking, and in cigarette smoke. It has been found in numerous foods and beverages, including drinking water.

Formaldehyde (gas) is listed in the *Eleventh Report on Carcinogens* (RoC) as *reasonably anticipated to be a human carcinogen* based on limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in laboratory animals (NTP 2005a); it was first listed in the *Second Annual Report on Carcinogens* (NTP 1981). Formaldehyde (all physical forms) was nominated by NIEHS for possible reclassification in the *Twelfth Report on Carcinogens* based on the 2004 review by the International Agency for Research on Cancer (IARC 2006), which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans.

1.1 Chemical identification

Formaldehyde is the simplest aldehyde. It is a highly reactive gas and is formed by oxidation or incomplete combustion of hydrocarbons (ChemIDPlus 2009a). Figure 1-1 shows the chemical structure of formaldehyde, and Table 1-1 provides some chemical identifying information.

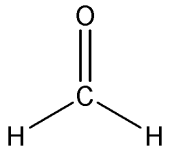


Figure 1-1. Chemical structure of formaldehyde

Commercially, formaldehyde is most often available as 30% to 50% (by weight) aqueous solutions commonly referred to as formalin (IARC 2006), to which have been added stabilizers, generally up to 15% methanol or lower concentrations (usually several hundred milligrams per liter) of various amine derivatives. In the absence of stabilizers, formaldehyde in solution oxidizes slowly to form formic acid and polymerizes to form oligomers, including paraformaldehyde (HSDB 2009a).

Table 1-1. Chemical identification of formaldehyde

Characteristic	Information	References
CAS Registry number	50-00-0	HSDB 2009a
IUPAC systematic name	methanal	IARC 2006
Molecular formula	CH_2O	HSDB 2009a
Synonyms	Fannoform, Formalith, formalin, formic aldehyde, Lysoform, methanal, methyl aldehyde, methylene oxide, Morbicid, oxomethane, oxymethylene, Superlysoform	HSDB 2009a

1.2 Physical-chemical properties

Formaldehyde exists at room temperature as a nearly colorless gas with a pungent, suffocating odor (ATSDR 1999, HSDB 2009a). Formaldehyde gas is generally stable in the absence of water, but it is flammable and can be ignited by heat, sparks, or flame. Vapors form explosive mixtures with air. Formaldehyde gas reacts violently with strong oxidizing agents and with bases and reacts explosively with nitrogen dioxide at around 180°C (Akron 2009). It reacts with hydrochloric acid to form bis(chloromethyl) ether (which is listed in the RoC as *known to be a human carcinogen*). In its pure state, formaldehyde is not easily handled, because it is extremely reactive and polymerizes readily.

The physical and chemical properties of formaldehyde are summarized in Table 1-2.

Table 1-2. Physical and chemical properties of formaldehyde

Property	Information	References
Molecular weight	30.0	HSDB 2009a
Melting point (°C)	–92	HSDB 2009a
Boiling point (°C)	–19.5	HSDB 2009a
Specific gravity	0.815 at –20°C/4°C	O'Neil *et al.* 2006
Vapor pressure (mm Hg)	3,890 at 25°C	HSDB 2009a
Vapor density (air = 1)	1.067	HSDB 2009a
Critical temperature (°C)	137.2 to 141.2	HSDB 2009a
Solubility water at 20°C acetone, alcohol, benzene, ether	 400 g/L soluble	HSDB 2009a
Octanol-water partition coefficient (log K_{ow})	0.35	HSDB 2009a
Dissociation constant (pK_a)	13.27 at 25°C	HSDB 2009a
Henry's law constant	3.4×10^{-7} atm-m^3/mol	HSDB 2009a
Unit conversion (air concentrations)	mg/m^3 = 1.23 × ppm (assuming normal temperature)	IARC 2006

The primary form of formaldehyde in dilute aqueous solutions is its monomeric hydrate, methylene glycol (methanediol) (Figure 1-2), and the primary forms in concentrated solutions are oligomers and polymers of polyoxymethylene glycols (IARC 2006). Formaldehyde can also exist as paraformaldehyde, a polymer with 8 to 100 units of formaldehyde, and as 1,3,5-trioxane, a cyclic trimer (Figure 1-2).

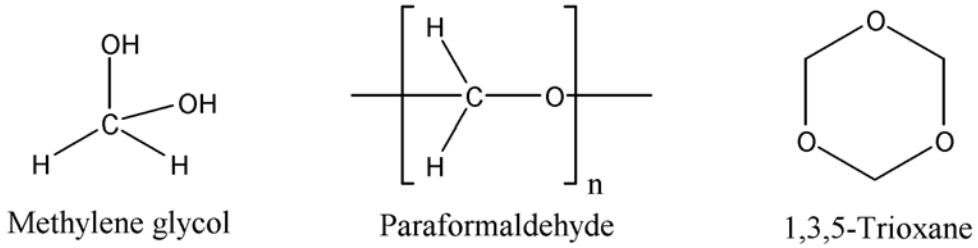


Figure 1-2. Chemical structures of hydrated and polymeric formaldehyde

1.3 Formaldehyde Polymers

Paraformaldehyde is a white crystalline powder with the odor of formaldehyde. It has the molecular formula $(CH_2O)_n$ and is a mixture of linear polyoxymethylene glycols containing 90% to 99% formaldehyde (O'Neil *et al.* 2006, HSDB 2009b). Paraformaldehyde dissolves slowly in cold water and more readily in hot water, with evolution to formaldehyde. It is soluble in fixed alkali hydroxide solution, but insoluble in alcohol and ether. Paraformaldehyde is used as an engineering plastic because it has good resistance to wear, chemicals, and temperature, a low coefficient of friction, and

good mechanical properties of strength and stiffness (Inventro 2009). Trioxane is a white crystalline solid with a chloroform-like odor and the molecular formula $(CH_2O)_3$ (HSDB 2009c). It is stable and easily handled. In acidic solutions, it will decompose to formaldehyde. Both paraformaldehyde and trioxane are used as low-water-content sources of formaldehyde. Table 1-3 shows chemical identifying information and some physical and chemical properties of paraformaldehyde and trioxane.

Table 1-3. Chemical identification and physical and chemical properties of paraformaldehyde and trioxane

Characteristic/Property	Paraformaldehyde	1,3,5-Trioxane
CAS Registry number	30525-89-4	110-88-3
Molecular formula	$(CH_2O)_n$[a]	$C_3H_6O_3$
Synonyms	Aldicide, Paraform, polyacetal, polyformaldehyde, polymethylene oxide, polyoxymethylene[b]	metaformaldehyde, *s*-trioxane, trioxymethylene
Molecular weight	30.03 (monomer)[a]	90.08
Melting point (°C)	164 (decomposes)	64
Boiling point (°C)	slowly sublimes, forming formaldehyde gas[c]	114.5 at 759 mm Hg
Density	1.46 at 15°C	1.17 at 65°C
Vapor pressure (mm Hg)	10.5 at 25°C	13.0 at 77.0°F[d]
Vapor density	1.03[c]	3.1[e]
Water solubility at 18°C	2×10^5 mg/L 500 mg/L[f,g]	1.7×10^5 mg/L
Octanol-water partition coefficient (log K_{ow})	NR	–0.43[h]
Dissociation constant (pK_a)	15.50 at 25°C	NR
Henry's law constant	NR	1.97×10^{-7}[h]

Source: HSDB 2009b,c unless otherwise noted.
NR = not reported.
[a]O'Neil *et al.* 2006.
[b]PolymerProcessing 2009 and HSDB 2009b.
[c]Mallinckrodt 2009.
[d]NOAA 2009.
[e]ScienceLab 2009a.
[f]ScienceLab 2009b.
[g]The higher-molecular-weight polymers are insoluble in water (ScienceLab 2009b).
[h]ChemIDPlus 2009b.

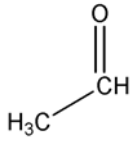
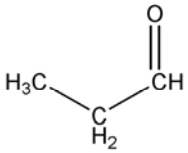
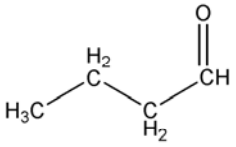
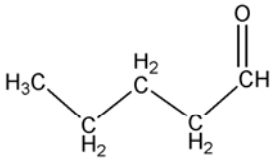
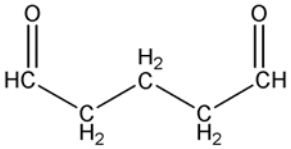
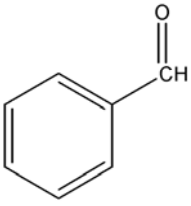
1.4 Metabolites and analogues

Formaldehyde is an endogenous metabolic product of *N*-, *O*-, and *S*-demethylation reactions and an essential metabolic intermediate in all cells (ATSDR 1999, Feick *et al.* 2006, IARC 2006). It is oxidized to formate, primarily by glutathione-dependent formaldehyde dehydrogenase. Formate may be excreted in the urine, further metabolized to carbon dioxide and water, or incorporated into the folic acid metabolic pathway for

synthesis of nucleic and amino acids. Formaldehyde metabolism and other biological reactions are discussed further in Section 5.

Analogues of formaldehyde include other low-molecular-weight aldehydes, such as acetaldehyde, propionaldehyde, butyraldehyde, *n*-pentanal, glutaraldehyde, and benzaldehyde. The chemical structures and molecular weights of these compounds are shown in Table 1-4, and carcinogenicity data for these analogues are discussed in Section 5.5.

Table 1-4. Some low-molecular weight formaldehyde analogues

Compound	Molecular weight	Chemical structure
Acetaldehyde	44.1	
Propionaldehyde	58.1	
Butyraldehyde	72.1	
n-Pentanal	86.1	
Glutaraldehyde	100.1	
Benzaldehyde	106.1	

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2 Human Exposure

Formaldehyde is an important chemical with numerous industrial and commercial uses. Annual U.S. industrial production in the early to mid 2000s averaged nearly 5 million tons. In addition to intentional industrial production, formaldehyde is produced unintentionally from human activities and from natural sources through the breakdown of hydrocarbons and other precursors. Formaldehyde is also produced endogenously in humans and other animals. Workers can be exposed to formaldehyde during its production or during the production or use of derivative products. The general population can be exposed to formaldehyde primarily from breathing indoor or outdoor air, from ingestion of food and water, from tobacco smoke, and from use of cosmetic products containing formaldehyde. In the natural environment, formaldehyde has been detected in indoor and outdoor air, surface water, rainwater, fog water, groundwater, soil, and food. Numerous U.S. federal agencies, including the Environmental Protection Agency (EPA), Food and Drug Administration (FDA), Department of Housing and Urban Development (HUD), and Occupational Safety and Health Administration (OSHA), have enacted regulations aimed at reducing formaldehyde exposures.

This section begins with a discussion of formaldehyde's various uses (Section 2.1). Section 2.2 discusses industrial production of formaldehyde and formalin, natural sources of formaldehyde, and endogenous production of formaldehyde in living organisms. Section 2.3 discusses the issues surrounding biological indices of exposure to formaldehyde. Occupational exposure levels are presented in Section 2.4 and environmental levels in Section 2.5. Section 2.6 provides data from studies that have estimated intake of formaldehyde by the general public from various sources. Section 2.7 provides regulations and guidelines that have been established with the intent of reducing exposure. Section 2 concludes with a summary (Section 2.8).

Several organizations have prepared review articles on formaldehyde (e.g., IARC, WHO, ATSDR); the most recent being a 2006 IARC monograph. These review articles have been used extensively in this section for information for the period before 2006. In addition to the review articles, an extensive literature search was conducted as recently as March 2009, and identified publications were reviewed for inclusion. Throughout this section, when data are cited from a review article, the primary citation is provided when available.

The occupational epidemiology studies presented in Section 3 of this document include a number of international studies; therefore, international occupational exposure data are included in Section 2.4 (occupational exposure) in addition to U.S. data. For environmental media, only U.S. levels are provided with the exception of levels that have been measured in food and bottled water because a possibility of exposure to these substances exists for the U.S. general public.

2.1 Use

Formaldehyde has many and varied uses; however, its predominant use in the United States is in the production of industrial resins, accounting for over 50% of formaldehyde use in the early to mid 2000s (Bizzari 2007, ICIS 2007). Other major uses include as a chemical intermediate (~29%), various agricultural uses (~5%), paraformaldehyde production (~3%), production of chelating agents (~3%), and various minor uses (~5%) such as in the medical field, in funeral homes, in histology, and in numerous consumer products (see Figure 2-1).

The predominant formaldehyde-based industrial resins consumed in the United States are urea-formaldehyde (UF) resins, accounting for 22% of the total formaldehyde consumed in 2006 (Bizzari 2007). The largest use of UF resins is as a wood adhesive in the manufacture of composite wood products, mainly particleboard and medium-density fiberboard (MDF). Bizzari (2007) reported that UF resins account for over 95% of the adhesives used in manufactured particleboard and that 45% of United States. UF consumption in 2006 was for particleboard manufacture. Wood adhesives made of UF resins are also used to produce MDF, hardwood plywood, and other composite-wood products. UF resins have also been used in the production of glass fiber roofing mats, as urea-formaldehyde foam for insulation (UFFI) in buildings, and in mining, where hollow areas are filled with foam (ATSDR 1999).

Three other major resins are produced from formaldehyde: phenol-formaldehyde (PF) resins, polyacetal resins, and melamine-formaldehyde (MF) resins. In the United States, PF resins accounted for roughly 18%, polyacetal resins for nearly 12%, and MF resins for roughly 3% of total formaldehyde consumption in 2006 (Bizzari 2007). Forecasts of U.S. demand through 2011 show little change in these patterns. Demand for PF, MF, and polyacetal resins is expected to grow between 0.1% and 3% annually through 2011, while consumption of UF resins is expected to decline by approximately 0.3% annually, primarily as a result of decreased particleboard production in the United States (Bizzari 2007).

Formaldehyde is also used as a chemical intermediate in the production of other chemicals and products. In 2006, the predominant chemicals produced from formaldehyde (based on the amount of formaldehyde consumed in production) were 1,4-butanediol (10% of total U.S. consumption) and methylenebis(4-phenyl isocyanate) (11% of total U.S. consumption) (Bizzari 2007). Formaldehyde also is used in the manufacture of chelating agents (2.7% of total U.S. consumption in 2006), primarily in the manufacture of ethylenediaminetetraacetic acid (EDTA) (57%), diethylenetriamine pentaacetic acid (DTPA) (20%), hydroxyethylethylenediaminetriacetic acid (HEDTA) (7%), and nitrilotriacetic acid (NTA) (16%) (Bizzari 2007).

Formaldehyde has many other varied uses that account for a small percentage of its total consumption. It has been used as a disinfectant in hospital wards and operating rooms and is used as a tissue preservative and disinfectant in embalming fluids (ATSDR 1999, IARC 2006, Dascalaki *et al.* 2008). It is used as an antimicrobial in many cosmetic products, at reported levels of up to 0.5% in lotions, cream rinses, and bubble-bath oils,

and up to 4.5% in nail hardeners. Other cosmetic products that may contain formaldehyde include suntan lotions, hand creams, bath products, mascara and eye make-up, cuticle softeners, nail creams, vaginal deodorants, shaving creams, soaps, shampoos, hair preparations, deodorants, and mouthwashes. The Agency for Toxic Substances and Disease Registry (ATSDR 1999) also noted that trace levels of formaldehyde may exist in cosmetic products as a result of its use as a disinfectant for the equipment used to manufacture the product. Formaldehyde has been used as a preservative in many consumer goods, including household cleaning agents, dishwashing liquids, fabric softeners, shoe-care agents, car shampoos and waxes, and carpet-cleaning agents; these products generally contain less than 1% formaldehyde. It has been found in moist toilet tissues for babies at levels exceeding 100 μg/g (100 ppm) (WHO 2002). It also has been added to finger paint as a preservative and has been measured at levels of 441 to 793 mg/kg in two types of finger paints; formaldehyde was undetectable (limit of detection = 189 ng) in two other types (Garrigós *et al.* 2001). It has been used in pet-care products at levels less than 0.5% and in various glues, epoxies, and adhesives intended for household use at levels up to 9% (HPD 2009).

In the food industry, formaldehyde has been used for preserving dried foods, disinfecting containers, preserving fish and certain oils and fats, and modifying starch for cold swelling (ATSDR 1999). Formaldehyde has been used as a bacteriostatic agent in cheese and other foods and in juice production, and paraformaldehyde has been implanted into maple syrup tap holes to deter bacterial growth. Formaldehyde has been used as a chemical germicide to control bacterial contamination in water distribution systems (IARC 2006). It also has been used in the animal feed industry as a preservative and to improve handling characteristics of feed (WHO 2002).

Although formaldehyde has many medical uses, consumption of formaldehyde in this industry is relatively small, reflecting only about 1.5% of total U.S. volume in the late 1980s (ATSDR 1999). Formaldehyde is used as an antibacterial agent delivered via hydrolysis of formaldehyde-releasing prodrugs, such as methenamine, used to treat urinary-tract infections (FDA 2006, MedScape 2006). Rectal instillation, topical application, and other techniques for administration of formalin solutions (typically 4% formalin) have been used to treat radiation proctitis (Haas *et al.* 2007, Leiper and Morris 2007). The synergy between doxorubicin and formaldehyde-releasing prodrugs in killing cancer cells has been shown to be due predominantly to formaldehyde (Rephaeli *et al.* 2007). Rephaeli *et al.* reported that these prodrugs also protected neonatal rat cardiomyocytes and adult mice against the toxicity of doxorubicin.

Other reported minor medicinal applications for formaldehyde have included its use during vasectomies, as a treatment for athlete's foot, as a sterilant for *Echinococcus* (tapeworm) cysts prior to their surgical removal, and in dentistry (IARC 1982, 2006).

Formaldehyde has had many uses in agriculture, including use as a fumigant, for prevention of mildew in spelt wheat and rot in oats, as a preservative in fodder, as a preplanting soil sterilant in mushroom houses, as a germicide and fungicide for plants and vegetables, as an insecticide for flies and other insects, as a disinfectant in brooding houses, in the production of herbicides, for seed treatment, and in the manufacture of

controlled-release fertilizers (used in agriculture and on residential lawns) (ATSDR 1999, WHO 2002). Formaldehyde also is used to produce glyphosate, which is the active ingredient in the herbicide Roundup (Bizzari 2007).

Additional uses of formaldehyde have been reported for the manufacture of glass mirrors, explosives, artificial silk, and dyes; as a bactericide in coating agents and other chemicals used in paper mills; for tanning and preserving animal hides; for hardening gelatin plates and papers, toning gelatin-chloride papers, and chrome printing and developing in the photography industry; as a biocide for latex, an adhesive additive, and an anti-oxidizer additive for synthetic rubber in the rubber industry; as a biocide in oil-well drilling fluids and as an auxiliary agent in petroleum refining; in chemical toilets; in the manufacture of crease-resistant and flame-retardant fabrics; as an anticorrosive agent for metals; and in formaldehyde-based resins often used as core binders in foundries (ATSDR 1999, WHO 2002).

Some products are not preserved with formaldehyde directly, but instead, with agents that break down and release formaldehyde under conditions of usage (WHO 2002, de Groot *et al*. 2009). The levels of decomposition and formaldehyde release depend mainly on temperature and pH (WHO 2002). de Groot *et al*. (2009) identified 42 substances that they determined, either unequivocally or with a high degree of certainty, were formaldehyde releasers (note that this includes chemicals that release formaldehyde as a result of decomposition, and chemicals synthesized from formaldehyde that may still contain residues of free formaldehyde, such as formaldehyde resins). Formaldehyde releasers that are used in cosmetics include quaternium-15, imidazolidinyl urea, diazolidinyl urea, DMDM hydantoin, and 2-bromo-2-nitropropane-1,3-diol (de Groot *et al*. 2009). Other products that often contain formaldehyde releasers are industrial and household cleaning agents, soaps, shampoos, paints, lacquers, and cutting fluids (WHO 2002). Examples of formaldehyde-releasing antimicrobial agents used in metalworking fluids are tris(*N*-hydroxyethyl) hexahydrotriazine, tris(hydroxymethyl)nitromethane and hexahydro-1,3,4, tris(2-hydroxyethyl)-*S*-triazine (NIOSH 2001, de Groot *et al.* 2009). No data were identified on formaldehyde levels resulting from formaldehyde releasers.

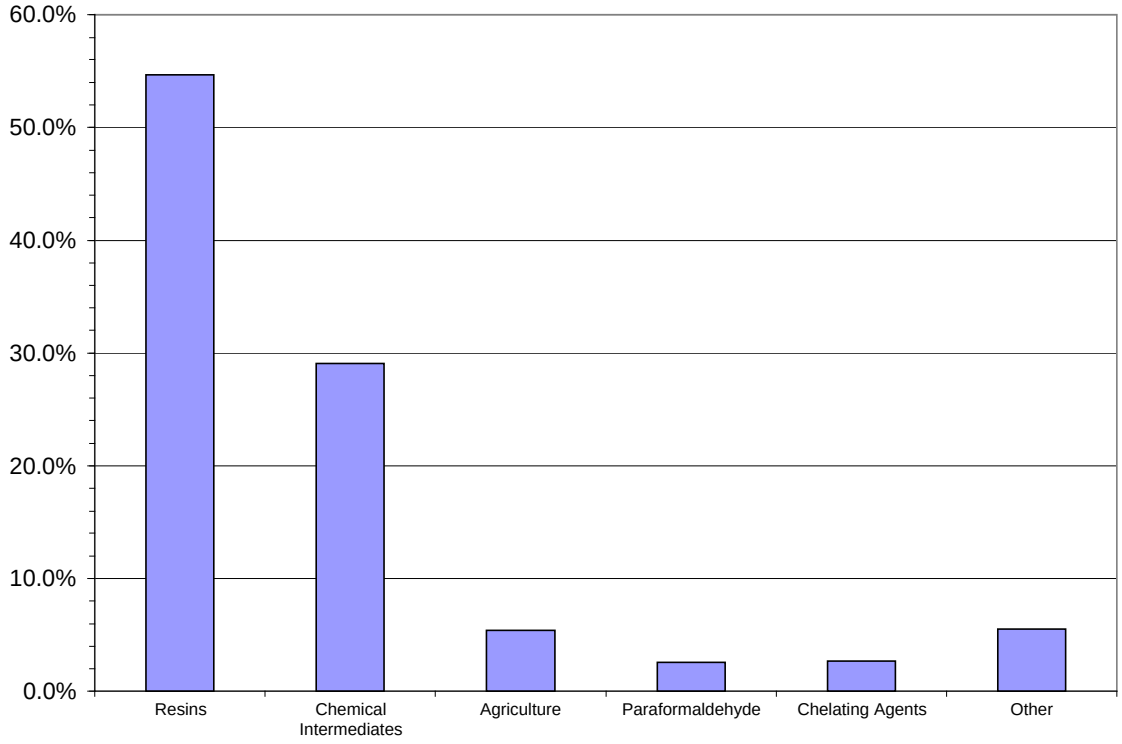

Figure 2-1. Major uses of formaldehyde in the United States

Resins = UF, PF, MF and polyacetal resins; chemical Intermediates = 1,4-butanediol, methylenebis(4-phenyl isocyanate), pentaerythritol, hexamethylenetetramine, trimethylolpropane; agriculture = controlled-release fertilizers and herbicides; chelating Agents = EDTA, DTPA, HEDTA, and NTA.
Source: Bizzari 2007.

Because formaldehyde is fairly easy to make, is costly to transport, and can become unstable during transport, it usually is produced to satisfy captive requirements for the production of derivatives or to supply local merchant sales (Bizzari 2007). The uses for formaldehyde vary regionally within the United States. Almost all formaldehyde produced in the West is consumed for wood adhesives; formaldehyde produced in the Gulf region is used primarily in chemical derivatives and to a lesser extent for wood adhesives; and production in the South and Southeast is used primarily for wood adhesives and to a lesser extent in chemical derivatives.

Paraformaldehyde is a high-formaldehyde-content product that is commercially available as 91% or 95% prills; roughly 2.6 metric tons of 37% formaldehyde are required to produce 1 metric ton of paraformaldehyde (Bizzari 2007). The main applications for paraformaldehyde are foundry resins and applications where the presence of water could interfere with a production process. Being a solid, paraformaldehyde is preferred over aqueous formaldehyde for shipping over long distances (Bizzari 2007). Paraformaldehyde has been used as a fumigant to decontaminate laboratories and to disinfect sickrooms, clothing, and linen; in pesticide applications; for making varnish resins, thermosets, and foundry resins; in the synthesis of chemical and pharmaceutical

products; in the preparation of disinfectants and deodorants; and in the production of textile products. In 2006, the production of paraformaldehyde accounted for almost 3% of U.S. formaldehyde consumption (Bizzari 2007, EPA 2007).

Formaldehyde is also marketed in solid form as its cyclic trimer, trioxane (Bizzari 2007). In acidic solutions, trioxane decomposes to generate three formaldehyde molecules (HSDB 2009c). Trioxane and hexamine ($C_6H_{12}N_4$) are the main components of solid fuel tablets, commonly known as Esbit, which are used by campers, hobbyists, the military, and relief organizations primarily for boiling water and cooking (ZenStoves 2009). Trioxane is also used in the production of polyacetal resins (Bizzari 2007) and has many other potential industrial applications (BASF 2006).

2.2 Production

2.2.1 Industrial production

Formaldehyde has been produced commercially since 1889 by catalytic oxidation of methanol. Currently, the two predominant production processes are a silver catalyst process and a metal oxide catalyst process (Bizzari 2007).

Formaldehyde is produced and consumed at various concentrations; the data on industrial levels presented here are based on a concentration of 37% unless otherwise noted. In 2006, worldwide formaldehyde production was around 28 million metric tons [31 million tons], with Western Europe being the highest producer, at 7.8 million metric tons [8.6 million tons], and China the second-highest producer, at 7 million metric tons [7.7 million tons] (Bizzari 2007). In the United States, production has gradually but steadily increased from 0.9 million metric tons [1 million tons] in 1960 to 4.5 million metric tons [5 million tons] in 2006. Figure 2-2 shows U.S. formaldehyde production from 1960 through 2006. Bizzari reported in 2007 that U.S. formaldehyde production capacity was 5.4 million metric tons [6 million tons] per year.

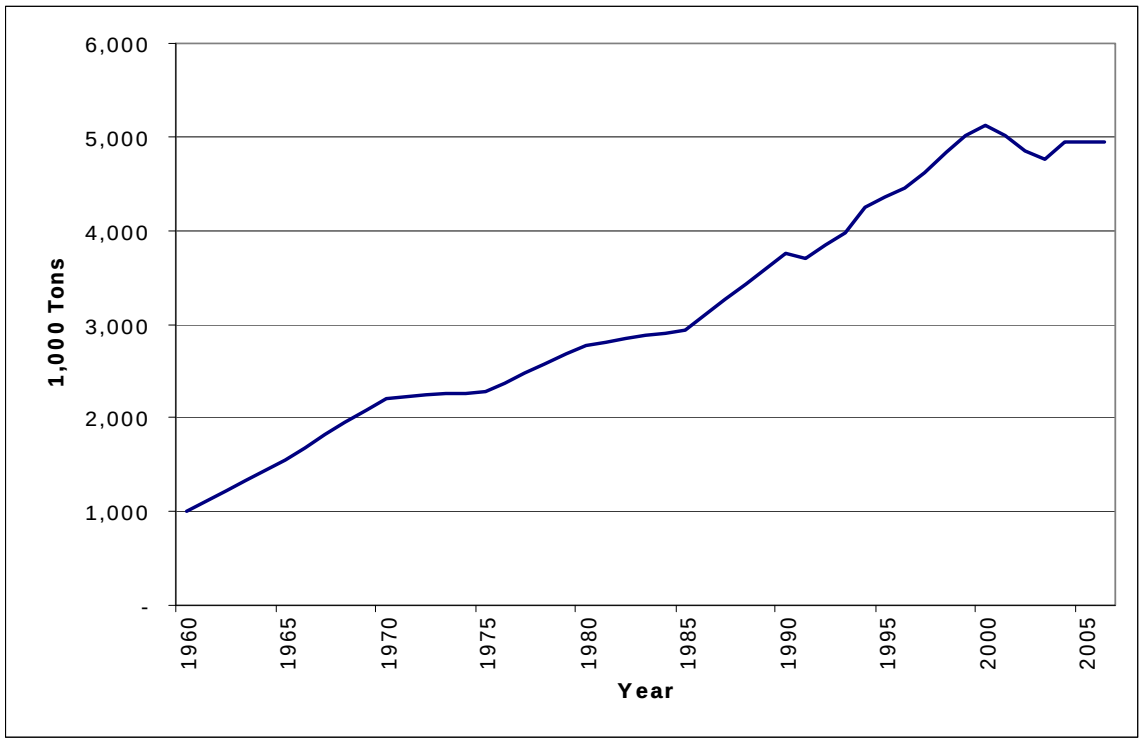

Figure 2-2. Formaldehyde production in the United States
Source: Bizzari 2007

In the United States in 2009, formaldehyde was reported to be produced at 39 manufacturing plants (SRI 2009a) by an estimated 12 companies (estimate based on Bizzari 2007), and paraformaldehyde and trioxane were each produced at one U.S. manufacturing facility (SRI 2009b,c). In 2009, 36 suppliers of formaldehyde, 25 suppliers of paraformaldehyde, and 11 suppliers of trioxane were identified in the United States; 152 formaldehyde suppliers in 25 countries were identified internationally, 59 paraformaldehyde suppliers in 15 countries, and 21 trioxane suppliers in 9 countries (ChemSources 2009a,b,c).

Because of transportation and storage issues associated with formaldehyde, it usually is produced close to the point of consumption; international trade in formaldehyde is therefore minimal, accounting for approximately 2% of worldwide production in 2006 (Bizzari 2007). In the United States, formaldehyde imports in 2006 were about 10,000 metric tons [11,000 tons], or roughly 0.2% of consumption, while exports were about 14,000 metric tons [15,400 tons], or about 0.3% of production.

2.2.2 Other production sources

In addition to intentional industrial production, formaldehyde is produced unintentionally from natural sources and from human activities. Combustion processes account either directly (i.e., release of formaldehyde) or indirectly (i.e., release of chemicals that are reduced to formaldehyde in the environment) for most of the formaldehyde entering the environment (Howard 1989, ATSDR 1999). Combustion sources include automobiles and other internal combustion engines, power plants, incinerators, refineries, forest fires,

wood stoves, and cigarettes. Photochemical oxidation of hydrocarbons and other precursors released from combustion processes can be a significant indirect source of formaldehyde. Formaldehyde may also be produced in the atmosphere by the oxidation of methane; this is probably the predominant source of formaldehyde in regions remote from hydrocarbon emissions. Formaldehyde is also formed in the early stages of decomposition of plant residues in soil (IARC 2006).

2.2.3 Endogenous production

In humans and other animals, formaldehyde is an essential metabolic intermediate in all cells and is produced endogenously from serine, glycine, methionine, and choline, and from the demethylation of *N*-, *O*-, and *S*-methyl compounds (IARC 2006) (see Section 5.1). Zhang *et al.* (2009a) reported that the endogenous concentration of formaldehyde in the blood of humans, monkeys, and rats is approximately 2 to 3 mg/L.

2.3 Biological indices of exposure

Direct measures of exposure to formaldehyde normally would involve determination of formaldehyde or its major metabolite formic acid (or formate) in blood or urine of exposed individuals. Neither formaldehyde nor formate has been very useful for direct biological monitoring, for several reasons. Levels of both of these molecules show large intrapersonal and interpersonal variation even in the absence of formaldehyde exposure (ATSDR 1999). Because both formaldehyde and formate are simple one-carbon molecules that are rapidly metabolized and incorporated into the one-carbon pathway or oxidized to carbon dioxide (Shaham *et al.* 2003), most of the formaldehyde taken into the body becomes unidentifiable as the parent molecule or major metabolite. A further complication is the formation of formaldehyde *in vivo* from the metabolism of many xenobiotics, including carbon tetrachloride, endrin, paraquat, dioxins, and dichloromethane (ATSDR 1999). Formate can also be part of the metabolic pathways of chemicals such as methanol, halomethanes, and acetone (ATSDR 1999, Shaham *et al.* 2003).

Formaldehyde can bind covalently to single-stranded DNA and protein to form crosslinks or with human serum albumin (HSA) or the *N*-terminal valine of hemoglobin to form molecular adducts, and these reaction products of formaldehyde might serve as biomarkers for exposure to formaldehyde. Pala *et al.* (2008) reported a significant relationship between levels of exposure to airborne formaldehyde and formaldehyde-HSA conjugate (FA-HSA); however, no relationship was observed between exposure levels and chromosomal aberrations, micronuclei, or sister chromatid exchanges. Metabolism of formaldehyde and adduct formation are discussed in Section 5.3, and the potential for these molecules as biomarkers for formaldehyde exposure is described in the remainder of this section.

Shaham *et al.* (1996a, 1997) conducted a pilot study to investigate the use of DNA-protein crosslinks as a biomarker for formaldehyde exposure in humans. DNA-protein crosslinks were measured in white blood cells from 12 exposed workers (physicians and technicians) and 8 unexposed controls. The workers had been exposed to formaldehyde from 2 to 31 years, with a mean of 13 years. Formaldehyde concentrations were

measured in the room air and in personal samples. Concentrations ranged from about 1.4 to 3.1 ppm. The levels of crosslinks were significantly higher ($P = 0.03$) in exposed workers than in controls and significantly higher ($P < 0.05$) in the most-exposed workers (technicians) than in less-exposed workers (physicians). Furthermore, the years of exposure and levels of crosslinks were linearly related. Smoking did not influence the results. The authors concluded that DNA-protein crosslinks can be used as a method for biological monitoring of formaldehyde exposure. Zhang *et al*. (2009a) reported that the level of DNA-protein crosslinks observed in the controls were an order of magnitude higher than those typically reported, and, therefore, the findings need to be replicated in other molecular epidemiology studies.

Shaham *et al.* (2003) conducted a follow-up study of the relationship of DNA-protein crosslinks to occupational exposure to formaldehyde. This study also investigated effects on p53 protein expression (see Section 5.6.4). The workers included physicians, laboratory assistants and technicians, and hospital orderlies at 14 hospital pathology departments, and the workers had a mean exposure period of 15.9 years (range = 1 to 51 years). The exposed group included 59 men and 127 women, who were further divided into low- and high-exposure subgroups. The low-exposure group, which consisted of laboratory assistants and technicians, had exposure levels ranging from 0.04 to 0.7 ppm, while the high-exposure group, which consisted of physicians and orderlies, had exposure levels ranging from 0.72 to 5.6 ppm. [Note that characterization of the exposure levels of physicians and technicians as being high or low differed between the two studies by Shaham *et al.*] The control group included 213 administrative workers (127 men and 86 women) at the same hospitals. Age distribution, sex, origin, and education differed significantly between the exposed and control groups; therefore, the data were adjusted for these variables. DNA-protein crosslinks were measured in the mononuclear-cell fraction of peripheral blood. The adjusted mean number of crosslinks was significantly higher ($P < 0.01$) in the total exposed group than in the control group. The mean number of crosslinks did not differ significantly by level of exposure or median years of exposure (≤ 16 vs. > 16 years).

Pharmacokinetic modeling suggests that the rate of formation of DNA-protein crosslinks is dose-dependent (IARC 2006), and it has been suggested that this rate can serve as a surrogate for the delivered dose of formaldehyde (Casanova *et al.* 1991, Shaham *et al.* 2003). DNA-protein crosslinks are also a marker for effect of exposure and are discussed further in Section 5.

Madison *et al.* (1991) reported that levels of immunoglobin M (IgM) and immunoglobin G (IgG) isotypes to FA-HSA were significantly higher in a group of subjects exposed to formaldehyde from an urea-formaldehyde spill than in a non-exposed group (see Section 5.4.2 for additional details). Carraro *et al.* (1999) later developed an indirect competitive enzyme immunoassay to titrate serum anti–FA-HSA antibodies using FA-HSA adducts conjugated *in vitro*. The assay was used to examine two groups of roughly 90 healthy adults each, using adducts with a different ratio of formaldehyde to HSA for each group (5:1 and 10:1). The assay was more sensitive and specific with the 10:1 adduct than with the 5:1 adduct. The authors noted that the results of this study supported the assertion that the FA-HSA adduct is a good marker for formaldehyde

exposure and concluded that this assay appeared to be able to evaluate immunological response against this adduct, in particular when the adduct with the 10:1 ratio was used. They suggested that the assay could be a useful tool for investigating formaldehyde exposure; however, no follow-up to this study was found in the literature.

Bono *et al.* (2006) found that the prevalence of *N*-methylenvaline (a molecular adduct formed by addition of formaldehyde to the *N*-terminal valine of hemoglobin) in blood was significantly higher in exposed workers than in non-exposed controls, and that levels of *N*-methylenvaline in blood were positively related to formaldehyde exposures. The authors concluded that its measurement in blood could be useful as a biomarker for occupational exposure to formaldehyde. For this study, 21 volunteers occupationally exposed to formaldehyde were recruited from a plywood factory and a laminate factory; 30 non-exposed workers served as a control group. The procedure for each subject consisted of the administration of a questionnaire, application of a passive sampler for one eight-hour working day, collection of a venous blood sample for *N*-methylenvaline determination, and collection of a urine sample to investigate the presence of cotinine (a biomarker for tobacco smoke exposure). Formaldehyde levels in personal air samples were significantly higher ($P = 0.0001$) for workers at both factories than for the controls, whereas the difference between the two factories was not statistically significant. Mean exposure levels were 0.092 mg/m^3 [0.075 ppm] for the plywood factory and 0.076 mg/m^3 [0.062 ppm] for the factory producing laminates. *N*-Methylenvaline distribution in blood showed a direct positive relationship to formaldehyde exposure ($r = 0.465$), and prevalence of the molecular adduct (as nanomoles per gram of globin) was significantly higher ($P < 0.04$) in the exposed group than in the control group.

Li *et al.* (2007a) investigated the formation of antibodies against formaldehyde-protein conjugates in rats as a potential biological marker for formaldehyde exposure. Male Sprague-Dawley rats were exposed to formaldehyde in their drinking water (1.6 mg/mL) for up to 6 months. Blood samples were collected at 3 and 6 months, and antibodies were measured in the serum. Antibodies were detected in half the animals at both 3 and 6 months, but the antibody titer was higher at 6 months. The antibodies were highly specific and did not cross-react with malondialdehyde or other albumin adducts. The antibody against formaldehyde-albumin adducts also recognized formaldehyde-human albumin conjugates, but only with about one-third the binding affinity. The authors concluded that anti-formaldehyde-protein conjugate antibodies are a potential biomarker for formaldehyde exposure.

Li *et al.* (2007c) monitored formaldehyde exposure by measuring urinary concentrations of thiazolidine-4-carboxylate (a stable cysteinyl adduct of formaldehyde). They also determined that six genes (*BHLHB2, CCNL1, SE20-4, C8FW, PLK2, and SGK1*) showed elevated expression in subjects with high urinary concentrations of thiazolidine-4-carboxylate, and they suggested that these genes might have the potential to be developed as biomarkers for formaldehyde exposure.

2.4 Occupational exposure

No current data were found on the number of U.S. employees who are exposed to formaldehyde; however, in the late 1980s, the Occupational Safety and Health Administration (OSHA) estimated that over 2 million U.S. workers were exposed to formaldehyde, with about 45% of these working in the garment industry (USDL 2009). OSHA estimated that about 1.9 million workers were exposed to formaldehyde at concentrations between 0.1 and 0.5 ppm, about 123,000 at concentrations between 0.5 and 0.75 ppm, and about 84,000 at concentrations between 0.75 and 1 ppm. It has been suggested that because formaldehyde is ubiquitous, occupational exposure occurs in all workplaces (WHO 2002). Additionally, Fishbein (1992) reported that about 107,000 employees were exposed to formaldehyde at concentrations greater than 1 ppm and about 430,000 employees at concentrations ranging from 0.5 ppm to 1 ppm (time-period of exposure not reported).

OSHA (1990) stated that formaldehyde exposure can occur in three ways: (1) exposure to liquid or solid formaldehyde (paraformaldehyde) and the accompanying vapors, (2) exposure to formaldehyde during primary processing of formaldehyde resins and other chemicals manufactured from formaldehyde, and (3) exposure to formaldehyde released from products that contain formaldehyde-based resins. In occupational environments, formaldehyde occurs mainly as a gas; however, formaldehyde particulates can be inhaled when paraformaldehyde or powdered resins are used, or when formaldehyde adsorbs to other particulates such as wood dust (IARC 1995).

Exposure also is possible when formalin solutions or liquid resins come in contact with the skin or eyes. Animal studies have shown low levels of radioactive excreted in urine and feces following topical application of ^{14}C-formaldehyde solutions (see Section 5.1.2). Dermal exposure to liquid formaldeyde solutions has been documented to cause dermal irritation, allergic contact dermatitis, and skin sensation (ATSDR 1999, de Groot *et al.* 2009). deGroot *et al.* (2009) noted that the frequency of positive patch tests to formaldehyde in the United States is around 8% to 9% of the patients with suspected contact dermatitis. Based on occupational exposure experience and results in controlled exposure studies in humans, airborne formaldehyde is a documented eye irritant (see Section 5.4.2). No data were found on occupational dermal or ocular exposures.

IARC (2006) noted that in the past, the highest continuous exposures have been measured during the varnishing of furniture and wooden floors, in the finishing of textiles, in the garment industry, during the treatment of furs, and in certain jobs within manufactured board mills and foundries. Short-term exposures to high levels have been reported for embalmers, pathologists, and paper workers. Lower levels have usually been encountered during the manufacture of synthetic vitreous fibers, abrasives, and rubber, and in formaldehyde production industries. A very wide range of exposure levels has been observed in the production of resins and plastic products.

Lavoué *et al.* (2008) extracted OSHA personal exposure monitoring data for formaldehyde from the U.S. Integrated Management Information System (IMIS) in order to develop a retrospective assessment of formaldehyde exposure and to determine what

factors affect exposure levels. Due to the database design, only detected personal measurement results (N = 5,228) were analyzed with linear mixed-effect models, which explained 29% of the total variance. This study did not include 28 measurements that were below the limit of detection. The authors noted that overall, short-term measurements were higher than time-weighted average (TWA) measurements. Short-term measurements decreased 18% per year until 1987, the year in which the OSHA permissible exposure limit (PEL) was implemented (see Section 2.7.1), and then 5% per year after that. TWA measurements decreased at a rate of 5% per year until 1987 and 4% per year thereafter.

Formaldehyde concentrations from IMIS were analyzed, and TWA and short-term levels were estimated for numerous industries. The highest estimated TWA concentrations were for the reconstituted wood products, structural wood members, and wood dimension and flooring industries (geometric mean = 0.2 mg/m^3 [0.16 ppm]), and the highest estimated short-term levels were for the funeral service and crematory and reconstituted wood products industries (geometric mean = 0.35 mg/m^3 [0.28 ppm]). Exposure levels in IMIS were marginally higher during non-programmed [non-scheduled] inspections compared with programmed [scheduled] inspections. Increasing exterior temperatures tended to cause a decrease in exposure levels for cold temperatures (−5% per 5°C increase for temperatures less than 15°C), but caused increases in exposure levels for warm temperatures (+15% per 5°C increase for temperatures greater than 15°C).

In a review of formaldehyde exposure in China, Tang *et al.* (2009) noted that the wood processing industry had the highest average industrial formaldehyde air concentration, caused in part by unventilated workshops and a lack of employee safety precautions.

This section provides information on various industries where occupational exposure to formaldehyde occurs: these include formaldehyde and formaldehyde-based resin production, wood-based products and paper production, manufacture of textiles and garments, foundries, production of formaldehyde-based plastics, embalming, histology, construction activities, fiberglass and mineral wool insulation production, firefighting and combustion-related exposures, agriculture, office-building exposures, and other exposures. Tables are provided with exposure levels; where available, information on sources of exposure and exposure reduction methods is included in the text. In addition to the review articles discussed above (i.e., WHO 1989, ATSDR 1999, and IARC 2006), Tang *et al*. (2009) performed an extensive review of occupational exposure to formaldehyde in China, and this article is used throughout the occupational exposure section. As with the other review articles, the primary reference is indicated for the data from Tang *et al*.

It is important to note that a variety of sampling and analytical techniques have been used to estimate formaldehyde air levels, and these differences could impact the comparability of data across studies. The occupational exposure levels that are presented in this section include data from both personal-sampling and area-sampling strategies. Although a number of parameters can impact the levels measured for each sampling strategy (Lavoue *et al.* 2006), [personal measurements are more relevant and in general, would be expected to be higher than area measurements].

Currently, six analytical methods are listed for the measurement of formaldehyde in the NIOSH Manual of Analytical Methods: three methods for formaldehyde in air, one for aldehydes screening in air, one for organic and inorganic gases in air, and one for formaldehyde on dust. The use of different analytical methods results in differences in sensitivity and error in the measurement of formaldehyde across studies. For example, the limits of detection across the three NIOSH methods that are specific to formaldehyde in air range from 0.07 to 1.0 μg/sample. Also, due to advances in analytical methods, there are temporal differences in sensitivity and error. In many reports, the sampling and analytical methods were not provided.

Often, information on the specific resin used in a process was not provided in the source document; where available, this information is provided with the exposure levels. Within the exposure-level tables, U.S. data are presented first; then the data generally are sorted by industry and then by year of publication of the study. Throughout the tables in this section, concentrations are presented in units of parts per million (ppm). If the concentrations were presented in milligrams per cubic meter (mg/m^3) in the source document, values were multiplied by a conversion factor of 0.81. The number of significant digits for the air concentrations varied across studies. Except for some instances where units were converted, the number of significant digits that were provided in the source document are provided in the tables.

2.4.1 Formaldehyde and formaldehyde-based resin production

As noted in Section 2.2.1, most industrial production of formaldehyde is in the form of formalin; an aqueous solution of formaldehyde with small amounts of stabilizers such as methanol added to prevent polymerization. The predominant industrial use of formaldehyde is in the production of urea-, phenol-, and melamine-formaldehyde resins, which are used primarily as binders for wood products such as particleboard, MDF, plywood, and wood-molding compounds and as laminates for flooring, cabinets, countertops, furniture, and similar items (Bizzari 2007). Another major use of formaldehyde is for the production of polyacetal resins, which are used widely in the production of plastics, industrial machinery, automotive components, and various consumer and industrial goods (IARC 2006, Bizzari 2007) (see Section 2.4.5).

Jobs with potential exposure during the production of formaldehyde or formaldehyde-based resins include machine operator, reception and shipping clerk, maintenance worker, laboratory technician, foreman, and office worker (IRSST 2006). Tasks that may result in formaldehyde exposure include collecting product samples for analysis, maintenance and repair operations, filter replacement, bagging, and filling trucks and barrels. The main factors that affect occupational exposures to formaldehyde include the condition of the piping and equipment, the presence and efficiency of fume hoods or local collection systems at the source of the emissions, and the efficiency of the general ventilation system.

IARC (2006) reported that mean air levels of formaldehyde were less than 1 ppm during the manufacture of formaldehyde and ranged from less than 1 ppm to more than 10 ppm during the manufacture of formaldehyde-based resins. Table 2-1 presents exposure data for formaldehyde and formaldehyde-based resin production. IARC (2006) noted that

while obvious differences have been seen in formaldehyde air levels among factories producing formaldehyde-based resins, no consistent seasonal variation has been demonstrated. Workers in formaldehyde production may also be exposed to methanol, carbon monoxide, carbon dioxide, and hydrogen as process gases.

In Canada, formaldehyde production is done in a continuous closed circuit and is completely automated (IRSST 2006); however, no information was found on whether processes used in the United States for formaldehyde or formaldehyde-resin production were open- or closed-circuit or on the potential for releases of formaldehyde to air.

The major steps that can be taken to reduce exposure in this industrial sector include confining operations that may result in formaldehyde exposure, such as sample collection, barrel filling, filter cleaning, and tanker-truck filling operations, and installing hoods above the emission sources. Ensuring proper general ventilation with outside air will also help reduce exposure levels, and personal protective equipment should be used where exposure levels are high (IRSST 2006).

Table 2-1. Formaldehyde exposure levels associated with formaldehyde production and formaldehyde-based resin production

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Formaldehyde production			
Formaldehyde manufacture (1983) Plant 2 summer Plant 10 summer	 15 9	 0.6 (0.03–1.9)[a] 0.7 (0.6–0.8)[a]	Stewart *et al.* 1987a[b] United States
Paraformaldehyde packaging (NR) Personal sampling Area sampling	 10 8	 0.55 (< 0.25–0.85) 1.17 (0.28–3.4)	Blade 1983[c] United States
Formaldehyde production (NR) Production operator Laboratory technician	 NR NR	 1.4 1.31	NIOSH 1980a[c] United States
Formaldehyde production (2001)	48	0.9 (0.4–2.8)	Li and Chen 2002[d] China
Formaldehyde production (1988–97) Oxidation Storage	 196 206	 1.0 (0.01–1.7) 1.1 (0.02–1.5)	Zhang *et al.* 1999[d] China
Formaldehyde workshops (1994) (1995) (1995) (1996) (2006)	 22 NR NR 12 21	 0.8 (NR) NR (0–2.3) NR (0–3.0) 2.1 (0.2–6.5) 0.024 (0.018–0.036)	 Cheng *et al.* 1995[d] Huan *et al.* 2001[d] Huan *et al.* 2001[d] Wang *et al.* 1997[d] Yang 2007a[d] China

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Factory producing formaldehyde and resins (1979–85)	62	0.2 (0.04–0.4)	Holmström *et al.* 1989b[b] Sweden
Formaldehyde production (1980s)	9	0.3 (NR)	Rosen *et al.* 1984[b] Sweden
Formaldehyde-based resin production			
Resin production (1983–84)			Stewart *et al.* 1987a[b]
Plant 1 summer	24	3.4 (0.2–13.2)[a]	United States
Plant 6 summer	6	0.2 (0.1–0.2)[a,e]	
Plant 7 summer	9	0.2 (0.1–0.3)[a]	
Plant 7 winter	9	0.6 (0.4–0.9)[a]	
Plant 8 summer	13	0.4 (0.2–0.8)[a,e,f]	
Plant 8 winter	9	0.1 (0.1–0.2)[a,e,f]	
Plant 9 summer	8	14.2 (4.1–30.5)[a,e,f]	
Plant 9 winter	9	1.7 (1.1–2.5)[a]	
Plant 10 summer	23	0.7 (0.3–1.2)[a,f]	
Resin and plastic materials production (NR)	NR	1.39 (NR)[g]	NIOSH 1980a[c] United States
Resin production (1981–82)			Heikkila *et al.* 1991[b]
Furan resin production	3	2.3 (1.0–3.4)	Finland
Maintenance	4	2.9 (1.4–5.5)	
UF resin production	7	0.7 (0.6–0.8)	
Resin production (1980s)	22	0.5 (NR)	Rosen *et al.* 1984[b] Sweden

NR = not reported.
[a]Mean and range of geometric means.
[b]Cited in IARC 2006.
[c]Cited in WHO 1989.
[d]Cited in Tang *et al.* 2009.
[e]Some of the sampling results were affected by simultaneous occurrence of phenol, which interferes with the measurement method, leading to artificially low values.
[f]Some of the sampling results were affected by a simultaneous occurrence of particulates "that contained nascent formadehyde (leading to high values)."
[g]Data also presented in Table 2-8.

2.4.2 Wood-based products and paper production

The predominant use for formaldehyde-based resins is in the production of wood-based composites; UF, MF, melamine-urea-formaldehyde (MUF), and PF resins all can be used, depending on the product being manufactured. Plywood and other laminated wood products often are referred to as composite-wood products; however, in this section, they are discussed separately from other wood-based composites, because of important differences in manufacturing processes and exposure potential. Wood furniture and paper-product manufacturing also are discussed in this section.

2.4.2.1 Wood-based composites

The product class of wood-based composites includes particleboard, fiberboard, and oriented strandboard (OSB), which are differentiated primarily by the type of wood fiber used (i.e., from large particles to small fibers). Regardless of the type of fiber used, the manufacturing process is basically the same: (1) the wood fiber is bonded together with a thermosetting resin to form a mat, (2) the mat is hot pressed, and (3) the pressed mat is then cooled and allowed to mature (IRSST 2006). The wood fibers typically are bonded with UF, MF, MUF, or PF resins. During hot pressing, the mat is heated and compacted to the desired density and thickness, and the resin polymerizes to bind the particles and stabilize the panel.

UF resins are primarily used in the manufacture of products where dimensional uniformity and surface smoothness are of primary concern. Conner (2001) reported that over 70% of the UF resin produced is used by the forest industry in the production of particleboard (61%), MDF (27%), hardwood plywood (5%), and as a laminating adhesive (7%). The popularity of UF resins results from a number of factors, including low cost, ease of use, water solubility, hardness, and lack of color. However, moist conditions, especially when combined with heat, lead to a reversal of the bond-forming reactions and result in the release of formaldehyde. For this reason, UF resins are unsuitable for most outdoor uses and are used almost exclusively for products intended for indoor use. MF and MUF resins are more resistant to breakdown in moist environments; however, melamine is much more expensive than urea. MF resins are used primarily for decorative laminates. PF resins are the most resistant to breakdown from moisture and thus typically are used in products requiring some degree of outdoor exposure durability, such as OSB. PF resins also have a darker color, making them generally less suitable for decorative products such as paneling and furniture (USDA 1999).

The major determinants of worker exposure levels are the type of resin used and the molar ratio of formaldehyde to the other components (IRSST 2006). IRSST noted that the emission rate is highest for UF resin and lowest for PF resin. Other parameters that affect exposure levels include process operating conditions, such as temperature, pressing time, panel thickness, and maturation time; the presence and efficiency of fume hoods or other collection systems; and the level of general ventilation. Production areas and processes associated with formaldehyde exposure include gluing (both glue preparation and application), board press operations, board cooling operations, maturing and drying, and storage. Jobs that may result in formaldehyde exposure include resin preparer, press operator, finisher, laminator, laboratory technician, and maintenance and office personnel. The main means of controlling exposure to formaldehyde are substitution (e.g., isocyanate-based products can be used for some applications but have high toxicity), the use of resins with lower emission rates, confinement of production steps that produce formaldehyde emissions, the use of hoods and capture devices, good general ventilation, and the use of personal protection where formaldehyde levels are high.

Process- and product-related changes over the past few decades have led to general reductions in levels of occupational exposure to formaldehyde, which is reflected in the data presented by Kauppinen and Niemelä (1985) (as cited in IARC 2006) (see Table 2-2). Lower mean exposure levels were seen for all operations that were assessed

during the 1975 to 1984 time period when compared with the 1965 to 1974 time period. These data indicate that tasks with the highest exposure levels include glue preparation, hot pressing, and sawing.

Table 2-2. Formaldehyde exposure levels associated with the production of wood-based composites

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Particleboard production MDF production OSB production	332 42 2	0.46[a] (NR) 0.33[a] (NR) 0.04[a] (NR)	Lavoue *et al.* 2007 Compiled data from various locations
Particleboard workers (NR)	NR	0.69 (0.17–2.93)[b]	Horvath *et al.* 1988[c] United States
Particleboard sanding (NR)	NR	NR (0.187–0.783)	Stumpf *et al.* 1986[c] United States
Fiberboard production (2003) (2005)	 60 NR	 0.34 (0.09–0.7) 0.33 (0.11–2.6)	 Geng *et al.* 2004[d] Jiang *et al.* 2006[d] China
Blocking (2002) (2005)	 40 NR	 0.9 (0.3–2.1) 0.15 (NR)	 Fan *et al.* 2004[d] Shi *et al.* 2006[d] China
Fiberboard sawing and sanding (1990s)	46	0.03–0.10 (0.01–0.14)[e]	Chung *et al.* 2000[f] United Kingdom
OSB plant (1990s)[g]	20	≤ 0.05 (NR)	Herbert *et al.* 1995[f] Canada
Particleboard mill (NR)	9	2.4 (1.2–3.5)	Malaka and Kodama 1990[f] Indonesia
Blockboard mill (NR)	6	0.5 (0.4–0.6)	Malaka and Kodama 1990[f] Indonesia
Chipboard production (1980–88)	24	1.5 (< 0.01–8.4)	Triebig *et al.* 1989[f] Germany
Two particleboard plants and a laminate plant (1980s)	NR	NR (0.08–0.9)[h]	Edling *et al.* 1988[c] Sweden

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Particleboard mills (1965–84)			Kauppinen and Niemelä 1985[f] Finland
Glue preparation 1975–84	10	2.2 (0.3–4.9)	
Blending 1965–74	10	1.0 (0.1–2.0)	
Blending 1975–84	8	0.7 (< 0.1–1.4)	
Forming 1965–74	26	1.7 (< 0.5–4.6)	
Forming 1975–84	32	1.4 (0.1–4.8)	
Hot press 1965–74	35	3.4 (1.1–9.5)	
Hot press 1975–84	61	1.7 (0.2–4.6)	
Sawing 1965–74	17	4.8 (0.7–9.2)	
Sawing 1975–84	36	1.0 (< 0.1–3.3)	
Coating 1965–74	7	1.0 (0.5–1.8)	
Coating 1975–84	12	0.4 (0.1–1.2)	
Particleboard and MDF production (1980s)	40	0.2–0.3 (NR)	Rosen *et al.* 1984[f] Sweden
Cork compression (1985)	28	2.5 (0.3–37.5)	Gao *et al.* 1988[d] China

NR = not reported.
[a]Median geometric mean from data compiled from 13 studies.
[b]Mean and range of TWAs. Data also presented in Table 2-8.
[c]Cited in ATSDR 1999.
[d]Cited in Tang *et al*. 2009.
[e]Includes both gaseous formaldehyde and formaldehyde extracted from dust for various products; maximum levels are for formaldehyde extracted from dust.
[f]Cited in IARC 2006.
[g]Includes debarking, pre-heat conveyor, post-heat conveyor, and packaging and storage.
[h]Data from the particleboard and laminate plants are not segregated. Presented is a range of estimated TWAs; peaks of up to 4 ppm were reported.

2.4.2.2 Plywood and other laminated veneer

This industrial sector involves the manufacture of plywood, veneer, laminated wood, and panel coating and generally involves gluing together panels of wood veneer or other materials. Regardless of the end product, the process generally consists of five steps: gluing, pressing, drying, finishing, and storage. Adhesives used in this industry can be made of UF, MF, MUF, or PF resins. UF, MF, or MUF resins are used primarily for decorative products intended for indoor use, while PF resins are used for structural plywood (softwood plywood) and weather-resistant materials (WSDE 1998, USDA 1999). Methods of applying the adhesives include spraying, curtain coating, roller coating, extrusion, and foaming (USDA 1999). The veneer panels are laid up by hand, machine, or a combination of both. The glue is then allowed to partially cure under pressure. Pressing operations can include cold pressing (pressing at ambient temperatures), hot pressing (pressing at high temperatures), or a combination of the two. Hot pressing is used for some UF glues and for all PF glues (WSDE 1998). Pressing times range from a few minutes to several hours depending on the temperature of the press, the size of the product, and the type of glue used.

Sources of exposure within this sector include glue preparation and application, press operations, drying and storage, maintenance operations, finishing operations, and packaging and transportation operations. The main factors that affect worker exposure include the type of resin and the molar ratio used; process operating conditions, such as temperature, amount of pressure applied and duration of pressing, panel thickness, and type of wood coating; the presence and efficiency of fume hoods and local collection systems; and the efficiency of the general ventilation system (IRSST 2006). Measures to control exposure include product substitution (e.g., isocyanate resins are available, but their toxicity is high), the use of resins with lower emission rates (PF resins release less formaldehyde during curing than UF resins), confinement of production steps that produce formaldehyde emissions, installation of fume hoods above the sources of emissions, sufficient levels of ventilation in the finishing and storage areas to dissipate residual formaldehyde emissions, and the use of personal protection where exposure levels are high. The extent to which these measures have been implemented in the United States is not clear, but large-scale replacement of UF by PF does not appear to have occurred over the last 30 to 40 years. The relative use of UF has remained consistently higher than that of PF since 1970 when they represented 27% and 23%, respectively, of total 37%-formaldehyde consumption in the United States compared with 22% and 18%, respectively, in 2006 (Bizzari 2007).

Numerous process- and product-related changes over the past few decades have led to general reductions in occupational exposure levels, as can be seen in Table 2-3. Of particular interest are data reported for several different processes for the periods 1965 to 1974 and 1975 to 1984 by Kauppinen (1986) (as cited in IARC 2006); mean exposure levels for all operations assessed during 1975 to 1984 had decreased from 1965 to 1974. Based on these data, tasks with the highest exposure levels include glue preparation and hot pressing, and major exposure-level reductions were seen for these tasks.

Table 2-3. Formaldehyde exposure levels associated with the manufacture of plywood and laminates

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Plywood paneling manufacture (1983–84)			Stewart *et al.* 1987a[b] United States
Winter	27	0.2[a] (0.08–0.4)	
Summer	26	0.08[a] (0.01–0.5)	
Plywood panels production	8	0.075 (NR)	Bono *et al.* 2006
Laminates production	13	0.062 (NR)	NR
Plywood mill (2000)			Fransman *et al.* 2003[b]
Dryers	14	0.06[a] (NR)	New Zealand
Composers	2	0.02[a] (NR)	
Pressing	5	0.13[a] (NR)	
Finishing end	1	0.03[a] (NR)	

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Plywood mill (1996–97)			Makinen *et al.* 1999[b]
Patching	6	0.06 (0.02–0.08)	Finland
Feeding of drying machine	6	0.05 (0.01–0.12)	
Forklift driving	6	0.06 (0.02–0.16)	
Scaring [scarfing]	6	0.11 (0.06–0.2)	
Assembly (machine 1)	4	0.24 (0.08–0.66)	
Assembly (machine 2)	6	0.12 (0.08–0.22)	
Hot pressing	5	0.11 (0.07–0.19)	
Glue preparation	2	0.12 (0.06–0.19)	
Finishing	4	0.07 (0.06–0.11)	
Carrying plywood piles	2	0.05 (0.04–0.06)	
Finishing	2	0.04 (0.01–0.06)	
Plywood factory (NR)			Ballarin *et al.* 1992
Warehouse	3	0.32 (0.17–0.49)	Italy
Shearing press	8	0.08 (0.07–0.11)	
Sawmill	1	0.07 (1 sample)	
Plywood mill (NR)	40	0.6 (0.2–2.3)	Malaka and Kodama 1990[b] Indonesia
Plywood mills (1964–84)			Kauppinen 1986[b]
Glue prep 1965–74	15	2.2 (0.6–5.0)	Finland
Glue prep 1975–84	19	0.7 (0.1–2.3)	
Assembly 1965–74	32	1.5 (< 0.1–4.4)	
Assembly 1975–84	55	0.6 (0.02–6.8)	
Hot press 1965–74	41	2.0 (< 0.1–7.7)	
Hot press 1975–84	43	0.5 (0.06–2.1)	
Sawing 1965–74	5	0.5 (0.3–0.8)	
Sawing 1975–84	12	0.1 (0.02–0.2)	
Coating 1965–74	7	1.0 (0.5–1.8)	
Coating 1975–84	28	0.3 (0.02–0.6)	
Plywood production (1980s)	47	0.3 (NR)	Rosen *et al.* 1984[b] Sweden

NR = not reported.
[a]Geometric mean.
[b]Cited in IARC 2006.

2.4.2.3 Wood furniture

Most furniture is manufactured from either wood-based composite or hardwood, and the manufacturing process can be generalized into four steps: (1) processing (sawing, sanding, assembly, inspection), (2) painting, staining, or varnishing (mixing, applying, drying, sanding, repair), (3) upholstery and installation of hardware, and (4) packaging and shipping (IRSST 2006). IRSST (2006) noted that most of the adhesives used in the industry do not emit formaldehyde; although wood-based composites and veneers may emit some formaldehyde, the main source of formaldehyde in this industry originates

from finishes used on the furniture. Formaldehyde-based resins often are used to crosslink more flexible resins, providing finishes that have good scratch and chemical resistance for use in furniture surface coatings (TIG 2005).

Exposure determinants include the type of varnish used; process operating conditions, such as the nature of the spraying systems, drying time, and the location of operations; work methods employed; the presence and efficiency of varnishing booths and other local collection systems at the source; and the efficiency of the general ventilation system (IRSST 2006). Tasks that can result in formaldehyde exposure include paint preparation, application of primers and varnishes, sanding between coats, unloading of furniture from ovens, repair tasks, installation of hardware, cleaning of application guns, and maintenance. Sources of formaldehyde release include releases from varnish use and storage, paint booths, furniture drying operations, and furniture storage. Jobs that may result in exposure include laborer, painter, finish operator, repair and maintenance personnel, finisher/shipper, supervisor, and office personnel.

Exposure control measures can include product substitution (i.e., use of formaldehyde-free coatings), confinement of operations with high emissions (e.g., preparation and application of varnish and paint in booths), good local and general ventilation, good work methods (such as proper use of capture devices), and the use of personal protection where formaldehyde levels are high (IRSST 2006). Table 2-4 provides formaldehyde levels that have been measured in the wood furniture manufacturing industry.

Table 2-4. Formaldehyde exposure levels associated with wood furniture manufacturing

Operation (year measured)	N	Exposure level mean (range) (ppm)	Reference Location
Wood processing			
(1995)	104	2.5 (0.6–15.6)	Feng *et al.* 1996[a]
(1990–98)	72	0.75 (NR)	Pan *et al.* 2000[a]
(1990–98)	90	0.71 (NR)	Pan *et al.* 2000[a]
			China
Woodworking shops (1990s)			Abdel Hameed *et al.* 2000[b]
Ventilated workshop	14	0.42 (0.28–0.54)	Egypt
Unventilated workshop	14	0.64 (0.48–0.84)	
Manufacture of furniture (NR)			Vinzents and Laursen 1993[b]
Painting	43	0.16 (2.25)[c]	Denmark
Gluing	68	0.12 (2.87)[c]	
Furniture factories (1981–86)			Heikkila *et al.* 1991[b]
Gluing	73	0.3 (0.07–1.0)	Finland
Machining in finishing department	9	0.3 (0.1–0. 9)	
Varnishing	150	1.1 (0.1–6.3)	
Furniture factory (NR)	NR	0.20[d] (0.16–0.4)	Holmström *et al.* 1989b[e]
			NR

Operation (year measured)	N	Exposure level mean (range) (ppm)	Reference Location
Furniture factories, finishing with paints (NR)			Alexandersson and Hedenstierna 1988[b]
Paint mixer/supervisor	6	0.2 (0.1–0.4)	Sweden
Mixed duties on the line	5	0.4 (0.3–0.5)	
Assistant painter	3	0.5 (0.2–0.7)	
Spray painter	10	0.4 (0.1–1.1)	
Feeder/receiver	13	0.2 (0.1–0.8)	
Furniture factory (1975–84)			Priha *et al.* 1986)[b]
Feeding painting machine	14	1.1 (0.3–2.7)	Finland
Spray painting	60	1.0 (0.2–4.0)	
Spray painting assistant	10	1.0 (0.2–1.6)	
Curtain painting	18	1.1 (0.2–6.1)	
Before drying of varnished furniture	34	1.5 (0.1–4.2)	
After drying of varnished furniture	14	1.4 (0.2–5.4)	
Furniture factory, varnishing (1980s)	32	0.7 (NR)	Rosen *et al.* 1984[b] Sweden
Wood furniture manufacture (NR)	> 33	0.12–2.75 (0.01–6.4)[f]	Herrick *et al.* 1983[g] NR
Cabinetmaking (NR)	48	max. = < 0.1	Sass-Kortsak *et al.* 1986[b] Canada

NR = not reported.
[a]Cited in Tang *et al*. 2009.
[b]Cited in IARC 2006.
[c]Geometric mean and standard deviation.
[d]Median.
[e]Cited in ATSDR 1999.
[f]Range of means and full range across four datasets.
[g]Cited in WHO 1989.

2.4.2.4 Paper products

Formaldehyde-based products can be used for various purposes in paper production. UF and MF resins can be added to fiber slurries before pressing to increase paper strength, and UF, MF, and PF resins often are used as coatings for various types of paper products (IARC 2006, TIG 2005). UF resins are used as adhesives in paper bags, cardboard, and sandpaper, and formaldehyde is used as a bactericide in some paper-coating agents.

In paper-coating operations, the primary sources of emissions are from the dipping or coating operations and from drying ovens (WSDE 1998), which is reflected in the data presented in Table 2-5. Emissions from storage tanks and from areas where resin blends are prepared can also be a source of exposure. In a large epidemiological study of workers in 12 countries employed in the production departments of paper and paperboard mills and recycling plants, the highest exposure levels were observed during the calendering or on-machine coating operations (IARC 2006).

Table 2-5. Formaldehyde exposure levels associated with the manufacture of paper and paper products

Industry (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Lamination and impregnation of paper with MF and PF resins (1983)			Stewart *et al.* 1987a[b] United States
Summer	53	0.7[a] (< 0.01–7.4)	
Winter	39	0.3[a] (0.05–0.7)	
Paper and paperboard manufacture, coating preparation (NR)	11	0.51, 1.0 (< 0.01–3)[c]	NIOSH 1980a[d] United States
Manufacture of treated paper products (NR)	101	0.34, 0.59[e] (0.14–0.99)[c]	NIOSH 1979b[d] United States
Paper and paperboard manufacture, resin impregnation (NR)	62	0.05–0.08 (0.01–0.28)[c]	NIOSH 1976b[d] United States
Pulp and paper industry (1950–94)			Korhonen *et al.* 2004[b] 12 countries (specific countries not reported by IARC)
Pulping, refining of stock	25	0.5 (0.0–3.1)	
Newsprint and uncoated paper machine	7	0.15 (0.04–0.46)	
Fine and coated paper machine	51	1.1 (0.01–9.9)	
Paperboard machine	8	0.5 (0.2–2.2)	
Paper/paperboard machine	228	0.4 (0.0–6.6)	
Calendering or on-machine coating	166	4.2 (0.0–50)	
Winding, cutting, and grading	111	0.2 (0.0–1.1)	
Repulping of waste paper	8	0.2 (0.05–0.4)	
Paper mill (1968–73)			FIOH 1994[b] Finland
Gluing, hardening, lamination, and rolling of paper	12	0.9 (0.3–2.5)	
Impregnation of paper with phenol resin	38	7.4 (< 1.0–33)	
Paper storage, diesel truck traffic	5	0.3 (0.2–0.4)	
Paper mill (1975–84)			Heikkila *et al.* 1991[b] Finland
Coating of paper	30	0.7 (0.4–31)	
Gum paper production	4	0.4 (0.3–0.6)	
Impregnation of paper with amino resin	6	3.1 (0.5–13)	
Impregnation of paper with phenol resin	20	0.1 (0.05–0.3)	
Paper production (1980s)			Rosen *et al.* 1984[b] Sweden
Laminated paper	23	0.3 (NR)	
Offset paper	8	0.2 (NR)	
Map printing (1985)	28	0.52 (0.03–1.46)	Gao *et al.* 1988[f] China

NR = not reported.
[a]Geometric mean. The authors noted that the simultaneous occurrence of phenol in summer interfered with the measurement method, resulting in artificially low values, and that occurrence of particulates (regardless of season) resulted in some high values due to off-gassing of formaldehyde from dust.
[b]Cited in IARC 2006.
[c]Range of means (or medians if denoted) and full range across two or three sets of data.
[d]Cited in WHO 1989.

[e]Median.
[f]Cited in Tang *et al*. 2009.

2.4.3 Manufacture of textiles and garments

Formaldehyde-based resins are used in the textile industry during the chemical finishing stage to impart crease-resistant and flame-retardant properties and to prevent shrinkage (IRSST 2006). Formaldehyde-based resins have been used for crease resistance since the 1950s. Early resins contained substantial amounts of extractable formaldehyde; however, modifications in the resins have decreased free formaldehyde levels from about 0.4% to 0.01% or less, which has also resulted in lower occupational exposure levels (IARC 2006). IARC (2006) reported the results of a study in which formaldehyde air levels increased from 0.1 to 1.0 ppm when formaldehyde content in the fabric increased from 0.015% to 0.04%. In another study, formaldehyde air levels in cutting rooms decreased from over 10 ppm in 1968 to less than 2 ppm in 1973 as a result of improvements in resin treatment processes (IARC 2006).

The finishing process involves impregnating the fabric in an aqueous solution and then pressing it to remove the excess solution (IRSST 2006). The main factors that affect worker exposure to formaldehyde include the types of processes and products used, the presence and efficiency of fume hoods and emission collection systems, and the level of general ventilation. Jobs that may result in formaldehyde exposure include resin preparer, process operators (various types), colorist, and maintenance worker. The main means of controlling exposure include use of formaldehyde-free finishes, the use of fume hoods at the source of emissions, sufficient general ventilation, and the use of personal protective equipment where formaldehyde levels are high.

In addition to gaseous formaldehyde exposure, workers can be exposed to formaldehyde bound to dust. IARC (2006) presented results of a study in a garment production facility in the United States where formaldehyde gas levels ranged from 26 to 36 $\mu g/m^3$ [0.02 to 0.03 ppm] and levels of formaldehyde bound to dust ranged from 0.2 to 0.7 $\mu g/m^3$ [0.0002 to 0.0006 ppm]. Workers in this industry may also be exposed to ammonia, dimethylthiourea, textile dyes, flame retardants, carrier agents, textile-finishing agents, and solvents (IARC 2006). The use of formaldehyde in garments can also result in formaldehyde exposure in retail shops and potentially of end users (ATSDR 1999, IARC 2006). Formaldehyde exposure levels associated with textile and garment manufacture are presented in Table 2-6.

Table 2-6. Formaldehyde exposure levels associated with the textile and garment industries

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Textile manufacture (NR)	19	0.53, 0.69 (0.11–1.33)[a]	NIOSH 1981[b] United States
Textile warehouse (NR)	22	0.25, 0.31 (0.04–0.73)[a]	NIOSH 1979a[b] United States
Textile facilities (NR)	43	0.7, 0.8 (< 0.1–1.4)[c]	NIOSH 1979b[b] United States
Textile and shoe industry Resin collar (1989, summer) Resin collar (1989, winter) Paint/production (2000)	 18 9 56	 NR (0.18–0.5) NR (1.13–4.5) 1.56 (0.33–3.5)	 Tao *et al.* 1990[d] Tao *et al.* 1990[d] Pan *et al.* 2001[d] China
Textile mills (1980s) Crease-resistance treatment Flame-retardant treatment	 29 2	 0. 2 (NR) 1.2 (NR)	Rosen *et al.* 1984[e] Sweden
Textile plant (1975–78) Finishing department mixing Crease-resistance treatment Flame-retardant treatment Other finish treatment Fabric store	 8 52 67 17 6	 0.8 (< 0.2– > 5.0) 0.4 (< 0.2– > 3) 1.9 (< 0.2– > 10) 0.3 (max. = 1.3) 0.8 (0.1–1.3)	Nousiainen and Lindqvist 1979[e] Finland
Garment manufacturing (NR)	32	0.16–0.24 (0.14–0.30)[a]	Echt and Burr 1997[e] United States
Sewing plant (NR) 0.04% formaldehyde fabric 0.015% formaldehyde fabric	 9 9	 1.0 (0.5–1.1) 0.1 (< 0.1–0.2)	Luker and Van Houten 1990[e] United States
Use of fabric treated with formaldehyde-based resins (1980s)	326	~0.2 (< 0.1–0.4)	Elliott *et al.* 1987[e] United States
Use of crease-resistant cloth (NR)	181	NR (< 0.1–0.9)	Blade 1983[e] United States
Clothing production warehouse (NR)	22	0.12, 0.39 (0.04–0.57)[a]	NIOSH 1979a[b] United States
Sewing machine operators (NR)	57	0.72, 1.2 (0.3–1.8)[a]	NIOSH 1979a[b] United States
Clothing pressers (NR)	40	0.07 (0.005–0.95)	NIOSH 1976a[b] United States
Permanent-press clothing production (NR)	41	0.31, 0.74 (0.0–2.7)[a]	USDHEW 1966, 1968[b] United States

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Cut & spread and turn & ticket operations (NR)	48	< 0.01–0.04 (NR)[f]	Kennedy *et al.* 1992[e] NR
Garment industry (1981–86)	50	0.1–0.2 (0.02–0.7)[a]	Heikkila *et al.* 1991[e] Finland
Shirt manufacturing (NR)	NR	NR (0.1–1.0)	Stayner *et al.* 1985, Stayner *et al.* 1988[g] NR
Garment manufacturing (NR)	168	0.19–0.46 (< 0.03–1.2)[a]	Blade 1983[b] NR
Fabric shops (NR)	77	0.14 (0.03–0.28)	McGuire *et al.* 1992[e] United States
Retail dress shops (1959)	NR	NR (0.1–0.5)	Elliott *et al.* 1987[e] United States
Fabric shops (1985–87)	3	0.17 (0.12–0.24)	Priha *et al.* 1988[e] Finland

NR = not reported.
[a]Means or range of means and full range across two to four datasets.
[b]Cited in WHO 1989.
[c]Medians and full range across two datasets.
[d]Cited in Tang *et al*. 2009.
[e]Cited in IARC 2006.
[f]Range of means for different measurements of formaldehyde as gas and bound to particulates.
[g]Cited in ATSDR 1999.

2.4.4 Foundries

The foundry process consists of pouring molten metal into a mold to obtain a cast product of specific shape. The mold can also contain a core that determines the dimensions of any internal cavity of the final product. Formaldehyde-based resins (both UF and PF) are commonly blended with sand to produce the molds and cores used in foundries (IARC 2006). Important manufacturing steps in the foundry process include manufacturing and assembling the molds and cores, melting the metal, pouring the metal into the mold, cooling the molded part, removing the mold and core (shake-out), and dressing and deflashing (IRSST 2006).

Tasks with potential formaldehyde exposure include molding-sand preparation, mold and core preparation, pouring of the molten metal into the mold, and shakeout operations (IRSST 2006). The main factors affecting worker exposure to formaldehyde include production variables (i.e., the molding and core-making processes employed and the types of metals processed), the percentage of free formaldehyde in the binder, the sizes of the molds and cores, the presence and efficiency of fume hoods and other emission collection systems, and the level of general ventilation (IRSST 2006). The main means of controlling formaldehyde exposure include use of mold and core-making materials that do not contain formaldehyde, replacement of hot-mold production processes with cold-hardening processes, using resins with lower emission rates, confinement of production

steps that produce formaldehyde emissions, installation of fume hoods at emission sources, sufficient general ventilation, and use of personal protective equipment for tasks where the formaldehyde concentration is high. In a study assessing formaldehyde levels in foundry sand, Oliva-Teles *et al*. (2009) reported that formaldehyde content in used foundry sands decreased with time, as formaldehyde was released to the occupational environment. Data presented by Heikkilä *et al.* (1991) (as cited in IARC 2006) showed major reductions in formaldehyde exposure levels for core-making operations from the 1970s to the 1980s (see Table 2-7).

Other chemicals to which workers potentially are exposed in the foundry industry include silica and other mineral dusts, polycyclic aromatic hydrocarbons, asbestos, metal fumes and dusts, carbon monoxide, isocyanates, phenols, organic solvents, and amines (IARC 2006).

Table 2-7. Formaldehyde exposure levels associated with foundries

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Iron foundry core machine operator (NR)	14	0.43[a] (< 0.02–18.3)	NIOSH 1979b[b] United States
Bronze foundry, core machine operator (NR)	15	0.39, 0.53 (0.12–0.80)[c]	NIOSH 1976c[b] United States
Foundries (before 1975 through 1986)			Heikkila *et al.* 1991[d]
Core-making before 1975	43	2.8 (< 0.1–> 10)	Finland
Core-making 1981–86	17	0.3 (0.02–1.4)	
Casting 1981–86	10	0.2 (0.02–0.2)	
Molding 1981–86	25	0.3 (0.04–2.0)	
Foundry molder (NR)	36	0.1 (0.02–0.22)	Ahman *et al.* 1991[d] Sweden
Foundry (1980s)			Rosen *et al.* 1984[d]
Hot-box method	5	1.5 (NR)	Sweden
Molding	17	0.1 (NR)	

NR = not reported.
[a]Median.
[b]Cited in WHO 1989.
[c]Means and full range across two datasets.
[d]Cited in IARC 2006.

2.4.5 Production of formaldehyde-based plastic products

Formaldehyde-based resins (UF, MF, and PF) are used as hardenable molding materials in plastics that are used to produce a number of end products, including electrical insulation, melamine tableware, lawn and garden equipment, plumbing fixtures, and various other products (WHO 1989, OSHA 1990, ATSDR 1999, IARC 2006). A growing application for UF and MF molded compounds is to cut the cured resin into small, granular-sized particles for use as an alternative to sand in sandblasting operations (TIG 2005). Polyoxymethylene (also called acetal resin, polytrioxane, or paraformaldehyde) is

a very strong and hard plastic that is formed through the polymerization of formaldehyde and is an important engineering polymer commonly used to make gears, bushings, and other mechanical parts (WHO 1989, ATSDR 1999, DuPont 2009). Because polyoxymethylene is lightweight and harder, tougher, and longer lasting than other plastics, it is used in many applications where metals previously were used, such as in motor vehicles, machine parts, household appliances, and plumbing fixtures. Formaldehyde also has been used for synthesizing polyols, such as pentaerythritol and trimethylolpropane, which are used to manufacture polyurethane plastic and alkydes [alkyds] (KEMI 1993); however, no information on formaldehyde release or occupational exposure was found for this use.

In 1990, OSHA noted that the plastics industry was the second-largest user of formaldehyde, behind the compressed-wood industry, and that formaldehyde-based resins used in the production process were capable of releasing formaldehyde when subjected to heat or compression during the molding process (OSHA 1990). IRSST (2006) noted that the plastics production industry is continually evolving and that various starting materials and manufacturing processes are used; however, regardless of the process or the type of plastic being manufactured, the heating stage will result in the most significant formaldehyde emissions.

Exposure levels depend primarily on the materials used, the processes employed, the presence and efficiency of emissions collection systems, and the level of general ventilation at the production facility (IRSST 2006). Exposure-reduction methods include confinement of production steps that produce formaldehyde emissions, installation of fume hoods above the emission sources, adequate general ventilation, and the use of personal protective equipment for tasks where formaldehyde concentrations are high.

IARC (2006) noted that plastic dust and fumes may be present in the atmosphere of molded-plastic plants, and exposures in these facilities are usually considerably higher than those in facilities where the products are used. It also was noted that workers in these plants might have been exposed to pigments, lubricants, and fillers (e.g., asbestos and wood flour) during some production processes. Table 2-8 presents formaldehyde exposure levels for this industry.

Table 2-8. Formaldehyde exposure levels associated with production of plastics and plastic products

Industry (year measured)	N	Exposure level mean (range) (ppm)	Reference Location
Particleboard and molded plastics plant (NR)	NR	0.69 (0.17–2.93)[a]	Horvath *et al.* 1988[b] United States
Production of molded plastic products (1983–84)			Stewart *et al.* 1987a[d] United States
Phenol resin	10	0.5[c] (0.1–0.9)	
Melamine resin	13	9.2[c] (< 0.01–26.5)	
Molding compound manufacture (1983–84)			Stewart *et al.* 1987a[d] United States
Plant 9, winter	9	2.8[c] (0.04–6.7)	
Plant 9, summer	18	38.2[c] (9.5–60.8)[e]	
Plant 1, winter	12	1.5[c] (0.9–2.0)	
Plant 1, summer	24	9.7[c] (3.8–14.4)	
Plant 8, winter	13	0.3[c] (0.07–0.7)	
Plant 7, summer	43	0.3[c] (0.05–0.6)	
Plant 2, summer	15	6.5[c] (0.3–20.6)	
Resin and plastic materials production (NR)	NR	1.39[f] (NR)	NIOSH 1980a[g] United States
Vinylon production	NR	2.0 (0.8–4.7)	Jin and Zhu 1992[h] China
Hexamine workshop	NR	0.6 (NR)	Dai and Bao 1999[h] China
Polyacetal workshop	NR	0.8 (NR)	Dai and Bao 1999[h] China
Plastics manufacturing (NR)	9	max. < 0.1	Tikuisis *et al.* 1995[d] Canada
Plastics production (1981–86)			Heikkila *et al.* 1991[d] Finland
Casting of polyacetal resin	10	0.3 (0.06–0.7)	
Casting of UF resin	4	0.4 (0.2–0.5)	
Casting of other plastics	29	< 0.1 (< 0.1–0.2)	

NR = not reported.
[a]Mean and range of TWAs. Data also presented in Table 2-2.
[b]Cited in ATSDR 1999.
[c]Geometric mean.
[d]Cited in IARC 2006.
[e]Some results were affected by the simultaneous occurrence in samples of particulates containing formaldehyde, leading to high values.
[f]Data also presented in Table 2-1.
[g]Cited in WHO 1989.
[h]Cited in Tang *et al*. 2009.

2.4.6 Embalming

Embalming is a procedure that delays the decomposition of a cadaver. To accomplish this, the embalmer injects into either the common carotid or femoral artery usually 12 to 18 L of an aqueous solution of formaldehyde at a concentration ranging from about 1.25% to 32%, depending on how much the body has changed since death (IRSST 2006). Formaldehyde is used as a tissue preservative and disinfectant in the embalming fluids, which contain smaller amounts of other chemicals such as methanol, diethylene glycol, propylene glycol, phenol, benzoic acid, and fragrances (ATSDR 1999, IARC 2006). Although embalming was one of formaldehyde's first and best-known uses, it now accounts for less than 1% of total consumption (GI 2006).

Exposure to formaldehyde can occur during the solution preparation and during the embalming operation. The main factors affecting exposure include the concentration of formaldehyde in the embalming fluid, the quantity of solution used, the number of workstations and the number of bodies handled daily, physical characteristics of the cadaver (e.g., condition, size, time since death), presence and efficiency of fume hoods or local collection systems at the emission source, and the level of general ventilation. Embalming of a normal intact body generally is completed within 1 to 1.5 hours, with 10 to 35 minutes spent using formaldehyde (IRSST 2006). In the case where the cadaver is in an advanced state of putrefaction or has undergone an autopsy, embalming can take up to 3 hours, with up to 2 hours spent using formaldehyde. Formaldehyde-based or paraformaldehyde-based jellies or powders can be prepared and applied to wounds of the cadaver.

IARC (2006) noted that mean formaldehyde exposure levels from embalming operations are generally around 1 ppm. Embalming of autopsied bodies generally results in higher exposure levels than embalming of intact bodies. Airborne formaldehyde concentrations in seven funeral homes in the United States in 1980 ranged from 0.12 to 0.42 mg/m^3 [0.1 to 0.34 ppm] during the embalming of non-autopsied bodies and from 0.6 to 1.4 mg/m^3 [0.49 to 1.14 ppm] during the embalming of autopsied bodies (Williams *et al.* 1984, as cited in WHO 1989). Table 2-9 summarizes exposure levels associated with embalming operations.

Methods to reduce formaldehyde exposure include product substitution and modifications of work areas and work practices. Although embalming solutions are available that do not contain formaldehyde (e.g., phenoxyethanol), none is the subject of consensus in the embalming industry (IRSST 2006). Work-station modifications that can reduce exposure include confining difficult embalming cases; physically separating embalming tasks from restoration tasks (i.e., aesthetic care and dressing in funeral homes); installation and proper use of capture equipment at the source, such as hoods over the injection equipment; and design of work stations to ensure adequate ventilation. In one study of 22 funeral-service embalming operations, formaldehyde levels were significantly lower (P = 0.0001) when general ventilation was turned on during the procedure (0.21 ppm) than when general ventilation was turned off (0.55 ppm) (Holness and Nethercott 1989).

General work practices that will reduce exposure include closing jars promptly when not in use, prompt disposal of formaldehyde soaked rags, proper storage and disposal of

products, and periodic equipment inspections (IRSST 2006). Personal protective equipment should be used during procedures involving high formaldehyde concentrations.

Embalmed cadavers and animals used in gross human and veterinary anatomy laboratories usually are prepared with a formaldehyde-based embalming fluid. During the process of dissection, formaldehyde vapors are emitted from the cadavers, resulting in the exposure of medical students and their instructors to potentially elevated formaldehyde levels (Ohmichi *et al.* 2006b). Levels have been shown to increase when body-cavity or deep structures were being dissected. Levels also have been shown to be higher in the center of the room than in the corners. Various types of exposure reduction technologies have been reported in the literature (Nacher *et al.* 2007, Ohmichi *et al.* 2007, Whitehead and Savoia 2008). Tang *et al.* (2009) presented the results of a study that demonstrated that even when anatomy laboratories were not in use, minimum formaldehyde concentrations were still above 0.25 mg/m^3 [0.2 ppm], with one measurement as high as 20.94 mg/m^3 [17 ppm]. Table 2-9 provides exposure levels seen in anatomy laboratories.

Table 2-9. Formaldehyde exposure levels associated with embalming or autopsies or in anatomy laboratories

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Embalming			
Embalming in funeral homes (NR) Personal samples Area samples	 4 4	 0.16 (NR) NR (< 0.1–0.15)	Korczynski 1996[a] United States
Embalming (NR)	75	2.2–2.6 (0.2–8.7)[b]	Stewart *et al.* 1992[a] United States
Embalming in mortuaries (NR)	NR	1.1 (0.03–3.2) 0.2 (0.01–0.5) (TWA)	Lamont Moore and Ogrodnik 1986[a] United States
Embalming in funeral homes (NR)	13	1.1, 2.7 (0.2–3.99)[b]	NIOSH 1980c[c] United States
Embalming in funeral homes: 6 facilities (NR)	187	0.74 (0.09–5.26)	Kerfoot and Mooney 1975[a,c] United States
Embalming (NR) Personal samples Area samples	 48 72	 0.6 (0.09–4.6) 0.5 (0.04–6.8)	Korczynski 1994[a] Canada
Embalming in funeral homes (1980) Intact bodies Autopsied bodies	 8 15	 0.3 (0.18–0.3)[d] 0.9 (0–2.1)	Williams *et al.* 1984[a] NR
Anatomy and biology laboratories and autopsies			
Anatomy laboratory, dissecting (NR)	15	0.9 (0.3–2.6)	Keil *et al.* 2001[a] United States

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Anatomy laboratory, dissecting (NR)			Akbar-Khanzadeh and Mlynek 1997[a]
Personal samples	44	1.9 (0.3–4.5)	United States
Area samples	76	1.0 (0.6–1.7)	
Anatomy laboratory, dissecting (NR)			Akbar-Khanzadeh *et al.* 1994[a]
Personal samples	32	1.2 (0.07–2.9)	United States
TWA personal samples	NR	0.4 (0.09–0.95)	
Area samples	13	1.4 (0.9–1.8)	
TWA area samples	2	1.7 (1.0–2.3)	
Anatomy laboratory, dissecting (1982–83)			Korky *et al.* 1987[a]
Laboratory	NR	NR (7.0–16.5)	United States
Stock room	NR	NR (2.0–2.6)	
Public hallway	NR	NR (< 1.0)	
Autopsy (NR)			Coldiron *et al.* 1983[a]
Personal samples	27	1.3 (0.4–3.3)	United States
Area samples	23	4.2 (0.1–13.6)	
Biology teaching (NR)	8	8.3 (2.75–14.8)	EPA 1981[c] United States
Pathology autopsy room (NR)	6	4.35 (2.2–7.9)	NIOSH 1979b[c] United States
Medical college anatomy labs			
(1998)	2	3.36 (NR)	Li *et al.* 1999[e]
(1999)	12	0.87 (NR)	Ye *et al.* 2000[e]
(2002)	3	6.8 (4.8–9.0)	Peng *et al.* 2003[e]
(2002)	2	NR (10.5–17.0)	Zhang *et al.* 2007d[e]
(2006)	9	0.27 (0.03–3.2)	Lu *et al.* 2007[e] China
Medical college teacher offices			
(1998)	2	0.31 (NR)	Li *et al.* 1999[e]
(1999)	12	0.16 (NR)	Ye *et al.* 2000[e]
(2006)	9	0.03 (NR)	Lu et al. 2007[e] China
Medical college corridors			
(1999)	14	0.26 (NR)	Ye *et al.* 2000[e]
(2006)	9	0.05 (NR)	Lu et al. 2007[e] China
Anatomy laboratory, dissecting (NR)	NR	NR (0.11–0.62)	Tanaka *et al.* 2003[a] Japan
Biology laboratory, dissecting (NR)	36	0.20, 0.51 (0.08–1.2)[b]	Dufresne *et al.* 2002[a] Canada
Anatomy laboratory, dissecting (NR)	NR	NR (max. < 4.0)	Burgaz *et al.* 2001[a] Turkey

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Anatomy laboratory, dissecting (NR)	NR	0.22 (0.11–0.33)	Wantke *et al.* 2000[a] Austria
Anatomy/histology laboratory, dissecting (NR)	48	3.0 (0.2–9.1)	Kim *et al.* 1999[a] NR
Anatomy laboratory, dissecting (NR)	25	0.4 (0.06–1.04)	Ying *et al.* 1997, Ying *et al.* 1999[a]
	NR	2.4 (NR)	He *et al.* 1998[a] China
Anatomy laboratory, dissecting (NR)	NR	0.12 (0.06–0.22)	Wantke *et al.* 1996b[a] Austria
Autopsy (1981–86)	5	0.7 (< 0.1–1.4)	Heikkila *et al.* 1991[a] Finland
Anatomical theater (1980–88)	29	1.1[f] (0.7–1.7)	Triebig *et al.* 1989[a] Germany
Animal dissection laboratory (NR)	24	0.15, 0.18 (0.05–1.04)[b]	Blade 1983[c] NR
Anatomy classrooms, 1998	4	2.0 (NR)	Li *et al.* 1999[e]
Pathology autopsy room (NR)	10	4.8 (0.06–7.9)	Covino 1979[c] NR
Autopsy room (NR)			Makar *et al.* 1975[c]
Personal sampling for a resident	10	1.58 (NR)	NR
Personal sampling for a pathologist	9	1.24 (NR)	
Personal sampling for a technician	2	0.57 (NR)	
Area sampling for assistants	23	0.72 (0.13–13.57)	

NR = not reported; TWA = time-weighted average.
[a]Cited in IARC 2006.
[b]Range of means and full range across two to three datasets.
[c]Cited in WHO 1989.
[d]No explanation provided for the mean being equal to the high end of the range.
[e]Cited in Tang *et al*. 2009.
[f]Median.

2.4.7 Histology

Histopathology laboratories receive organ, tissue, or cell specimens in which to study structural modifications in support of diagnosis and prognosis of disease, and formalin is commonly used to preserve these samples (IARC 2006, IRSST 2006). The main steps in the process include preparing formaldehyde solutions (diluting the formalin solution to roughly 4% formaldehyde), macroscopic examination of the specimen with the naked eye, placing the samples in cassettes (for the tissue preparer), and microscopic observation (IRSST 2006). Specific tasks that may result in exposure to formaldehyde include preparing the formaldehyde solution, handling and disposing of specimens, handling waste (such as draining specimens), handling and cleaning used jars, handling bags of medical waste, maintaining equipment, and recycling and discarding

formaldehyde solution. Equipment leaks are another potential source of exposure (e.g., leaks from the tissue preparer, formaldehyde recycler, specimen storage, and storage of new and waste formaldehyde solutions). Workers who might be occupationally exposed include pathologists, technicians, technical assistants, and administrative personnel (IRSST 2006).

IARC (2006) noted that the typical mean formaldehyde exposure level in pathology operations is approximately 0.5 ppm. Table 2-10 summarizes exposure levels associated with histology operations.

One way in which formaldehyde exposure can be reduced in histology operations is through substitution of other chemicals. Because of increasing concern about health effects associated with formaldehyde exposure, a number of proprietary fixatives have been developed that do not contain formaldehyde. Although a number of these fixatives have been successfully used in the United States, none are the subject of consensus, and formaldehyde-based fixatives generally are considered superior (Titford and Horenstein 2005, IRSST 2006). Other exposure-reduction methods include the use of hoods and other ventilation methods and wearing of personal protective equipment for tasks where the formaldehyde concentration is high (IRSST 2006).

Table 2-10. Formaldehyde exposure levels associated with histology and pathology laboratories

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Histopathology teaching laboratory (NR)	16	0.3 (NR)	Tan *et al.* 1999[a] United States
Histology laboratory, tissue specimen preparation and sampling (NR)	NR	NR (0.2–1.9)	Kilburn *et al.* 1985a[a] United States
Hospital pathology rooms (2005) (2003) (2003)	 8 40 85	 NR (0.07–1.5) NR (0.15–0.76) 1.3 (0.15–4.8)	 Li and Li 2007[b] Cheng *et al.* 2004[b] Fan *et al.* 2006[b] China
Histology laboratory (NR) Laboratory assistants/technicians Physicians and orderlies	 NR NR	 0.4 (0.04–0.7) 2.2 (0.7–5.6)	Shaham *et al.* 2002[a] Israel
Pathology laboratory (NR)	10	NR (max. < 2.0)	Burgaz *et al.* 2001[a] Turkey
Medical college specimen workshops (1998)	2	0.9 (NR)	Li *et al.* 1999[b] China
Medical college specimen rooms (1998)	2	10.4 (NR)	Li *et al.* 1999[b] China

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Histology laboratory (NR) Area samples Personal samples	 NR NR	 NR (1.4–1.6) NR (2.8–3.1)	Shaham *et al.* 1996a, Shaham *et al.* 1996b[a] Israel
Hospital histopathology laboratories (1981–86)	80	0.5 (0.01–7.3)	Heikkila *et al.* 1991[a] Finland
Pathology laboratories (1980–88)	21	0.5[c] (< 0.01–1.6)	Triebig *et al.* 1989[a] Germany
Pathology laboratory (1980s)	13	0.5 (NR)	Rosen *et al.* 1984[a] Sweden

max. = maximum; NR = not reported.
[a]Cited in IARC 2006.
[b]Cited in Tang *et al*. 2009.
[c]Median.

2.4.8 Construction-related exposures

There are many potential sources of exposure to formaldehyde in the construction industry; however, data are limited on exposure levels for most of these sources. Construction workers who varnish floors can have high exposures. IARC (2006) noted that formaldehyde levels during varnishing with UF-based varnishes have been measured at levels ranging from 2 to 5 ppm during a 30-minute application period, and that workers may apply 5 to 10 coats per day. These workers are also potentially exposed to wood dust and various solvent vapors from varnishes, putties, and adhesives.

Working with UFFI or fiberglass insulation manufactured using formaldehyde-based resins also can result in formaldehyde exposure (IARC 2006); however, no data on exposure levels associated with this activity were identified.

Since the 1980s, glass-fiber mats have become an important material for roof shingles, asphalt roofing tiles, and roll roofing (TIG 2005). UF and occasionally PF resins are used as binders to hold the glass fibers together until an asphalt coating is applied. No information was found on exposure levels from their use.

Machining of wood-based composites and other formaldehyde-containing wood products are other sources of exposure in the construction industry; however, IARC (2006) noted that formaldehyde exposure levels from this activity are consistently low. Formaldehyde exposure levels associated with construction-related activities are presented in Table 2-11.

Table 2-11. Formaldehyde levels associated with construction-related activities

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
UFFI dealing and installation (NR)	82	1.05–1.56 (0.3–3.1)[a]	NIOSH 1979b[b] United States
Fiberglass insulation installation (NR)	13	0.023 (0.007–0.033)	NIOSH 1980a[b] United States
Varnishing parquet with UF varnish (1976 & 1987)	16	2.9, 4.3 (0.3–6.6)[c]	Heikkila *et al.* 1991[d] and Riala and Riihimaki 1991[d] Finland
Insulating buildings with UFFI (1980s)	6	0.1 (NR)	Rosen *et al.* 1984[d] Sweden
UFFI dealing and installation (NR)	NR	NR (0.07–2.0)	Herrick *et al.* 1983[b] NR
Sawing particleboard at construction site (1967)	5	< 0.5 (NR)	FIOH 1994[d] Finland

NR = not reported.
[a]Range of means and full range across three datasets.
[b]Cited in WHO 1989.
[c]Means and full range across two studies.
[d]Cited in IARC 2006.

2.4.9 Fiberglass and mineral-wool insulation manufacturing

PF resins commonly are used to bind fiberglass, mineral wool, or shredded waste products such as cotton, wool, or polyester for use as structural and acoustical insulation for residential and commercial buildings, pipes, and industrial equipment. Fiberglass insulation accounts for 90% of formaldehyde consumption in this industry (Bizzari 2007). In fiberglass and mineral-wool insulation, UF resins often are used in conjunction with PF resins to inhibit the burning potential of the PF resins (TIG 2005).

Fiberglass insulation manufacturing involves six general steps: melting glass, spinning the molten glass into fibers, cooling and coating the fibers with a binder, forming the fibers into a pad, curing the binder (i.e., heating at 400°F to 600°F to set the binder), and packaging the insulation (Milton *et al.* 1996). The primary sources of formaldehyde release are from the fiber-coating process and the curing process. IARC (2006) described measurements taken in the 1980s and noted that very high levels occasionally were measured in close proximity to these two operations. Measured formaldehyde levels associated with fiberglass insulation are presented in Table 2-12. No data were found on exposure levels associated with manufacture of insulation from materials other than fiberglass or synthetic vitreous fibers.

Table 2-12. Formaldehyde exposure levels associated with fiberglass manufacturing

Industry (year measured)	N	Exposure level mean (range), in ppm	Comment	Reference Location
Fiberglass manufacturing plant (NR)				Milton *et al.* 1996
Area sampling	50	0.04–0.42 (max. = 1.02)	Range of means for area sampling at four different locations; maximum concentration found at forehearth.	United States[a]
Personal sampling	197	0.017–0.070 (NR)	Range of mean TWA concentrations from personal sampling of 37 workers.	
Synthetic vitreous fiber plant (1981–86)	60	0.09, 0.20 (0.01–1.5)	Means and full range across production and form-pressing operations.	Heikkila *et al.* 1991[b] Finland
Insulation manufacture				Tao *et al.* 1990[c]
(1989, summer)	8	NR (0.12–0.32)		China
(1989, winter)	8	NR (0.52–0.76)		
Synthetic vitreous fiber plant (1980s)	20	0.15, 0.16 (NR)	Mean values for production and form-pressing operations.	Rosen *et al.* 1984[b] Sweden

NR = not reported; TWA = time-weighted average.
[a]Cited in ATSDR 1999 and IARC 2006; data presented here are from the original article, which was reviewed because of questions raised during review of IARC and ATSDR documents.
[b]Cited in IARC 2006.
[c]Cited in Tang *et al*. 2009.

2.4.10 Firefighting and other combustion-related exposures

As noted in Section 2.2.2, combustion processes are one of the major sources of formaldehyde in the environment. IARC (2006) reviewed three studies that assessed firefighters' levels of personal exposure to formaldehyde during various stages of firefighting, with concentrations measured up to 8.3 ppm (see Table 2-13). Formaldehyde was detected in 6 of 24 samples (25%) in one study and 73% of samples in a second study; the percentage was not reported for the third study. In a comprehensive air-monitoring study to characterize exposure of firefighters during 25 structure fires, formaldehyde levels exceeded 0.1 ppm (which was cited as the National Institute for Occupational Safety and Health [NIOSH] ceiling recommended exposure limit [see Section 2-7]) at 22 of the 25 fires. Firefighters might also be exposed while fighting wildfires. Results of two studies, in which formaldehyde was detected in all samples, showed concentrations that ranged from 0.02 to 0.3 ppm.

Because formaldehyde is emitted from internal combustion engines, workers in any occupation that involves exposure to exhaust from automobile or other internal combustion engines potentially are exposed to formaldehyde. In a study of occupational

exposure to volatile organic compounds (VOCs) and aldehydes in the U.S. trucking industry, Davis *et al.* (2007) measured formaldehyde at the perimeter of trucking terminal yards (i.e., considered background levels), at indoor work areas (i.e., at loading docks and mechanic shops), and in on-road truck cabs (i.e., driver exposures). The mean background level was reported to be 3.33 μg/m^3 [0.002 ppm], and higher exposure levels were reported for the indoor work areas than in on-road truck cabs (Table 2-13). Zhang *et al.* (2003) (as cited in IARC 2006) reported a slightly higher mean level for automobile garages (0.03 ppm) than the mean level for the mechanics shop (13.72 μg/m^3 [0.01 ppm]) reported by Davis *et al.* (2007). Pang and Mu (2007) assessed carbonyl exposures from public vehicles in Beijing, China, noting that taxi and bus drivers can have high levels of formaldehyde exposure as a result of high concentrations and long work hours. They also noted that in-vehicle carbonyl concentrations were loosely associated with vehicular service years and type of fuel used. All drivers were asked to refrain from smoking during this study. Formaldehyde exposure levels for these studies are presented in Table 2-13.

IARC (2006) reported exposure levels ranging up to 0.5 ppm for lumberjacks using chainsaws and up to 21 μg/m^3 [0.017 ppm] in personal air samples from French policemen working close to traffic. Pilidis *et al.* (2009) reported exposure levels for policemen in outdoor environments (car, motorcycle, and foot patrol, guards, and traffic regulation) that ranged from about 3 to 25 μg/m^3 [0.002 to 0.02 ppm].

Table 2-13. Formaldehyde exposure levels associated with firefighting and other combustion sources

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Firefighting, city fire (1998)	96	0.25 (0.02–1.2)	Bolstad-Johnson *et al.* 2000[a] United States
Firefighting, city fire (NR)	(22 fires)		Jankovic *et al.* 1991[a] United States
Knockdown[b]		NR (ND–8.0)	
Overhaul[b]		NR (ND–0.4)	
Inside mask		NR (ND–0.3)	
Firefighting, city fire (1986)	24	0.55 (0.1–8.3)[c]	Brandt-Rauf *et al.* 1988[a] United States
Wildland fire fighting (1990 & 1989)	35	0.05, 0.13 (0.02–0.3)[d]	Reh *et al.* 1994[a] and Materna *et al.* 1992[a] United States
Trucking industry (2004–06)			Davis *et al.* 2007 United States
In cab (nonsmokers)	234	0.007 (NR)	
In cab (smokers)	62	0.008 (NR)	
Loading dock	65	0.021 (NR)	
Mechanic shop	17	0.011 (NR)	

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Public transportation vehicles (NR)			Pang and Mu 2007
Taxis	35	0.020, 0.023 (0.011–0.028)	China
Buses	15	0.013–0.033 (0.011–0.076)	
Chain-sawing (NR)	NR	< 0.1 (< 0.1–0.5)	Heikkila *et al.* 1991[a] Finland
Chain-sawing (NR)	NR	0.05 (0.02–0.11)	Hagberg *et al.* 1985[a] Sweden
Automobile garage (NR)	53	0.03 (NR)	Zhang *et al.* 2003[a] NR
Policemen working close to traffic center (NR)			Maitre *et al.* 2002[a] France
Summer	[32][e]	0.011[f] (NR)	
Winter	[32][e]	0.017[f] (NR)	
Policemen (2006)			Pilidis *et al.* 2009
Vehicle patrol	5	~0.02–0.028 (0.016–0.031)[g]	Greece
Motorcycle patrol	4	~0.022–0.028 (0.016–0.032)[g]	
Foot patrol	2	~0.015, 0.015 (0.014–0.024)[g]	
Guards	2	~0.011, 0.019 (0.010–0.021)[g]	
Traffic regulation	3	~0.017–0.030 (0.015–0.034)[g]	

ND = not detected; NR = not reported.
[a]Cited in IARC 2006.
[b]"Knockdown" is when the main body of the fire is brought under control; "overhaul" refers to searching for and extinguishing hidden fires.
[c]The mean and range do not include 18 values that were noted as 0 in the original paper.
[d]Means and full range across two studies.
[e]Personal sampling performed for 8 policemen, four days each in summer and winter.
[f]Median.
[g]Estimated from graph.

2.4.11 Agriculture and aquaculture

In agricultural settings, formaldehyde has been used as a preservative for fodder, a disinfectant in brooding houses, a sterilant in mushroom houses, and a preservative for produce (ATSDR 1999, IARC 2006). Levels as high as 7.8 ppm have been reported when formaldehyde was used for disinfection of eggs in brooding houses; however, IARC (2006) noted that annual exposures are likely to be low, because the operation is performed only intermittently (roughly 5 to 10 times per year). Formalin solutions have been used in aquaculture to treat fish eggs to control infection (IARC 2006), with treatment times ranging from 15 to 90 minutes. Urea-formaldehyde concentrates are used in the manufacture of controlled-release fertilizers (Bizzari 2007); however, no information was found on exposure to formaldehyde from application of these products. [Although there is the potential for occupational exposure from agricultural applications of controlled-release fertilizers, their primary uses are nonagricultural, such as on lawns and turfs and in nurseries (Bizzari 2007).] Formaldehyde exposure levels associated with agriculture and aquaculture are presented in Table 2-14.

Table 2-14. Formaldehyde exposure levels associated with agriculture and aquaculture

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Fish hatchery, treating fish eggs (NR)			Lee and Radtke 1998[a]
Personal monitoring of 6 employees	6	NR (NQ–0.8)	United States
Area monitoring during treatment operations	6	NR (< 0.05–0.7)	
TWA concentrations	6	0.02 (0.006–0.038)	
Mushroom farming (NR)	18	2.68 (ND–> 10)[b]	NIOSH 1980b[c] United States
Handling of fodder (1982)	NR	NR (0.02–0.4)	Heikkila *et al.* 1991[a] Finland
Disinfection of eggs (1981–86)	11	2.6 (0.2–7.8)	Heikkila *et al.* 1991[a] Finland

ND = not detected; NQ = not quantifiable; NR = not reported.
[a]Cited in IARC 2006.
[b]Upper end of range reported as "12+" (mg/m^3) in WHO 1989. Range is across three datasets; the mean was reported for only one of these datasets.
[c]Cited in WHO 1989.

2.4.12 Office buildings and nonindustrial work places

There are numerous sources of formaldehyde in office buildings, restaurants, commercial buildings, and other nonindustrial work places. These sources include paint and varnish, carpeting, wallpaper, insulation, furniture, and laser printers (ATSDR 1999, IARC 2006). In a study that assessed exposure of policemen performing several types of activities (i.e., vehicle or foot patrol, traffic regulation, guarding outside the police station building, and office work), Pilidis *et al.* (2009) found that officers working indoors had significantly higher exposure than those working outdoors. Table 2-15 presents exposure-level data for offices and other nonindustrial work places. IARC (2006) noted that laser printers have been found to be a source of formaldehyde exposure as a result of ozonolysis reactions with VOCs emitted from the toner. IARC (2006) also noted that newer-technology laser printers did not produce detectable levels of formaldehyde.

Table 2-15. Formaldehyde exposure levels in offices and other nonindustrial work places

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Office buildings: 6 buildings (1996–97)	72	0.001–0.011[a] (NR)	Reynolds *et al.* 2001[b] United States
Offices (1981–84)	25	0.065[c] (NR)	Shah and Singh 1988[b] United States
Offices and commercial buildings: 4 establishments (NR)	NR	NR (0.01–1.01)	Konopinski 1983[d] United States
Office buildings: 23 buildings for which air-quality complaints had been filed but for which there were no clear, unusual sources for chemical pollutants (2001–06)	76	0.009 (max. = 0.036)	Salonen *et al.* 2009 Finland
Offices: summary of results from 9 studies (1996–2005)	351	0.21 (0.047–1.83) (Overall mean and range of individual means)	Tang *et al*. 2009 China
Office buildings: 5 buildings, 8-hour average concentrations (NR)	54	0.11–0.97 (NR)	Wu *et al.* 2003[b] Taiwan, China
Offices (NR) Conventional offices (18 sites) Portable office buildings (20 sites)	 NR 40	 0.022 (0.01–0.08) 1.1 (0.4–2.1)	Dingle *et al.* 2000[b] Australia
Offices (1995–96) Recently painted with low-emitting paint Three months after painting Control	NR	 0.015 (0.013–0.016) 0.007 (0.006–0.008) 0.007 (0.0065–0.0073)	Wieslander *et al.* 1999a[b] Sweden
Offices (1995)	11	0.033 (0.01–0.08)	Brickus *et al.* 1998[b] Brazil
Nonindustrial workplaces and restaurants (1995)	12	0.017 (0.004–0.05)	Miguel *et al.* 1995[b] Brazil
Office work (NR)	NR	0.07[c] (0.07–0.13)[e]	Holmström *et al.* 1989b[d] NR
Office building (NR) Nonsmoking office Office that allowed smoking	NR	 NR (ND–0.22) NR (ND–0.6)	Sterling *et al.* 1987[d] NR
Offices (NR) Aged 1–3 years Aged 11–43 years	NR	 0.12 (NR) 0.07 (NR)	Kalinic *et al.* 1985[f] Yugoslavia
Offices (NR) Smokers Nonsmokers	NR	 0.04 (0.01–0.11) 0.04 (0.02–0.08)	Prescher 1984[f] Germany

Operation (year measured)	N	Exposure level mean (range), in ppm	Reference Location
Office work (NR)	48	< 0.04, 0.06 (0.02–0.12)[g]	Blade 1983[f] NR
Commercial buildings (NR) Offices Stores Furniture stores	NR	 0.88 (NR) 2.11 (NR) 0.12 (NR)	Kuljak 1983[f] Yugoslavia

ND = not detected; NR = not reported.
[a]Geometric means.
[b]Cited in IARC 2006.
[c]Median.
[d]Cited in ATSDR 1999.
[e]The median is a year-round median concentration, but the range is only for late summer.
[f]Cited in WHO 1989.
[g]Means for two studies. The range is from one dataset; the other dataset reported the range as < 0.04 ppm.

2.4.13 Other occupational exposures

Formaldehyde has been used in the treatment of furs and leather (IARC 2006). Its use in the treatment of furs resulted in the highest formaldehyde exposure levels for all jobs and industries studied in a large Swedish survey in the early 1980s. The eight-hour TWA concentration of formaldehyde was reported to be 0.8 to 1.6 ppm, and high peak exposures occurred several times per day. Formaldehyde concentrations of 0.5 to 7 ppm have been measured in leather-tanning facilities (ATSDR 1999), and a mean level of 0.2 ppm has been reported for taxidermy operations in Sweden (IARC 2006).

Formaldehyde has been used extensively in hospitals and healthcare facilities (IARC 2006). ATSDR (1999) noted that numerous types of healthcare professionals (e.g., pharmacists, physicians, veterinarians, dentists, nurses) can be exposed to formaldehyde vapors during the preparation, administration, or cleanup of various medicines. IARC (2006) reported exposure levels associated with the use of formaldehyde as a disinfectant in hospitals, showing mean levels ranging from 0.05 to 0.8 ppm, with levels as high as 5.1 ppm. Formaldehyde levels as high as 288 $\mu g/m^3$ [0.23 ppm] were measured in a hospital operating room where it was used as a disinfectant (Dascalaki *et al.* 2008). Formaldehyde also has been detected in the plume of surgical smoke produced by electrocautery, harmonic scalpel, and argon beaming (Krones *et al.* 2007).

Formaldehyde has been used as a biocide in the oil processing industry (Steinsvag *et al.* 2007); however, the authors noted that formaldehyde appears to have been replaced by other biocides and was phased out before 2002. Mean measured airborne exposure levels were 0.13 mg/m^3 [0.11 ppm] (range = 0.06 to 0.29 mg/m^3 [0.05 to 0.24 ppm]) for personal sampling and 0.21 mg/m^3 [0.17 ppm] (range = 0.05 to 0.53 mg/m^3 [0.04 to 0.43 ppm]) for stationary monitoring of Norwegian offshore oil drilling installations during 1999 and 2000.

In a study assessing exposure of nail technicians to formaldehyde and toluene, a mean airborne formaldehyde exposure level of 0.022 ppm was calculated based on personal air sampling at 30 nail salons in California (McNary and Jackson 2007).

Formaldehyde has been measured in studies assessing exposure of workers to metalworking fluids in a secondary aluminum plant (Godderis *et al.* 2008) and in machine shops (Lillienberg *et al.* 2008). Godderis *et al*. reported airborne formaldehyde at a concentration of 0.03 mg/m^3 [0.02 ppm], and Lillienberg *et al.* reported mean levels of 0.003, 0.012, and 0.128 mg/m^3 [0.002, 0.01, 0.1 ppm] for three facilities (the full range across the three facilities was 0.001 to 0.154 mg/m^3 [0.0008 to 0.13 ppm]). Lillienberg *et al.* suggested that use of recirculating air probably was responsible for the higher levels observed in one machine shop. Godderis *et al*. postulated that the airborne formaldehyde in the aluminum plant originated either from the combustion of metalworking fluids or from formaldehyde-releasing triazines used as biocides.

Formaldehyde levels in spacecraft have been found to consistently exceed 0.05 mg/m^3 [0.04 ppm] (IARC 2006). ATSDR (1999) noted that the laser cutting of felt, woven fabrics, formica, plexiglass, and acrylic materials has been found to release formaldehyde; however, no air levels were identified for these activities. Concentrations ranging from less than 0.01 to 2.0 mg/m^3 [0.008 to 1.6 ppm] have been measured at coal and pitch-coking plants in the former Czechoslovakia. Levels up to 1.1 mg/m^3 [0.9 ppm] have been measured at plants producing photographic film.

2.5 Environmental occurrence and fate

Formaldehyde is ubiquitous in the environment and can occur in outdoor and indoor air, drinking water, groundwater, surface water, sediment, soil, and food. This section discusses the sources of formaldehyde, its fate and transport, and occurrence of formaldehyde in air (Section 2.5.1), water (Section 2.5.2), land and soil (Section 2.5.3), and food (Section 2.5.4).

A potential source of contamination for all environmental media and for general population exposure is from inadvertent spills of formaldehyde-containing materials. A 2009 search of the National Response Center (NRC 2009) on-line database using the keyword “formaldehyde” yielded 802 results. The NRC serves as the sole national point of contact for the reporting of all oil, chemical, radiological, biological, and etiological (i.e., biologically hazardous) spills into the environment anywhere in the United States and its territories. The level of information provided in the query results was not sufficient to estimate the extent of environmental contamination or the number of people exposed; however, it does suggest the potential for environmental contamination and general public exposure from inadvertent spills of formaldehyde or chemical mixtures containing formaldehyde.

2.5.1 Air

In air, formaldehyde is a gaseous pollutant that is produced both naturally and from human activities and occurs as a primary or secondary pollutant. In outdoor air, primary sources include direct emissions of formaldehyde from industrial processes and products

and its release during the combustion of organic materials. Occurrence of formaldehyde as a secondary pollutant results from the photochemical breakdown of hydrocarbons, which occur both naturally and as a result of human activities. In indoor air, the main sources of formaldehyde are indoor combustion sources, including tobacco smoke, and off-gassing from various materials.

Because formaldehyde air levels generally are higher in occupational settings than in nonoccupational settings, this section reports air concentrations in units of parts per billion (ppb) rather than the units of parts per million (ppm) used to describe occupational exposure (Section 2.4). If the source document reported concentrations in units of micrograms per kilogram (µg/kg), the values were multiplied by a conversion factor of 0.81.

Four studies were found in the literature that estimated time-weighted daily exposure levels for indoor and outdoor exposures. Probabilistic methods were used to estimate a 24-hour TWA exposure concentration for the general Canadian public, taking into account the amount of time spent indoors and outdoors and the associated formaldehyde concentrations (WHO 2002). Although this study applies specifically to the Canadian population, it was noted that the sources of formaldehyde are ubiquitous and are likely similar in most countries, and the overall magnitude of relative contributions from indoor air and outdoor air are expected to be similar in other parts of the world. Based on two different assumptions regarding the statistical distribution of formaldehyde concentrations, mean values were 24 and 29 µg/m^3 [20 and 24 ppb], median values were 33 and 36 µg/m^3 [27 and 29 ppb], and 95th-percentile values were 94 and 80 µg/m^3 [77 and 65 ppb].

More recently, in a review of production, consumption, exposure levels, and health effects of formaldehyde in China, Tang *et al.* (2009) provided data from numerous studies that had measured formaldehyde air levels. From these data, Tang *et al.* calculated average concentrations of formaldehyde in various locations including outdoor air, in newly remodeled homes, new office buildings, and public places. Based on these levels and time-activity pattern assumptions, the authors estimated an effective concentration for a hypothetical person of 0.21 mg/m^3 [170 ppb] during workdays and 0.17 mg/m^3 [140 ppb] over the course of the weekend. The authors noted that this level of exposure was higher than the WHO recommended indoor level of 0.1 mg/m^3 [80 ppb]. They further noted that higher levels would be associated with occupational exposures: 0.58 mg/m^3 [470 ppb] per day for industrial exposures and 0.61 mg/m^3 [490 ppb] per day for professional exposures (e.g., exposures associated with anatomy or pathology labs).

Dodson *et al.* (2007) developed a personal exposure model using VOC data (including data on formaldehyde) collected for teachers and office workers as part of the Boston Exposure Assessment in Microenvironments study. Included in the final model were data on participants' time-activity and concentration measurements for residential outdoor, residential indoor, and workplace microenvironments, along with average concentrations in various dining, retail, and transportation microenvironments. The authors noted that even with the full model, exposures to formaldehyde were not fully characterized, based on comparison with personal monitoring data; they emphasized the need for additional

time-activity and concentration data. Measured time-weighted personal exposure levels ranged from roughly 8 to 88 μg/m^3 [6.48 to 71.3 ppb] across 62 observations.

Boström *et al.* (1994) derived ratios of nitrogen oxide (NO_x) levels to levels of other pollutants in urban air, including formaldehyde, and used time-activity data together with NO_x levels to estimate exposure of the Swedish population to various pollutants. The overall mean exposure level for formaldehyde was estimated at 1.2 μg/m^3 [0.97 ppb].

The remainder of this section discusses outdoor air and indoor air separately.

2.5.1.1 Outdoor air

Formaldehyde in outdoor air has many natural and anthropogenic sources. Natural sources of formaldehyde include forest fires, animal waste, microbial products of biological systems, and plant volatiles. In Riverside, CA, airborne formaldehyde levels were twice as high during a wildfire as after the wildfire had ended (Na and Cocker 2008). However, the majority of formaldehyde in outdoor air is from anthropogenic activities, primarily combustion processes; therefore, higher levels are seen in urban environments than in rural environments (ATSDR 1999, WHO 2002). Major anthropogenic sources of formaldehyde in outdoor air include power plants, refineries, manufacturing facilities, incinerators, automobile exhaust, and other combustion sources.

In 2007, U.S. industrial air emissions of more than 9.2 million pounds [4,173 metric tons] of formaldehyde were reported to the U.S. EPA's Toxics Release Inventory (TRI) as either fugitive (1 million pounds [454 metric tons]) or point-source (8.2 million pounds [3,719 metric tons]) emissions (TRI 2009). Total air emissions reported to TRI trended downward slightly between 1988 and 2007, with a maximum of 13.2 million pounds [5,987 metric tons] in 1989 and a minimum of 9 million pounds [4,082 metric tons] in 2006. Reported emissions were lowest in 2005, 2006, and 2007.

It has been suggested that formaldehyde levels due to secondary formation might be much larger than levels from direct emissions. One study reviewed by the World Health Organization (WHO 2002), estimated that 70% to 90% of atmospheric formaldehyde was the result of secondary formation.

Formaldehyde is not present in gasoline; however, it is a product of incomplete combustion and is therefore released from internal combustion engines (WHO 2002). Automobiles are a major source of formaldehyde in outdoor air through direct formaldehyde emissions and through emission of precursors that form formaldehyde via atmospheric oxidation. Formaldehyde levels have been found to be correlated with traffic activity (ATSDR 1999). In the mid 1970s, the U.S. EPA estimated that automobiles emitted about 610 million pounds [276,691 metric tons] of formaldehyde annually. Emission levels depend on the fuel composition, the type of engine, the type of emission controls, the operating temperature, and the age and state of repair of the vehicle; therefore, emission rates are quite variable. The introduction of catalytic converters reduced automobile emissions of formaldehyde; however, the use of oxygenated fuels increases emissions. With the increased use of both catalytic converters and oxygenated fuels, the net effect on formaldehyde emissions is uncertain. Tractors and back-up

generators are additional sources of substantial amounts of formaldehyde in outdoor air (Sawant *et al.* 2007).

In a study of emissions from diesel engines operating on standard diesel fuel or on various blends of biodiesel, Liu *et al.* (2009a) reported that emissions of carbonyl compounds (including formaldehyde) increased when the engines were run on biodiesel fuels; however, the total concentration of the emitted carbonyls did not increase with biodiesel content. Sawant *et al.* (2007) noted that for tractors and back-up generators, engine operating mode and application appear to strongly influence the absolute mass emission rate of carbonyls (including formaldehyde); however, they do not appear to exert as strong an influence on the relative mass emission rates of individual carbonyl compounds.

No consistent seasonal variation has been demonstrated for formaldehyde levels, which could be explained in part by the fact that photo-oxidation is both an important source of formaldehyde (i.e., photo-oxidative breakdown of hydrocarbons to form formaldehyde) and an important pathway for degradation of formaldehyde.

Chen *et al*. (2004) measured formaldehyde levels continuously over several days and reported that peak formaldehyde levels occurred during daylight hours due to photochemical oxidation of VOCs caused by intense sunlight, and that minimum levels occurred during nighttime (Chen *et al.* 2004).

Formaldehyde half-lives in air can vary considerably under different conditions (WHO 2002). Atmospheric residence times in several U.S. cities ranged from 0.3 hours under conditions typical of a rainy winter night to 250 hours under conditions typical of a clear summer night. ATSDR (1999) reported half-lives in the atmosphere ranging from 1.6 to 19 hours. Reaction with the hydroxyl radical is the most important photo-oxidation process in the degradation of formaldehyde (WHO 2002). Factors that influence formaldehyde's atmospheric half-life, such as time of day, intensity of sunlight, and temperature, are mainly those factors that affect the availability of the hydroxyl radical. Based on hydroxyl radical reaction rate constants, the atmospheric half-life of formaldehyde has been calculated to be between 7.1 and 71.3 hours. Photolysis is another degradation pathway; however, it accounts for only about 2% to 5% of formaldehyde removal. At night, the degradation of formaldehyde is expected to occur through reactions with nitrate radicals. This process tends to be more significant in urban areas, where concentrations of the nitrate radical are higher.

Formaldehyde is highly soluble in water and will transfer into clouds, precipitation, and surface water. WHO (2002) noted that formaldehyde has a washout ratio (concentration in rain/concentration in air) of 73,000, and thus is expected to be efficiently scavenged from the atmosphere by atmospheric water.

Table 2-16 summarizes data on outdoor formaldehyde air levels in the United States that have been reported in review articles by Zhang *et al.* (2009a), IARC (2006), ATSDR (1999), and WHO (1989). Both IARC and Zhang *et al.* reported levels for some other countries that were higher than those seen in the United States. The highest mean ambient

level reported in the IARC review was 80 ppb in Salvador, Bahia, Brazil, and the highest single measurement (based on the upper end of the reported range) was 176 ppbv in Budapest, Hungary. Ambient levels exceeding those reported for the United States were also seen in Italy, China, Mexico, France, England, Egypt, and other parts of Brazil, all in urban areas. The highest levels reported by Zhang *et al.* were from Rio de Janeiro, Brazil (151 ppb) and Mexico City, Mexico (110 ppb). In addition to Brazil and Mexico, Zhang *et al.* reported concentrations for seven countries that exceeded the maximum U.S. concentration. The ATSDR (1999) and WHO (1989) reviews reported similar levels for the United States and other countries.

Table 2-16. Occurrence of formaldehyde in outdoor air in the United States

Location (sampling period)	N	Concentration mean (range), in ppb	Reference
Urban[a]			
Boston, MA (1993)			Reiss *et al.* 1995[b]
Winter measurements outside 4 residences	8	3.1 (0–3.1)	
Summer measurements outside 9 residences	18	2.6 (1.2–5.9)	
New Jersey, 4 cities (1974)	NR	3.8–6.6 (means) 14.0–16.3 (maxima)	Cleveland *et al.* 1977[c]
New York City, NY (1999)			Sax *et al.* 2004
Winter	36	1.7 (0.4–3.3)	
Summer	36	4.3 (1.5–10.6)	
Schenectady, NY (June–August 1983)	NR	NR (1.0–31)	Schulam *et al.* 1985[d]
Atlanta, GA, 4 urban areas (July and August 1992)	217	2.7–3.0 (max. = 8.3)	Grosjean *et al.* 1993[b]
Baton Rouge, LA, FEMA trailer-staging area (2006)	NR	4.9 (0.8–70.7)	ATSDR 2007a
OH urban centers (June–July 1989)	48	3.0 (max. = 15.5)	Spicer *et al.* 1996[d]
Houston, TX: Range of peak levels across the 3 sampling periods (2002)	NR	NR (< 7.0–30)	Chen *et al.* 2004
Denver, CO (1987–91)	NR		Anderson *et al.* 1996[b]
Winter		3.9 (NR)	
Spring		2.3 (NR)	
Summer		2.7 (NR)	
Los Angeles, CA (2000)			Sax *et al.* 2004
Winter	40	3.2 (1.9–6.8)	
Fall	35	3.6 (2.0–6.3)	
Los Angeles, CA (1999–2000)	69	7.2 (4.3–14)	Delfino *et al.* 2003[b]
Los Angeles, CA (1993)			Grosjean *et al.* 1996[b]
Measured at urban locations during smog season (September)	32	5.3 (1.4–10.6)	
Measured at 1 background location	NR	0.8 (0.7–1.0)	
Los Angeles, CA (Cal State University) (May–June 1980)	NR	NR (2.0–40)	Grosjean 1982[d]
Los Angeles, CA downtown (1960–61)	31		Altschuller and McPherson 1963[c]
July–November (1960)		40 (NR)	
September–November (1961)		45 (NR)	

Location (sampling period)	N	Concentration mean (range), in ppb	Reference
California, during air pollution episode (NR)			Grosjean and Swanson 1983[c]
Lennox	36	NR (0.5–39.5)	
Azusa	36	NR (0.7–35)	
Los Angeles	20	NR (3.7–57)	
Claremont, CA (September–October 1980)	NR	NR (3.0–48)	Grosjean 1982[d]
Riverside, CA (NR)	32	NR (< 4.1–9.8)	Tuazon *et al.* 1978[c]
Rural			
Albany, NY, rural and semi rural (October 1991)	NR	NR (0.6–3.7)	Khwaja 1995[b]
Whiteface Mountain, Wilmington, NY (1983)	NR	NR (0.8–2.6)	Schulam *et al.* 1985[d]
Mixed locations			
USA, mixed locations in TX, LA, VT, and NJ (1996–97)	NR	NR (1.5–7.4)	Mohammed *et al.* 2002
USA, mixed locations (1975–85)			Shah and Singh 1988[b]
Nationwide	629	4.1[e,f] (NR)	
Urban – mixed locations	332	6.5[e] (NR)	
Suburban – mixed locations	281	2.7[e] (NR)	
Rural and semirural – mixed locations	12	2.7[e] (NR)	
United States, ambient air measurements at 58 locations (NR)	1,358	2.5[e] (NR)	Kelly *et al.* 1994[d]
United States, 9 datasets from 8 cities (1980–84)	NR	2.3–19 (means) 5.5–67.7 (maxima)	Salas and Singh 1986 and Singh *et al.* 1982[d]
Minnesota, 25 sites throughout the state (1991–98)	2,494	1.7 (< 0.05–21)	Pratt *et al.* 2000[b]
California, multiple locations (NR)	NR	3.2–4.9 (NR)	Seiber 1996[d]

NR = not reported.
[a]Data within this section are sorted geographically, generally from east to west across the United States.
[b]Cited in IARC 2006.
[c]Cited in WHO 1989.
[d]Cited in ATSDR 1999.
[e]Median.
[f]The nationwide mean value was 8.3 ppb.

2.5.1.2 Indoor air

Formaldehyde levels generally are higher in indoor air than in outdoor air, often by an order of magnitude or more (ATSDR 1999, IARC 2006). Sources of formaldehyde in indoor air include off-gassing from various products (e.g., building materials, composite-wood-based furnishings, carpets, various consumer products, clothing, fabrics, UFFI, and paints and varnishes) and indoor combustion sources (e.g., gas burners and ovens, kerosene heaters, cook stoves, and cigarettes) (WHO 1989, ATSDR 1999, IARC 2006). In indoor air, formaldehyde can form due to reactions of ozone with indoor materials such as latex paints and carpets (Sax *et al*. 2004) and due to degradation of other organic compounds in indoor air (ATSDR). Important determinants of indoor air levels include the sources of the formaldehyde, the age of the source materials, temperature, humidity, and ventilation rates (IARC 2006).

Formaldehyde levels in indoor air have been shown to be associated with the age and structural type of the building; however, these factors are not independent and reflect more fundamental variables such as the overall emission potential of the source materials and the air-exchange rate of the dwelling (WHO 1989). In one study reviewed by WHO (1989), the amount and dynamics of formaldehyde migration into indoor air was assessed in relation to the age of the material, air temperature, and air-exchange rate. Age of the material was found to be the most important factor influencing formaldehyde levels, followed by temperature elevation, and then air-exchange rate.

In a study assessing secondary VOC emissions from flooring material, Kagi *et al.* (2009) exposed a low-formaldehyde type of flooring material to UV radiation and found that chemical transformations occurred resulting in the emission of a number of secondary products, including formaldehyde. Similar results were found when the flooring material was exposed to ozone.

Emission rates due to off-gassing have been assessed for various consumer products and are presented in Table 2-17. (Measured indoor formaldehyde levels are discussed below.) The highest emission rates were seen for UF floor finishes; this finding is supported by data showing high exposure levels for workers who varnish floors (see Section 2.4.8). Other products with high emission rates include fingernail hardener and polish, various types of composite wood products (i.e., particleboard, plywood, UF wood products), latex paints, permanent-press fabrics, and insulation. In general, UF resins have the highest emission rates and PF resins the lowest emission rates (IRSST 2006). Generally, emission rates from these products decrease over time (WHO 1989). It has been shown that formaldehyde emission rates increase with higher ozone concentrations, temperature, and relative humidity (Sax *et al*. 2004).

Table 2-17. Formaldehyde off-gassing emission rates from building materials, home furnishings, and consumer products

Product	Emission rate, in μg/m^2 per day	Comment	Reference
Building supplies and home furnishings			
Commercially applied UF floor finish Base coat Top coat	 [10,104] [25,200,000]	Reported by ATSDR as 421 and 1,050,000 μg/m^2 per hour	ATSDR 1999
Particleboard	36,000–168,000	Range of releases based on varying a number of parameters in a test chamber	Pickrell *et al.* 1984
Plywood	31,000–68,000	Range of releases based on varying a number of parameters in a test chamber	Pickrell *et al.* 1984
Pressed wood products (including particle-board, plywood, and paneling)	BD–36,000	Minimum is for exterior plywood, and maximum is for paneling	Pickrell *et al.* 1983
Bare UF wood products	210–37,900	Results from a variety of products	ATSDR 1999
Bare PF wood products	100–220		ATSDR 1999
Coated UF wood products	24–11,100	Results from a variety of products	ATSDR 1999
Low-formaldehyde-emitting flooring Natural wood flooring without adhesives	96–2,000 2,000–6,900	Rates span flooring material exposed to ozone, infrared lamp, sun lamp, UVA lamp, and UVB lamp Reference rates were "not detected" for the low-emitting flooring and 48 μg/m^2 per day for the natural wood flooring	Kagi *et al.* 2009
Insulation products	52–620	Includes various fiberglass products, air ducts, blackface insulation sheathing	Pickrell *et al.* 1983
Insulation	3,000	Measured release rate from a test chamber; details on type of insulation not provided	Pickrell *et al.* 1984
Carpet	BD–65	Both foam-backed and non-foam-backed carpets (highest level from foam-backed and lowest level from non-foam backed)	Pickrell *et al.* 1983
Carpet	1,500	Measured release rate from a test chamber (carpet type not specified)	Pickrell *et al.* 1984
Carpet	440–1,375	Measured rates from a test chamber; the maximum rate was at 24 h, and the minimum rate was at 168 h (carpet type not specified)	ATSDR 1999

Product	Emission rate, in μg/m^2 per day	Comment	Reference
Latex paints	7,800–14,200	From two brands of paints; the lower value was for a more expensive paint	ATSDR 1999
Decorative laminates	100–1,200		ATSDR 1999
Consumer products			
Fingernail hardener	5,172,000		ATSDR 1999
Nail polish	496,800		ATSDR 1999
Paper products	75–1,000	Paper plates and cups	Pickrell *et al.* 1983
Paper grocery bags	10		ATSDR 1999
Clothes	15–550	Unwashed new clothing	Pickrell *et al.* 1983
Fabric	BD–350	Includes drapery fabric and upholstery fabric of cotton, nylon, olefin, and rayon/cotton blends	Pickrell *et al.* 1983
Permanent press fabrics	1,000–5,100		ATSDR 1999
Towels	< 7		ATSDR 1999
Fiberglass products	380–770		ATSDR 1999

BD = below detection; UVA = ultraviolet A; UVB = ultraviolet B.

Off-gassing from UFFI is another potential source of formaldehyde in indoor air. No emission rates were found in the literature; however, studies have indicated that formaldehyde levels in homes increase immediately after foaming, but return to pre-foaming levels after a few weeks (WHO 1989). As noted above, changes in home-construction methods have significantly reduced the use of UFFI since the mid 1980s.

Paint can be a source of formaldehyde in indoor air. In one study, the average formaldehyde level was 18 μg/m^3 [15 ppb] in office buildings that had recently been painted with a low-formaldehyde-emitting paint. Three months later, the concentration had fallen to 8 μg/m^3 [6.5 ppb], which was the average level in a control area in the same building that had not been painted (IARC 2006) (data are presented in occupational exposure section, Table 2-15). A study in Swedish homes showed significantly increased formaldehyde levels in houses where wood paint had been used. This study also noted that wall-to-wall carpeting had contributed almost the same amounts of formaldehyde to indoor air as paint had (13 μg/m^3 [11 ppb] for carpeting vs. 16 μg/m^3 [13 ppb] for paint).

Indoor combustion sources of formaldehyde include wood stoves, gas stoves, kerosene heaters, open fireplaces, furnaces, and burning tobacco products. Combustion sources generally are considered to be weak emitters to indoor air, but tobacco smoke can be an important source of formaldehyde in indoor air, potentially accounting for 10% to 25% of indoor air exposure (ATSDR 1999) (see below and Table 2-19).

Other potential sources of formaldehyde in indoor air include cooking and formation from other chemicals in the air. In one study, an emission rate of 1.38 μg/g was estimated for charbroiling meat over a natural-gas-fired grill (WHO 2002). Another study showed

emission rates for fish that ranged from 0.48 µg/g for mackerel to 5.31 µg/g for sardines (IARC 2006). Formaldehyde has also been shown to be released from cooking oils that were heated to 240°C to 280°C [464°F to 536°F].

Formaldehyde may form through degradation of organic compounds commonly found in indoor air. Formaldehyde has been found to form through this process at a rate of 0.87 µg/sec in winter and 2.43 µg/sec in summer (ATSDR 1999) [which is reflected in the higher indoor formaldehyde levels in summer than in winter shown in Table 2-18 for studies with measurements in both seasons].

Park and Ikeda (2006) found that air levels of VOCs in new homes decreased markedly after one year; however, formaldehyde required a longer flushing period in new homes. The authors concluded that decreases in indoor formaldehyde levels depend more on time than on ventilation rates. Gold *et al.* (1993) noted that older conventional homes had the lowest indoor concentrations of formaldehyde (compared with new conventional homes and mobile homes), with values typically less than 50 ppb. This is consistent with the expected decrease in release of latent formaldehyde from wood-based building materials as they age. Interior remodeling can also result in increased formaldehyde levels. Tang *et al.* (2009) reported that in China, indoor formaldehyde concentrations typically decrease with time, usually falling below 0.1 mg/m^3 [0.08 ppm] about 6 months after remodeling; however, the authors noted that levels can remain high even up to 1 year after remodeling.

In 2008, the Centers for Disease Control and Prevention (CDC) released *Final Report on Formaldehyde Levels in FEMA-Supplied Travel Trailers, Park Models, and Mobile Homes* (CDC 2008). The report summarized a study of a stratified random sample of 519 occupied travel trailers, park models, and mobile homes provided by the Federal Emergency Management Agency (FEMA) for use as temporary shelter for Louisiana and Mississippi residents displaced by hurricanes Katrina and Rita. The overall geometric mean indoor formaldehyde level was 77 ppb (range = 3 to 590 ppb). The CDC reported that formaldehyde levels varied by trailer type (travel trailers had significantly higher levels than park models or mobile homes), but all types tested had some levels greater than 100 ppb. Levels also varied by manufacturer. Temperature was the most important determinant of indoor levels. Other statistically significant determinants of formaldehyde levels included relative humidity; opened windows, doors, and scuttles; and presence of mold. Indoor cooking and tobacco smoking contributed to formaldehyde levels, although not significantly. The CDC noted that since indoor formaldehyde levels tend to be higher in warmer weather and in newly constructed trailers, the results of this study could have underestimated long-term exposure levels (many of the trailers were around 2 years old, and the study was undertaken in winter).

In 2006, ATSDR evaluated data on formaldehyde levels in FEMA temporary housing units in Baton Rouge, LA. Two different ventilation methods were tested in the study: Method A relied on running the air conditioning and opening the bathroom vents only, and Method B relied on opening all windows and vents. The authors found that Method B was more effective at lowering formaldehyde levels (see Table 2-18) (ATSDR 2007a). ATSDR (1999) also noted that the generally increased levels of formaldehyde in mobile

homes would be expected because of their generally lower air-exchange rates. IARC noted that formaldehyde in the air of mobile homes has a half-life of about 4 or 5 years.

Residential indoor air levels of formaldehyde have been documented extensively by IARC (2006), ATSDR (1999), and WHO (1989). U.S. levels from these assessments are presented in Table 2-18. Residential indoor air levels reported for other countries were very similar to U.S. levels, and except for one instance (in which > 500 ppb was reported in Austrian apartments), all data points fell within the range of mean concentrations reported for the United States. Zhang *et al.* (2009a) presented graphs showing indoor formaldehyde air levels for several countries, noting that in general, indoor levels (including U.S. levels) were below the WHO recommended indoor limit of 0.1 mg/m^3 [81 ppb]. However, mean levels for Cairo, Egypt, and Tianjin, China, were slightly higher than the WHO recommended level (100 ppb for both cities), and levels in Beijing, China, were roughly 170 ppb in winter and 225 ppb in summer. The ATSDR review included many measurements made in the mid 1980s or earlier; the authors noted that production methods have changed since that time period and have reduced formaldehyde levels in plywood and particleboard; also, the use of UFFI has decreased. The authors also noted that formaldehyde levels in mobile homes appear to have been decreasing since about 1980, probably as a result of the use of these reduced-emission products.

Table 2-18. Occurrence of formaldehyde in U.S. residential indoor air

Location (year measured)	N[a]	Concentration mean (range), in ppb	Reference
Manufactured housing			
LA & MS, 519 FEMA-supplied temporary housing units (Dec. 2007–Jan. 2008)	519*	77 (3.0–590)	CDC 2008
Baton Rouge, LA, 96 FEMA-supplied temporary housing units (2006)			ATSDR 2007a
Ventilation with air conditioning and bathroom vents only	1,090	400 (2.8–2,440)	
Ventilation with open windows and vents	1,117	140 (2.4–3,659)	
Florida, new manufactured house (2000)	NR	77.2 (NR)	Hodgson *et al.* 2002[b]
United States, East and Southeast (1997–98)			Hodgson *et al.* 2000[b]
Indoor level	4	34 (21–47)	
Outdoor level		2.0[c] (NR)	
California, mobile homes (1984–85)	470	70–90 (NR)	Sexton *et al.* 1989[d]
Texas, mobile homes whose residents requested testing (1979–82)	443*	NR (ND–8,000)	Norsted *et al.* 1985[d]
Homes < 1 yr old		> 2,000 for 27% of homes	
Homes > 1 yr old		> 2,000 for 11.5% of homes	

Location (year measured)	N[a]	Concentration mean (range), in ppb	Reference
United States (NR)	430*	> 1,000 for 4% of samples 500–1,000 for 18% of samples 100–500 for 64% of samples < 100 for 14% of samples	Breysse 1984[e]
United States (NR)	431*	382 (9.8–2,926)	Ulsamer *et al.* 1982[e]
United States (NR)			Stone *et al.* 1981[e]
Complaint homes, WA, < 2 yr old	110*	772 (NR)	
Complaint homes, WA, 2–10 yr old	77*	472 (NR)	
Complaint homes, MN, < 2 yr old	66*	846 (NR)	
Complaint homes, MN, 2–10 yr old	43*	276 (NR)	
Complaint homes, WI, < 2 yr old	38*	724 (NR)	
Complaint homes, WI, 2–7 yr old	9*	455 (NR)	
Random sample, WI, < 2 yr old	NR	537 (NR)	
Wisconsin, complaint homes, 0.2–12 yr old (NR)	65*	480[f]	Dally *et al.* 1981[e]
Traditional housing or unspecified			
New York City, NY (1999)			Kinney *et al.* 2002[b]
Winter	38	9.8 (NR)	
Summer	41	17.0 (NR)	
United States, East and Southeast, site-built houses (1997–98)	7	36[c] (14–58)	Hodgson *et al.* 2000[b]
Louisiana, 53 houses: 75% urban and 25% rural (NR)	419	374 (ND–5,365)	Lemus *et al.* 1998[b]
Boston, MA (1993)			Reiss *et al.* 1995[b]
Winter, 4 residences	14	11.1 (6.0–16.1)	
Summer, 9 residences	26	16.1 (5.9–53.8)	
Colorado (1992–93)	9		Lindstrom *et al.* 1995[b]
Prior to occupancy		21 (6.5–54)	
After occupancy for 5 months		40 (26.8–66)	
New Jersey, residential houses (1992)	6*		Zhang *et al.* 1994b[d]
Indoor		54.56 (NR)	
Outdoor		12.53 (NR)	
Arizona, houses (NR)	202*	26 (max. 140)	Krzyzanowski *et al.* 1990[d]
United States, residential, various locations (1981–84)	273	35.8[f] (NR)	Shah and Singh 1988[b]
San Francisco, CA, Bay Area (1984)			Sexton *et al.* 1986[b]
Kitchen	48	41.0 (NR)	
Main bedroom	45	36 (NR)	
Pullman, WA, houses (NR)	NR	5.0–72 (NR)	Lamb *et al.* 1985[d]

Location (year measured)	N[a]	Concentration mean (range), in ppb	Reference
United States (NR)			Breysse 1984[e]
UFFI houses	244*	> 1,000 for 2.8% of samples 500–1,000 for 1.9% of samples 100–500 for 24.1% of samples	
Non-UFFI houses and apartments	59*	< 100 for 71.2% of samples > 1,000 for 1.8% of samples 500–1,000 for 1.8% of samples 100–500 for 36.3% of samples < 100 for 60.1% of samples	
United States (1982)			Hawthorne *et al.* 1983[e]
Houses 0–30 yr old	40*	61.7 ± 77.2[g]	
Houses 0–5 yr old	18*	83.7 ± 91.1[g]	
Houses 5–15 yr old	11*	42.3 ± 42.3[g]	
Houses > 15 yr old	11*	31.7 ± 42.3[g]	
Houses 0–5 yr old	18*		
spring		87.0 ± 92.7[g]	
summer		111 ± 102[g]	
autumn		47.2 ± 55.3[g]	
Houses 5–15 yr old	11*		
spring		43.1 ± 39.8[g]	
summer		48.8 ± 48.0[g]	
autumn		34.1 ± 35.0[g]	
Houses > 15 yr old	11*		
spring		35.8 ± 51.2[g]	
summer		29.3 ± 37.4[g]	
autumn		26.0 ± 22.8[g]	
United States (1983)			Grimsrud *et al.* 1983[e]
Energy-efficient new houses	20*	61.8 (NR)	
Low-ventilation modernized houses	16*	30.1 (NR)	
United States (1981)			Ulsamer *et al.* 1982[e]
Houses without UFFI	41*	32.5 (9.8–79.7)	
Houses with UFFI	636*	122 (9.8–3,415)	
United States (1980–81)			Offerman *et al.* 1982[e]
Houses averaging 2 yr old	9*		
air-tight construction		35.8 ± 17.9[g]	
mechanical ventilation		26.8 ± 16.3[g]	
Houses averaging 6 yr old (loose construction)	1*	13.8 (NR)	
United States (1978–79)	13*	97.6[f] (NR)	Dally *et al.* 1981[e]

Location (year measured)	N[a]	Concentration mean (range), in ppb	Reference
United States (1979)	2*		Berk *et al.* 1980[e]
Energy-efficient house		79.7 (32.5–122)	
Unoccupied house without furniture		65.9 ± 5.7[g]	
Unoccupied house with furniture		182.9 ± 13.0[g]	
Occupied house			
day		213.8 ± 21.1[g]	
night		114.6 ± 35.8[g]	

ND = not detected; NR = not reported.
[a]Number of samples unless denoted with an asterisk (*), which indicates number of houses.
[b]Cited in IARC 2006.
[c]Geometric mean.
[d]Cited in ATSDR 1999.
[e]Cited in WHO 1989.
[f]Median.
[g]Standard deviation.

A number of studies have estimated formaldehyde levels in cigarette mainstream smoke, sidestream smoke, and indoor air due to smoking. Levels in sidestream smoke have been estimated to be from 5 to 50 times the levels in mainstream smoke (ATSDR 1999). Table 2-19 summarizes formaldehyde levels in tobacco smoke and resultant exposure levels.

Table 2-19. Formaldehyde levels associated with cigarette smoke

Source or setting	Average or range	Comment	Reference
Formaldehyde levels in cigarettes and cigarette smoke			
Total per cigarette	~1,500–2,000 µg	Low end of range reported in WHO 1989 and upper end reported in ATSDR 1999	ATSDR 1999, WHO 1989
Sidestream smoke, total per cigarette	958–2,360 µg (range)	The range represents the minimum and maximum values reported across numerous studies. The low end is the low end of a range from one study. The high end is the mean value from another study (the range for that study was not provided).	WHO 1989, 2002
Mainstream smoke Total per cigarette Total per puff Concentration	 8–284 µg 5.1–8.9 µg 49,000–105,000 ppb	Total per cigarette includes data from numerous studies involving numerous brands and types of cigarettes. Total per puff data from 6 American filter-tip brands.	WHO 2002, 1989, ATSDR 1999
Formaldehyde air concentrations due to smoking			
50-m^3 chamber	97 ppb	Six cigarettes smoked over 15 minutes; chamber averaged 1 air exchange per hour	WHO 1989
30-m^3 chamber 0.2–0.3 air exchanges/h 1 air exchange/h	 170–284 ppb 40–57 ppb	Formaldehyde yield from 5–10 cigarettes smoked in the chamber at the two different exchange rates	WHO 1989
Nonsmoking office building Smoking section of building	BD–220 ppb BD–600 ppb		ATSDR 1999

BD = below detection.

The interior of automobiles can be a significant source of formaldehyde exposure as a result of off-gassing from interior materials. Using data from chamber tests that showed an average formaldehyde concentration of 48 µg/m^3 [39 ppb] at 23°C [73°F], Schupp *et al.* (2005) extrapolated a car concentration of 1,680 µg/m^3 [1,370 ppb] at a temperature of 65°C [150°F], which is easily reached in the interior of a car sitting in the sun with the windows rolled up. Based on air samples taken inside 802 new cars (manufactured in and after 2003) parked in an underground parking garage, Zhang *et al*. (2008b) reported a mean airborne formaldehyde level of 80 µg/m^3 [65 ppb] (range = 20 to 1,110 µg/m^3 [16 to 900 ppb]). Samples also were taken inside 20 older cars (manufactured before 2003) for comparison; levels were slightly lower in the older cars.

2.5.2 Water

Formaldehyde has been detected in bottled drinking water, treated drinking water, and various types of environmental water, including groundwater, surface water, fog, and

mist. This section discusses formaldehyde levels in these various types of water. Because drinking water is the most likely potential source of exposure, it is discussed first, followed by a discussion of formaldehyde levels in other types of environmental waters.

2.5.2.1 Drinking water

Formaldehyde in treated drinking water occurs primarily through the oxidation of organic matter during ozonation or chlorination (WHO 2005); however, formaldehyde can also be present in the water before treatment. Krasner *et al.* (1989) reported the results of a study on the occurrence of disinfection by-products in U.S. drinking-water supplies. Formaldehyde and several other disinfection by-products were measured both pre- and post-treatment at 35 drinking-water treatment facilities in 1988 and 1989. To ensure that the facilities chosen for analysis were representative, selection was based on the type of source water, type of treatment process, population served, geographic location, and the disinfectants used (i.e., free chlorine, chloramines, chlorine dioxide, or ozone). Levels of disinfection by-products were assessed quarterly (spring, summer, fall, and winter, 1988 to 1989), and the data for formaldehyde are presented in Table 2-20 note that formaldehyde was not assessed in the spring. To determine whether the formaldehyde was produced during the disinfection process or originated from the source water, formaldehyde was measured in the influents of all 35 facilities. It was detected in 16 influent samples at levels ranging from 1.2 to 13 µg/L, with a median of 2.8 µg/L. The median for all samples (including samples in which no formaldehyde was detected) was less than 1 µg/L. The authors suggested that the presence of formaldehyde in treated drinking water depends on a combination of the disinfection process and the influent water quality. It was noted, however, that formaldehyde clearly was a product of the oxidation-disinfection process, and that formaldehyde levels were higher at facilities that used ozone treatment.

Formaldehyde can also contaminate drinking water through leaching from polyacetal plastic fittings whose protective coatings have been compromised (Tomkins *et al.* 1989, Owen *et al.* 1990, WHO 2002). Concentrations ranging from roughly 20 to 100 µg/L have been reported to result from this process; levels were positively associated with the residence time of the water in the pipe (Owen *et al.* 1990).

WHO (2002) noted that based on limited U.S. data, formaldehyde concentrations in drinking water may range up to approximately 10 µg/L in the absence of contributions from ozone treatment during water treatment or from leaching of formaldehyde from polyacetal plumbing fixtures.

Formaldehyde has also been detected in bottled drinking waters. Mutsuga *et al.* (2006) purchased 20 polyethylene terephthalate (PET) bottles of mineral water and analyzed the water for formaldehyde and acetaldehyde. Of the 20 bottles of water, 6 were bottled in Japan, 11 in Europe, and 3 in North America. All of the Japanese bottled-water samples contained detectable levels of formaldehyde, whereas 3 of the 11 European samples and 2 of the 3 North American samples had detectable formaldehyde levels (see Table 2-20). The authors concluded that formaldehyde in the water was due to leaching from the PET bottles. In further investigations to explain the absence of formaldehyde from some of the water samples, the authors discovered that the water samples without formaldehyde were

unsterilized and contained heterotrophic bacteria. Based on these findings, the authors suggested that formaldehyde probably had leached from the PET bottles but had been decomposed by the bacteria.

Tsai *et al.* (2003) measured formaldehyde levels in 63 brands of packed drinking water and 13 brands of barreled drinking water in Taiwan. The authors reported that all concentrations were below 129 ppb [129 μg/L] [specific levels not reported] and noted that these levels were well below the WHO water-quality guidelines of 900 μg/L. No additional information was found specifically for bottled water in the United States.

Table 2-20. Formaldehyde concentrations in drinking water

Water type	Concentration, in µg/L	Comments	Reference
U.S. drinking water at treatment facility Summer 1988 Fall 1988 Winter 1988–89	 5.1[a] 3.5[a] 2.0[a]	Formaldehyde was detected at concentrations ranging from 1.2 to 13 µg/L in influents of 16 of 35 treatment facilities; however, authors noted that it was also created through treatment by ozonation or chlorination	Krasner *et al.* 1989
U.S. domestic drinking water	~ 20–100	Concentrations observed in a study assessing the leaching of formaldehyde from domestic polyacetal plumbing fixtures. [The low end is assumed to represent normal conditions and the high end to represent a reasonable worst-case scenario.]	WHO 2002
U.S. domestic drinking water	~ 10	Levels expected without contributions from ozone treatment during water treatment or by leaching from polyacetal plumbing fixtures	WHO 2002
U.S. drinking water	BD	U.S. EPA's 1975 report on National Organics Reconnaissance Survey of Suspected Carcinogens in Drinking Water	ATSDR 1999
Drinking water (location not reported)	< 100	Noted as generally less than this level	WHO 1989
Drinking water (treated with ozone; location not reported)	< 50	Noted as unlikely to exceed this level	WHO 2005
Bottled water Bottled in Japan Bottled in Europe Bottled in North America	 10.1–27.9 7.8–13.7 13.6, 19.5	Range of levels detected in water from 20 PET bottles. Detectable levels were found in 6 of 6 Japanese, 3 of 11 European, and 2 of 3 North American bottled waters.	Mutsuga *et al.* 2006
63 brands of packed drinking water and 13 brands of barreled drinking water in Taiwan	< 129	Specific levels not reported	Tsai *et al.* 2003

BD = below detection; PET = polyethylene terephthalate.
[a]Median; range not reported.

2.5.2.2 Environmental water

Groundwater can be contaminated by formaldehyde leaching from surface soils into the water table and through underground injection of wastes. In 2007, underground injection of formaldehyde was the predominant source of industrial release to the environment, based on TRI reporting data; 11.9 million pounds [5,398 metric tons] were released to on-site and off-site underground injection wells, accounting for 54% of total U.S. releases reported for the TRI (TRI 2009). As a percentage of total releases, underground injection

has trended upward since 1988, with a minimum of 29% in 1992 and a maximum of 55% in 2006. ATSDR (1999) reported that formaldehyde had been detected in groundwater at 4 of 26 hazardous waste sites at which at least one environmental medium was contaminated with formaldehyde. No information was found on the fate of formaldehyde in groundwater.

Surface water can be contaminated via the direct discharge of formaldehyde-containing wastes, the use of formaldehyde in aquaculture, formaldehyde runoff from hazardous waste sites, and land disposal of formaldehyde-containing wastes. Formaldehyde releases to U.S. surface waters totaling 278,335 pounds [126 metric tons] were reported to the TRI for 2007 (TRI 2009), accounting for roughly 1% of all formaldehyde releases reported to the TRI. Discharges to surface water have declined steadily since 1988 when 904,547 pounds [410 metric tons] were reported. The minimum amount reported from 1988 through 2007 was 277,083 pounds [126 metric tons] in 2003. Formaldehyde-containing wastes may also be sent to publicly owned treatment works (POTWs) and subsequently released to surface waters. For example, formaldehyde has been found in hospital effluent at a 24-hour average concentration of 0.07 mg/L (Boillot *et al.* 2008). As a result of treatment at POTWs, only a fraction of formaldehyde received is expected to be released to surface waters (ATSDR 1999); however, no data on treatment efficiency or resultant discharge levels were found.

Formalin is commonly used in fish-culture activities to treat fish with fungal or ectoparasitic infections; after use, formaldehyde solutions often are discharged into the hatchery effluent (WHO 1989). No data were found on formaldehyde levels in water due to such discharges.

In 1999, ATSDR (1999) noted that formaldehyde had been detected in surface water at 5 of 26 hazardous waste sites at which at least one environmental medium was contaminated with formaldehyde. In 2007, roughly 373,000 pounds [169 metric tons] of formaldehyde was disposed of in U.S. landfills, surface impoundments, land treatment sites, and other land disposal sites, accounting for less than 2% of total U.S. releases reported to the TRI for that year (TRI 2009). No information was available to estimate the impacts to surface water from these land disposals.

Although volatilization of formaldehyde from surface waters is expected to be low, biodegradation in surface water is a significant degradation process; formaldehyde is biodegraded to low levels within a few days. In one study, formaldehyde was completely biodegraded in water from a stagnant lake within 30 hours under aerobic conditions and within 48 hours under anaerobic conditions (ATSDR 1999). Based on its low K_{ow}, adsorption of formaldehyde to sediment is expected to be low (Howard 1989). Biotic and abiotic degradation are expected to be significant fate processes in sediment.

Table 2-21 provides data on formaldehyde levels in U.S. environmental waters. ATSDR's HazDat database provided the only data found for U.S. groundwater levels. (The on-line HazDat database provides only maximum values measured at Superfund sites or other facilities where ATSDR has performed a site assessment.} Three data points were provided for formaldehyde: 0.1 ppm [~0.0001 μg/L] measured in 1979 at a

facility in New Jersey, 0.0005 µg/L measured in 1980 at a facility in North Carolina, and 140 µg/L at a facility in California (year not reported). WHO (2002) presented results of groundwater monitoring at two industrial facilities in Canada where groundwater had been contaminated with formaldehyde. For one facility, which produced and used formaldehyde, formaldehyde was detected in 43 samples at concentrations ranging from 65 to 690,000 µg/L and was not detected in 10 samples (detection limit = 50 µg/L). This site was monitored from November 1991 to February 1992 as part of a program to delineate the boundaries of groundwater contamination at the facility. At the other facility, which produced UF resins, quarterly analyses of five on-site monitoring wells in 1996 and 1997 showed formaldehyde concentrations ranging from below the limit of detection to 8,200 µg/L, with an overall median of 100 µg/L. It was noted that concentrations measured in various wells indicated little dispersion from the source of contamination. Groundwater samples collected down gradient from six cemeteries in Ontario, Canada, contained formaldehyde at levels ranging from 1 to 30 µg/L (WHO 2002).

Table 2-21. Formaldehyde levels in U.S. environmental water

Water type	Concentration, in µg/L	Comments	Reference
Groundwater	100–500	Range of maximum values from 3 locations in ATSDR's HazDat database	ATSDR 2007b
Surface water	2,100, 7,400	Maximum values from two locations in ATSDR's HazDat database	ATSDR 2007b
Surface water	BD–12	Of 204 sites in 14 heavily industrialized U.S. river basins, 1 site had detectable formaldehyde	Howard 1989
Rainwater	BD–0.06	California	ATSDR 1999
Fog water	1,800[a] (400–3,000)[b]	Corvallis, OR	ATSDR 1999
Fog water	3,000[c] (120–6,800)[b]	Riverside, CA	ATSDR 1999
Mist water	250 560	Long Beach, CA Marina del Ray, CA	ATSDR 1999
Snow	18–901	California	WHO 2002

BD = below detection.
[a]Volume-weighted mean.
[b]Range.
[c]Median.

As with groundwater, ATSDR's HazDat database provided the only data on U.S. surface-water levels of formaldehyde providing maximum levels at two locations in California of 7,400 µg/L and 2,100 ppb [~2,100 µg/L].

Because of its high solubility in water, formaldehyde is efficiently transferred into clouds, fog, and precipitation, leading to potentially high levels in these media (Table 2-21). WHO (2002) noted that formaldehyde has a washout ratio (concentration in rain to

concentration in air) of 73,000, and thus is estimated to be efficiently removed from the atmosphere by atmospheric water. Levels of formaldehyde in rainwater in California have been reported to range from below detection (level of detection not reported) to 0.06 μg/L (ATSDR 1999). WHO (1989) reported levels in rainwater ranging from 8 μg/L (a mean level reported for the central equatorial Pacific Ocean) to 1,380 μg/L (location not reported). No information was provided that would explain why these levels were so much higher than the levels reported by ATSDR (1999).

No data were found on formaldehyde levels in water sediment.

2.5.3 Land and soil

Formaldehyde occurs in soil through its use in controlled-release fertilizers, its use as a fumigant, and land disposal of industrial, construction, demolition, and other wastes. Formaldehyde could be released to soil from hazardous waste sites (ATSDR 1999). It is also formed naturally in soil during decomposition of plants (WHO 1989).

Based on TRI data, 373,000 pounds [169 metric tons] of formaldehyde were released to land in 2007: 82% to landfills, 14% to surface impoundments, 3% to land treatment sites, and 1% to other land disposal sites (TRI 2009). Land disposal has declined considerably but has fluctuated widely since TRI data were first reported, from a maximum disposal of 1.25 million pounds [567 metric tons] in 1988 to a minimum of about 205,000 pounds [93 metric tons] in 1997. As noted above, over 11.9 million pounds [5,398 metric tons] of formaldehyde were released to underground injection wells in 2007: 98% to on-site wells and 2% to off-site wells. Since 1988 (the first year in which data were reported), underground injection releases have ranged from around 5 million pounds [2,268 metric tons] in 1992 to over 13.6 million pounds [6,169 metric tons] in 2004.

Formaldehyde is degradable under both aerobic and anaerobic conditions (Howard 1989); however, no soil degradation rates were found in the literature. It has a low soil-adsorption coefficient, meaning that it is very mobile in soils (WHO 1989). Based on its Henry's law constant, it is not expected to volatilize appreciably (Howard 1989).

Although large amounts of formaldehyde are disposed of on land and in the ground, no U.S. soil concentration data were found. In Canada, soil levels were measured in 1991 at a plywood manufacturing facility that used PF resins. Six soil samples contained formaldehyde concentrations ranging from 73 to 80 mg/kg, with a mean of 76 mg/kg (WHO 2002).

2.5.4 Food

Formaldehyde can occur in food naturally, through direct addition as a preservative, as a result of cooking or smoking of foods, or through inadvertent contamination (e.g., from its use as a fumigant or from the use of utensils made from formaldehyde resins) (Howard 1989, WHO 1989, ATSDR 1999). Formaldehyde has also been shown to be eluted from formaldehyde-resin plastic dishes by water, acetic acid, and ethanol at temperature-proportionate levels (ATSDR 1999). Formaldehyde levels in fresh fruit have been found to increase after refrigeration (Tang *et al.* 2009).

As shown in Table 2-22, generally higher formaldehyde levels have been seen in fish and seafood than in other foods, aside from smoked ham. Formaldehyde develops postmortem in marine fish and crustaceans via enzymatic reduction of trimethylamine oxide (WHO 2002). Formaldehyde will accumulate in some fish species, including cod, pollack, and haddock, during frozen storage. The formaldehyde formed in fish reacts with protein, causing muscle toughness, and it has been suggested that fish containing the highest levels of formaldehyde may not be palatable for human consumption. Li *et al*. (2007b) observed variable formaldehyde levels among four species of squid; levels generally were far higher in viscera than in muscle of frozen squid. The authors also noted that formaldehyde levels increased with increasing cooking temperature.

Tang *et al.* (2009) reported that an illegal use of synthetic formaldehyde (Rongalite [Rongalit, a registered trademark of BASF; i.e., sodium formaldehyde sulfoxylate]) as a food preservative is common in Chinese markets, and that formaldehyde-induced food poisoning remains a huge problem in China because of this practice. Based on data from seven independent studies, Tang *et al.* reported high formaldehyde levels in seafood due to this practice (Table 2-22).

Table 2-22. Formaldehyde levels in food

Food	Concentration, in mg/kg	Comment	Reference
Fruits and vegetables			
60 different fresh fruits: Without refrigeration With refrigeration	 < 2.74 [< 6.3–10.4]	Reported that fruits had levels below 2.74 but the levels increased 2.3 to 3.8 times with refrigeration	Tang *et al.* 2009
Pear	38.7, 60	Values based on two different analytical methods	WHO 1989
Apple	17.3, 22.3		WHO 1989
Cabbage	4.7, 5.3		WHO 1989
Carrot	6.7, 10		WHO 1989
Green onion	13.3, 26.3		WHO 1989
Spinach	3.3, 7.3		WHO 1989
Tomato	5.7, 7.3		WHO 1989
White radish	3.7, 4.4		WHO 1989
Meat			
Pig	20		WHO 1989
Sheep	8		WHO 1989
Poultry	5.7		WHO 1989
Smoked ham	267	Value for the outer layer of ham	WHO 2002
Milk and milk products			
Goat's milk	1		WHO 1989
Cow's milk	≤ 3.3		WHO 1989
Cow's milk	0.22	Maximum value from cows fed formalin; it was noted that this was roughly 10 times the level in milk from cows without added formalin in the diet	WHO 2002
Cow's milk (fresh) Processed 2% milk	0.013–0.057 0.027 (mean) 0.075–0.255 0.164 (mean)	Higher levels in processed milk were attributed to processing technique, packaging, and storage	WHO 2002
Cheese	≤ 3.3		WHO 1989

Food	Concentration, in mg/kg	Comment	Reference
Fish and seafood			
Squid	10.7–165	Levels across the muscle and viscera and for dried squid thread for 4 species	Li *et al.* 2007b
Freshwater fish (fumigated)	8.8	Fumigation process not described in the source	WHO 1989
Ocean fish (fumigated)	20		
Cod (frozen)	20		WHO 1989
Shrimp (live)	1		WHO 1989
Crustaceans (Mediterranean)	1–60		WHO 1989
Crustaceans (ocean)	3–98		WHO 1989
Fresh marine products	2.177 ± 1.41 (mean ± std. dev.)	Includes products such as mackerel, squid, pomfret, hairtail, sea cucumber, red shrimp, yellow croaker, scallop and octopus	Tang *et al.* 2009
Marine products illegally treated with formaldehyde preservative	~300–4,250	Results of 7 independent studies in 6 Chinese cities	Tang *et al.* 2009
Beverages			
Fruit and vegetable juices	≤ 800	It was reported that concentrations up to 800 mg/kg have been reported in fruit and vegetable juices in Bulgaria	WHO 2002
Alcoholic beverages	0.02–3.8 mg/L	Concentrations from a variety of alcoholic beverages from a study in Japan and a study in Brazil	WHO 2002
Canned or bottled beer	0.1–1.5		WHO 2002
Beer	0.1–0.9	Levels in China across domestic and imported beers	Tang *et al.* 2009
Canned or bottled cola	7.4–8.7		WHO 2002
Brewed coffee	3.4–4.5		WHO 2002
Instant coffee	10–16		WHO 2002
Other			
Shiitake mushroom	40–380	Range of base concentration measurements	Tang *et al.* 2009
Vermicelli noodles	0.011–3.38	Full range across two studies	Tang *et al.* 2009
Maple syrup Untreated trees Treated trees	 < 1 up to 14	Trees treated with paraformaldehyde to deter bacterial growth	WHO 2002

The artificial sweetener aspartame consists of 10% methanol, which Humphries *et al*. (2008) reported can be converted to formaldehyde and other derivatives. The authors also noted that research has shown that formaldehyde adducts accumulate in the tissues after aspartame ingestion.

Formaldehyde can be added to ruminant feeds to improve handling characteristics. It has been estimated that animals may ingest as much as 0.25% formaldehyde in their diets (WHO 2002). Formalin has been added as a preservative to skim milk fed to pigs in the United Kingdom and to liquid whey fed to cows and calves in Canada. Formaldehyde levels in milk from cows fed formalin at the highest concentration were up to 10 times the level in milk from control cows. No data were found on levels in meat due to formaldehyde in animals' diets.

2.6 Exposure estimates

Exposure to formaldehyde can occur from breathing of air and tobacco smoke; ingestion of food, drinking water, and other beverages; dermal contact; and, rarely, direct entry of aqueous solution into the bloodstream (e.g., during medical procedures in which machines or tubing have been disinfected with formaldehyde) (WHO 1989, ATSDR 1999, IARC 2006). As noted above, there are no widely accepted biomarkers for formaldehyde exposure and, therefore, very few data on human intake levels. Exposure can be estimated by combining media concentration information with assumed ingestion and inhalation rates and making various assumptions about the duration of exposure periods. Exposure estimates found in the literature are provided in Table 2-23.

Table 2-23. Estimated formaldehyde exposure levels

Source	Intake, in mg/day	Comment	Reference
Food	1.5–14	Range based on meal composition	WHO 1989
Workplace air Without occupational exposure With occupational exposure	 0.2–0.8 5.0–8.0	Assumes 25% of day at work. Without occupational exposure assumes normal concentrations in conventional buildings; with occupational exposure assumes 1 mg/m^3 [810 ppb] air concentrations. Ranges are across two datasets.	Fishbein 1992, WHO 2002
Tobacco smoke Smoking 20 cigarettes/day Environmental tobacco smoke Home Work	 0.9–2.0 0.5–3.5 0.4–2.8	Environmental tobacco smoke exposure assumes 25% of the day at work and 65% of the day at home, with concentrations of 50–350 µg/m^3 [40–280 ppb]	WHO 2000
Smoking 20 cigarettes/day Environmental tobacco smoke	1.0 0.1–1.0	Authors noted that environmental tobacco smoke can contribute 10%–25% of indoor exposure	Fishbein 1992
Residential indoor air Conventional home Mobile home	 0.3–0.6 1.0	Assumes 65% of time at home, 30–60 µg/m^3 [24–50 ppb] for conventional home, and 100 µg/m^3 [81 ppb] for mobile home	WHO 2000
Residential indoor air Conventional home Prefabricated home Outdoor air	 0.5–2.0 1.0–10.0 0.02	Assumes 65% of day spent in residence and 10% of day spent outdoors	Fishbein 1992
Indoor air Outdoor air	1.0 0.1	Estimates for the Finnish population	HSDB 2007
Outdoor air	0.002–0.04	Assumes 10% of time spent outdoors and 2 m^3/d intake at 1–20 µg/m^3 [0.8–16 ppb] concentration	WHO 2000
Drinking water	< 0.2	Assumes that concentrations in drinking water are normally less than 0.1 mg/L	WHO 1989
Cosmetics Hand cream Suntan lotion	 0.1[a] 0.85[a]	Hand-cream exposure assumes 2-g/application containing 2 mg of formaldehyde and 5% absorption; same assumptions for suntan lotion except 17 g applied	ATSDR 1999

[a]Milligrams absorbed per application.

2.7 Regulations and Guidelines

2.7.1 Regulations

Coast Guard, Department of Homeland Security

46 CFR 150 and 151 detail procedures for shipping formaldehyde, formaldehyde solution, and 1,3,5-trioxane with incompatible chemicals.

Minimum requirements have been established for safe transport of formaldehyde solutions on ships and barges.

Consumer Product Safety Commission (CPSC)

Formaldehyde and products containing 1% or more formaldehyde are considered "strong sensitizers" and must display a warning label.

Department of Agriculture (USDA)

Limits have been established for the amount of residual formaldehyde in inactivated bacterial products and killed-virus vaccines.

Department of Transportation (DOT)

Formaldehyde, formalin, and paraformaldehyde are considered hazardous materials, and special requirements have been set for marking, labeling, and transporting these materials, as prescribed in 49 CFR 172.

Environmental Protection Agency (EPA)

Clean Air Act

Clean-Fuel Vehicles: Formaldehyde emissions limits have been established for various classes of clean-fuel vehicles.

Control of Emissions from New and In-Use Highway Vehicles and Engines: Formaldehyde emissions limits have been established for various classes of vehicles.

Mobile Source Air Toxics: Listed as a mobile source air toxic for which regulations are to be developed.

National Emissions Standards for Hazardous Air Pollutants (NESHAP): Listed as a hazardous air pollutant.

New Source Performance Standards (NSPS): Manufacture of formaldehyde is subject to certain provisions for the control of VOC emissions.

Prevention of Accidental Release: Threshold quantity (TQ) = 15,000 lb.

Regulation of Fuels and Fuel Additives: Under reformulated gasoline certification requirements, formaldehyde emissions levels must not be exceeded.

Urban Air Toxics Strategy: Identified as one of 33 HAPs that present the greatest threat to public health in urban areas.

Clean Water Act

Designation of Hazardous Substances: Formaldehyde and paraformaldehyde both are listed as hazardous substances.

Comprehensive Environmental Response, Compensation, and Liability Act

Formaldehyde reportable quantity = 100 lb.

Paraformaldehyde reportable quantity = 1,000 lb.

Emergency Planning and Community Right-To-Know Act

Toxics Release Inventory (TRI): Listed substance subject to reporting requirements.

Reportable quantity = 100 lb.

Threshold planning quantity = 500 lb.

Resource Conservation and Recovery Act

Listed hazardous waste: Waste codes in which listing is based wholly or partly on formaldehyde — U122, K009, K010, K038, K040, K156, and K157.

Listed as a hazardous constituent of waste.

Food and Drug Administration (FDA)

Numerous formaldehyde-based chemicals may be used as components of adhesives and coatings in packaging, transporting, or holding food provided that conditions prescribed in 21 CFR 175 are met.

Numerous formaldehyde-based chemicals may be safely used as articles intended for use in contact with food provided that conditions prescribed in 21 CFR 177 are met.

Numerous formaldehyde-based chemicals may be used in the production of paper products intended for use in producing, processing, preparing, treating, packaging, transporting, or holding food provided that conditions prescribed in 21 CFR 176 are met.

Formaldehyde and formaldehyde-based chemicals may be used as adjuvants, production aids, and sanitizers that come in contact with foods provided that conditions prescribed in 21 CFR 178 are met.

Formaldehyde-based ion-exchange resins may be used in the treatment of food provided that conditions prescribed in 21 CFR 173 are met.

Formaldehyde may be safely used in the manufacture of animal feeds in accordance with conditions prescribed in 21 CFR 573.460.

Formalin, containing approximately 37% formaldehyde gas by weight, can be used in environmental waters for the control of fungi and parasites for certain finfish and shellfish as prescribed in 21 CFR 529.

U.S. Department of Housing and Urban Development (HUD)

All plywood and particleboard materials bonded with a resin system or coated with a surface finish containing formaldehyde shall not exceed the following emission levels

when installed in manufactured homes: 0.2 ppm for plywood and 0.3 ppm for particleboard.

Manufactured homes must prominently display a notice which provides information on formaldehyde sources, levels, health effects, and remedial actions to reduce indoor levels.

Mine Safety and Health Administration

Approval Requirements for Permissible Mobile Diesel-Powered Transportation Equipment: Engine exhaust from mobile diesel-powered transportation equipment must be diluted with air so that the mixture contains no more than 0.001% by volume of aldehydes, calculated as equivalent formaldehyde.

Occupational Safety and Health Administration (OSHA)

Permissible exposure limit (PEL) = 0.75 ppm [0.92 mg/m^3] (8-h TWA).

Short-term exposure limit = 2 ppm [2.46 mg/m^3] (15-min exposure).

Action level = 0.5 ppm [0.61 mg/m^3] (8-h TWA).

Comprehensive standards have been developed for occupational exposure to formaldehyde gas, its solutions, and materials that release formaldehyde.

Requirements for preventing or minimizing the consequences of catastrophic releases of toxic, reactive, flammable, or explosive chemicals are prescribed in 29 CFR 1910.119; the threshold quantity (TQ) for formaldehyde is 1,000 lb.

2.7.2 Guidelines

American Conference of Governmental Industrial Hygienists (ACGIH)

Threshold limit value – ceiling (TLV-C) = 0.3 ppm [0.37 mg/m^3].

Listed as a suspected human carcinogen.

National Institute for Occupational Safety and Health (NIOSH)

Recommended exposure limit (REL) = 0.016 ppm [0.02 mg/m^3] (10-h TWA).

Immediately dangerous to life and health (IDLH) level = 20 ppm [24.56 mg/m^3].

Ceiling recommended exposure limit = 0.1 ppm [0.12 mg/m^3] (15-min exposure).

Listed as a potential occupational carcinogen.

2.8 Summary

Formaldehyde has numerous industrial and commercial uses and is produced in very large amounts (billions of pounds per year in the United States) by catalytic oxidation of methanol. Its predominant use, accounting for roughly 55% of consumption, is in the production of industrial resins, which are used in the production of numerous commercial products. Formaldehyde is used in industrial processes primarily as a solution (formalin) or solid (paraformaldehyde or trioxane), but exposure is frequently to formaldehyde gas, which is released during many of the processes. Formaldehyde gas is also created from the combustion of organic material and can be produced secondarily in air from photochemical reactions involving virtually all classes of hydrocarbon pollutants. In some instances, secondary production may exceed direct air emissions. Formaldehyde is also produced endogenously in humans and animals.

Formaldehyde is a simple, one-carbon molecule that is rapidly metabolized, is endogenously produced, and is also formed through the metabolism of many xenobiotic agents. Because of these issues, typical biological indices of exposure, such as levels of formaldehyde or its metabolites in blood or urine, have proven to be ineffective measures of exposure. Formaldehyde can bind covalently to single-stranded DNA and protein to form crosslinks, or with human serum albumin or the *N*-terminal valine of hemoglobin to form molecular adducts, and these reaction products of formaldehyde might serve as biomarkers for exposure to formaldehyde.

Occupational exposure to formaldehyde is highly variable and can occur in numerous industries, including the manufacture of formaldehyde and formaldehyde-based resins, wood-composite and furniture production, plastics production, histology and pathology, embalming and biology laboratories, foundries, fiberglass production, construction, agriculture, and firefighting, among others. In fact, because formaldehyde is ubiquitous, it has been suggested that occupational exposure to formaldehyde occurs in all work places.

Formaldehyde is also ubiquitous in the environment and has been detected in indoor and outdoor air; in treated drinking water, bottled drinking water, surface water, and groundwater; on land and in the soil; and in numerous types of food.

The primary source of exposure is from inhalation of formaldehyde gas in indoor settings (both residential and occupational); however, formaldehyde also may adsorb to respirable particles, providing a source of additional exposure. Major sources of formaldehyde exposure for the general public have included combustion sources (both indoor and outdoor sources including industrial and automobile emissions, home cooking and heating, and cigarette smoke), off-gassing from numerous construction and home furnishing products, and off-gassing from numerous consumer goods. Ingestion of food and water can also be a significant source of exposure to formaldehyde.

Numerous agencies, including the Department of Homeland Security, CPSC, DOT, EPA, FDA, HUD, the Mine Safety and Health Administration, OSHA, ACGIH, and NIOSH, have developed regulations and guidelines to reduce exposure to formaldehyde.

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3 Human Cancer Studies

This section reviews the epidemiologic literature on formaldehyde exposure and human cancer risk. As mentioned in Section 1, formaldehyde was nominated for review by the RoC based on an evaluation by the International Agency for Research on Cancer (IARC). In 2004 and 2009, IARC working groups classified formaldehyde as *carcinogenic to humans* (Group 1) (IARC 2006, Baan *et al.* 2009), based on sufficient evidence for the carcinogenicity of formaldehyde in humans for leukemia and nasopharyngeal cancer.

The vast majority of epidemiologic studies on formaldehyde and cancer have focused on occupational, rather than recreational or environmental, exposures. Industries known to involve formaldehyde exposure include (but are not limited to) formaldehyde production or other chemical manufacture using formaldehyde resins; wood, plywood, particleboard, and paper manufacture; garment and other textile manufacture; work in foundries; production of glass fibers, plastics, and rubber products; and health professions, including pathology and embalming (see Section 2.4 for more information about exposed occupations). To date, only one study has evaluated residential formaldehyde exposure and cancer risk among individuals living in mobile homes constructed with formaldehyde-treated material (Vaughan *et al.* 1986b); however, this study is excluded from this review because the exposed number of cases was too small for meaningful analysis.

Epidemiologic studies evaluating formaldehyde exposure and cancer risk were identified by searching databases (primarily Medline and Web of Science) initially using the search terms “formaldehyde” in combination with “epidemiologic studies” or “mortality” and “neoplasm” or “cancer.” Online searches were supplemented through the bibliographies of retrieved papers (original research papers, reviews, and meta-analyses). Case reports and letters to the editor were excluded from this review. In general, studies were excluded if a more recent study completely subsumed a previous analysis conducted within the same study population; reference is made to the results of earlier studies where the population or analysis differs or substantially different findings were reported. Also, some analytic studies were excluded from this review for one or more of the following reasons: (1) they were not peer reviewed (Robinson *et al.* 1987, Matanoski 1991), (2) they had excessively small sample size (Hernberg *et al.* 1983a,b, Brinton *et al.* 1984, Vaughan *et al.* 1986b Fondelli *et al.* 2007), (3) the authors did not provide any cancer risk estimates for formaldehyde (Nisse *et al.* 2001, Ambroise *et al.* 2005), (4) the extent or effects of potential exposure to formaldehyde cannot be evaluated due to exposure to complex mixtures containing formaldehyde (McDuffie *et al.* 2001, Chen *et al.* 2008), or (5) no English translation was available (Andersen *et al.* 1982). While meta-analyses and pooled analyses were included in the review, descriptive reviews were generally excluded. Further exclusions are cited in the corresponding sections relevant to these studies.

Section 3.1 provides background information on head and neck cancers, which, due to the potential carcinogenic effects of direct contact with inhaled formaldehyde, are among the tumor sites of primary interest. That section also discusses other potential tumor sites.

Sections 3.2 to 3.5 describe the individual epidemiologic studies, and are organized primarily by study population and study design, as follows: (1) Section 3.2 describes historical cohort and nested case-control studies among industrial workers; (2) Section 3.3 reviews historical cohort and nested case-control studies among health professional workers; (3) Section 3.4 describes population-based cohort and cancer registry studies; and (4) Section 3.5 describes population-based case-control studies, and is organized by tumor sites. Section 3.6 summarizes findings organized by tumor site, and Section 3.7 is an overall summary of the entire body of epidemiologic literature included in the review.

3.1 Cancer sites reviewed in Sections 3.2 and 3.3

3.1.1 Upper respiratory system (head and neck) cancers

Head and neck cancers associated with the upper respiratory tract include cancers of the paranasal sinuses and nasal cavity, nasopharynx, oral (or buccal) cavity and salivary glands, pharynx, larynx, and trachea. Cancers of the brain, eye, and thyroid are not usually defined as cancers of the head and neck. The estimated incidence of new cases of head and neck cancer in the United States in 2009 was 48,010 people (35,260 men and 12,850 women), and the estimated mortality was 11,260 deaths (8,140 men and 3,120 women) (Perez *et al.* 2009). See Figure 3-1 for an illustration of the upper respiratory system.

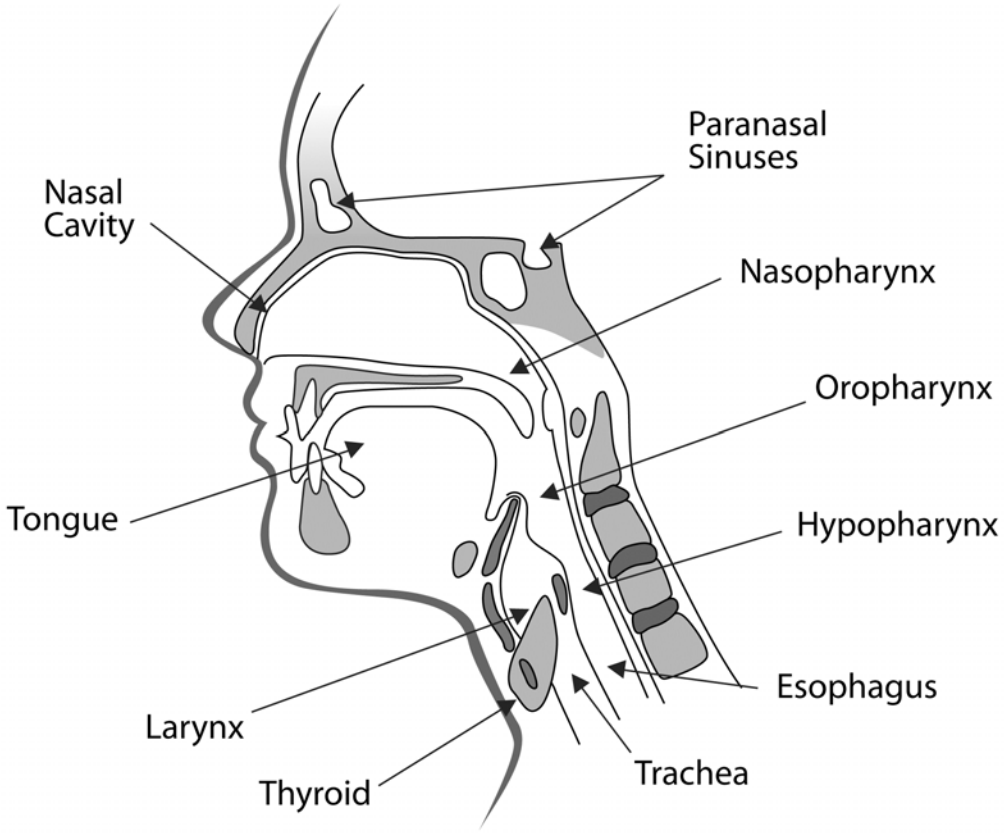

Figure 3-1. Upper respiratory system
(Illustration prepared by Donna Jeanne Corocran, Image Associates, Durham, NC.)

Sinonasal carcinoma comprises all cancers of the paranasal sinuses and nasal cavity, which are small hollow spaces lined with mucosal tissue in and around the nose. The histology of these tumors is primarily squamous-cell (60% to 70%). These carcinomas have been a particular focus in formaldehyde studies as the nasal sinuses are the initial site of contact with inhaled formaldehyde. Pharyngeal carcinomas (also known as throat cancer) are also primarily squamous-cell type and include nasopharyngeal, oropharyngeal, and hypopharyngeal carcinomas. Oro- and hypopharyngeal carcinomas are often grouped together in epidemiologic studies. Many studies of formaldehyde exposure and pharyngeal cancer have focused only on nasopharyngeal cancers since the nasopharynx is thought to be the primary site of contact in the pharynx following inhalation exposure to formaldehyde.

3.1.2 Lower respiratory system cancers

The lower respiratory tract begins after the larynx at the start of the trachea. The trachea enters the left and right lung as primary bronchi which bifurcate into secondary and tertiary bronchi and, finally, to bronchioles. The alveoli (air sacs) are attached to the bronchioles (see Figure 3-2).

Lung cancers are the most common type of cancer associated with the lower respiratory tract. The American Cancer Society estimated that cancer of the lung and bronchus accounted for approximately 15% of all cancers in the United States in 2009 (Jemal *et al.* 2009). Lung cancers are divided into two classes: non-small-cell lung cancer and small-cell lung cancer. Non-small-cell lung cancers are the more common of the two types and may have the histological description of squamous-cell carcinoma, adenocarcinoma, large-cell carcinoma, or may be grouped together. Small-cell carcinomas make up approximately 15% of the bronchogenic cancers and are the more aggressive of the two forms of tumor.

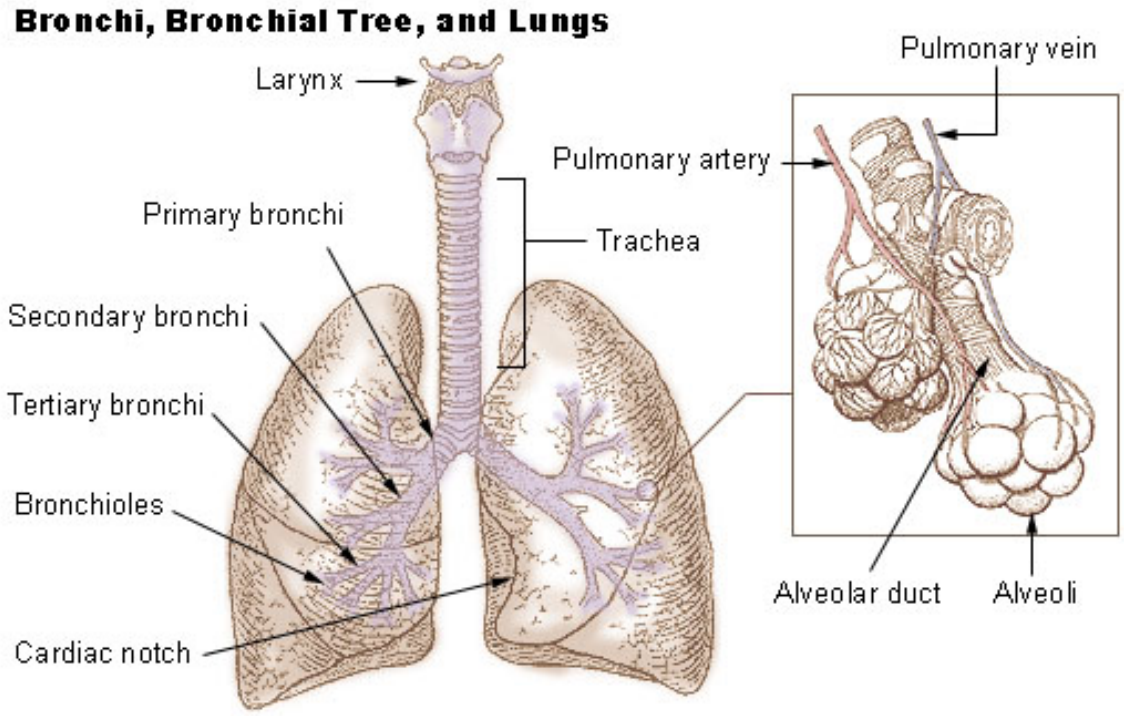

Figure 3-2. Lower respiratory system
Source: http://upload.wikimedia.org/wikipedia/commons/d/db/Illu_bronchi_lungs.jpg.

3.1.3 Lymphohematopoietic cancers

Malignant blood diseases (leukemia, lymphomas, and myeloma) are a heterogenous group of neoplasms that arise from stem cells at different hierarchical levels of hematopoietic and lymphoid cell development (Greaves 2004, Kumar *et al.* 2010). Blood cells arise from a common pluripotent progenitor cell (stem cell). In the bone marrow, this stem cell forms two multipotent progenitor cells, the common myeloid stem cell and the common lymphoid stem cell (For more details, see Section 5.7.6 and Figure 5-4). Examples of lymphoid neoplasms are chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma, and an example of myeloid neoplasm is myeloid leukemia. The terms leukemia and lymphoma are used to describe the usual tissue distribution of the disease (bone marrow and peripheral blood vs. discrete mass in lymphoid tissue) at the time of clinical presentation, but both types of neoplasms can be present in bone marrow, circulating blood, and lymphoid tissues. There are four major types of leukemia: acute lymphocytic leukemia, chronic lymphocytic leukemia, acute myeloid leukemia and chronic myeloid leukemia.

The estimated incidence of new cases of head and neck cancer in the United States in 2009 was 48,010 people (35,260 men and 12,850 women), and the estimated mortality was 11,260 deaths (8,140 men and 3,120 women) (Perez *et al.* 2009).

3.1.4 Brain and central nervous system cancers

The central nervous system (CNS) consists of the brain, spinal cord, and meninges (mesenchymal tissue that covers the brain and spinal cord). Brain tumors account for approximately 85% of all primary CNS tumors, 38% are gliomas (astrocytoma and glioblastoma), and 27% are of mesenchymal origin (Levin *et al.* 2001). Other less common tumors in decreasing incidence include: pituitary gland tumors, schwannomas, CNS lymphomas, oligodendrogliomas, ependymomas, astrocytomas (low grade), and medulloblastomas. According to NCI, brain metastases outnumber primary brain tumors 10 to 1 with metastases from the lung the most common. Nasopharyngeal cancers can extend along cranial nerves or through the foramina at the base of the skull to the brain.

3.2 Industrial cohort and nested case-control studies

This section reviews historical cohort and nested case control studies that have examined the association between occupational exposure to formaldehyde and cancer among industrial workers. The three largest cohort studies (NCI, NIOSH and British chemical workers study) are described first, followed by a review of the smaller studies, which are organized by industrial sector: workers in the fiberglass, woodworking, mixed manufacturing industries, resin, chemical, plastics, other industries which use formaldehyde (abrasive materials, tannery, iron foundry, and textile industries). Several of the cohort studies have been updated recently, and the results presented in this review will generally be limited to the most recent findings from each cohort and unique re-analyses within the cohort. Information on suspected confounding factors (e.g., smoking) is noted in each study summary whenever such information was collected or analyzed by the study investigators.

Table 3-1 summarizes the characteristics of the major cohort and nested case-control studies among industrial workers. Findings for the tumor sites of interest from these studies are reported in Tables 3-4 to 3-9 (see Section 3.6).

Table 3-1. Characteristics of cohort studies and nested case-control studies among industrial workers

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
Andjelkovich *et al.* 1995, Andjelkovich *et al.* 1994	Workers at an iron foundry in Michigan, USA N = 8,147 Subcohort of formaldehyde–exposed workers: N = 3,929 1959–87 or 89	Occupational histories obtained from employment records and classified using a JEM *Exposure level (ppm)* low 0.05 medium 0.5 high 1.5	Standardized mortality analysis on formaldehyde exposed workers Nested case-control study of lung cancer (N = 220) from entire cohort
Beane Freeman *et al.* 2009) Hauptmann *et al.* 2003, 2004 (update of Blair *et al.* 1986)	NCI cohort, USA N = 25,619 *Hauptmann* et al. *2003* Follow-up 1966–94 median 35 yr Person-yr 865,708 *Beane Freeman* et al. Follow-up 1966–2004 median 42 yr Person-yr 998,106	Occupational histories obtained from company records, interviews, and industrial hygiene monitoring from 1980; exposure was classified by level and frequency of peak exposure, average exposure, cumulative exposure, and duration *Exposure levels and duration for exposed workers (median and range)* Average intensity, in ppm 0.3 (0.01–4.25) Cumulative (ppm-yr) 0.6 (0–107.4) 8-h TWA 0.45 (0.01–4.25) Duration 2 yr (0–46) All workers 82.5% exposed to formaldehyde 4.7% employed in jobs with ≥ 2 ppm average intensity 22.6% employed in jobs involving ≥ 4 ppm peak exposure	Standardized mortality and internal analysis Beane Freeman *et al.* Lymphohematopoietic malignancies Hauptmann *et al*. solid tumors Potential confounding from exposure to 11 occupational substances and working as a chemist or lab technician was evaluated Reanalysis of lung, leukemia (1994 follow-up) and NPC by Marsh and Youk 2005, Marsh *et al.* 2007b Follow-up of Wallingford cohort by Marsh *et al.* 2007a, cohort findings and nested case-control study on pharyngeal cancer (N = 17)
Bertazzi *et al.* 1989 (update of Bertazzi *et al.* 1986)	Workers at a resin manufacturing plant in Italy N = 1,332 1959–86 Subcohort exposed to formaldehyde N not reported 73 deaths (total cohort had 179)	Occupational histories obtained from plant employment records and classified by job title and task *Exposure levels* Air sampling 1974, 1978, 1979 Average 0.16–3.1 ppm Maximum 0.33–6.5 ppm	Standardized mortality study for selected cancer sites Employment length and time since first exposure available for lung and digestive tract

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
Bond *et al.* 1986	Male workers employed at Dow Chemical production facility in Texas N = 19,608 1940–80	Occupational histories and potential for exposure obtained from records, and information on smoking from interviews *Exposure levels not reported*	Nested case-control study on lung cancer (N = 308)
Chiazze *et al.* 1997	Male workers employed at an Owens Corning fiberglass manufacturing plant in South Carolina, USA N = 4,631 1951–91	Occupational histories obtained by interview and a historical exposure reconstruction; exposure was classified by a committee of experts *Exposure levels* Each process was assigned to 1 of 4 exposure levels with mid-points ranging from 0.05 to 1.5 ppm Cumulative exposure (level times duration) was estimated for each worker	Nested case-control study of lung cancer (N = 47)
Coggon *et al.* 2003 (update of Acheson *et al.* 1984)	British Chemical Workers (males), UK N = 14,014 1941–2000	Occupational histories obtained from company employment records and classified using plant-specific JEMs *Exposure levels* Estimated from measurements taken after 1970 and recall of workers' irritant symptoms Level (ppm) % of workers < 0.1 27.6% 0.1–0.5 27.2% 0.6–2.0 9.7% > 2.0 28.5% Most workers with the highest exposure were from the British Industrial Plastics plant	Standardized mortality study SMRs provided for ever exposed and highly exposed; SMR provided for employment in jobs with high exposure to lung cancer, and for low, moderate and high exposure for lung and stomach cancer

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
Dell and Teta 1995	Male workers employed at a Union Carbide plastics manufacturing plant in New Jersey, USA N = 5,932 1946–88	Occupational histories obtained using employment records Exposure levels not reported	Standardized mortality study Workers exposed to formaldehyde (N = 111)
Edling *et al.* 1987b	Male and female workers at an abrasive materials manufacturing plant, Sweden N = 506 blue collar workers Mortality 1958–83 Incidence 1958–81	Exposure monitoring in plant from 1970 No individual exposure assessment reported *Exposure levels* Grinding wheel manufacturing [0.08–0.8 ppm] Abrasive belts (N = 59 workers) Peaks [16–25 ppm)]	Standardized mortality and incidence study Unknown number of workers exposed to formaldehyde in grinding wheel process; 59 making abrasive belts Results reported for males only, and for few cancer sites
Hansen and Olsen 1995, 1996	Danish workers at 265 companies producing or using 1 kg/individual year N = 2,041 men, and 1,263 women 1970–84	Occupational information obtained from Danish product Registry Individuals assigned to low or high exposure based on "white or blue collar" status based on pension records Exposure levels not reported	Record linkage study Workers were included in study if their longest employment was 10 years prior to cancer diagnosis (Original study population = 126,347 men and women) Findings for some cancer sites provided for low formaldehyde exposure, and formaldehyde and woodworkers (combined)
Marsh *et al.* 2001, Stone *et al.* 2001, Youk *et al.* 2001 (update of Marsh *et al.* 1990)	Workers employed at 10 fiberglass manufacturing facilities in the USA N = 32,110 1946–92	Occupational histories obtained from company employment records and relevant industrial hygienic literature; exposure estimated using job location-weighted measures *Exposure level* Median average intensity 0.066 ppm Median cumulative exposure 0.173 ppm-yr	Nested case control of cancers of the respiratory system

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
Ott *et al.* 1989	Workers employed in 2 Union Carbide Corporation chemical manufacturing facilities and a research and development center, USA N = 29,139 1940–78	Occupational histories obtained from company employment records and classified using a JEM Exposure levels not reported	Nested case-control study of lymphohematopoietic malignancies (N = 129): NHL, multiple myeloma, nonlymphocytic leukemia, lymphocytic leukemia
Partanen *et al.* 1990, 1993, 1985	Workers employed in 135 particleboard, plywood, and formaldehyde glue factories and sawmills in Finland N = 7,703 1944–65	Occupational histories and air quality monitoring data obtained from company employment records and classified using a JEM Exposure levels determined from hygienic data (ppm) Low 0.1–1 Medium 1–2 Heavy > 2 Workers considered exposed to formaldehyde if minimum exposure was 0.1 ppm and cumulative exposure was > 3 ppm-month 83% of subjects in respiratory case-control study exposed to cumulative exposure of less than < 0.25 ppm-yr	Nested case-control studies of lymphohematopoietic malignancies (N = 24 in 1993 study) and respiratory cancer (N = 136)
Pinkerton *et al.* 2004 (update of Stayner *et al.* 1985 [PMR study] and 1988 [SMR study])	NIOSH cohort of garment workers, USA N = 11,039 SMR 1955–98 PMR 1959–82	All workers considered exposed; personal exposure levels available from plant monitoring programs *Exposure levels* 3 plants in 1981 or 1984 Geometric mean 8-h TWA (ppm) 0.15 (0.09–0.20) Median duration = 3.3 years In other garment factories, exposures prior to the 1970s were estimated to be as high as 10 ppm	Standardized mortality study Analysis by duration of exposure, time since first exposure, and time of first exposure performed for a few selected cancer sites PMR study included 256 deaths, PCMR ratios were also calculated to correct for healthy worker effect

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
Boffetta *et al.* 1989, Stellman *et al.* 1998	Workers employed in the wood industry American Cancer Society Cancer Prevention Study, USA N = 362,823 Formaldehyde-exposed workers NR (1,238 deaths from all causes) Formaldehyde-exposed woodworkers (N = 387) 1982–88	Occupational histories obtained by interview and classified by job title and task Exposure levels not reported Findings reported for ever exposed	Mortality study Internal analyses using non-woodworkers or workers not exposed to wood dust as the reference group Nested case-control study of multiple myeloma (N = 282) (Boffetta *et al.*)
Stern 2003 (update of Stern *et al.* 1987)	Workers employed in two chrome leather tannery plants, USA N = 9,352 1940–93 Formaldehyde exposed workers in the finishing dept. (no. of workers not stated, 1,050 deaths from all causes, 2,332 cancer deaths observed)	Occupational history obtained from work records Exposure levels obtained from industrial hygiene surveys *Exposure levels in finishing department (ppm)* Mean (range) 2.45 (0.5–7)	Standardized mortality study Analysis by duration of employment for entire cohort but not for workers in the finishing department
Li *et al.* 2006, Ray *et al.* 2007, Wong *et al.* 2006	Chinese female textile workers in 526 factories N= 267,400 1958–98	Historical exposure estimated by industrial hygienists using a JEM based on job histories and production process data	Nested case-cohort studies of thyroid (Wong *et al.*), nasopharyngeal cancer (Li *et al.*), and breast cancer (Ray *et al.*) Age adjusted hazard ratios calculated using Cox proportional hazards methods

8-h TWA = 8-hour time-weighted average; JEM = job-exposure matrix; NHL = non-Hodgkin's lymphoma; PCMR = proportionate cancer mortality ratio; PMR = proportionate mortality ratio; SMR = standardized mortality ratio.

3.2.1 National Cancer Institute (NCI) Cohort: mixed industries

Blair and colleagues at the National Cancer Institute (NCI) assembled the largest cohort of industrial workers to date to assess the risk of several cancers suspected of being associated with exposure to formaldehyde, including leukemia and cancer of the brain, lung, oral cavity, and pharynx (Blair *et al.* 1986). This cohort includes workers from various industries that used formaldehyde, including plants that manufactured resin, plastic, photographic film, and plywood. The authors also assessed several concurrent occupational exposures (and potential confounding agents), such as asbestos, wood dust, and solvents.

Previous studies (Marsh 1982, Fayerweather *et al.* 1983, Wong 1983, Liebling *et al.* 1984, Marsh *et al.* 1994a, Marsh *et al.* 1994b) included workers who were later included in the NCI study; the findings of these studies are considered to be subsumed by NCI analyses for the purposes of this review. Likewise, earlier analyses of the NCI cohort (Robins *et al.* 1988, Sterling and Weinkam 1988, 1989a,b, 1994, Blair and Stewart 1989, Stewart *et al.* 1989, Blair *et al.* 1990b, Marsh *et al.* 1992a,b, Marsh *et al.* 1994a,b, Callas *et al.* 1996) will not be discussed in detail since more recent and updated analyses are available on the same study population.

3.2.1.1 Cohort and methods

Study population and follow-up. Using records from the Formaldehyde Institute, trade organizations, and other sources, including chemical producers, approximately 200 companies reported to use or produce formaldehyde were identified. The 10 industrial plants with the largest number of employees and longest history of formaldehyde use were selected for inclusion into the cohort. Three of the plants produced formaldehyde, six produced formaldehyde resins, six produced molding compounds, two produced molded plastic products, two produced photographic film, and one produced plywood (some plants produced more than one product). The study cohort consisted of all workers of known sex and race first employed at the selected plants before January 1, 1966 (N = 25,619; 93% white, 12% female). Workers were originally followed through January 1, 1980 to determine vital status and cause of death. Hauptmann *et al.* (2003, 2004) extended the mortality follow-up through December 31, 1994 (median follow-up of 35 years, representing a total of 865,708 person-years) for analyses of lymphohematopoietic malignancies (N = 178 deaths) and solid cancers (N = 1,921 deaths). The NCI cohort was most recently extended through December 31, 2004, resulting in a median follow-up time for workers of 42 years, representing 998,106 person-years of follow-up among 25,619 workers, 4,359 of whom were classified as never exposed to formaldehyde (Beane Freeman *et al.* 2009). A total of 13,951 deaths were identified from 1943 to December 31, 2004, and findings for lymphohematopoietic cancers (but not solid cancers) have been published by Beane Freeman *et al.* (2009). Findings for solid cancers are from the 1994 follow-up as reported by Hauptmann *et al.* (2004).

Exposure assessment. Exposure to formaldehyde was reconstructed using comprehensive work histories collected through 1980 on the basis of job titles, tasks, plant visits by industrial hygienists, information from workers and plant managers, as well as monitoring data (Blair *et al.* 1986, Stewart *et al.* 1986, 1987a, Blair and Stewart 1990). Peak exposures that occurred in both routine and non-routine tasks were defined as short-term exposures (generally less than 15 minutes) that exceeded the 8-hour time-weighted average (TWA) formaldehyde exposure intensity, and were estimated by an industrial hygienist based on knowledge of the job tasks. For jobs in which peak exposures did not exceed the 8-hour TWA exposure intensity, the job-specific 8-hour TWA exposure intensity was assigned as the peak exposure. Four maximum peak exposure categories were used in the statistical analyses: unexposed, 0.1 to 1.9 ppm, 2.0 to 3.9 ppm, and ≥ 4 ppm. In addition to peak exposure and frequency of peak exposure (none, hourly, daily, weekly, monthly), time-dependent estimates also were calculated for duration of exposure (years), average exposure (ppm), and cumulative exposure (ppm-years). Several

important cofactors were assessed, including exposure to particulates and 11 other widely used chemicals in the plants (i.e., antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust, and benzene), routine use of respirators by workers, and duration of employment as a chemist or laboratory technician. No data on formaldehyde exposures after 1980 were available, and in the primary analyses, exposures after 1980 were considered to be zero.

Among jobs considered exposed to formaldehyde (83.4%), the median 8-hour TWA exposure was 0.45 ppm (range = 0.01 to 4.25 ppm); median values were 2 years (range = 0 to 46 years) for duration, 0.3 ppm (range = 0.01 to 4.25 ppm) for average intensity, and 0.6 ppm-years (range = 0.0 to 107.4 ppm-years) for cumulative exposure. Average intensity was 2 ppm or higher for nearly 3% of jobs, and peak exposures reached 4 ppm or higher for over 14% of jobs. Approximately 0.5% (N = 133) of workers ever used a respirator routinely.

The authors noted that smoking information was not available for most of the cohort. Smoking was not considered to be a source of confounding in internal analyses, however, since analysis of a sample of workers revealed no major differences in smoking prevalence by cumulative formaldehyde exposure.

Statistical methods. Standardized mortality ratios (SMRs) were calculated using sex-, race, age-, and calendar-year-specific U.S. mortality rates. To investigate the association between levels and duration of exposure to formaldehyde and cancer mortality, internal comparisons were conducted using log-linear Poisson regression, stratified by calendar year, age, sex, and race, and adjusted for pay category. Potential confounding was evaluated for exposure to 11 concomitant occupational substances (ever/never), as well as working as a chemist or lab technician (years). Exposure lags ranging from 2 to 20 years were considered to account for latency; all exposures were subsequently calculated using a 2-year lag interval for the analyses of lymphohematopoietic malignancies (Beane Freeman *et al.* 2009, Hauptmann *et al.* 2003) and a 15-year lag interval for the analyses of solid cancers (Hauptmann *et al.* 2004).

Overall results. Person-years at risk (456,635) among exposed workers and person-years (409,074) among unexposed workers were compared in external analyses in the 1994 cohort update, lagged by 15 years. Compared with the U.S. population, Hauptmann *et al.* (2004) found that mortality from all cancers was lower than expected both in unexposed (SMR = 0.65, 95% confidence interval [CI] = 0.56 to 0.75, 183 deaths for 2-year lag) and exposed workers (SMR = 0.90, 95% CI = 0.86 to 0.94, 1,916 deaths for 2-year lag), regardless of length of the lag interval.

3.2.1.2 Lymphohematopoietic cancers: Beane Freeman *et al.* (2009)

Beane Freeman *et al.* (2009) conducted external and internal analyses of lymphohematopoietic cancers through the 2004 follow-up. The authors noted that a total of 1,006 deaths were identified that had been missed in the previous 1980 to 1994 analysis of Hauptmann *et al.* (2003). In addition, four subjects had been previously misclassified as deaths but were found to be living. Lastly, several deaths for lymphohematopoietic cancers that were included in the Hauptmann *et al.* analysis were

recoded: six deaths (one multiple myeloma, one myeloid leukemia, one non-Hodgkin's lymphoma, and three myelofibrosis deaths) were re-classified as non-lymphohematopoietic cancers, and two non-lymphohematopoietic cancer deaths were recoded as multiple myelomas. The data reported below are confined to the 2004 update reported by Beane Freeman *et al.* (2009) unless clear differences between findings in this update and the earlier (1994) update were observed. In the text, *P* values for trends for lymphohematopoietic cancer exposure-response relationships refer to the exposed group only, using the lowest exposure group as the referent, unless otherwise stated; *P* values for trends both across the unexposed and exposed groups, and within exposed groups only, using the lowest exposed group as referent, are reported in Tables 3-2 and 3-8a (see Section 3.6).

A total of 319 deaths from all lymphohematopoietic cancers were identified to the end of follow-up in 2004; 286 among ever-exposed and 33 among never-exposed workers. In external analyses, the SMRs indicated that the rates of lymphohematopoietic cancers in the cohort were similar to national rates in both the exposed (SMR = 0.94, 95% CI = 0.84 to 1.06, 286 deaths) and nonexposed groups (SMR = 0.86, 95% CI = 0.61 to 1.21, 33 deaths). An increased risk for Hodgkin's lymphoma among exposed workers was observed (SMR = 1.42, 95% CI = 0.96 to 2.10, 25 deaths), but mortality from other subtypes of lymphohematopoietic cancers among the exposed workers did not indicate increased mortality rates compared with the U.S. population. Findings were generally similar to the 1994 findings (Hauptmann *et al.* 2003).

In internal analyses of exposed workers, using Poisson logistic regression stratified by age, sex, race, calendar year, and pay category, peak exposures in the highest exposure category were associated with a significant increase in all lymphohematopoietic deaths combined (RR = 1.37, 95% CI = 1.03 to 1.81, 108 deaths, comparing peaks of ≥ 4 ppm with > 0 to 2.0 ppm; P_{trend} = 0.02; Table 3-2). No association was observed for all lymphohematopoietic cancers in the 2004 update for average intensity of exposure (Table 3-8a) or cumulative exposure.

With respect to leukemia, risks for leukemia (P_{trend} = 0.12) and the subgroup myeloid leukemia (P_{trend} = 0.13) increased with increasing peak exposure (P_{trend} = 0.12), although the trends were not statistically significant. At the highest exposure category of peak exposure (peaks ≥ 4 ppm vs. > 0 to 2.0 ppm), RRs were 1.42 (95% CI = 0.92 to 2.18, 48 deaths) for leukemia and 1.78 (95% CI = 0.87 to 3.64, 19 deaths) for myeloid leukemia. There were no clear trends toward increasing risk with increasing average or cumulative exposure to formaldehyde for leukemia or myeloid leukemia, although an elevated RR for myeloid leukemia was observed for the highest category of average intensity of exposure (≥ 1 ppm) vs. the lowest category (RR = 1.61, 95% CI = 0.76 to 3.39, 11 deaths, P_{trend} = 0.43) (see Table 3.8a).

Table 3-2. Lymphohematopoietic (LH) cancers in formaldehyde-exposed workers and highest peak exposure: NCI cohort, 1994 and 2004 updates

Cancer type	2004 Update RR (95% CI); N[a]	P_{trend}[b]	P_{trend}[c]	1994 Update RR (95% CI); N[a]	P_{trend}[b]	P_{trend}[c]
All LH	1.37 (1.03–1.81); 108	0.02	0.04	1.48 (1.04–2.12); 68	0.025	0.025
All leukemia	1.42 (0.92–2.18); 48	0.12	0.02	1.60 (0.90–2.82); 29	0.09	0.02
Myeloid leukemia	1.78 (0.87–3.64); 19	0.13	0.07	2.79 (1.08–7.21); 14	0.02	0.008
Lymphatic leukemia	1.15 (0.54–2.47); 14	> 0.50	0.30	0.74 (0.28–1.94); 7	> 0.50	> 0.50
Other leukemia	1.15 (0.53–2.53); 13	> 0.50	0.50	1.79 (0.55–5.89); 7	0.33	0.42
Hodgkin's lymphoma	3.96 (1.31–12.02); 11	0.01	0.004	3.30 (0.98–11.10); 8	0.04	0.009
Multiple myeloma	2.04 (1.01–4.12); 21	0.08	> 0.50	2.03 (0.89–4.64); 15	0.14	> 0.50
NHL	0.91 (0.55–1.49); 28	> 0.50	> 0.50	0.95 (0.49–1.86); 16	> 0.50	> 0.50
LH (lymphoid origin)	1.35 (0.97–1.89); 74	0.06	0.10	NR	NR	NR
LH (nonlymphoid origin)	1.80 (0.91–3.57); 21	0.09	0.09	NR	NR	NR

Source: Beane Freeman *et al.* 2009: 1994 follow-up is based on the reanalysis that accounted for additional and recoding of deaths. See Table 3-8a for detailed data on peak and average exposure for the 2004 update. LH = lymphohematopoietic; N = number of deaths; NHL = non-Hodgkin's lymphoma; RR = relative risk.

[a]Data for peak (≥ 4 ppm vs. > 0–2.0 ppm) exposures, 2-year exposure lag used.

[b]P_{trend} for 2-sided likelihood ratio for exposed person-years only.

[c]P_{trend} for 2-sided likelihood ratio for exposed and unexposed person-years.

Deaths from Hodgkin's lymphoma were significantly elevated in the highest peak vs. the lowest peak exposure group and the relative risks increased with increasing peak exposure. (RR = 3.96, 95% CI = 1.31 to 12.02, 11 deaths, P_{trend} = 0.01). RRs for Hodgkin's lymphoma increased with increasing average intensity of exposure (P_{trend} = 0.05) and cumulative exposure (P_{trend} = 0.08). Elevated RRs were found for the highest category of exposure vs. lowest category of exposure: RR = 2.48 (95% CI = 0.84 to 7.32, 6 deaths, for ≥ 1 ppm average intensity of exposure and RR = 1.30 (95% CI = 0.40 to 4.19, 4 deaths for ≥ 5.5 ppm-years cumulative exposure). Peak exposure (highest category compared with the lowest category) was also associated with deaths from multiple myeloma (RR = 2.04, 95% CI = 1.01 to 4.12, 21 deaths, P_{trend} = 0.08), but no association was found with average or cumulative exposure. Relative risks were also computed for unexposed workers in comparison with the lowest exposure groups for peak, average, and cumulative exposure, and subjects with no estimated exposure to formaldehyde were found to be at significantly increased risk of multiple myeloma compared with low-exposed workers for peak and average exposure, but not for cumulative exposure. For other lymphohematopoietic cancers, unexposed workers had similar or lower risks in comparison with the lowest exposed group. Non-Hodgkin's lymphoma was not associated with peak, average, or cumulative exposure (see Table 3.2 and 3.8a in Section 3.6).

In general, the 2004 update confirmed the findings of the 1994 update; however, the magnitude of the risks estimates for the highest category of peak exposure were higher in the 1994 update compared with the 2004 update, and some of the exposure-response relationships were stronger in the earlier update (see Table 3-2). Analyses due to recoding of some of the lymphohematopoietic cancers did not substantially affect the previously reported results. The 1994 update (Hauptmann *et al.* 2003) also reported findings by duration of exposure (not presented in the 2004 update), and found no statistically significant risk estimates by specific categories of exposure duration and no overall trends with increasing duration.

As mentioned previously, the primary analysis assumed zero exposures after 1980. The authors conducted two sensitivity analyses to evaluate this assumption. If exposure was considered to continue at 1980 levels, risk patterns for all lymphohematopoietic cancers were similar to those observed in the primary analysis. If the cohort follow-up was censored two years after the last job for the 2,810 individuals who were still exposed in 1979 and alive two years later (instead of 2004), however, the association for myeloid leukemia with peak and average intensity of exposure was stronger than that observed in the primary analyses.

Controlling for duration of exposure or for 11 other co-exposures with possible associations with lymphohematopoietic cancers did not alter the findings for leukemia, myeloid leukemia, or other subtypes of lymphohematopoetic cancer, and excluding 586 workers with possible exposure to benzene (a known leukemogen) did not alter the results for lymphatic or myeloid leukemia and the highest peak exposure category (data not reported). Similarly, adjusting for plant type did not substantively alter the results.

Additional analyses considered calendar time periods and the effects of time since first exposure (Figure 1 and supplemental tables in Beane Freeman *et al.* 2009). When time period analyses for trends in relative risk were examined, statistically significant excesses of risk were observed for myeloid leukemia in relation to peak exposures > 4.0 ppm (compared with peaks of > 0 to < 2.0 ppm) up to 1994 (RR = 2.79, 95% CI = 1.08 to 7.21, P_{trend} = 0.02); RRs for earlier follow-ups were 3.92 (95% CI = 0.78 to 19.67, 6 deaths, P_{trend} = 0.12) prior to 1981 and 2.70 (95% CI = 0.79 to 9.17, 9 deaths, P_{trend} = 0.21) from 1981 to 1994. From 1995 through 2004, the risks for myeloid leukemia declined (RR = 0.71, 95% CI = 0.20 to 2.50, P_{trend} = > 0.50). According to the authors, the cumulative risks in the highest peak category for myeloid leukemia (calculated by extending the calendar year of follow-up by one year) were elevated over the entire period of follow-up (P_{trend} values were statistically significant starting in 1990). Similarly, cumulative risks among medium and high peak exposure categories were elevated over most of the study follow-up period for Hodgkin's lymphoma and for all lymphohematopoietic cancers combined. Risks for average exposure showed a similar pattern but at generally lower levels of risk.

With respect to time since any first exposure, based on unlagged exposure, the risk for myeloid leukemia was highest for 15 to 25 years since first exposure (RR = 2.44, 95% CI = 0.45 to 13.25) compared with < 15 years since first exposure). Similar patterns, i.e., risks that were highest 15 to 25 years since first exposure, were observed for all

lymphohematopoietic cancers combined (RR = 1.30, 95% CI = 0.68 to 2.49, 46 deaths), leukemia (RR = 2.13, 95% CI = 0.64 to 7.15), and Hodgkin's lymphoma (RR = 1.54, 95% CI = 0.42 to 5.62). Beane Freeman *et al.* (2009) concluded that the pattern of lymphohematopoietic risk over time was consistent with the relatively short induction periods characteristic of leukemogenesis, and suggest an association between lymphohematopoietic cancer and formaldehyde exposure, particularly for myeloid leukemia and possibly Hodgkin's lymphoma and multiple myeloma.

3.2.1.3 Solid cancers: Hauptmann et al. *(2004)*

The follow-up for solid tumors was conducted through 1994 (Hauptmann *et al.* 2004). Mortality from solid tumors was lower than expected compared with U.S. rates (SMR among unexposed = 0.78, 95% CI = 0.70 to 0.86, 341 deaths; SMR among exposed = 0.91, 95% CI = 0.87 to 0.96, 1,580 deaths). A statistically significant excess of mortality from nasopharyngeal cancer was observed among the exposed group (SMR = 2.10, 95% CI = 1.05 to 4.21, 8 deaths). One death from nasopharyngeal cancer was subsequently re-classified as oropharyngeal cancer and excluded from internal analysis of average, peak, and cumulative exposure, however. SMRs exceeding 1.0 were observed for cancers of the buccal cavity (SMR = 1.01, 95% CI = 0.77 to 1.34, 49 deaths), nose and nasal cavity (SMR = 1.19, 95% CI = 0.38 to 3.68, 3 deaths) and bone (SMR = 1.57, 95% CI = 0.75 to 1.18, 7 deaths). Lung cancer was not elevated among exposed workers (SMR = 0.97, 0.90 to 1.05, 641 deaths), although it was slightly higher than among the unexposed workers (SMR = 0.79, 95% CI = 0.65 to 0.96, 103 deaths).

In an internal analysis of exposure-response relationships between average, peak, cumulative, and duration of exposure to formaldehyde and solid cancers, lagged by 15 years, the following results were reported. *P* values for trends for exposure-response relationships refer to the exposed group only, using the lowest exposure group as the referent, unless otherwise stated (The non-exposed group was used as the referent group when there were no deaths observed in the lowest exposed group.) Cancer of the nasopharynx was elevated at the highest category of average exposure intensity (RR = 1.67 for ≥ 1.0 ppm vs. the non-exposed group, 6 deaths); the trend among exposed workers was $P_{trend} = 0.066$, and across exposed and unexposed workers, $P_{trend} = 0.126$. For peak exposure, the RR was 1.83 at the maximum peak category of ≥ 4.0 ppm (7 deaths) vs. the non-exposed group, and the tests for trend were $P_{trend} < 0.001$ among exposed workers and $P_{trend} = 0.044$ across exposed and unexposed workers. For cumulative exposure, the RR was 4.14 (vs. the lowest exposed group) for the highest exposure category of ≥ 5.5 ppm-years, 3 deaths); the P_{trend} was 0.025 among exposed workers and $P_{trend} = 0.029$ across exposed and unexposed workers. For duration of exposure, the RR was 4.18 (vs. the lowest exposed group) for the longest duration of ≥ 15 years, 2 deaths), and the trends were $P_{trend} = 0.147$ and $P_{trend} = 0.206$, respectively. Because five of the nine nasopharyngeal cancer cases occurred at the Wallingford, CT plant, the authors conducted analyses adjusted for plant and found increasing risks for peak exposure ($P_{trend} = 0.008$), cumulative exposure ($P_{trend} = 0.007$), and duration of exposure ($P_{trend} = 0.043$). Plant-adjusted relative risks were also higher among worker with higher average exposure (RR = 8.51 for workers exposed to 0.5 to < 1 ppm, and 23.54 for workers exposed to > 1 ppm), but the test for trend was not statistically

significant (P_{trend} = 0.404). [Plant 1, which had the second highest level of median exposure, appeared to have the largest numbers of workers exposed to the highest levels of formaldehyde of all the 10 plants. According to Stewart *et al.* 1990 (which is an earlier follow-up of the cohort), 1,391 (93% of 1,496) short-term workers and 1,401 (88% of 1,592) long-term workers were exposed to formaldehyde levels greater than 0.5 ppm in their first jobs. (Plant 2, which had the highest exposure levels, was much smaller and had fewer people (578, 80% of 722 long- and short-term workers combined) exposed to formaldehyde levels greater than 0.5 ppm in their first jobs. However, no information was provided for all jobs held by these workers.]

Combining cancers of the upper respiratory tract (i.e., cancers of the salivary gland, mouth, nasopharynx, nasal cavity, and larynx) yielded increasing relative risks with increasing average intensity of exposure (RR = 1.69 for 0.5 to < 1.0 ppm, 11 deaths; RR = 2.21 for ≥ 1.0 ppm, $P < 0.05$, 15 deaths, CI excluded 1.0; P_{trend} = 0.122). Cancer of the upper respiratory tract was also associated with peak exposure (RR = 1.24, 12 deaths, for 2.0 to < 4.0 ppm; RR = 1.65, 18 deaths, for ≥ 4.0 ppm; P_{trend} = 0.142) but not with cumulative exposure or duration of exposure. No evidence was observed of a positive association between lung cancer mortality and any of the exposure measures, except for a statistically significant relative risk associated with peak exposure of 2.0 to < 4.0 ppm (RR = 1.45, 227 deaths). A statistically significant decrease in lung cancer risk was observed for duration of exposure of 5 to 15 years (RR = 0.80, 123 deaths). The only other observed statistically significant elevation in risk was a RR of 1.61 for 42 deaths from prostate cancer in association with a peak exposure of 2.0 to < 4.0 ppm. (All RRs were calculated using the lowest exposure group as the referent group.)

The authors noted that RR estimates were not adjusted by plant because plants were highly correlated with exposure. However, findings from repeated analyses where each plant was selectively removed from the model one at a time were similar to those from the analysis including all plants (data not presented).

3.2.1.4 Re-analyses

Marsh and Youk (2004) conducted a re-analysis of the updated cohort of Hauptmann *et al.* (2003) to re-examine mortality risk from leukemia. Exposure-specific SMRs using both local and national reference rates were calculated by highest peak exposure, average intensity, cumulative exposure, and duration, and by categorizing formaldehyde exposure into tertiles based on the exposure distribution among all leukemia deaths in exposed workers. Generally, the SMRs increased in magnitude with increasing peak and average intensity of exposure for all leukemias combined and for myeloid leukemia. An internal analysis that applied alternative regression modeling yielded RRs similar to those observed by Hauptmann *et al.* (2003); a significant exposure-response relationship was observed for all leukemias (P_{trend} = 0.001) and myeloid leukemia (P_{trend} = 0.003) by peak exposure. Tests for trend by average intensity for all leukemias (P_{trend} = 0.193) or myeloid leukemias (P_{trend} = 0.086) were not statistically significant. Exposure tertiles were also examined in these models, and results were similar to that of the NCI exposure categorization (P_{trend} = 0.145 for all leukemia; P_{trend} = 0.092 for myeloid leukemia). Duration of time worked in the highest category of peak exposure was not associated with leukemia mortality.

Marsh and Youk (2005) conducted a re-analysis of nasopharyngeal cancer data from the Hauptmann *et al.* (2004) study. They noted that the Wallingford, Connecticut plant (Plant 1) contributed five of the nine nasopharyngeal cancer deaths in the NCI study. Marsh and Youk (2005) reported that when the SMR for nasopharyngeal cancers in Plants 2 to 10 combined was re-calculated it was not elevated (SMR = 0.65, 95% CI = 0.8 to 2.3, 4 deaths), in comparison with that of Plant 1 alone (SMR = 10.3, 95% CI = 3.8 to 22.5, 6 deaths). (Also, see separate analyses of the Wallingford plant by Marsh *et al.* 2007a, below). In a further re-analysis of the nasopharyngeal cancers observed in the Hauptmann *et al.* (2004) study, Marsh *et al.* (2007b) examined the interaction between the plant and peak exposures to formaldehyde, since the elevated SMR for nasopharyngeal cancers in the NCI cohort was largely driven by an association with peak (> 4 ppm) exposure to formaldehyde in the Wallingford plant. By examining the interaction between a new 2-factor variable (Plant 1 vs. Plants 2–10) and a continuous variable for peak exposure, Marsh *et al.* concluded that the observed increase in risk of nasopharyngeal cancers in the NCI cohort could be attributable to the effect of an association between peak exposure in Plant 1 and nasopharyngeal cancers and was not generalizable within the entire NCI cohort. In addition, they concluded that the internal analysis of the NCI cohort was not robust (i.e., the risk estimates obtained were subject to considerable instability depending on the addition of one or more nasopharyngeal cancer death to the cohort) and did not warrant the conclusion of a causal relationship between formaldehyde and nasopharyngeal cancer.

3.2.1.5 Related studies

Marsh *et al*. (2007a) followed 7,328 male, mostly white, workers employed between 1941 and 1984 at the Wallingford plant through the end of 2003, updating an earlier follow-up to 1998. Vital status was ascertained for 98% of the cohort, and cause of death was determined for 95% of 2,872 deaths. Worker exposures to formaldehyde were reconstructed and unlagged and lagged exposure metrics computed. Approximately half of the individuals in the cohort were employed for less than one year. Exposure estimation was based on available sampling data (sporadic measurements were taken between 1965 and 1987), job descriptions, and information from plant personnel including the plant industrial hygienist. Exposure to formaldehyde was estimated for each job and task, yielding measures of average intensity, cumulative exposure, and duration of exposure. Though the exposure assessment for formaldehyde was developed to maximize comparability with the NCI study, the authors noted that exposure estimates were generally less than one tenth of the corresponding values estimated for the same workers in the NCI study. External (SMR) analyses and a nested case-control analysis of nasopharyngeal cancers and all other pharyngeal cancers (AOPC) were conducted, taking into account demographic variables, smoking, and also the external employment of cases and controls before, during, and after employment at the Wallingford plant, using various sources such as city directories, employment applications and genealogical searches. Based on the frequency of external employment, three external occupational groups were established: silver smithing, other metal work, and military service. In external analyses, a statistically significant increase in lung cancer was observed (SMR = 1.18, 95% CI = 1.05 to 1.32, 322 deaths) and increases in laryngeal (SMR = 1.51, 95% CI = 0.85 to 2.50, 15 deaths), sinonasal cancers (SMR = 2.64, 95% CI = 0.54 to 7.71, 3 deaths), lip (SMR =

7.08, 95% CI = 0.18 to 39.45, 1 death), floor of the mouth (SMR = 1.41, 95% CI = 0.17 to 5.07, 2 deaths) and gum + other mouth (SMR = 1.18, 95% CI = 0.32 to 3.02, 4 deaths) were also observed. With respect to pharyngeal cancers, 7 nasopharyngeal cancer cases and 16 other pharyngeal cancers (AOPC) were observed (SMR = 4.43, 95% CI = 1.78 to 9.13, 7 nasopharyngeal cancer deaths and SMR = 1.71, 95% CI = 1.01 to 2.72, 16 AOPC deaths; both compared with local rates). In internal analyses, a statistically significant risk of nasopharyngeal cancer (OR = 14.41, 95% CI = 1.30 to 757.8, 4 deaths), was observed in association with ever working in silver smithing, and an OR of 7.31 (95% CI = 1.08 to 82.1, 5 deaths) for ever working in silver smithing and/or other metal work. No association with external employment was observed for AOPC, with the exception of a statistically nonsignificant increase in risk for workers with a history of employment in other metal work (OR = 1.40, 95% CI = 0.31 to 5.1, 4 deaths). The risk of nasopharyngeal cancer associated with formaldehyde exposure before adjustment for smoking and external employment was 1.51 (95% CI = 0.20 to ∞ (infinity), 7 deaths) and after adjustment for smoking and silver smithing and/or metal working employment was 2.87 (0.21 to ∞). An interaction model suggested that neither nasopharyngeal cancer nor AOPC was associated with formaldehyde in the presence of these external occupations, according to the authors.

There was no clear or statistically significant monotonic trend towards increasing nasopharyngeal cancer risk with increasing duration, average intensity, or cumulative exposure to formaldehyde before and after adjustment for smoking and silver smithing and/or other metal working employment, although some increase in risk was observed in each exposure category both before and after adjustment.

3.2.2 National Institute for Occupational Safety and Health (NIOSH) cohort: garment industry

Study population and follow-up. Stayner and colleagues led a NIOSH-sponsored investigation of formaldehyde exposure and cancer among garment workers at three shirt-manufacturing facilities located in Pennsylvania and Georgia where formaldehyde was used to treat fabrics. This proportionate mortality study (Stayner *et al.* 1985) was based on 256 decedents identified from a death-benefit insurance fund, which comprised mostly long-term workers. Stayner *et al.* (1988) subsequently conducted a retrospective cohort standardized mortality study of 11,039 workers at three shirt-manufacturing facilities (two of which were included in the previous PMR study) in which vital status was ascertained through December 31, 1982, and which included both long-and short-term workers. In both studies, cause of death was coded by a trained nosologist.

Follow-up for vital status was later updated through December 31, 1998 (Pinkerton *et al.* 2004). However, work histories were not updated and were truncated for approximately 11% of subjects. To be eligible for the updated retrospective cohort study (N = 11,039; 82% female, 76% white) workers must have served as production workers for at least three months at one of the three facilities between the time formaldehyde was first introduced into the facility (1955 or 1959, depending on the facility) and December 1977. Of 2,206 total deaths observed in the updated retrospective cohort, 608 deaths were due to cancer (Pinkerton *et al.* 2004).

Exposure assessment. Company personnel records were used to obtain information about demographics and occupational history for each worker. Union records or Internal Revenue Service quarterly earning files were used to verify completeness of plant records. The median 8-hour TWA concentration of formaldehyde obtained during air monitoring across all departments at three plants in 1981 (Plant 1) and 1984 (Plants 2&3) ranged from 0.09 to 0.20 ppm (overall geometric mean = 0.15 ppm), and levels did not vary appreciably between facilities. Previous exposures were assumed to be higher at every facility since improvements in the resins have greatly reduced the amount of free formaldehyde contained in the fabrics; formaldehyde levels at other garment factories in the 1970's and earlier were estimated to be as high as 10 ppm (Stayner *et al.* 1988). The authors also noted that workers were not thought to be exposed to any other potentially carcinogenic agents at the work site.

Statistical methods. PMRs were estimated based on U.S. rates (standardized for sex, race, age, and calendar time). Proportionate cancer mortality ratios (PCMR) were also calculated to address the potential for healthy worker bias. SMRs were calculated using United States and state rates. SMRs were stratified by duration of exposure, time since first exposure, and year of first exposure. Poisson regression was used to estimate age-adjusted rate ratios by exposure duration for selected cancer sites including the lung, leukemia, and brain. In the 2004 update (Pinkerton *et al.* 2004), additional analyses using all causes listed on the death certificate (instead of only the underlying cause) were performed using multiple-cause mortality methods.

Results. Results of the earlier proportionate cancer mortality analysis (Stayner *et al.* 1985) showed a statistically significant excess of deaths from buccal cavity (PCMR = 6.82, 90% CI = 1.85 to 17.58, 3 deaths) and "other lymphohematopoietic cancers" (three multiple myeloma and one lymphoma) (PCMR = 3.42, 90% CI = 1.17 to 7.82, 4 deaths). Other excess cancer mortalities (PCMRs > 1.0) were noted, including biliary passages and liver (PCMR = 2.74, 90% CI = 0.94 to 6.27, 4 deaths), unspecified liver (PCMR = 3.70, 90% CI = 0.66 to 11.66, 2 deaths), skin (PCMR = 1.50, 90% CI = 0.27 to 4.73, 2 deaths), pancreas (PCMR = 1.07, 90% CI = 0.37 to 2.46, 4 deaths), all lymphohematopoietic cancers (PCMR = 1.44, 90% CI = 0.78 to 2.44, 10 deaths), and leukemia and aleukemia (PCMR = 1.52, 90% CI = 0.52 to 3.47, 4 deaths).

In the updated retrospective cohort SMR analysis (Pinkerton *et al.* 2004), a statistically significant deficit in mortality (underlying causes of death) from all cancers was observed (SMR = 0.89, 95% CI = 0.82 to 0.97, 608 deaths). Statistically nonsignificant elevated SMRs were observed for cancer of the buccal cavity (SMR = 1.33, 95% CI = 0.36 to 3.41, 4 deaths), other respiratory (non-lung or larynx) (SMR = 1.21, 95% CI = 0.15 to 4.37), prostate (SMR = 1.58, 95% CI = 0.79 to 2.83, 11 deaths), other male genital (non prostate) (SMR = 3.89, 95% CI = 0.47 to 14.04, 2 deaths), brain (SMR = 1.09, 95% CI = 0.66 to 1.71, 19 deaths), thyroid (SMR = 1.16, 95% CI = 0.14 to 4.18, 2 deaths), connective and soft tissue (SMR = 1.57, 95% CI = 0.63 to 3.24, 7 deaths), other unspecified sites (SMR = 1.19, 95% CI = 0.89 to 1.55, 54 deaths), and leukemia (SMR = 1.09, 95% CI = 0.70 to 1.62, 24 deaths). No deaths from cancers of the nasopharynx (0.96 expected) or nose (0.16 expected) were observed. Further analysis showed an excess in myeloid leukemia (SMR = 1.44, 95% CI = 0.80 to 2.37, 15 deaths), which was

greatest among workers first exposed prior to 1963 when exposures to formaldehyde were presumably higher (SMR = 1.61, 95% CI not reported), or with at least 10 years of exposure (SMR = 2.19, lower bound of 95% CI value less than 1), or exposed at 20 or more years since first exposure (SMR = 1.91, lower bound of 95% CI greater than 1).

Seven additional leukemia deaths (two myeloid leukemia and 5 lymphocytic leukemia deaths) were identified in the multiple-cause analysis. Deaths from all leukemia and myeloid leukemia were significantly elevated among workers with 10 or more years of exposure in the multiple-cause analysis (SMR = 1.78, 95% CI = 1.04 to 2.86, 17 leukemia deaths, and SMR = 2.24, 95% CI = 1.02 to 4.23, 9 myeloid leukemia deaths), and deaths from lymphoid leukemia were also elevated in this group (SMR = 2.12, 95% CI = 0.78 to 4.62, 6 deaths). Among workers with at least 10-years exposure and 20 or more years since first exposure, multiple-cause mortality from all leukemia was significantly elevated (SMR = 1.92, 95% CI = 1.08 to 3.17, 15 deaths), as was that for myeloid leukemia (SMR = 2.55; 95% CI = 1.10 to 5.03; 8 deaths). Multiple-cause mortality from acute myeloid leukemia in this group was elevated but not statistically significant (SMR =1.84, 95% CI = 0.84 to 3.49, 9 deaths).

3.2.3 British Chemical Workers Study

Study population and follow-up. Acheson *et al.* (1984) assembled a large industry-based cohort of approximately 7,680 male workers first employed before 1965 at one of six factories in the British chemical and plastics industry where formaldehyde had been first manufactured or used from the 1920s to 1950s. This cohort was updated by Gardner *et al.* (1993) and expanded with the addition of 6,357 workers first employed since 1964. More recently, Coggon *et al.* (2003) reported on an updated analysis of the total cohort of 14,014 men employed after 1937 (which subsumed findings by Gardner *et al.*), extending the original cohort with 11 additional years of follow-up. Workers were followed for mortality and cancer incidence through December 31, 2000 using the National Health Service Central Register and social security records.

Exposure assessment. Occupational histories extracted from employment records were used to classify formaldehyde exposure for each job into five categories (background, low, moderate, high, or unknown). Exposure measurements taken after 1970, as well as workers' recall of irritant symptoms, were used to estimate exposure levels for each exposure category. According to Gardner *et al.* (1993), a total of 3,872 (27.6%) workers were exposed to background levels of formaldehyde corresponding to time-weighted average concentrations of less than 0.1 ppm; 3,815 (27.2%) were classified in the low exposure category (0.1 to 0.5 ppm); 1,362 (9.7%) in the moderate-exposure category (0.6 to 2.0 ppm), and 3,993 (28.5%) in the high-exposure category (greater than 2.0 ppm). Job-exposure matrices were constructed for each factory. Within each factory, each job was assigned to the same exposure category for all time periods; however, jobs were not necessarily assigned to the same exposure category across factories. Workers were individually classified as having no, low, moderate, high or unknown exposure. For workers with more than one job, their exposure classification was based on the job with the highest exposure. In one factory, no workers were classified as highly exposed; the portion of highly exposed workers in the other five factories ranged from 3% to 7%. Of 14,014 workers, 13,865 (99%) were successfully traced through the follow-up period:

5,185 (37%) had died (99% with a known cause of death), and 859 (6%) were lost to follow-up.

Statistical methods. Person-year analysis was used to calculate SMRs; expected numbers of deaths were obtained from national rates for England and Wales in 5-year age strata for 5-year calendar periods. Adjustments for local geographic variations in mortality were made by multiplying the expected numbers of deaths from national rates by the SMRs for the localities in which each factory was located. [This method of adjustment may underestimate the risk if rates are higher among workers, and these workers live in the areas surrounding the factories.] Exposure-response trends were evaluated using Poisson regression.

Results. (Coggon *et al.* 2003 update). Mortality from all cancers was somewhat elevated in the cohort (SMR = 1.10, 95% CI = 1.04 to 1.16, 1,511 deaths), especially among workers ever classified as highly exposed to formaldehyde (SMR = 1.31, 95% CI = 1.21 to 1.42, 621 deaths). Statistically significant increases in the number of deaths from stomach (SMR = 1.31, 95% CI = 1.11 to 1.54, 150 deaths) and lung cancer (SMR = 1.22, 95% CI = 1.12 to 1.32, 594 deaths) were observed among all workers. SMRs were higher among workers with high exposure (SMR for stomach = 1.53, 95% CI = 1.17 to 1.95, 63 deaths; SMR for lung = 1.58, 95% CI = 1.40 to 1.78, 272 deaths). A positive trend was noted for the SMR for lung cancer (but not stomach cancer) by increasing exposure level when compared with national rates ($P_{trend} < 0.001$), though the trend was no longer statistically significant when adjusted for geographic location. No relationships between lung cancer mortality and years of employment in high-exposure jobs or years since first employment in a high-exposure job were observed (results for stomach cancer or other sites were not reported). However, lung cancer mortality was highest among workers who were highly exposed before 1965 (SMR = 1.61, 95% CI = 1.41 to 1.82, 243 deaths). The authors noted that during this time period, occupational exposures to formaldehyde would have been higher.

Excess cancer mortality at several other tumor sites was also observed among highly exposed workers, though estimates were not statistically significant. These tumor sites included: lip (SMR = 5.62, 95% CI = 0.14 to 31.30, 1 death), tongue (SMR = 1.91, 95% CI = 0.39 to 5.68, 3 deaths), mouth (SMR = 1.32, 95% CI = 0.16 to 4.75, 2 deaths), pharynx (SMR = 1.91, 95% CI = 0.70 to 4.17, 6 deaths), esophagus (SMR = 1.28, 95% CI = 0.81 to 1.92, 23 deaths), large intestine (SMR = 1.30, 95% CI = 0.93 to 1.77, 40 deaths), rectum (SMR = 1.26, 95% CI = 0.82 to 1.84, 26 deaths), larynx (SMR = 1.56, 95% CI = 0.63 to 3.22, 7 deaths), bone (SMR = 3.38, 95% CI = 0.92 to 8.65, 4 deaths), genital excluding breast, testis, and prostate (SMR = 1.42, 95% CI = 0.04 to 7.90, 1 death), bladder (SMR = 1.25, 95% CI = 0.79 to 1.88, 23 deaths), kidney (SMR = 1.37, 95% CI = 0.73 to 2.35, 13 deaths), and multiple myeloma (SMR = 1.18, 95% CI = 0.48 to 2.44, 8 deaths). No elevated risks were observed for leukemia, Hodgkin's lymphoma, or non-Hodgkin's lymphoma among all workers or workers with high exposure. No deaths from cancer of the nose or nasal sinuses were observed among men with high exposure (0.8 deaths expected), and two deaths were reported in the entire cohort versus 2.3 expected. However, a review of contributory causes of death revealed two additional cases of sinonasal cancer in individuals with high exposure to formaldehyde. One death

from nasopharyngeal cancer was observed (in a man with no recorded high exposure to formaldehyde) versus 2 expected. (No additional cases of nasopharyngeal cancer were found on review of contributory causes of death.)

3.2.4 Studies of fiberglass workers

In this section, two studies of workers in the fiberglass industry are reviewed. Workers in this industry may be exposed to formaldehyde in addition to respirable fibers during the fiberglass manufacturing process. Evaluation of the association between formaldehyde exposure and cancer outcomes was not a primary objective of either study. Therefore, the description of the study methods and results are limited to formaldehyde-related analyses only.

3.2.4.1 United States: Nested case-control study of respiratory cancer in a historical cohort of 10 fiberglass manufacturing plants

The following analyses draw from a large historical cohort study established in 1975 of production and maintenance workers from some of the largest and oldest fiberglass and rock/slag wool manufacturing plants in the United States. Marsh *et al.* (2001) updated and expanded upon a sub-cohort of workers employed at the 10 fiberglass manufacturing facilities, which was originally assembled and studied by Enterline *et al*. (1983, 1984, 1987). This review covers the most recent follow-up analyses by Marsh *et al.* (2001) as well as additional analyses reported by Youk *et al.* (2001) and Stone *et al.* (2001, 2004). (Note that the primary focus of these studies was the relationship between glass wool exposure and cancer mortality, and specifically of respiratory (lung and laryngeal) cancers.]

Study population and follow-up. Marsh *et al.* (2001) led an effort to expand this historical cohort to capture female workers, workers employed after the original 1963 cohort end date, and workers from additional manufacturing sites. The expanded cohort included 32,110 production or maintenance workers (84% white, 82% female) employed for at least one year between 1945 and 1978 in any of the 10 facilities. Vital status was ascertained through December 31, 1992, and the cause of death was determined for nearly all deceased workers (98.8%) using the National Death Index or death certificates. Using this updated cohort, Marsh *et al*. (2001) conducted a nested case-control analysis to investigate occupational exposures at the fiberglass manufacturing plants and respiratory system cancers (lung and larynx) among male workers. Cases were defined as workers who died from respiratory system cancer between 1970 and 1992; 96% of cases were diagnosed with cancer of the bronchus, trachea, or lung. Controls were eligible if they were at risk during 1970 to 1992 as well as alive and at risk at the age when the case died. Cases were matched to one control by date of birth (within one year). Smoking information was collected as ever/never having used any form of tobacco via telephone interview with the worker or proxy; the response rate was 88% for 716 eligible cases and 80% for 713 controls.

Exposure assessment. Potential exposures to known or suspected carcinogens, including formaldehyde, were estimated from plant start-up until closing or the end of the study period (Quinn *et al.* 2001). Exposure data were developed by integrating industrial hygiene data with worker histories to estimate exposures over time for all unique

production areas and their associated jobs. A job-exposure matrix was used to produce job-location-weighted exposure measures and three summary exposure metrics: duration, cumulative exposure, and average intensity. Exposure to formaldehyde was the second most prevalent exposure (22.4% of total person-years) after respirable glass wool or continuous glass filament fibers (28.5% of total person-years) among workers. The median average intensity of exposure to formaldehyde was 0.066 ppm for all plants (range = 0.030 to 0.130); the median cumulative exposure was 0.173 ppm (range = 0.063 to 0.469).

Statistical methods. Complete data were available for 502 of 713 matched pairs, and unmatched cases and controls were combined with the matched set nearest in age to form 516 matched pairs (631 cases and 570 controls) for analysis. Conditional logistic regression was used to estimate RRs adjusted for smoking.

Results. Marsh *et al.* found that, compared with unexposed workers, exposure to formaldehyde was associated with a statistically significant increase in respiratory system cancer (RR = 1.92, 95% CI = 1.25 to 2.94, 591 exposed deaths, global test *P* value = 0.003) which remained after adjustment for estimated smoking (RR = 1.61, 95% CI = 1.02 to 2.57, global test *P* value = 0.04). However, tests for trend by exposure duration, cumulative exposure, and average intensity of exposure were not statistically significant.

Related analyses. Youk *et al.* (2001) analyzed the Marsh *et al.* nested case-control study using exposure weighting as an alternative form of exposure characterization to explore a possible exposure-response relationship between respiratory system cancer and formaldehyde. Nine different configurations of exposure lag and window periods were considered. The RR for respiratory system cancer among exposed workers was 1.62 (95% CI = 1.04 to 2.54, 588 exposed cases) with a 5-year lag and 1.46 (95% CI = 0.96 to 2.23, 581 exposed cases), with a 10-year lag. Estimates from other combinations of lag and window periods were otherwise closer to the null compared with the unweighted estimate (OR = 1.61, 95% CI = 1.02 to 2.56) noted by Marsh *et al.* (2001).

Stone *et al*. (2001) also analyzed data from the nested case-control study by further adjusting conditional logistic regression models for exposure to respirable particles in addition to smoking, and by considering exposure to formaldehyde as a continuous quantitative term in piecewise linear functions (i.e., linear splines) with knots placed at the deciles of the distribution of formaldehyde exposure among cases. Application of the linear splines allowed for multiple exposure-response functional forms to be evaluated. Cumulative exposure to formaldehyde was not significantly associated with an increased risk of respiratory system cancer in any of the models. A positive association was observed between relatively high average exposure intensity and respiratory system cancer risk; the authors noted, however, that the dramatic increase in risk was only predicted for the small number of workers with average exposure intensity at levels above 0.4 ppm. [Estimated exposure to formaldehyde in this cohort of fiberglass production workers was considerably below the current OSHA permissible exposure limit of 0.75 ppm based on an 8-hour time-weighted average.]

Stone *et al.* (2004) performed an analysis of respiratory system cancer among the 4,008 female fiberglass workers included in the updated cohort of fiberglass workers followed until 1992 (Marsh *et al.* 2001). (Previous analyses were restricted to male workers.) Fifty-three deaths due to respiratory cancer were observed. Estimated relative risks were calculated for a 1 ppm-year increase in cumulative formaldehyde exposure score using multiplicative models fit to the internal cohort cancer rates. Estimated RRs ranged from 1.10 to 1.21 depending on adjustment factors (e.g., fiberglass production group, year of hire, duration of employment, or time since first employment); none of the estimates was statistically significant. The authors noted that very few women had a cumulative exposure score for formaldehyde of greater than 3 ppm-years in this study.

3.2.4.2 South Carolina: Nested case-control study in a historical cohort of one fiberglass manufacturing plant

Study population and follow-up. Chiazze *et al.* (1997) conducted a nested case-control study evaluating lung cancer mortality among continuous filament fiberglass manufacturing workers at an Owens Corning facility in Anderson, South Carolina. This plant was not included among those studied by Marsh *et al.* (2001). The cohort from which the subjects were selected included 4,631 current and former employees (74% male; 87% white) who had worked for at least one year between 1951 and 1991. Follow-up for vital status was completed through 1991 (96% complete), and cause of death was obtained from death certificates (96% complete). Cases (N = 47) included white male members of the cohort for whom lung cancer was the underlying cause of death; controls (N = 122) included any white male non-case cohort member and were matched to cases (case to control ratio = 1:2) on year of birth (within 2 years) and survival to end of follow-up or death (within 2 years).

Exposure assessment. Exposure to occupational substances including formaldehyde was estimated by an exposure assessment committee composed of former and current employees knowledgeable in industrial hygiene and plant processes (Chiazze *et al.* 1993). For each process, one of four ranges of estimated potential exposure for each substance was assigned based on 8-hour time-weighted averages. Cumulative exposure was then estimated for each employee based on the number of days spent performing each process; cumulative exposure days for formaldehyde ranged from none to 2,585 days (only one case and three controls had cumulative exposure greater than 1,000 days). In addition, a telephone interview was used to obtain demographic information, lifetime residence history, lifetime occupational history, smoking and alcohol use, and medical history.

Statistical methods. Conditional logistic regression was applied to estimate the association between formaldehyde and lung cancer death, adjusted for smoking (adjusted models used information from 33 cases and 82 controls who were smokers).

Results. Compared with 15 workers with no exposure to formaldehyde, the unadjusted ORs for smokers + nonsmokers with 0.25 to 99.99, 100 to 999 and 1000+ cumulative days of exposure were 0.94 (95% CI = 0.38 to 2.36, 14 cases), 1.27 (95% CI = 0.50 to 3.21, 15 cases), and 1.14 (95% CI = 0.11 to 12.1, 1 case, a smoker), respectively. Among smokers only, the respective estimates were 0.92 (95% CI = 0.29 to 2.88, 10 cases), 1.72 (95% CI = 0.57 to 5.23, 11 cases), and 2.07 (95% CI = 0.17 to 25.5, 1 case).

3.2.5 Studies of woodworking and related industries

In this section, the findings from two nested case-control studies of a cohort of Finnish workers are reviewed. Workers in these industries are commonly exposed to wood dust, which is a known risk factor for sinonasal cancer and nasopharyngeal cancer. This review will focus on study findings for formaldehyde exposure only, though other occupational exposures such as wood dust were also evaluated. Industries related to woodworking that were examined in these studies included sawmills, particleboard and plywood manufacture, construction carpentry, and formaldehyde adhesive production for furniture.

3.2.5.1 Description of historical cohort of woodworkers from various industries

Partanen *et al.* (1985) assembled a retrospective cohort of 3,805 male workers at 19 particleboard, plywood, and formaldehyde glue factories and sawmills in Finland. This cohort was later expanded (N = 7,303) with additional years of follow-up and additional factories to re-evaluate the association between formaldehyde exposure, respiratory cancer (Partanen *et al.* 1990), and lymphohematopoietic malignancies (Partanen *et al.* 1993) in nested case-control studies.

Study population. The Finnish woodworker cohort included 7,307 workers from 35 Finnish factories employed for at least one year between January 1944 and December 1965 in various woodworking facilities. Approximately 9% of cohort members worked at particleboard plants, 24% at plywood plants, 12% at construction carpentry plants, 20% at furniture manufacturing plants, 35% at sawmills, and less than 1% at a formaldehyde glue manufacturing plant (Partanen *et al.* 1990). Cohort members were followed for vital status from January 1957 to December 1982.

Exposure assessment. Job-exposure matrices were constructed by industrial hygienists for each factory using factory records that included information on exposures, ventilation, work procedures, and actual air quality monitoring data (Kauppinen and Partanen 1988). The job-exposure matrices were linked with worker histories using factory registers, interviews with factory personnel, and questionnaires conducted with cases, controls, or their next of kin (control histories were obtained from company records only). For each of the 73 uniquely classified jobs, exposure to formaldehyde and several other concurrent agents was estimated by cumulative dose and level: unexposed, low (0.1 to 1 ppm-months), moderate (1 to 2 ppm-months), and heavy (> 2 ppm-months). Both exposure to formaldehyde fumes and formaldehyde attached to wood dust was considered. Exposure were also categorized dichotomously (ever/never) and lagged by 10 years to account for latency. Workers were considered ever exposed to formaldehyde if their estimated cumulative exposure reached 3 ppm-months.

3.2.5.2 Nested case-control study of respiratory cancers (Partanen et al. *1990)*

Study population. In this study, respiratory cancer was defined by the authors as primary malignant neoplasms of sites with which inhaled formaldehyde was thought to come into direct epithelial contact, including: oral cavity, pharynx, nasal and sinus cavities, larynx, lung, and trachea. Cases of respiratory cancer (N = 136) were ascertained using the Finnish Cancer Registry; three controls were randomly selected from the cohort and matched to each case by year of birth (N = 408).

Results. Odds ratios and 90% CIs were estimated using conditional logistic regression and, in most cases, adjusted for vital status and smoking (< 35 years vs. ≥ 35 years). Comparing workers with at least 3 ppm-months of exposure to formaldehyde with workers with less than 3 ppm-months, the OR for all respiratory cancers combined was 1.11 (90% CI = 0.40 to 3.11, 11 exposed cases, adjusted for vital status and smoking) with no latency period, and 1.39 (90% CI = 0.40 to 4.10, 9 exposed cases, adjusted for vital status and smoking) with a minimum latency period of 10 years. Corresponding estimates were lower for lung cancer (OR = 0.69, 90% CI = 0.21 to 2.24, 9 cases, no latency, adjusted for vital status and smoking; and OR = 0.89, 90% CI = 0.26 to 3.00, 7 cases, 10-year latency, adjusted for vital status and smoking), and higher for combined upper respiratory cancers only (OR = 2.38, 90% CI = 0.43 to 13.2, 2 cases, no latency, adjusted for vital status only, and OR = 2.40, 90% CI = 0.31 to 18.6, 2 cases, 10 year latency, adjusted for vital status only). Exposure to dust-borne formaldehyde (yes or no) was also estimated; ORs ranged from 1.33 to 1.42, depending on the latency period, but none was statistically significant. No evidence of an association was observed between peak exposure to formaldehyde and all respiratory cancers combined, nor was any evidence observed of an exposure-response relationship for all respiratory cancers combined and any exposure indicator including cumulative dose, duration of exposure to peak levels, and duration of exposure to dust-borne formaldehyde. [Adjustment for smoking substantially reduced the sample size and consequently reduced statistical power for estimation of effects, because smoking history was unknown for approximately 35% of workers in this study. Further, estimates were not adjusted for wood dust or phenol exposure, both factors that the authors noted were correlated with formaldehyde exposure in this study population.]

3.2.5.3 Nested case-control study of lymphohematopoietic malignancies (Partanen et al. *1993)*

Study population. Twelve cases of leukemias and 12 of malignant lymphoma (4 of Hodgkin's lymphoma and 8 of non-Hodgkin's lymphoma) were ascertained using the Finnish Cancer Registry; between 1 and 8 non-cancer controls were matched to each case by year of birth and vital status in 1983.

Statistical methods and results. Odds ratios and 95% CIs were estimated using conditional logistic regression. For the lymphohematopoietic cancers combined, the OR associated with at least 3 ppm-months of formaldehyde was 2.49 (95% CI = 0.81 to 7.59, 7 exposed cases), which did not change markedly after controlling for exposure to wood dust or solvents. Corresponding (unadjusted) ORs for specific lymphohematopoietic cancers were 1.40 (95% CI = 0.25 to 7.91, 2 exposed cases) for leukemia, and 4.24 (95% CI = 0.68 to 26.6, 4 exposed cases) for non-Hodgkin's lymphoma. An OR for Hodgkin's lymphoma alone could not be estimated because only one case was considered exposed to formaldehyde. The OR for all lymphomas combined (Hodgkin's and non-Hodgkin's lymphomas) was 4.02 (95% CI = 0.87 to 18.6, 5 exposed cases). The authors noted that more sensitive exposure assessment among cases than controls could have biased the observed effect estimates away from the null.

3.2.6 Denmark: Proportionate cancer incidence study of mixed industry workers

Study population and follow-up. Hansen and Olsen (1995, 1996) conducted a standardized proportionate cancer incidence study of workers in Denmark born between 1897 and 1964 whose cancer was diagnosed between 1970 and 1984; eligible workers were identified using the national Danish Cancer Registry and then linked with the compulsory Supplementary Pension Fund to obtain employment history (N = 91,182 men and 73,423 women). Using the national Danish Product Register, 265 companies in which more than one kilogram of formaldehyde was used or manufactured per employee per year since 1970 were identified. Workers (2,041 men and 1,263 women) whose longest work experience since 1964 had started at one of the 265 companies at least 10 years prior to diagnosis (N = 2,041, 2.2% of study population) were considered exposed to formaldehyde.

Exposure assessment. Based on job title, exposed workers were further classified as having low (white-collar workers), high (blue-collar workers), and unknown (no information on job title) exposure.

Statistical methods and results. Standardized proportionate incidence cancer ratios (SPIR) adjusted for age (5-year strata) and calendar time (per year) were estimated using all Danish workers in the study population as the referent group. Among the 2,041 men, who had worked in companies where formaldehyde was used (Hansen and Olsen 1995), a statistically significant excess in incidence was noted for tumors of the colon (SPIR = 1.2, 95% CI = 1.1 to 1.4, 166 exposed cases), nasal cavity (SPIR = 2.3, 95% CI = 1.3 to 4.0, 13 cases), and kidney (SPIR = 1.3, 95% CI = 1.0 to 1.6, 60 cases). Statistically nonsignificant increases in cancer incidence (SPIRs > 1.0) were also observed among men for the nasopharynx (SPIR = 1.3, 95% CI = 0.3 to 3.2, 4 exposed cases), buccal cavity and pharynx (excluding nasopharynx) (SPIR = 1.1, 95% CI = 0.7 to 1.7, 23 deaths), liver (SPIR = 1.2, 95% CI = 0.9 to 1.8, 29 exposed cases), rectum (SPIR = 1.1, 95% CI = 0.9 to 1.3, 117 cases), melanoma of the skin (SPIR = 1.1, 95% CI = 0.8 to 1.5, 39 cases), brain (SPIR = 1.1, 95% CI = 0.9 to 1.5, 54 cases) and breast (SPIR = 2.2, 95% CI = 0.9 to 4.3, 8 exposed cases). Other sites had SPIRs of 1.0 or less. Among lymphohematopoietic cancers, data were reported only for non-Hodgkin's lymphoma (32 cases), Hodgkin's lymphoma (12 cases) and leukemia (39 cases); no increase in risk was observed. Data were also presented on selected cancers (nasal, colon, lung, breast, kidney, brain and CNS, and leukemia) among workers with estimated exposure to low or high formaldehyde, the latter with or without potential wood dust exposure. No differences by estimated exposure category were observed, with the exception of nasal cavity cancers; among those estimated to be more highly exposed to formaldehyde and unexposed to wood dust (based on job industry and title), the SPIR was 3.0 (95% CI = 1.4 to 5.7, 9 cases), compared with 5.0 (95% CI = 0.5 to 13.4, 2 cases) for both higher formaldehyde and wood dust exposure and 0.8 (95% CI = 0.02 to 4.4, 1 case) for low formaldehyde exposure. Among women (Hansen and Olsen 1996), an increase was found for nasal cancer (SPIR = 2.4, 95% CI = 0.6 to 6.0. 4 exposed cases), lung cancer (SPIR = 1.2, 95% CI = 0.96 to 1.4, 108 deaths), leukemia (SPIR = 1.2, 95% CI = 0.7 to 1.8, 21 deaths), Hodgkin's cancer (SPIR = 1.1, 95% CI = 0.3 to 2.7, 4 deaths), and brain cancer (SPIR = 1.2, 95% CI = 0.8 to 1.6, 39 deaths). No deaths from nasopharyngeal cancer were observed versus 0.8 expected.

3.2.7 Studies of resin, chemical, and plastics manufacturing workers

In this section, historical cohort studies of workers in the formaldehyde-based resin (Bertazzi *et al.* 1989, Bertazzi *et al.* 1986), chemical (Bond *et al.* 1986, Ott *et al.* 1989), and plastics (Dell and Teta 1995) manufacturing industries are reviewed. Bond *et al.* (1986) evaluated lung cancer specifically, and Ott *et al.* (1989) evaluated lymphohematopoietic malignancies. [Collectively, the studies reviewed in this section are limited by small numbers of study participants exposed to formaldehyde. Note also that in these studies formaldehyde was not the primary occupational exposure of interest. Workers in these cohorts were exposed to various other agents such as asbestos, styrene, and solvents.] The following review will focus on study findings for formaldehyde only.

3.2.7.1 Italy: Historical cohort of formaldehyde-based resin production workers

Study population and follow-up. Bertazzi *et al.* (1986, 1989) studied mortality among male workers at a resin manufacturing plant in Italy where formaldehyde-based resins, including urea- and melamine-formaldehyde resins, were primarily produced since 1959. A cohort of workers was assembled including 1,332 men ever employed in the plant for at least 30 days between 1959 and 1980 (Bertazzi *et al.* 1986), which was revised to 1,330 men in the 1989 update (Bertazzi *et al.* 1989). Vital status was ascertained as of December 31, 1986 through the local vital statistics offices, and death certificates were obtained for cause of death (follow-up was complete for nearly 98% of the cohort) (Bertazzi *et al.* 1989). The number of formaldehyde-exposed workers was not provided, but 73 of the 179 deaths from all causes were exposed to formaldehyde.

Exposure assessment. Work histories for each worker were reconstructed using incomplete plant employment records and interviews with current and retired workers as well as foremen. Work histories were completed for over 80% of the cohort, and each worker was assigned to one of three exposure categories based on their work history: (1) exposed to formaldehyde, (2) exposed to other compounds (including styrene and solvents), and (3) exposure not noted. Air sampling was conducted at the plant in 1974, 1978, and 1979; mean levels of formaldehyde ranged from 0.2 to 3.8 mg/m^3 [0.16 to 3.1 ppm]. The authors noted that formaldehyde-based resins were produced in a separate area from other resins, and also that job mobility was low, especially among workers engaged in formaldehyde-based resin production [these factors reduce the potential for exposure misclassification] (Bertazzi *et al.* 1986).

Statistical methods and results. Mortality in the cohort was compared with national and local rates using the person-years method, adjusting for sex, age (5-year strata), and calendar time (5-year intervals). Among workers "definitely" exposed to formaldehyde statistically nonsignificant excess mortality was observed for cancers of the digestive system (SMR = 1.34, 11 observed deaths vs. 8.2 expected), stomach (SMR = 1.64, 5 observed deaths vs. 3 expected,), liver (SMR = 2.44; 2 observed deaths vs. 0.8 expected), and lymphohematopoietic cancers (SMR = 1.73, 3 observed deaths vs. 1.7 expected); all comparisons with local rates. Note that only selected cancer sites were reported in these studies.

3.2.7.2 Texas: Nested case-control study in a historical cohort of chemical production workers

Study population and follow-up. A nested case-control study of workers was conducted to investigate elevated lung cancer mortality rates at a chemical production facility (Dow Chemical) in Texas (Bond *et al.* 1986). A retrospective cohort was assembled including 19,608 male workers hired between 1940 and 1980 and who had worked at the Texas facility for at least one year. Vital status was ascertained for 97% of the cohort; death certificates were obtained for 96% of the 3,444 deceased workers. Cases (N = 308) were defined as former workers who had died before December 1980 and whose death certificate listed cancer of the respiratory system as the underlying or contributing cause of death. Two control series (of 308 each) without lung cancer were randomly selected and individually matched by race, year of birth (within 5 years), and year of hire (case to control ratio = 1:1). One series included workers alive when the matched case died of lung cancer, and the other series included workers who had died of other causes within five years after the matched case had died. A total of 588 unique controls were identified, and pooled controls were used in the analysis.

Exposure assessment. For each subject, exposure to 171 chemical and physical agents (yes/no), including formaldehyde, was estimated by an industrial hygienist blinded to case/control status using information from employee work history records about work areas, tasks, agents handled, and duration of employment. Information on potentially confounding variables such as smoking and vitamin A intake was obtained from interviews (82% response rate) conducted with subjects or their next-of-kin.

Statistical methods and results. Stratified analyses and conditional logistic regression were used to calculate ORs and 95% CIs. Reported risk estimates for formaldehyde were unadjusted for exposure to other agents and other potential confounders like smoking. The estimated OR between exposure to formaldehyde (9 exposed deaths) and lung cancer mortality was less than 1.0; the negative association remained after accounting for a 15-year latency period (4 exposed deaths). [Eligible controls included participants with cancers suspected to be associated with formaldehyde exposure, which might have attenuated observed effect estimates.]

3.2.7.3 West Virginia: Nested case-control study in a historical cohort of chemical manufacturing workers

Study population and follow-up. Ott *et al.* (1989) conducted a nested case-control study of lymphohematopoietic cancer within a cohort of nearly 30,000 male workers employed in two chemical manufacturing facilities and a research and development center (Union Carbide Corporation). Cases of non-Hodgkin's lymphoma (N = 52), multiple myeloma (N = 20), nonlymphocytic leukemia (N = 39), and lymphocytic leukemia (N = 18) among workers in the cohort were identified by reviewing both underlying and contributory causes of death noted on death certificates from 1940 through 1978; follow-up was complete for 96% of the cohort. Controls were selected from the cohort using group-matched incidence density sampling so that controls were first employed in the same decade and survived to at least the same 5-year period as cases (case to control ratio = 1:5).

Exposure assessment. Work history information was used to link work areas and assignments with records of departmental usage for each substance; a worker was considered exposed to formaldehyde (ever/never) if he worked for at least one day with the chemical or in a work area specified as exposed.

Statistical methods and results. Unadjusted ORs were obtained using unconditional logistic regression. Elevated but statistically nonsignificant risks were found for non-Hodgkin's lymphoma (OR = 2.0, 95% CI not reported, 2 exposed deaths), nonlymphocytic leukemia (OR = 2.6, 2 exposed deaths), and lymphocytic leukemia (OR = 2.6, 1 exposed death). The OR for multiple myeloma was 1.0 (1 exposed death). Very few workers were exposed to formaldehyde, and workers with only one day of exposure in their occupational lifetime were considered exposed.

3.2.7.4 New Jersey: Historical cohort of plastics manufacturing workers

Study population and follow-up. Cancer mortality among male workers at a plastics manufacturing plant (Union Carbide Corporation) in New Jersey was studied by Dell and Teta (1995). This plant is not included among those studied by Ott *et al.* (1989). The cohort included 5,932 male employees who worked more than six months between January 1, 1946 and December 31, 1967. Vital status was ascertained through December 31, 1988 (94% complete) using company records, Social Security files, and information from the National Death Index. Underlying causes of death were obtained from death certificates (98% complete).

Exposure assessment. Exposure to asbestos, polyvinyl chloride, and formaldehyde was assigned (yes/no) based on the major work department for each worker. One hundred eleven (111) workers were assigned exposure to formaldehyde.

Statistical methods. Mortality in the cohort was evaluated using person-years analysis, with age- and alendar-year-specific mortality rates among white males for the United States (1940 to 1989) and New Jersey (1950 to 1989) as the referents.

Results. An excess of lung cancer was noted among 57 workers exposed to formaldehyde during hexamethylenetetramine production (4 observed cases vs. 1.1 expected, no risk estimate reported). No cases of sinonasal or nasopharyngeal carcinoma were observed. As noted by the authors, the power of this study is limited with regard to formaldehyde because of small sample size. [Further, the potential effect of individual exposures cannot be distinguished within each work area.]

3.2.8 Other studies: abrasive material manufacturing, Iron foundry chrome leather tannery workers, and textile workers

In this section, four historical studies examining the association between formaldehyde exposure and cancer among abrasive material manufacturing, iron foundry, mixed industry, and chrome leather tannery workers are summarized.

3.2.8.1 Sweden: Cohort mortality and incidence study of abrasive materials manufacturing workers (Edling et al. *1987b)*

Study populations and statistical methods. 911 workers (211 women) at a plant manufacturing abrasive materials and employed between 1955 and 1983 for at least five years were enrolled in the study. Workers were traced through the Swedish national death registry (from 1958 to 1983) and the national cancer registry (from 1958 to 1981). Deaths occurring at ages 74 and older were excluded, based on less reliable diagnostic validity. Age-, sex- and calendar year-stratified expected rates were calculated using the person-year method based on national data.

Exposure assessment. The plant manufactured grinding wheels from aluminum oxide and silicon carbide as abrasives bound with clay or phenol formaldehyde resins. Industrial hygiene measurements were available since the 1970s; during the manufacture of formaldehyde resins, exposure to formaldehyde ranged from 0.1 to 1.0 mg/m^3 [0.08 to 0.8 ppm]. According to the authors, 59 workers had heavy intermittent exposure to peaks of 20 to 30 mg/m^3 [16.3 to 24.4 ppm] of formaldehyde during the manufacture of abrasive belts. No exposure assessments were conducted for individual workers.

Results. Findings were reported for 506 male "blue collar" workers only. No statistically significant increases in mortality or incidence for all cancers combined (observed/expected = 0.93, 95% CI = 0.5 to 1.5, 17 deaths; and observed/expected = 0.84, 95% CI = 0.5 to 11.3, 24 cases). Elevations in cancer incidence were observed for pancreas (observed/expected = 1.8, 95% CI = 0.2 to 6.6, 2 cases), lymphoma (observed/expected = 2.0, 95% CI = 0.2 to 7.2, 2 cases) and multiple myeloma (observed/expected = 4.0; 95% CI = 0.5 to 14.4, 2 cases). One incident case of nasopharyngeal cancer was observed in a worker with formaldehyde exposure of < 1.0 mg/m^3 [< 0.8 ppm] and less than 5 years of employment.

3.2.8.2 Michigan: Historical cohort of iron foundry workers

Mortality among workers at an iron foundry in Michigan was investigated in a retrospective cohort study assembled by Andjelkovich *et al*. (1990). Workers (N = 8,147) were employed at an automotive gray iron foundry for at least six months between 1950 and 1979. During the period of observation from 1950 to 1984, an excess of lung cancer deaths among these workers was observed. Though the authors suspected that the excess could have been in part explained by smoking, other hypotheses related to occupational exposures at the plant were proposed, including exposure to formaldehyde. To further evaluate these hypotheses, the investigators conducted a nested case-control study of lung cancer in the entire cohort (Andjelkovich *et al.* 1994) as well as a standardized mortality analysis of a subset of the cohort exposed to formaldehyde between 1960 and 1987 (Andjelkovich *et al.* 1995). A summary of the major methods and findings from these two studies follows.

Nested case-control study

To investigate the potential association between lung cancer and relevant exposures at the iron foundry, including silica and formaldehyde, a nested case-control study was conducted with additional years of follow-up through December 1989 (Andjelkovich *et al.* 1994). Cases (N = 220, 51% white) were defined as primary lung cancer deaths among men in the cohort between January 1, 1950 and December 31, 1989. For each

case, 10 controls matched on race and attained age were selected from the cohort using incidence density sampling (52% of controls were alive at the end of the study period). Smoking information was obtained by questionnaire or records (including plant records and death certificates) for 76% of cases and 69% of a random sample of controls. Detailed work histories within the foundry were used to identify 107 unique occupational titles, which were then characterized by an industrial hygienist according to exposure to silica (high, medium, low) and formaldehyde (high, medium, low, none). For analyses, exposure to formaldehyde was dichotomized (ever/never) because only 25% of workers were considered ever exposed to formaldehyde (57 cases and 538 controls).

Conditional logistic regression was applied to estimate the effect of exposure to formaldehyde on lung cancer mortality adjusting for smoking, birth cohort (< 1915 *vs.* ≥ 1915), and silica exposure (quartiles). Using the subset of controls for which collection of smoking information was attempted, the OR for exposure to formaldehyde was 1.31 (95% CI = 0.83 to 2.07, number of cases not specified). Effect estimates consistently decreased in magnitude with increasing lag periods (10, 15, and 20 years) to 0.84 (95% CI = 0.44 to 1.60) with a 20-year lag. Effect estimates were slightly higher and more precise when all controls were included, though the same decrease in risk was observed with increasing lag periods. No evidence was observed of an interaction between smoking and formaldehyde.

Cohort mortality sub-analysis

A subsequent analysis examined mortality among a subset of foundry workers (N = 3,929, 67% white) exposed to formaldehyde for 6 months or more during core making operations between 1960 and 1987 (Andjelkovich *et al.* 1995). An internal referent group included a sample of workers (N = 2,032) from the original cohort who were unexposed to formaldehyde during the same time period. Cumulative exposure to formaldehyde was estimated for each worker by an industrial hygienist based on job-specific exposure levels (low = 0.05 ppm; medium = 0.55 ppm; and high = 1.5 ppm) and duration of exposure. Smoking information was obtained by questionnaire or records (including plant records and death certificates) for 65% of exposed workers and 55% of the unexposed referent group.

Mortality among the exposed workers through December 1989 was compared with mortality among the U.S. population; SMRs adjusted for sex, race, age, and calendar period were obtained using the person-years method. To address the potential for healthy worker bias, mortality among all the workers was compared with that of an occupational referent population assembled by the NCI and NIOSH, using Poisson regression adjusted for race, smoking, and silica exposure. Statistically nonsignificant excess mortality was observed among the exposed workers for cancers of the buccal cavity and pharynx (SMR = 1.31, 95% CI = 0.48 to 2.86; 6 deaths), esophagus (SMR = 1.07, 95% CI = 0.39 to 2.33, 6 deaths), stomach (SMR = 1.64, 95% CI = 0.82 to 2.94, 11 deaths), rectum (SMR = 1.17, 95% CI = 0.23 to 3.41, 3 deaths), trachea, bronchus, and lung (SMR = 1.20, 95% CI = 0.89 to 1.58, 51 deaths) and other and unspecified genital organs (SMR = 1.13, 95% CI = 0.23 to 3.31, 3 deaths). SMRs below 1.0 were reported for all other cancer sites, including, but not limited to, larynx (2 deaths), and all lymphohematopoietic cancers (7 deaths). No deaths from nasopharyngeal cancer were observed among formaldehyde-

exposed workers (deaths from sinonasal cancers were not presented). Directly adjusted relative risks (comparing exposed workers with unexposed workers) were elevated for laryngeal cancer (RR = 1.50, 95% CI not reported, $P \geq 0.05$) and cancer of the trachea, bronchus, or lung (RR = 1.13, 95% CI not reported, $P \geq 0.05$). The authors report that the majority of SMRs increased when the NCI/NIOSH referent population was applied (data not presented). In the Poisson regression analysis of men for whom smoking status was known, cumulative exposure to formaldehyde (third and fourth quartiles combined vs. unexposed) was not associated with cancers of the lung or oral cavity and pharynx (data for other cancer sites not presented).

3.2.8.3 United States: Chrome leather tannery plant workers

Study population and follow-up. Stern and coworkers (Stern *et al.* 1987, Stern 2003) conducted a retrospective cohort mortality study of 9,352 workers employed from 1940 to June 1979 (Plant A) or May 1980 (Plant B) in two chrome leather tannery plants in the United States. Approximately 76% of the cohort were male, and approximately 82% were white. The 1987 study followed workers until 1982, and the 2003 update extended the follow-up for 11 years until 1993, yielding a total of 2,735 deaths. At the last follow-up, vital status had been ascertained for 96% of the cohort, using Social Security and National Death Index records. Death certificates were obtained for 96.1% of all deaths. Workers in the finishing department were exposed to formaldehyde; the number of workers was not stated, but there were 1,050 observed deaths.

Exposure assessment. No exposure monitoring data were available from the plants. Industrial hygiene surveys were conducted by the investigators and used to assess exposures by process and department. Duration of employment was used as a surrogate for cumulative exposure. Multiple potentially hazardous agents were used in the tannery process, including nitrosamines, chromates, benzidine-based dyes, leather dust, and organic solvents, as well as formaldehyde, which was used in the finishing process. Ambient formaldehyde levels were measured in the finishing department at the time of the study and ranged from 0.5 to 7 ppm (mean 2.45 ppm). (Other potential exposures at detectable levels in this department included acetone, toluene, methyl isobutyl ketone, butyl cellusolve, and ambient leather fibers.)

Statistical methods. A modified life-table analysis was used to construct person-years at risk from the start of employment to the end of 1993. Expected mortality rates were computed from age-, sex-, race-, and calendar-year-specific rates in the two states in which the plants were located.

Results. No statistically significant increases in SMRs for any site-specific cancers among the entire cohort of workers in either Tannery A or B were observed (Stern 2003). (Note, however, that not all cancer sites were reported.) With respect to the workers in the finishing department, who were the subgroup of workers potentially exposed to formaldehyde, the SMR for all causes of deaths was somewhat decreased (SMR = 0.95) and that of cancer deaths was significantly decreased (SMR = 0.86), [which may suggest a possible healthy worker effect]. A statistically nonsignificant increase in bladder cancer (SMR = 1.20, 95% CI not reported, 7 deaths) and digestive system cancers (SMR = 1.02, 95% CI not reported, 68 deaths) was observed. SMRs were not increased for leukemia + aleukemia (SMR = 0.93, 95% CI not reported, 9 deaths) or for all lymphatic and

hematopoietic cancers (SMR = 0.91, 95% CI not reported, 22 deaths). One death from squamous-cell carcinoma of the nasal cavity was noted in the 1987 study in a man who had worked in the finishing department for over 18 years and died 55 years after the start of employment; the SMR was not estimated, but the annual incidence rate among white males in the United States cited by the authors was approximately 8 in one million at the time of the study).

3.2.8.4 China: female textile workers; Wong et al. *2006, Li* et al. *2006, and Ray* et al. *2006*

A series of nested case-cohort studies of cancer outcomes was conducted among a large cohort of currently employed and retired female textile workers in 526 factories in the Shanghai region of China who had originally been enrolled in a randomized breast self-examination trial. The cohort, consisting of 267,400 workers born between 1925 and 1958, was recruited from 1989 to 1991 and followed for cancer incidence and mortality from 1989 to 1998 or later. Workers received routine health care through their factories, and cancer diagnoses were reported to a registry operated by the Shanghai Textile Industry Bureau. Diagnoses were confirmed by record linkage with the Shanghai Cancer Registry or medical records. Historical exposures were estimated by industrial hygienists using a job-exposure matrix constructed from individual job histories and production process data. Stratified analysis was conducted using a weighting scheme for the stratified case-cohort design. Age-adjusted hazard ratios (HR) were calculated using Cox proportional hazards methods with robust variance estimation.

Thyroid cancer

Wong *et al*. (2006) conducted a nested case-cohort study of thyroid cancer among the cohort of female textile workers.Incident thyroid cases (N = 130) and non-case controls (N= 3,187) randomly selected from the cohort of all eligible textile workers and matched by year of birth in 5-year strata were identified. The HR for only 2 cases of thyroid cancer was considered to have exposure to formaldehyde compared with 11 controls; the HR was 8.33 (95% CI = 1.16 to 60.0, 2 exposed cases, with > 10 years of exposure).

Nasopharyngeal cancer

Li *et al.* (2006) identified 76 incident cases of primary nasopharyngeal cancer among the textile workers, of which occupational histories could be constructed for 67, were identified. Non-case controls (N = 3,188) were randomly selected from the cohort of all eligible textile workers and matched by year of birth in 5-year strata. No cases of nasopharyngeal cancer were considered to have exposure to formaldehyde, compared with 10 controls. The authors stated that there were no measurement data on formaldehyde exposure, which could have resulted in exposure misclassification. The study also included 10 cases of nasal or paranasal sinus cancer, but risk estimates (or number of expected and observed cases) for formaldehyde exposure and sinonasal cancer were not reported.

Breast cancer

In a follow-up of breast cancer incidence among the textile workers until 2000, Ray *et al.* (2007) identified 1,709 incident breast cancer cases, and 3,155 non-case subcohort controls, randomly selected from the cohort of all eligible textile workers and matched by

year of birth in 5-year strata. Women with an *a priori* history of breast cancer or mastectomy at baseline were excluded. Only two cases of breast cancer (both with > 10 years exposure) were considered to have exposure to formaldehyde, compared with 11 controls; the HR was 0.85 (95% CI = 0.14 to 5.23, 2 exposed cases), with > 10 years of exposure.

3.3 Studies of health professionals, embalmers, and funeral directors

This section covers multiple studies of health professionals (e.g., anatomists, pathologists, and medical lab technicians), embalmers, and funeral directors. These occupations are known to involve exposure to formaldehyde, which is used as a human tissue preservative (see Section 2.4.6 for more information on exposure levels). This section includes studies of health professionals (Hall *et al.* 1991, Harrington and Oakes 1984, Harrington and Shannon 1975, Stroup *et al.* 1986) and studies of embalmers and funeral directors (Walrath and Fraumeni 1983, 1984, Levine *et al.* 1984, Hayes *et al.* 1990, Hauptmann *et al.* 2009). One study of pathologists was excluded from this review because its primary objective was to examine low-level ionizing radiation among pathologists with membership in the Radiation Registry of Physicians (Logue *et al.* 1986). A small case-control analysis of lung cancer among Danish physicians (Jensen and Andersen 1982) is reported in Section 3.5.4.

Studies included in this section examined the association between occupational groups assumed to be exposed to formaldehyde and excess mortality from cancer (compared with cancer mortality among internal or external reference populations). Most of these studies did not attempt to quantify or characterize exposure or estimate exposure-response relationships, but rather examined cancer outcomes by occupation and occupational characteristics (e.g., duration of employment) only. The case-control study of Hauptmann *et al.* (2009), however, examined exposure-response relationships for lymphohematopoietic and brain cancers among embalmers and funeral directors by average, cumulative, peak, and duration of exposure based on estimated exposure levels and individual work histories. Table 3-3 summarizes the characteristics of the major studies. Findings for the tumor sites of interest from these studies are reported in Tables 3-4 to 3-9 (see Section 3.6).

Table 3-3. Characteristics of cohort and nested case-control studies among health professionals

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
Hall *et al.* 1991 (update of Harrington and Oakes 1984, Harrington and Shannon 1975)	Pathologists, members of professional organizations in the UK N = 4,512 1974–87	Employment status No information on exposure levels	Standardized mortality study
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046 1975–85	Employment status No information on exposure levels	Proportionate mortality study Lymphohematopoietic and brain cancer analyzed by type of license (embalmer or funeral director).
Levine *et al.* 1984	Licensed embalmers in Ontario, Canada N = 1,413 1950–77	Licensing records No information on exposure levels	Standardized mortality study
Stroup *et al.* 1986	Anatomists who were members of the American Association of Anatomists, USA N = 2,317 1888–1979	Employment status No information on exposure levels	Standardized mortality study Findings for brain and lung analyzed by length of membership and subspecialty
Walrath and Fraumeni 1983	All licensed embalmers in New York, USA N = 1,263 1902–80	Licensing records No information on exposure levels	Proportionate mortality study Specific cancer sites analyzed by age at first license, time since first license, and type of license (embalmers only and funeral directors and embalmers)
Walrath and Fraumeni 1984	All licensed embalmers in California, USA N = 1,109 1916–80	Licensing records No information on exposure levels	Proportionate mortality study Employment duration estimated by length of licensure
Hauptmann *et al.* 2009	*Nested case-control study* *Cohort*: 6,808 death certificates from 1960–86 identified from (1) registries of the National Funeral Directors Association,	Occupational history obtained by interviews with next of kin and multiple co-workers using detailed questionnaires Exposure was assessed by linking questionnaire responses to a validated exposure assessment model validated by	Cohorts include Hayes *et al.* (1990), Walrath and Fraumeni e*t al.* (1983, 1984) Analyses included duration of working in jobs with embalming, number of embalmings,

Reference	Study population and follow up	Exposure assessment and exposure levels	Analyses and related studies
	(2) licensing board and state funeral director's associations, (3) NY State Bureau of Funeral Directors and CA Department of Health Division of Funeral Directors and Embalmers *Nested case-control study* Cases: 168 lymphohematopoietic cancer, 48 brain cancer, and 4 nasopharyngeal cancer (underlying or contributory cause of death) Controls: 264 randomly selected from cohort with other causes of disease except for cancer of the buccal cavity or pharynx, respiratory system, or eye	monitoring data. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure-response data.	and exposure to formaldehyde including cumulative, peak, average intensity, and 8-hour time-weighted average exposure. Only one case of myeloid leukemia was observed in reference to never exposed, so analysis was repeated using embalmers with fewer than 500 lifetime embalmings as the referent group.

Pathologists: United Kingdom

A series of overlapping studies of pathologists in the United Kingdom were reported in three publications from 1975 to 1991.The methods and findings for the earlier study are mentioned briefly, and findings for the latest update are presented in greater detail. Harrington and Shannon (1975) studied mortality among pathologists and medical laboratory technicians who were members of professional organizations in the United Kingdom at some time between 1955 and 1973 (N = 2,079, 156 deaths among pathologists and 154 deaths among technicians), and followed until.1968. Harrington and Oakes (1984) extended the previous study to include 2,307 males (110 deaths) and 413 females (16 deaths). Pathologists active in one of the professional organizations from January 1974 through December 1980 were followed until 1980. Statistically significant increases in lymphohematopoietic cancers were observed among male pathologists (8 observed deaths vs. 3.3 expected, $P < 0.05$) in the 1975 study and in brain cancer among men (SMR = 3.31, 90% CI = 1.13 to 7.58, 4 deaths) in the 1984 study; no cases were observed among women.

Hall *et al.* (1991) further updated this cohort of British pathologists, adding new members of the Pathological Society and extending follow-up to 1987. A total of 4,512 pathologists were included: 3,872 from England and Wales (3,069 men, 803 women), and 409 males from Scotland; references rates were not available for the remaining members,

which included females from Scotland or members from Northern Ireland. Sex-specific SMRs adjusted for age (5-year strata) and calendar time (2-year intervals) were calculated based on expected mortality rates from England and Wales (males and females), or Scotland (males only). Compared with national rates, mortality from all causes (SMR for men in England and Wales = 0.43, 95% CI = 0.37 to 0.50, 176 deaths; SMR for women in England and Wales = 0.65, 95% CI = 0.38 to 1.03, 18 deaths, SMR for men in Scotland = 0.50, 95% CI = 0.34 to 0.72, 29 deaths) and also from all cancers was substantially less than expected. No statistically significant excesses were observed for cancer at any site. However, increases in mortality were noted for lymphohematopoietic cancer (SMR = 1.44, 95% CI = 0.69 to 2.65, 10 deaths) and leukemia (SMR = 1.52, 95% CI = 0.41 to 3.89, 4 deaths) among all pathologists in England and Wales, brain cancer (SMR = 2.40, 95% CI = 0.88 to 5.22, 6 deaths) among male pathologists from England and Wales, prostate cancer (SMR = 3.30, 95% CI = 0.39 to 11.80, 2 deaths) among pathologists from Scotland, and breast cancer (SMR = 1.61, 95% CI = 0.44 to 4.11, 4 deaths) among female pathologists from England and Wales. Among all pathologists, nonstatistically significant excesses were also observed for liver, Hodgkin's lymphoma and tongue, each based on one death only. (Only nine deaths were observed among Scottish pathologists.)

3.3.1 Anatomists: United States

Stroup *et al*. (1986) conducted a retrospective cohort study of mortality among members of the American Association of Anatomists. Eligible subjects included 2,317 male residents of the United States who joined the professional organization between 1888 and 1969; each subject was followed from date of initial membership through December 1979. Death certificates were obtained and coded by a trained nosologist for underlying and contributing causes of death. SMRs were calculated using 5-year age-specific and 5-year time-specific mortality rates among U.S. white males from 1925 to 1979. A second referent group consisting of 5-year age-specific mortality rates among 19,000 male members of the American Psychiatric Association between 1900 and 1969 was also used to reduce any influence of the "healthy-worker effect." Compared with the general U.S. population of white males, this cohort of anatomists experienced less-than-expected numbers of death from all causes (SMR = 0.65, 95% CI = 0.60 to 0.70, 738 deaths) and all cancers (SMR = 0.64, 95% CI = 0.53 to 0.76, 118 deaths). Despite these overall deficits, a statistically significant excess of brain cancer was observed (SMR = 2.7, 95% CI = 1.3 to 5.0, 10 cases), and SMRs increased in magnitude with duration of membership. Excess mortality was also noted for lymphohematopoietic cancers in comparison with the U.S. population (SMR = 1.2, 95% CI = 0.7 to 2.0, 18 deaths), including leukemia (SMR = 1.5, 95% CI = 0.7 to 2.7, 10 deaths) and other lymphohematopoietic cancer of other lymphatic tissues (SMR = 2.0, 95% CI = 0.7 to 4.4, 6 deaths). The authors noted that of the 10 leukemia deaths, 5 were from myeloid leukemia, and the SMR for chronic myeloid leukemia was statistically significantly elevated (SMR = 8.8, 95% CI = 1.8 to 25.5, 3 deaths) during the period from 1969 to 1979 when cell-type-specific mortality rates were available. Slight increases in cancers of the colon (SMR = 1.1, 95% CI = 0.7 to 1.7, 20 deaths) and pancreas (SMR = 1.1, 95% CI = 0.6 to 2.0, 11 deaths) were also observed. No deaths were observed from cancer of the nasal cavity and sinuses or nasopharynx. Brain cancer was also statistically significantly

elevated when compared with the referent group of psychiatrists (SMR = 6.0, 95% CI = 2.3 to 15.6); the SMR for leukemia was not elevated in comparison with the referent group of psychiatrists, however (SMR = 0.8, 95% CI = 0.2 to 2.9, 3 deaths). (The authors did not state whether both underlying and contributory causes of deaths, which were both recorded by a nosologist in this study, were used in analyses, either for the exposed subjects or for calculating expected rates for U.S. males or members of the American Psychiatric Association.)

3.3.2 Embalmers: New York

Using records obtained from the New York Bureau of Funeral Directing and Embalming, Walrath and Fraumeni (1983) assembled a cohort of all embalmers licensed to practice in New York between 1902 and 1980 and known to have died between 1925 and 1980. Death certificates were obtained for 1,263 eligible subjects (75% of cohort), and the underlying cause of death was coded by a trained nosologist. Deaths observed among the embalmers were compared with expected numbers calculated by applying the age-, race-, and calendar-year-specific proportions of deaths for each cause among the U.S. male population to the total number of deaths in the cohort by 5-year age and calendar periods. Time since first licensure was used to approximate duration of exposure.

Results focused on findings from 1,132 white men (10 women and 42 men of unknown race were excluded). Among white male embalmers, a statistically nonsignificant increase in PMR for all cancers was observed (PMR = 1.11, 243 observed deaths vs. 218.9 expected). A statistically significant ($P < 0.05$) excess mortality was observed for cancers of the colon (PMR = 1.43, 29 observed deaths vs. 20.3 expected) and skin (PMR = 2.21, 8 observed deaths vs. 3.6 expected). Mortality was also greater than expected for cancers of the kidney (PMR = 1.50, 8 observed deaths vs. 5.4 expected), brain (PMR = 1.56, 9 observed deaths vs. 5.8 expected), liver and gallbladder (PMR = 1.06, 5 observed deaths vs. 4.7 expected), pancreas (PMR = 1.05, 13 observed deaths vs. 12.3 expected), lung (PMR = 1.08, 72 observed deaths vs. 66.8 expected; 2 of these deaths were pleural cancers), buccal cavity and pharynx (PMR = 1.13, 8 observed deaths vs. 7.1 expected), and lymphohematopoietic cancers (PMR = 1.21, 25 observed deaths vs. 20.6 expected) including leukemia (PMR = 1.40; 12 observed deaths vs. 8.5 expected). (PCMRs were calculated and were similar to PMRs in most cases, although estimates were less stable for cancers with small numbers of deaths.) No deaths from cancer of the nasal cavity or sinuses or nasopharynx were observed. Among non-white males (N = 79), the authors noted that significantly higher mortality from cancers of the larynx (2 observed deaths) and lymphohematopoietic system (3 observed deaths) was found (data not presented).

Analysis by time since first licensure did not produce markedly different results, with the exception of mortality from skin cancer (PMR = 1.73 for less than 35 years, 4 deaths; and PMR = 3.08, 35 deaths for greater than 35 years). Statistically significant increases in brain (PMR = 2.94, 5 observed deaths) and skin cancer mortality (PMR = 3.87, 5 observed deaths) were found among white embalmers who were first licensed at 30 years or older. Stratification by type of license among the white male embalmers showed that cancer mortality was generally more elevated among the 546 subjects who practiced only as embalmers than among the 586 who practiced both as embalmers and funeral directors; the authors considered embalmers to be more highly exposed to formaldehyde

than funeral directors. Among those who practiced only as embalmers, increases in mortality were observed for oral cavity and pharyngeal cancer (PMR = 2.01, 7 observed deaths vs. 3.5 expected, $P > 0.05$), skin (PMR = 3.26, 5 observed cases vs. 1.5 expected, $P < 0.05$), kidney (PMR = 2.47, 6 observed cases vs. 2.4 expected, $P < 0.05$) and brain (PMR = 2.34, 6 observed cases vs. 2.6 expected, $P < 0.05$). Statistically nonsignificant increases were seen only for lymphohematopoietic cancers (PMR = 1.39, 16 observed deaths vs. 11.5 expected), bladder cancer (PMR = 1.32, 5 observed deaths vs. 3.8 expected), gastrointestinal and peritoneal cancers (PMR = 1.33, 42 observed deaths vs. 31.7 expected), skin (PMR = 1.44, 3 observed deaths vs. 2.1 expected) and respiratory system cancers (PMR = 1.12, 47 observed deaths vs. 42.1 expected).

3.3.3 Embalmers: California

The study design and analysis used by Walrath and Fraumeni (1983) was replicated by Walrath and Fraumeni (1984) using a second cohort including all embalmers licensed to practice in California between 1916 and 1978 and known to have died between 1925 and 1980. Licensing records were obtained from the Bureau of Funeral Directing and Embalming in Sacramento, California, and death certificates were obtained for 1,109 eligible subjects (94% male, 96% white). Reported results excluded 63 women and 39 non-white men. Mortality from all malignant neoplasms was significantly higher than expected in this cohort (PMR = 1.21, 205 observed deaths vs. 169.9 expected; $P < 0.05$). A statistically significant ($P < 0.05$) excess mortality was observed for cancers of the colon (PMR = 1.87, 30 observed deaths vs. 16 expected), prostate (PMR = 1.75, 23 observed deaths vs. 13.1 expected), brain and central nervous system (PMR = 1.94, 9 observed deaths vs. 4.7 expected), and leukemia (PMR = 1.75, 12 observed deaths vs. 6.9 expected). The excess of leukemia cases was noted largely among embalmers with greater than 20-years licensure (PMR = 2.21, 8 observed deaths; $P < 0.05$). Statistically nonsignificant increases (greater than 5%) were also noted for cancers of the buccal cavity and pharynx (PMR = 1.31, 8 observed deaths vs. 6.1 expected), pancreas (PMR = 1.35, 12 observed cases vs. 8.9 expected), bladder (PMR = 1.38, 8 observed deaths vs. 5.8 expected), all lymphohematopoietic cancers (PMR = 1.22, 19 observed deaths vs. 15.6 expected), and other (unspecified) cancers (PMR = 1.37, 21 observed deaths vs. 15.3 expected). No deaths from nasal cancer were observed (0.6 expected).

3.3.4 Embalmers: Canada

Levine *et al.* (1984) assembled a cohort of 1,413 male embalmers first licensed by the Ontario Board of Funeral Services between 1928 and 1957 and known to have died between 1950 and 1977. Death certificates were obtained from the Canadian Mortality Database and coded for underlying and contributing cause of death by trained nosologists. Numbers of observed and expected deaths were enumerated for each underlying cause of death. Standardized mortality ratios were calculated using expected deaths determined by applying age- and calendar-year-specific mortality rates among all males in Ontario from 1950 to 1977. A statistically nonsignificant increase in deaths from all lymphohematopoietic cancers was noted (SMR = 1.24, 8 observed deaths vs. 6.5 expected, including 4 leukemia deaths vs. 2.5 expected), [though this finding was based on small numbers]. SMRs were less than 1.0 for all other major cancer sites reported. SMRs were not calculated for cancer sites where either observed or expected numbers of

deaths were less than five. Three deaths from brain cancer were observed (vs. 2.6 expected), and no deaths from sinus and nasal cancers were observed (vs. 0.2 expected).

3.3.5 Embalmers and funeral directors: United States

Hayes *et al.* (1990) conducted a proportionate mortality study of 4,046 (90% white) male embalmers and funeral directors from multiple locations in the United States who had died between 1975 and 1985. Information on occupation and cause of death was ascertained from death certificates, licensing board, and state funeral directors association. Observed numbers of deaths by cause were compared with expected numbers using sex-, race-, 5-year age- and calendar-year-specific proportions of deaths among the U.S. general population. Results were stratified by race. An increase in all cancers combined was observed among whites (PMR = 1.07, 95% CI = 1.01 to 1.15, 900 deaths) and non-whites (PMR = 1.08, 95% CI = 0.87 to 1.31, 102 deaths). Colon cancer was statistically significantly elevated among non-whites (PMR = 2.31, 95% CI = 1.32 to 3.76, 16 deaths) but not whites (PMR = 1.18, 95% CI = 0.95 to 1.44, 95 deaths), as were lymphohematopoietic cancers among both whites (PMR = 1.31, 95% CI = 1.06 to 1.59, 100 deaths) and non-whites (PMR = 2.41, 95% CI = 1.35 to 3.97, 15 deaths). Mortality from lymphohematopoietic cancers did not vary substantially between embalmers and funeral directors. Among all subjects with lymphohematopoietic cancers, PMRs were statistically significant for myeloid leukemia (PMR = 1.57, 95% CI = 1.01 to 2.34, 24 deaths) and unspecified leukemias (PMR = 2.28, 95% CI = 1.39 to 3.52, 20 deaths); statistically nonsignificant excesses were observed for several other histologic subtypes, including non-Hodgkin's lymphoma (PMR = 1.26, 95% CI = 0.87 to 1.76, 34 deaths) and multiple myeloma (PMR = 1.37, 95% CI = 0.84 to 2.12, 20 deaths). PMRs were nonsignificantly elevated for several other cancer sites, including the oral cavity and pharynx (whites: PMR = 1.19, 95% CI = 0.78 to 1.74, 26 deaths; non-whites: PMR = 1.25, 95% CI = 0.34 to 3.20, 4 deaths); nasopharynx (whites: PMR = 1.89, 95% CI = 0.39 to 5.48, 3 deaths; non-whites: PMR = 4.00, 95% CI = 0.10 to 22.29, 1 death); esophagus (whites: PMR = 1.15, 95% CI = 0.72 to 1.73, 22 deaths; non-whites: PMR below 1.0); pancreas (whites: PMR = 1.19, 95% CI = 0.89 to 1.57, 51 deaths; non-whites: PMR = 1.67, 95% CI = 0.72 to 3.29, 8 deaths); skin (whites: PMR = 1.34, 95% CI = 0.81 to 2.09, 19 deaths; non-whites: no observed deaths), breast (whites: PMR = 2.00, 95% CI = 0.24 to 7.22, 2 deaths; non-whites: no observed deaths); prostate (whites: PMR = 1.06, 95% CI = 0.84 to 1.32, 79 deaths; non-whites: PMR = 1.35, 95% CI = 0.82 to 2.12, 9 deaths); kidney (whites: PMR = 1.26, 95% CI = 0.82 to 1.87, 25 deaths; non-whites: PMR = 1.52, 95% CI = 0.18 to 5.50, 2 deaths), eye (whites: PMR = 3.62, 95% CI = 0.44 to 13.08, 2 deaths; non-whites: no observed deaths), brain and other central nervous system (whites: PMR = 1.23, 95% CI = 0.80 to 1.84, 24 deaths; non-whites: no observed deaths), and thyroid (whites: PMR = 2.37, 95% CI = 0.49 to 6.93, 3 deaths; non-whites: no observed deaths).

3.3.6 Nested case control study of embalmers and funeral directors: United States

Study population. Hauptmann *et al.* (2009) conducted a case-control study of lymphohematopoietic, brain and nasopharyngeal cancers that included embalmers and funeral directors from previous mortality studies (Walrath and Fraumeni 1983, 1984, Hayes *et al.* 1990) and for whom vital status could be determined. Death certificates were

obtained from state vital statistics offices for 6,808 embalmers and funeral directors who had died between January 1 1960 and January 1 1986 and coded for underlying cause and contributory of death. All cases in which lymphohematopoietic, (N = 168, 85% coded as underlying cause of death, consisting of 99 for lymphoid origin, 48 for nonlymphoid origin, and 34 for myeloid leukemia), brain (N = 48, 92% coded as underlying cause of death) and nasopharyngeal cancer (N = 4, all coded as underlying cause of death) was an underlying or contributing cause of death were included in the study. Three cases in which more than one of these cancers occurred among the underlying and contributing causes of death were coded to the underlying cause of death for analysis. Cases were matched on data source, sex, and 5-year date of birth and death interval with 265 controls randomly selected from workers in the funeral industry with other causes of death, except for cancers of the buccal cavity or pharynx, respiratory system, or eye, brain or other central nervous system.

Exposure assessment. Work histories and practices of the subjects were obtained by in-person interviews with both next of kin and several co-workers to ascertain frequency and duration of embalmings for jobs held more than five years, spills, and ventilation of the premises. These data were linked to a predictive exposure model that took into account exposure levels validated from repeated real-time measurements of independent embalmings, ventilation, spills, and other covariates to estimate lifetime 8-hour time-weighted average, cumulative, and peak exposures to formaldehyde.

Statistical methods and results. Unconditional logistic regression analysis was used to calculate odds ratios for categories of exposure (frequency and duration of embalming and exposure to formaldehyde metrics) with a 2-year lag interval, and adjusted for calendar year of birth, age at death, sex, and data source, and smoking status (ever vs. never). Continuous exposure metrics (peak, average lifetime 8-hour time-weighted average and cumulative exposure) were grouped into four categories: non-exposed and approximate tertiles of exposed controls. Wald tests for trend were based on estimated slopes of continuous variables. Using a 15-year lag for exposure compared with the 2-year interval used in primary analyses did not alter the results.

Lymphohematopoietic cancers

Risk estimates were calculated for all lymphohematopoietic cancers combined, cancers of the lymphoid origin cancers of nonlymphoid origin, and specifically for myeloid leukemia for each of the following exposure metrics: ever embalming, number of embalmings and number of years of working in embalming, and the four quantitative estimates of exposure to formaldehyde. Ever embalming was associated with a statistically nonsignificant increased risk for all lymphohematopoietic cancers combined (OR = 1.4, 95% CI = 0.8 to 2.6, 144 exposed cases) and a borderline statistically significant increased risk for lymphohematopoietic cancers of non-lymphoid origin (OR = 3.0, 95% CI = 1.0 to 9.5, $P = 0.059$, 44 exposed cases). Among the latter cases, a statistically significant trend with increasing number of years of working in embalming was observed ($P_{trend} = 0.046$). In addition, statistically significant increases were observed among lymphohematopoietic cancers of non-lymphoid origin for the highest exposure categories for cumulative exposure (OR = 4.0, 95% CI = 1.2 to 13.2, 22 exposed cases, for > 9,253 ppm-hours), 8-hour TWA intensity of exposure (OR = 4.2,

95% CI = 1.2 to 14.3, 20 cases, for > 0.10 to 0.18 ppm and OR = 3.4, 95% CI = 1.0 to 11.8, 15 exposed cases for > 0.18 ppm) and peak exposure (OR = 3.8, 95% CI = 1.1 to 12.7, 18 exposed cases, for peaks > 9.3 ppm), although exposure-response trends were not significant (see Table 3-8b).

The increases in risk for non-lymphoid origin cancers were attributable mainly to the risk for myeloid leukemia (OR = 11.2, 95% CI = 1.3 to 95.6, $P = 0.027$, 33 exposed cases). Among deaths from myeloid leukemia, a statistically significant trend was observed for duration of employment in jobs with embalming ($P_{trend} = 0.020$); the trend for peak exposure was 0.036 and for average exposure the trend was 0.058. No exposure response relationship was observed with cumulative or 8-hour TWA exposure; however, statistically significant increases in risk were observed for myeloid leukemias for each category of cumulative exposure of between > 0.0 and > 9,253 ppm-hours, for average intensity of exposure while embalming of > 0.0 to 1.4 ppm, > 1.4 to 1.9 ppm, and > 1.9 ppm, and for 8-hour TWA exposures > 0.10 ppm. Risks for myeloid and other subtypes of leukemia were compared between subjects who had performed more than 500 embalmings with those performing less than 500 over a lifetime because there was only one myeloid leukemia in the reference group of non-embalmers. [This analysis reduced the ORs for exposed cases but yielded more stable risk estimates of effect.] For myeloid leukemia (N = 34 for > 500 embalmings vs. 5 for < 500 embalmings), increased risks were associated with high-level exposures of more than 34 years of employment (OR = 3.9, 95% CI = 1.2 to 12.5, $P = 0.024$), more than 3,068 embalmings (OR = 3.0, 95% CI = 1.0 to 9.2, $P = 0.057$) and > 9,253 ppm-hours cumulative exposure to formaldehyde (OR = 3.1, 95% CI = 1.0 to 9.6, $P = 0.047$) (see Table 3-8b). Adjustment for smoking did not alter the results. With respect to lymphohematopoietic cancers of lymphoid origin, no associations with the various estimates of formaldehyde exposure were observed (ORs for ever embalming compared with never embalming were 0.9, 95% CI = 0.4 to 2.1 for non-Hodgkin's lymphoma; 0.5, 95% CI = 0.1 to 2.6, 8 exposed cases for Hodgkin's lymphoma; 1.4, 95% CI = 0.4 to 5.6 for multiple myeloma; and 1.0, 95% CI = 0.5 to 1.9 for all lymphoma including chronic lymphocytic leukemia).

Brain cancers

Embalming was associated with an increased but not statistically significant risk for these tumors (OR = 1.9, 95% CI = 0.7 to 5.3, 42 exposed cases). There were no clear exposure-response trends with duration, cumulative, average intensity, or peak exposures.

Nasopharyngeal cancers

Four cases of nasopharyngeal cancer were identified in this population, of whom two had ever engaged in embalming (OR = 0.1, 95% CI = 0.01 to 1.2, 2 exposed cases). Average exposure levels among these two cases were equal or higher than exposure levels among exposed controls for most exposure metrics, however.

3.4 Population-based cohort and cancer registry studies

One population-based cohort study, in which cancer mortality in association with occupational histories was prospectively investigated in a large, nationwide cancer study of U.S. males (Stellman *et al.* 1998), together with a case-control analysis of multiple

myeloma nested within this study (Boffetta *et al.* 1989), and one cancer registry study of the buccal cavity, tongue, and pharynx from Finland (Tarvainen *et al.* 2008) were identified. Findings for cancer outcomes among men who reported exposure to formaldehyde and for a nested case-cohort analysis of multiple myeloma conducted within the larger U.S. cohort are reviewed

3.4.1 United States: American Cancer Society Cancer Prevention Study

Study population and follow-up. Stellman *et al.* (1998) studied the association between mortality and occupational exposure to wood dust in the second phase (CPS II) of the American Cancer Society's population-based Cancer Prevention Study. The entire cohort consisted of over half a million males from all 50 states, Washington, D.C., and Puerto Rico who were enrolled in 1982 and completed questionnaires on demographic and lifestyle characteristics including smoking, medical history, and occupational history, and were followed for 6 years. Stellman *et al.* reported findings for 45,399 men who reported employment in a wood-related occupation or exposure to wood dust, some of whom were exposed to formaldehyde.

Exposure assessment and statistical analysis. Exposure to 12 occupational substances including formaldehyde, was self-indicated on a check-list. The analysis included 11,541 woodworkers, of whom 387 reported exposure to formaldehyde. Risk estimates for selected cancer sites were also calculated for non-woodworkers exposed to formaldehyde (number not stated but 1,238 deaths from all causes were observed). Site-specific cancer mortality information was obtained from death certificates during six years of follow-up (September 1982 to August 1988). Incidence density ratios adjusted by age and smoking status were calculated for subjects reporting formaldehyde exposure employed in any occupation, and for subjects reported formaldehyde exposure employed in a wood-related occupation. The reference group for all estimates consisted of the 317,424 men who did not report either employment in a wood-related occupation or regular exposure to wood dust. The analysis focused on cancer sites considered to be of *a priori* concern based on excesses observed among woodworkers in other studies.

Results. Woodworkers who reported regular exposure to formaldehyde had a statistically significant increase in lung cancer mortality (RR = 2.63, 95% CI = 1.25 to 5.51, 7 exposed cases) and leukemia (RR = 5.79, 95% CI = 1.44 to 23.25, 2 exposed cases). Effect estimates were elevated for rectal cancer (RR = 5.77, 95% CI = 0.81 to 41.22) and non-Hodgkin's lymphoma (RR = 2.88, 95% CI = 0.40 to 20.50), though both estimates were based on only one exposed case and were not statistically significant. Among non-woodworkers exposed to formaldehyde, increased risk of cancer mortality was observed for stomach cancer (RR = 1.63, 95% CI = 0.94 to 2.86, 11 exposed cases) and all lymphohematopoietic cancers combined (RR = 1.22, 95% CI = 0.84 to 1.77, 28 exposed cases). Results for cancers of the paranasal sinuses and nasal cavity were not presented for the formaldehyde-exposed workers; two cases of SNC and one case of NPC were observed among all workers.

Nested case-cohort study. A population-based nested case-cohort study of 282 deaths from multiple myeloma observed in the second stage of the American Cancer Society's Cancer Prevention prospective cohort study and matched with up to 4 within-cohort

controls was conducted by Boffetta *et al.* (1989). Of the 282 deaths, 128 were considered to be incident cases, on which analyses were based. The association between multiple myeloma, occupational groups and selected exposures was examined, based on questionnaires completed by enrollees and assignment of exposure status by the investigators. Using conditional logistic regression, a statistically nonsignificant association between multiple myeloma incidence and formaldehyde exposure was observed (OR = 1.8, 95% CI = 0.6 to 5.7, 4 exposed cases).

3.4.2 Cancer registry study of the buccal cavity, tongue, and pharynx: Finland

Study population. The association between oral cavity, tongue, and pharyngeal cancers and occupational exposures was investigated in a standardized incidence study by Tarvainen *et al.* (2008), using all diagnosed cases identified among all Finnish men and women, born between 1906 and 1945 and followed from 1971 to 1995, through the Finnish Cancer Registry. A total of 46.8 million person-years were represented by the cohort, and a total of 2,708 cases of oral cavity, tongue and pharyngeal cancers (excluding nasopharyngeal cancers) were identified.

Exposure assessment. The occupation held the longest according to the 1970 census was converted via a national job-exposure matrix to semi-quantitative (low, medium, and high) estimates of cumulative exposure to 43 separate chemical agents.

Statistical methods and results. Standardized incidence ratios for combined oral, tongue, and pharyngeal cancers were calculated based on national rates. Exposure to low, medium, and high estimated cumulative levels of formaldehyde was associated with statistically nonsignificant SIRs of 0.79 (95% CI = 0.6 to 1.03, 59 cases), 1.01 (95% CI = 0.43 to 1.98, 8 cases) and 0.73 (95% CI 0.27 to 1.59, 6 deaths), respectively.

3.5 Case-control studies

Over 40 case-control studies have examined the relationship between occupational exposure to formaldehyde and various cancers. Most are population based with the exception of the study of physicians by Jensen and Anderson (1982) and the study of workers in woodworking industries by Pesch *et al.* (2008). This section reviews epidemiological case-control studies chronologically by major cancer site. The review covers head and neck cancers, lung cancer, lymphohematopoietic malignancies, and cancers at all other sites that have been studied in relation to formaldehyde. Head and neck cancers are further divided into three distinct sections: cancers of the paranasal sinuses and nasal cavity (i.e., sinonasal cancer), cancer of the nasopharynx, and all other head and neck cancers. See Tables 3-4 to 3-9 for cancer-specific tumor site findings.

Some studies evaluated cancer risk at more than one tumor site; results from these studies will be presented for each tumor site individually, though the study population and methods will be described only at the first citation.

3.5.1 Cancers of the paranasal sinuses and nasal cavity

This section reviews six case-control studies and a pooled analysis of workers from 12 case-control studies (Luce *et al.* 2002) that examined the association between

formaldehyde and sinonasal carcinoma. Four studies were conducted in Europe (Hayes *et al.* 1986, Luce *et al.* 1993, Olsen and Asnaes 1986, Olsen *et al.* 1984, Pesch *et al.* 2008), and two in the United States (Vaughan *et al.* 1986a, Roush *et al.* 1987). [In a number of these studies, exposure to wood dust might have occurred in addition to formaldehyde. Wood dust is a known human carcinogen with a strong association with sinonasal cancers, predominantly of the adenocarcinoma type; some studies have also reported associations with squamous-cell carcinomas (IARC 1995, NTP 2005a, Baan *et al.* 2009)]

3.5.1.1 Denmark: Olsen et al. *(1984), Olsen and Asnaes (1986)*

Study population. The association between occupational formaldehyde exposure and sinonasal and nasopharyngeal cancers was explored in a population-based case-control study in Denmark (Olsen *et al.* 1984). Cases of non-sarcoma carcinomas of the sinonasal cavity (N = 488, 66% male) and nasopharynx (N = 266, 68% male) diagnosed between 1970 and 1982 were identified using the Danish Cancer Registry (see Section 3.5.2 for results on nasopharyngeal cancer). Eligible controls (N = 2,465) diagnosed with colorectal, prostate, or breast cancer were also selected from the registry and matched to cases (case to control ratio = 1:3) by sex, age (within 5 years), and year of diagnosis (within 5 years). In 1986, Olsen and Asnaes performed a re-analysis after conducting additional data collection to obtain histological information for each case included in their original case-control study. Seven hundred fifty-nine (759) histologically verified cancers of the nasal cavity (N = 287), paranasal sinuses (N = 179), and nasopharynx (N = 293) were included in the analysis. [Presumably, many of these cases were included in the Danish record linkage study by Hansen and Olsen 1996 (see Section 3.2.6)].

Exposure assessment. Information on occupational history since 1964 was obtained by linking subjects with national pension and population registries with information including job title, industry, job description, company of employment, and period of employment for each worker. These data, in addition to information about Danish industries and occupations supplied by the national Labor Inspection Service, were used by three industrial hygienists blinded to case/control status to classify each subject by exposure (ever/never) to certain agents including formaldehyde. Each reported job was further classified as unexposed, certainly exposed, probably exposed, or unknown.

Statistical methods and results. Odds ratios were estimated with tabular analysis, and Mantel-Haenszel summary estimates were calculated to assess confounding and interaction with wood dust. Among controls, 4.2% of men and 0.1% of women were considered exposed to formaldehyde (percentage of cases exposed not reported); further analyses were thus restricted to men only. Olsen *et al.* (1984) reported that the RR for sinonasal cancers among men considered certainly exposed to formaldehyde compared with those unexposed was 2.8 (95% CI = 1.8 to 4.3, 33 exposed cases). When a lag time was applied by excluding exposures within 10 years of diagnosis, the corresponding RR increased to 3.1 (95% CI = 1.8 to 5.3, 23 exposed cases). Effect estimates among men considered probably exposed were closer to the null. Exposure to wood dust was evaluated both as a potential confounding factor and as an effect modifier. Among subjects unexposed to wood dust, the RR for any formaldehyde exposure and sinonasal cancers was 1.8 (95% CI = 0.7 to 4.9, 5 cases). Among those unexposed to formaldehyde, the RR for any wood dust exposure and sinonasal cancers was 2.0 (95% CI = 1.1 to 3.7, 8

cases). The RR for the joint effect of exposure to both formaldehyde and wood dust was 3.5 (95% CI = 2.2 to 5.6, 28 cases). Adjusting for wood dust to evaluate whether the effect of formaldehyde alone was confounded by wood dust, the pooled RR for any formaldehyde exposure was 1.6 (95% CI not reported; $P \geq 0.05$). When a 10-year exposure lag time was applied, the adjusted summary measure was unchanged; however, the joint effect of both exposures increased to 4.1 (95% CI = 2.3 to 7.3, 20 cases). Effect estimates for formaldehyde did not markedly change after adjustment by occupational exposure to paint, lacquer, and glue. The authors noted that this study had 80% power to detect an OR of 2.0 for sinonasal cancer.

Olsen and Asnaes (1986) reported findings by histological type of cancer. For squamous-cell type sinonasal cancers, the RR among men ever exposed to formaldehyde was 2.3 (95% CI = 0.9 to 5.8, 13 exposed cases) after adjusting for exposure to wood dust. Among those unexposed to wood dust, the RR was 2.0 (95% CI = 0.7 to 5.9, 4 exposed cases). For adenocarcinoma of the sinonasal cavities, the RR among men exposed to formaldehyde vs. unexposed was 2.2 (95% CI = 0.7 to 7.2, 17 exposed cases) after adjusting for wood dust. Among those unexposed to wood dust, the RR was 7.0 (95% CI = 1.1 to 43.9, 1 exposed case). Restricting exposures to those occurring at least 10 years before diagnosis did not markedly change the magnitude of the effect of formaldehyde on either histologic type of sinonasal cancers.

3.5.1.2 The Netherlands: Hayes et al. *(1986)*

Study population. One hundred sixteen (116) male residents of the Netherlands aged 35 to 79 and diagnosed with histologically confirmed primary epithelial sinonasal cancers between 1978 and 1981 were identified from six major cancer treatment centers in 1982 for a case-control study of occupational formaldehyde exposure and other environmental risk factors for sinonasal cancers (Hayes *et al.* 1986). Sixty–seven (67) of the cases (58%) were squamous-cell carcinomas, 28 (24%) adenocarcinomas, and 21 (18%) of other types, mostly undifferentiated. At the start of study implementation, 74 (64%) patients were alive and 42 were deceased. Controls were frequency matched by age and randomly selected from living resident males in 1982 (case to control ratio = 1:2 for living cases, yielding 223 living controls), and from deceased resident males in 1980 (case to control ratio = 1:1 for deceased cases, yielding 36 deceased controls).

Exposure assessment. Interviews were conducted in person or on the phone (10%) to obtain occupational histories for all jobs held at least six months including information such as year(s) of employment, industry and company, and type of work. Interviews were completed for 91 cases and 195 controls. Each reported job was first classified by industry and occupational title. Two industrial hygienists blinded to case status (IH_A and IH_B) then independently classified each occupation and assigned scores of 0 (no exposure) to 9 (highest exposure) based on the level and probability of exposure to formaldehyde. Exposure to wood dust was similarly assessed by one hygienist.

Statistical methods and results. Relative risks were estimated along with 90% confidence intervals, and exposure-response trends were evaluated using the Breslow-Day chi-square test for trend. Of the 286 subjects, 65 (23%) were considered exposed to formaldehyde by IH_A and 125 (44%) by IH_B. Among the 224 subjects considered unlikely to be exposed

to wood dust (scores 0 to 2), 15% and 30% were considered exposed to formaldehyde by IH_A and IH_B, respectively. The age-adjusted RR for nasal cancer associated with any formaldehyde exposure was 2.5 (90% CI = 1.5 to 4.3) for IH_A and 1.9 (90% CI = 1.2 to 3.0) for IH_B. These effect estimates did not change after adjustment for smoking or alcohol use. Restricting this analysis to subjects with low exposure to wood dust (scores 0 to 2), the age-adjusted RRs for nasal cancer and different levels of exposure to formaldehyde were as follows: (1) any exposure, RR = 2.5 (90% CI = 1.2 to 5.0, 15 exposed cases) for IH_A and 1.6 (90% CI = 0.9 to 2.8, 24 exposed cases) for IH_B; (2) low exposure (scores 1 to 2), RR = 2.2 (90% CI = 0.8 to 5.4, 8 exposed cases) for IH_A and 1.0 (90% CI = 0.4 to 2.5, 7 exposed cases) for IH_B; and (3) high exposure (scores 3 to 9), RR = 3.0 (90% CI = 1.0 to 8.7, 7 exposed cases) for IH_A and 2.1 (90% CI = 1.1 to 4.1, 17 exposed cases) for IH_B. Among subjects with low exposure to wood dust, elevated RRs for squamous-cell nasal carcinoma were also observed: (1) any exposure, RR = 3.0 (90% CI = 1.3 to 6.4, 12 exposed cases) for IH_A and 1.9 (90% CI = 1.0 to 3.6, 19 exposed cases) for IH_B; (2) high exposure, RR = 3.1 (90% CI = 0.9 to 10.0, 5 exposed cases) for IH_A and 2.4 (90% CI = 1.1 to 5.1, 13 exposed cases) for IH_B. There were insufficient numbers of cases of adenocarcinomas with low wood dust exposure to permit a separate analysis of formaldehyde exposure, according to the authors.

3.5.1.3 Washington State: Vaughan et al. *(1986a)*

Study population. A population-based case-control study was conducted by Vaughan *et al.* (1986a) to determine whether occupational exposure to formaldehyde in 13 counties in Washington state was associated with sinonasal or pharyngeal cancer (see Sections 3.5.2 and 3.5.3 for results on the different types of pharyngeal cancer). Incident cases were identified through a population-based cancer registry operated as part of the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. Eligible cases were aged 20 to 74 years at enrollment, resided in the study area, and were diagnosed during the period 1979 to 1983 for sinonasal cancer, and 1980 to 1983 for pharyngeal cancer. Controls from the study area were identified using random-digit dialing and frequency-matched to cases by age and sex. Information about medical, smoking, alcohol, residential, and occupational histories was either self-reported or reported by next-of-kin (for deceased cases) in a telephone interview. Two hundred eighty-five cases (285) (69% of eligible cases), including 53 sinonasal, 27 nasopharyngeal, and 205 oro- or hypopharyngeal cases, were included in the analysis; half the case interviews were conducted with next-of-kin. Of 690 eligible controls, 552 (80%) were included in the analysis.

Exposure assessment. Occupational formaldehyde exposure was assessed using a job-exposure linkage system in which each unique job is identified by the 3-digit U.S. Census occupation and industry codes. Estimates of the likelihood and intensity of formaldehyde exposure for each job were combined to create a 4-level summary exposure metric: (1) high = probable exposure to high levels, (2) medium = probable exposure to low levels, (3) low = possible exposure at any level, and (4) background = no occupational exposure. Four estimates of exposure to formaldehyde were then calculated for each subject: lifetime maximum exposure for any job, total lifetime duration of exposure, cumulative exposure, and lagged (15 years) cumulative exposure. Cumulative exposure scores of 0 to

20 were calculated based on the duration of exposure per job and weighted by the 4-level exposure category for each job. Exposure assignments were made blinded to case status.

Statistical methods and results. Unconditional logistic regression was used to produce ORs adjusted for sex, age, smoking, alcohol use, and race. Over 90% of sinonasal cancers occurred among subjects with cumulative exposure scores less than 5 because most cases were classified as being unexposed (0 years lifetime exposure) and having a lifetime maximum exposure intensity level of "background." Effect estimates were based on very small numbers of exposed cases (12 cases exposed at any level, 3 cases exposed for at least 10 years) and showed no increase in risk associated with formaldehyde exposure. Analysis of cumulative exposure, lagged 15 years, resulted in only one case of sinonasal cancer in the highest exposure category and did not produce interpretable estimates. The authors noted some methodological limitations including low statistical power, non-differential exposure misclassification, and bias due to recall error by next-of-kin. This latter limitation was explored by examining data obtained from live cases only; live cases reported a higher mean number of jobs than proxies, and most ORs increased in magnitude when restricted to live cases only.

3.5.1.4 Connecticut: Roush et al. *(1987)*

Study population. From the Connecticut Tumor Registry, Roush *et al.* (1987) identified 198 cases of sinonasal cancer and 173 cases of nasopharyngeal cancer (see Section 3.5.2 for results on nasopharyngeal cancer) among male residents of Connecticut who had died of any cause between 1935 and 1975. Controls (N = 605) were randomly selected without stratification or matching from male residents who died during the same time period.

Exposure assessment. Occupational information including job title, industry, and year(s) of employment was obtained from death certificates and from annual city directories; the latter were examined for the years corresponding to 1, 10, 20, 25, 30, 40 and 50 years before death (as long as the subject was ≥ 20 years old at each assessment). An industrial hygienist blinded to case/control status classified each reported job by probability and level of exposure to formaldehyde, and subsequently categorized each subject into 4 exposure groups: (1) probably exposed to some level for most of working life, (2) probably exposed to some level for most of working life and probably exposed to some level at 20+ years prior to death, (3) probably exposed to some level for most of working life and probably exposed to high level in some year, and (4) probably exposed to some level for most of working life and probably exposed to high level at 20+ years prior to death. This latter exposure category was intended to capture short-term high exposures and account for the latency period necessary for sinonasal cancers to develop.

Statistical methods and results. Logistic regression was applied to estimate ORs and 95% confidence intervals. Approximately 47% of sinonasal cancer cases had occupational information for three or more jobs; 11% of sinonasal cancer cases were categorized into exposure level 1 (N = 21), 8% in level 2 (N = 16), 4.5% in level 3 (N = 9), and 3.5% in level 4 (N = 7). No association between occupational exposure to formaldehyde and sinonasal cancers was observed for levels 1 to 3. The OR for men who were probably exposed to some level for most of their working life and probably exposed to high levels at some point 20 years or more before death (level 4) was 1.5 (95% CI = 0.6 to 3.9, 7

exposed cases). [The ability to detect an effect was limited by the use of death certificates and city directories for occupational information, potentially resulting in non-differential exposure misclassification.]

3.5.1.5 France: Luce et al. *(1993)*

Study population. Luce *et al.* (1993) reported on a case-control study of primary sinonasal cancer in France. Cases of sinonasal cancers (N = 303) diagnosed between January 1986 and February 1988 among male and female residents of France were identified at 27 hospitals; 207 (67%) cases were enrolled in the study. All but one case was histologically confirmed. Two control series were enrolled. A hospital-based control series included patients with cancers other than sinonasal cancers diagnosed during the same time period as cases at the same or nearby hospitals; of 340 eligible hospital controls, 323 (95%) were enrolled and frequency matched by age and sex (case to control ratio = 2:3). A population-based control series was selected from lists of friends and family provided by cases; of 103 eligible convenience controls, 86 (84%) were enrolled and matched to cases by sex, age (within 10 years), and residence.

Exposure assessment. Interviews were conducted by trained physicians to elicit information on socio-demographic characteristics, smoking and alcohol intake, medical history and nasal diseases, and occupational history. An additional questionnaire was administered to assess occupational exposure to a pre-determined list of substances including formaldehyde. Exposure assessment was performed by an industrial hygienist blinded to case/control status and involved classifying each subject according to probability of exposure based on information from the questionnaires. Jobs considered exposed to formaldehyde were further classified by exposure frequency, concentration, and cumulative exposure.

Statistical methods and results. Multivariate logistic regression was used to estimate ORs and 95% confidence intervals and to evaluate confounding by occupational and non-occupational factors. Odds ratios were stratified by histologic subtype (squamous-cell carcinoma and adenocarcinoma) and sex (regression results were reported for 166 men only), and adjusted by age and exposure to wood dust, glues, and adhesives. The two control series were combined for analysis. [Eligible controls included participants with cancers suspected to be associated with formaldehyde exposure, which might have attenuated observed effect estimates.] The authors stated that among cases, 55% of males and 25% of females were exposed to formaldehyde; among controls, 36% of males and 29% of females were exposed. (According to data presented in the Table 2 of the paper, 68% of male cases and 23% of female cases were exposed to formaldehyde.) Among men, no association was found between possible exposure to formaldehyde and squamous-cell carcinoma (OR = 0.96, 95% CI = 0.38 to 2.42, 7 cases). Analyses by different exposure variables were based on 16 squamous-cell carcinoma cases in males with probable or definite exposure and 81 controls. The proportion of subjects with at least one probable or definite exposure was higher among exposed cases than among exposed controls; however, regression results showed no relationship between any formaldehyde exposure index and squamous-cell sinonasal cancers among males. In contrast, ORs for adenocarcinoma-type sinonasal cancer increased with higher levels of average and cumulative exposure, longer duration of exposure and earlier date of first

exposure among men with probable or definite exposure to formaldehyde (N = 69 cases) (see Table 3.4b). Statistically significant risk estimates were observed for the highest exposure category of average exposure (OR = 5.22, 95% CI = 1.28 to 22.20; 43 exposed cases), cumulative exposure (OR = 6.91, 95% CI =1.69 to 28.23, 52 exposed cases) and duration of exposure (OR = 6.86, 95% CI = 1.69 to 27.80, 57 exposed cases). The authors also evaluated combined effects for formaldehyde and wood dust exposure. The ORs for adenocarcinoma-type sinonasal cancers and any exposure to formaldehyde were 8.1 (95% CI = 0.9 to 72.9, 4 exposed cases) among those unexposed to wood dust, 130 (95% CI = 14.2 1,191, 6 exposed cases for wood dust only), and 692 (95% CI = 91.9 to 5,210, 71 exposed cases) among those jointly exposed to wood dust and formaldehyde. [The association between formaldehyde and adenocarcinoma-type sinonasal cancers independent of exposure to wood dust could not be estimated with any precision in this study because the majority of subjects with probable or definite exposure to formaldehyde were also exposed to wood dust (97% of subjects were jointly exposed).] Among subjects with "other" histologies (7 esthesioneuromas, 3 sarcomas, 2 melanomas, 1 lymphoma, and 4 unspecified cases), a positive association was generally observed for subjects with probable or definite exposure to formaldehyde. For the highest index exposure levels of these other histologies, ORs ranged from 1.62 (exposure duration > 20 years) to 3.27 (date of first exposure ≥ 1955); only the latter estimate was statistically significant (95% CI = 1.15 to 9.33, 6 cases). The authors noted that adjustment by smoking and re-analysis taking into account a 15-year induction period did not markedly change the reported effect estimates.

3.5.1.6 Multi-country pooled analysis: Luce et al. *(2002)*

Study population. A pooled analysis (Luce *et al.* 2002) combining 12 case-control studies from seven countries was conducted to further evaluate the relationship between sinonasal cancers and occupational exposure to formaldehyde. The studies were selected on the basis of availability of information on histologic type, age, sex, smoking, and occupational histories. They differed according to the source and vital status of cases and controls as well as the method of interview. This analysis includes some of the studies described in this section, including Luce *et al.* (1993), Hayes *et al.* (1986) and Vaughan *et al.* (1986a). In addition, the following studies were included in the pooled analysis: Zheng *et al.* (1992), Bolm-Audorff *et al.* (1990), Comba *et al.* (1992a, 1992b), Magnani *et al.* (1993), Merler *et al.* (1986), Hardell *et al.* (1982), Brinton *et al.* (1984, 1985), and unpublished data by Mack and Preston-Martin. [These studies were excluded from the present review based on one or more of very small numbers of cases, no estimate of formaldehyde exposure, or sourcing from a non-peer-reviewed publication.] The study population included 195 cases (169 men and 26 women) with sinonasal adenocarcinoma cases, 432 (330 men and 102 women) sinonasal squamous-cell carcinoma and 3,136 controls (2,349 men and 787 women).

Exposure assessment. Exposures were independently assessed for each study by the authors of the pooled analysis using a job-exposure matrix designed specifically for the analysis, and industrial hygiene data were used to determine semi-quantitative exposure indices (only 3 of the 12 studies had originally conducted exposure assessments for formaldehyde).

Statistical methods and results. Logistic regression was applied to estimate ORs adjusted for age, study, and additional occupational factors that were found to be confounders (smoking was not found to be a confounder). Only 11 cases exposed to formaldehyde were estimated to have never been exposed to wood dust. Among men, the ORs for adenocarcinoma sinonasal cancers by cumulative exposure to formaldehyde (adjusted for wood dust exposure) were 0.7 (95% CI = 0.3 to 1.9, 6 pooled exposed cases) for low exposure, 2.4 (95% CI = 1.3 to 4.5, 31 pooled exposed cases) for medium exposure, and 3.0 (95% CI = 1.5 to 5.7, 91 pooled exposed cases) for high exposure. The estimates for squamous-cell sinonasal cancers were 1.2 (95% CI = 0.8 to 1.8, 43 pooled exposed cases), 1.1 (95% CI = 0.8 to 1.6, 40 pooled exposed cases), and 1.2 (95% CI = 0.8 to 1.8, 30 pooled exposed cases), respectively. Effect estimates among women were generally higher. To investigate the potential for residual confounding by wood dust, the authors repeated the analyses for adenocarcinoma including only subjects who had never been exposed to wood or leather dusts; effect estimates were reduced though still elevated (OR for high cumulative exposure = 1.9, 95% CI = 0.5 to 6.7). The authors also evaluated combined effects from exposure to wood dust and formaldehyde for adenocarcinoma. The highest risks were found for those with high exposure to both agents; among individuals with medium or high exposure to wood dust (OR = 7.7, 95% CI = 2.6 to 22.8 for medium exposure to formaldehyde and OR = 17.0, 95% CI = 6.3 to 45.6 for high exposure to formaldehyde).

3.5.1.7 Germany: Pesch et al. *(2008)*

Study population. Pesch *et al.* (2008) conducted a case-control study of woodworkers insured by a specific insurance company in Germany. Cases with a histologically confirmed diagnosis of adenocarcinoma of the nasal cavity or paranasal sinuses were identified from workers diagnosed with a recognized occupational disease between 1994 and 2003, and 86 cases (57 survivors and 29 next of kin) agreed to participate. Frequency-matched controls (204, including 69 next of kin) were also employed in the wood working industry and were chosen randomly from a database of cases with accidents either on the way between the workplace and home or fall accidents during their shift.

Exposure assessment. A semi-quantitative job-exposure matrix was constructed for each subject based on occupational histories, job titles and types of materials used within the woodworking industry, together with previously monitored wood dust exposure measurements conducted within the industry to assess exposure to wood dust. Exposures to wood preservatives, stains, and varnishes, and formaldehyde were categorized by experts as none, low, medium, and high.

Statistical methods and results. Logistic regression conditional on age and adjusted for smoking and other demographic variables was used to calculate odds ratios for low, medium and high levels of average and cumulative exposures, duration of exposure, and time since first exposure to select agents. Inhalable wood dust exposure was associated with a highly significant increase in the risk of adenocarcinoma of the nasal cavity and paranasal sinuses, but formaldehyde exposure (either pre- or post 1985) adjusted for wood dust exposure was not associated with a significant increase in risk (ORs were less than 1.0 and statistically nonsignificant). [The study was limited by the selection of cases

of adenocarcinoma from among workers with occupational diseases and controls from among workers with reported accidents, which might result in selection bias, as well as by the small number of formaldehyde-exposed cases and possible residual confounding due to wood dust exposure.]

3.5.2 Cancer of the nasopharynx

Section 3.5.2 reviewed case-control studies that examined the association between formaldehyde and nasopharyngeal cancer. Three studies were conducted in Asia (West *et al.* 1993, Armstrong *et al.* 2000, Hildesheim *et al.* 2001), one in Europe (Olsen *et al.* 1984, Olsen and Asnaes 1986), and three in the United States (Vaughan *et al.* 1986a, Roush *et al.* 1987, Vaughan *et al.* 2000). Some of these studies were described previously in Section 3.5.1 (Olsen *et al.* 1984, Olsen and Asnaes 1986, Vaughan *et al.* 1986a, Roush *et al.* 1987). A nested case-control study among embalmers was discussed in Section 3.3 (Hauptman *et al.* 2009) and a nested case-cohort study among Chinese textile workers was discussed in Section 3.2 (Li *et al.* 2006).

3.5.2.1 Denmark: Olsen et al. *1984, Olsen and Asnaes 1986*

Olsen *et al.* (1984) also evaluated the association between formaldehyde exposure in the workplace and risk of nasopharyngeal carcinoma (N = 266 cases, 2,465 controls) in a population-based case-control study in Denmark (see Section 3.5.1 for complete study description). Among controls, 4.2% of men and 0.1% of women were considered exposed to formaldehyde (percentage of cases exposed not reported). The RR for nasopharyngeal carcinoma comparing those ever exposed vs. never exposed was 0.7 (95% CI = 0.3 to 1.7, number of exposed cases not reported) among men and 2.6 (95% CI = 0.3 to 21.9) among women. Analysis of nasopharyngeal cancers (N = 293 cases) by histologic subtype did not show any association with either formaldehyde or wood dust (Olsen and Asnaes 1986).

3.5.2.2 Washington state: Vaughan et al. *(1986a)*

The association between nasopharyngeal cancers (N = 27) and occupational formaldehyde exposure was also examined by Vaughan *et al.* (1986a) in the population-based case-control study in Washington state (see Section 3.5.1 for complete study description and results on sinonasal cancers; see Section 3.5.3 for results on oro- and hypopharyngeal cancer). Approximately 60% of nasopharyngeal cancers occurred among subjects classified as unexposed; cumulative exposure scores less than 5 were estimated for over 75% of cases. Adjusting for race and smoking, the ORs for nasopharyngeal cancers for low and medium/high exposure were 1.2 (95% CI = 0.5 to 3.3, 7 exposed cases) and 1.4 (95% CI = 0.4 to 4.7, 4 exposed cases), respectively, compared with subjects with a background level maximum lifetime exposure (unexposed). Compared with subjects with zero years of lifetime exposure, the ORs for 1 to 9 years duration were 1.2 (95% CI = 0.5 to 3.1, 8 exposed cases) and for 10+ years 1.6 (95% CI = 0.4 to 5.8, 3 exposed cases). Cumulative exposure estimates were 0.9 (95% CI = 0.2 to 3.23, 3 exposed cases) for scores 5 to 19 and 2.1 (95% CI = 0.6 to 7.8, 3 exposed cases) for scores 20+ compared with scores less than 5. Cumulative exposure scores were also analyzed excluding job histories within 15 years of the date of diagnosis to account for a

cancer latency period. The OR for the 5 to 19 exposure score group was 1.7 (95% CI = 0.5 to 5.7, 4 exposed cases); the point estimate for the 20+ group did not change.

3.5.2.3 Connecticut: Roush et al. *(1987)*

Occupational exposure to formaldehyde and mortality from nasopharyngeal cancers among men (N = 173) was also investigated by Roush *et al.* (1987) in their population-based case-control study in Connecticut (see Section 3.5.1 for complete study description). The OR for nasopharyngeal cancer mortality among men was 1.0 (95% CI = 0.6 to 1.7, 21 exposed cases) for level 1, 1.3 (95% CI = 0.7 to 2.4, 17 exposed cases) for level 2, 1.4 (95% CI = 0.6 to 3.1, 9 exposed cases) for level 3, and 2.3 (95% CI = 0.9 to 6.0, 7 exposed cases) for level 4 exposure category.

3.5.2.4 The Philippines: West et al. *(1993)*

Study population. West *et al.* (1993) investigated non-viral risk factors, including occupational exposure to formaldehyde for nasopharyngeal cancers in the Philippines. This hospital-based case-control study included 104 incident cases of histologically confirmed nasopharyngeal cancers (100% participation rate, 73% male) recruited from the Philippine General Hospital, and two control series: 104 hospital controls (100% participation rate) matched to cases by sex, age, and hospital ward type (public vs. private), and 101 community controls (77% participation rate) matched to cases by sex, age, and neighborhood.

Exposure assessment. During interviews conducted with a trained nurse, information was collected on socio-demographics, diet, smoking, occupational history, and use of herbal medicines, betel nut, and anti-mosquito coils. Reported occupations were classified by an industrial hygienist blinded to case/control status as likely or unlikely to involve exposure to formaldehyde, solvents, wood dust and other dusts, and pesticides. This classification was then combined with information from the complete occupational history to obtain for each individual four estimates of exposure: (1) overall duration of exposure, (2) duration excluding exposure in the 10 years preceding diagnosis (for cases) or interview (for controls), (3) years since first exposure, and (4) age at first exposure.

Statistical methods and results. Conditional logistic regression was applied to estimate ORs and 95% CIs. The authors reported that results of the occupational analyses were similar for each control series and thus combined controls for analyses. Estimates of association for formaldehyde and nasopharyngeal cancers were reduced toward the null after adjusting for years since first exposure to dusts and/or exhaust fumes. Overall duration of exposure was not clearly associated with nasopharyngeal cancers after adjusting for exposure to dusts and/or exhaust; however, duration of exposure lagged by 10 years yielded an increased risk (RR = 2.1, 95% CI = 0.70 to 6.2, 8 exposed cases) for subjects with at least 15 years exposure. Statistically significant effects were observed for formaldehyde with 25+ years since first exposure (RR = 2.9, 95% CI = 1.1 to 7.6, 14 cases) and among subjects who were < 25 years old at first exposure (RR = 2.7, 95% CI = 1.1 to 6.6, 16 cases), adjusted for years since first exposure to dusts and/or exhaust (unlagged estimates). The RR for subjects jointly exposed to both formaldehyde (25+ years since first exposure) and dust/exhaust (35+ years since first exposure) compared

with subjects with neither exposure was 15.7 (95% CI = 2.7 to 91.2, number of exposed subjects not reported). In further models, a statistically significantly increased risk of nasopharyngeal cancers was also observed with increasing years since first exposure to formaldehyde after adjusting for other confounding factors including education, exposure to dust and exhaust, diet, smoking, and use of herbal medicines and anti-mosquito coils. Compared with subjects never exposed to formaldehyde, the RRs were 1.2 (95% CI = 0.41 to 3.6, 12 exposed cases) for subjects first exposed less than 25 years before diagnosis or interview, and 4.0 (95% CI = 1.3 to 12.3, 14 exposed cases) for subjects first exposed 25 years or more ago.

3.5.2.5 Malaysia: Armstrong et al. *(2000)*

Study population. Histologically confirmed cases of nasopharyngeal cancers (all squamous-cell carcinomas) diagnosed or treated in Kuala Lumpur and Selangor from January 1987 to June 1992 were assembled for a case-control study of nasopharyngeal cancers and work-site inhalation of dust and smoke particles, formaldehyde, and certain aromatic hydrocarbons among Malaysian Chinese (Armstrong *et al.* 2000). Of 530 eligible cases who had lived in the study area for at least 5 years, 282 (53%) were enrolled (31% female). Each case was matched by sex and age (within 3 years) to one control with no history of head, neck, or respiratory system cancer; controls were selected from the general population using a house-to-house multistage area sampling.

Exposure assessment. Data on residential history, occupational history, diet, and tobacco and alcohol use were collected by trained interviewers during two in-home structured interviews. Occupational history included information about job description, tasks, workplace characteristics, use of industrial equipment and substances, and exposure to dusts, smoke, gases, and chemicals at each job. Additional information about exposures to industrial heat and 20 inhalants known to be deposited or absorbed in the nasopharynx were collected by trade or profession, calendar time, frequency and duration. Jobs were classified according to official Malaysian occupational codes, and exposure for each occupational code was assigned by a study investigator blinded to case/control status and familiar with Malaysian industry. Industries considered exposed to formaldehyde included adhesives, foundries, latex processing, metalworking and welding, plywood manufacturing, rubber tire manufacturing, sawmilling, shoe-making (glues), and textiles (permanent press fabrics). Four categories of exposure to inhalants (never, low, medium, high) were created based on job type, task, mode of exposure (inhalation and/or dermal), interview data on exposure, years of exposure, frequency, and duration. To account for latency, cumulative exposure was evaluated using 5 lag time periods: > 1, 5, 10, 15, and 20 years prior to diagnosis. Exposure intensity was also assessed by categorizing participants according to cumulative years exposed. The authors presented air monitoring data for formaldehyde levels within 10 industries (42 worksites) reported by participants in this study. Samples were taken in 1991 to 1992 and showed that formaldehyde levels exceeded the recommended limit (0.37 mg/m^3) in the adhesives industry only, and the range of levels for all other industries sampled was wide (mean 8-hour concentration = 0.16 to 0.35 mg/m^3 [0.13 to 0.28 ppm]).

Statistical methods and results. For analysis, Armstrong *et al.* examined exposure dichotomously (ever/never) as well as by cumulative duration using conditional logistic

regression. Approximately 10% of cases were considered exposed to formaldehyde compared with 8.2% of controls. The unadjusted OR for ever/never formaldehyde exposure and nasopharyngeal cancers was 1.24 (95% CI = 0.67 to 2.32, cases not specified); the diet- and smoking-adjusted estimate was 0.71 (95% CI = 0.34 to 1.43). The authors assessed dose-response in relation to a 10-fold increase in ratio of hours exposed; no dose-response trend was observed with increasing duration of formaldehyde exposure. No differences in effect estimates were observed in analyses by lag time or intensity. The participation rate among diagnosed cases was low (53%); according to the authors, the possibility of prevalence-incidence or other forms of selection bias could not be excluded. [In addition, although some inhalants (wood dust, for example) were found to be significantly associated with nasopharyngeal cancers in these data, these factors were not evaluated as potential confounders when evaluating the relationship between formaldehyde and the outcome.]

3.5.2.6 United States – SEER: Vaughan et al. *(2000)*

Study population. To further investigate whether occupational exposures to formaldehyde and wood dust increase the risk of nasopharyngeal cancers, Vaughan *et al.* (2000) conducted a population-based (cancer registry) case-control study that identified 294 nasopharyngeal cancer cases (diagnosed between April 1987 and June 1993 among persons 18 to 74 years of age) from five cancer registries (Connecticut, Detroit, Iowa, Utah, and Washington) in the National Cancer Institute's SEER program. This study focused on a subset of 196 interviewed cases (68% male) diagnosed with epithelial carcinoma including epithelial not-otherwise-specified (N = 24), undifferentiated or non-keratinizing (N = 54), and differentiated squamous-cell types (N = 118). Controls were identified from the same geographic locations using random-digit dialing, and were frequency matched to cases by age (within 5 years), sex, and cancer registry. Of 2,885 households contacted, 244 of 324 eligible controls were successfully enrolled and interviewed.

Exposure assessment. Structured telephone interviews were conducted with study participants or proxies (44 case and 3 control interviews by proxy) collecting information on demographics, personal and family medical history, tobacco and alcohol use, and lifetime history of occupational and chemical exposure; information since diagnosis for cases or since ascertainment for controls was excluded. Information collected about occupational history for any job held at least 6 months included job title, tasks, industry type, calendar dates, and exposure to specific chemicals or other agents including wood dust and formaldehyde. Participants were also asked specifically about any jobs held in particular industries including furniture manufacturing, construction, foundry, and smelting. Industrial hygienists blinded to case/control status used these data combined with estimates from both published and unpublished literature to assess exposure to formaldehyde for each unique reported job. Each job was assigned a probability of formaldehyde exposure based on the percentage of workers with a similar job profile expected to be exposed: definitely not or unlikely (< 10%), possible (10% to < 50%), probable (50% to < 90%), and definite (≥ 90%). Using information about frequency (days/year) and duration (hours/day), jobs with potential exposure were further classified by the estimated concentration of exposure representing an 8-hour time-weighted average

(8-h TWA): low (< 0.10 ppm), moderate (0.10 to < 0.50 ppm), and high (≥ 0.50 ppm). Twenty-four (24) reported jobs (of 2,209 unique reported jobs) were considered to entail exposure to formaldehyde; 19 were classified as definitely exposed (16 low-level and 3 moderate), 3 as probable (all low-level), and 2 as possible (1 low-level and 1 moderate). Exposure to wood dust was assessed by identifying jobs in occupational or industry codes considered exposed, and by using interview data of subjects self-reported as exposed to wood dust; jobs were assigned total wood dust 8-h TWA estimates. Using results from the exposure assessment, exposure to formaldehyde and wood dust were coded using the following variables: ever exposed, maximum concentration exposed, duration exposed, and cumulative exposure. Duration and cumulative exposure were further evaluated with a 10-year lag.

Statistical methods and results. Multivariate logistic regression was used to estimate the association between nasopharyngeal cancers and exposure to formaldehyde and wood dust. Confounding and effect measure modification by age, sex, race, SEER site, smoking, alcohol intake, education, and proxy status were evaluated. Forty-three percent (43%) of cases were potentially exposed to formaldehyde, compared with 32% of controls. The adjusted (age, sex, race, SEER site, smoking, education, and proxy status) OR for nasopharyngeal cancers comparing ever occupationally exposed with unexposed by histological subtype was 1.3 (95% CI = 0.8 to 2.1, 79 exposed cases) for all epithelial, 0.9 (95% CI = 0.4 to 2.0, 18 exposed cases) for undifferentiated or non-keratinizing, 1.5 (95% CI = 0.8 to 2.7, 49 exposed cases) for differentiated squamous-cell, and 3.1 (95% CI = 1.0 to 9.6, 12 exposed cases) for epithelial not otherwise specified (NOS). No consistent pattern of association or trend in risk was observed with maximum lifetime exposure concentration. For lifetime duration of exposure and risk of nasopharyngeal cancers, there was some evidence of an increased risk of nasopharyngeal cancers with increasing lifetime duration of exposure among all subjects with any possibility of exposure (P_{trend} = 0.014, 79 exposed cases); the OR for subjects who had worked at least 18 years in potentially exposed jobs was 2.7 (95% CI = 1.2 to 6.0, 25 exposed cases). A trend was observed with increasing years of exposure (P_{trend} = 0.070); the adjusted OR for subjects who had worked at least 18 years in potentially exposed jobs was 2.1 (95% CI = 1.0 to 4.5, 29 exposed cases). This trend was stronger for differentiated squamous-cell (P_{trend} = 0.033) and epithelial NOS (P_{trend} = 0.036) histologies than undifferentiated or non-keratinizing types (P_{trend} = 0.820). The adjusted ORs for 61 cases of nasopharyngeal cancers (excluding undifferentiated or non-keratinizing type) for estimated probability of formaldehyde exposure were 1.6 (95% CI = 1.0 to 2.8, 61 exposed cases) for ever having a job classified as possibly, probably, or definitely exposed, 2.1 (95% CI = 1.1 to 4.2, 27 exposed cases) for probably or definitely exposed, and 13.3 (95% CI = 2.5 to 70.0, 10 exposed cases) for definitely exposed. Again, among the group of cases excluding undifferentiated and non-keratinizing types, there was evidence of an increased risk of nasopharyngeal cancers with increasing lifetime duration of exposure among all subjects with any potential exposure (P_{trend} = 0.014); the OR for subjects who had worked at least 18 years in any potentially exposed jobs was 2.7 (95% CI = 1.2 to 6.0, 25 exposed cases). The risk of nasopharyngeal cancers also increased with increasing cumulative exposure (P_{trend} = 0.033) among all potentially exposed subjects. The OR for subjects in the highest category of cumulative exposure (> 1.10 ppm-years) was 3.0 (95% CI = 1.3 to 6.6, 24 exposed cases). The authors reported that

estimates were similar when exposures were lagged by 10 years, and that adjustment by exposure to wood dust did not affect results for exposure to formaldehyde. However, some evidence of effect measure modification by smoking was observed; measures of association as well as estimates of trend were generally stronger among current and former smokers than non-smokers. [A strength of this study is its large sample size, which improved the precision of the effect estimates and allowed for adjustment of the effect estimates by a number of potentially confounding factors, after which a positive association between formaldehyde exposure and nasopharyngeal cancers still remained.]

3.5.2.7 Taiwan: Hildesheim et al. *(2001)*

Study population. Hildesheim *et al.* (2001) conducted a population-based case-control study of nasopharyngeal cancers and occupational exposure to wood dusts, formaldehyde, and solvents in Taipei, Taiwan. Incident cases of histologically confirmed nasopharyngeal cancers diagnosed between July 1991 and December 1994 were identified from two tertiary care hospitals in Taipei; eligible cases (N = 378) were residents of Taipei city or county for at least six months, and were less than 75 years of age. Ninety-nine percent (99%) of eligible cases (N = 375, 69% male) agreed to participate. Over 90% of cases were diagnosed with non-keratinizing or undifferentiated carcinomas and the remainder with squamous-cell carcinomas. Controls were identified using a National Household Registration System and were individually matched to cases (case to control ratio = 1:1) on age (within 5 years), sex, and area of residence. Eligible controls (N = 376) lived in Taipei city or county for at least six months and had no history of nasopharyngeal cancer; 87% (N = 327) agreed to participate.

Exposure assessment. Interviews administered to each participant by a trained nurse collected information about occupational, medical, and residential histories, demographics, diet, and smoking and alcohol use. Occupational histories were collected for all jobs held for at least one year and included information on job title, industry, duties/activities, and tools/materials used on the job. Exposure assessment was conducted by an industrial hygienist blinded to case/control status; jobs were first classified into Standard Industry Classification/Standard Occupational Classification codes, and then each code was evaluated for probability and intensity of exposure to formaldehyde, wood dusts, and solvents and assigned a score of 0 (unexposed) to 9; < 4 was considered low, and ≥ 4 high. For each subject, this score plus information about duration were combined to produce six estimates of exposure: (1) years of exposure, (2) average intensity, (3) average probability, (4) cumulative exposure, (5) age at first exposure, and (6) years since first exposure. Duration of exposure was also calculated excluding exposures occurring within 10 years of diagnosis (for cases) or interview (for controls). Occupational data were available for 100% of cases and over 99% of controls. Of the 2,034 jobs reported by all 700 subjects, 156 (7.7%) were classified as exposed to formaldehyde; 74 cases and 41 controls were considered "ever" exposed. Some of the reported occupations considered exposed to formaldehyde included farmers (N = 68), barbers, hairdressers, and cosmetologists (N = 15), carpenters (N = 14), and health professionals (N = 13).

Statistical methods and results. Unconditional logistic regression was used to estimate ORs (reported as risk ratios) for the association between formaldehyde exposure and nasopharyngeal cancers. Exposure-response trends were assessed by entering exposure

into the model as a continuous variable and testing the resulting ß-coefficient. Stratification was used to examine effects by age, sex, Epstein-Barr virus (EBV) seroprevalence (established as a risk factor for the development of nasopharyngeal cancers), and histologic subtype. After adjustment by age, sex, education, and ethnicity, the OR for subjects ever exposed to formaldehyde vs. never exposed was 1.4 (95% CI = 0.93 to 2.2, 74 exposed cases). Risk increased with increasing duration of exposure (P_{trend} = 0.08 among all subjects and P_{trend} = 0.09 among subjects not exposed to wood dust). The observed trend was lower when a 10-year exposure lag was applied. Risks also increased with increasing cumulative exposure (P_{trend} = 0.10 among all subjects). Increased risks were observed among subjects with high average intensity or high probability of exposure compared with low exposure intensity or probability. No clear pattern of risk was observed in analyses by age at first exposure or years since first exposure. The authors noted that estimates were unaffected by adjustment for wood dust or solvent exposure. The OR estimating the joint effect of formaldehyde and wood dust was 1.8 (95% CI not reported). Among subjects who were seropositive for EBV, the adjusted OR for ever exposure to formaldehyde exposure was higher than among nonseropositive individuals (RR = 2.7, 95% CI = 1.2 to 5.9, number of exposed cases not specified, but 360 of the total of 375 nasopharyngeal cancer cases were EBV positive). Results of stratified analysis suggested that the effect of formaldehyde exposure was the same across age ranges and histologic subtype (excluding squamous-cell type because sample size was too small for meaningful analysis).

3.5.3 Other head and neck cancers

Section 3.5.3 reviews case-control studies that examined the association between formaldehyde and head and neck cancer at sites including the oro- and/or hypopharynx (OHPC) (Vaughan *et al.* 1986a, Laforest *et al.* 2000, Berrino *et al.* 2003), the whole pharynx combined and oral cavity (Gustavsson *et al.*1998), oral cavity and oropharynx combined (Merletti *et al.* 1991), salivary glands (Wilson *et al.* 2004), and larynx (Wortley *et al.* 1992, Gustavsson *et al.* 1998, Laforest *et al.* 2000, Berrino *et al.* 2003, Elci *et al.* 2003, Shangina *et al.* 2006, Elci and Akpinar-Elci 2009). Pharyngeal carcinomas can include nasopharyngeal (see Section 3.5.2), oropharyngeal, and hypopharyngeal carcinomas. Six studies were conducted in Europe (Merletti *et al.* 1991, Gustavsson *et al.* 1998, Laforest *et al.* 2000, Berrino *et al.* 2003, Elci *et al.* 2003, Shangina *et al.* 2006, Elci and Akpinar-Elci 2009) and three in the United States (Vaughan *et al.* 1986a, Wortley *et al.* 1992, Wilson *et al.* 2004). Most studies evaluated more than one type of cancer. Details on the study methodology for one study was described in Section 3.5.1 (Vaughan *et al.* 1986a). A nested case-cohort study of upper respiratory cancer among formaldehyde-exposed workers at sawmills and manufacturers of particleboard, plywood, furniture, or glue was discussed in Section 3.2 (Partanen *et al.* 1990), and a cancer registry study of the oral cavity, tongue, and pharynx was discussed in Section 3.4 (Tarvainen *et al.* 2008). In this section, studies are organized by tumor site.

3.5.3.1 Various head and neck cancers: Sweden, Gustavsson et al. *(1998)*

Study population. Occupational risk factors for squamous-cell carcinoma of the upper gastrointestinal tract among men 40 to 70 years of age were investigated in an incident case-control study in Sweden (Gustavsson *et al.* 1998). From weekly health-care facility

reports and regional cancer registries, 605 cases of head and neck squamous-cell carcinoma were identified between 1988 and 1991. Ninety percent (90%) of cases (N = 545) were enrolled: 138 with pharyngeal cancer, 128 with oral cancer, 122 with esophageal cancer, and 157 with laryngeal cancer. Controls (N = 756) were selected from the same study base by stratified random sampling from population registries; 641 (85%) eligible controls were enrolled and frequency matched to cases by region and age.

Exposure assessment. Subjects were interviewed by one of two trained nurses about lifestyle and environmental factors including oral hygiene, smoking, alcohol and snuff use, and occupational history. Questions about occupational history covered all jobs ever held for more than one year and included information about title, task, duration, industry, and potential exposures. An industrial hygienist blinded to case/control status coded each job according to the Swedish standard occupational classifications and then further classified each occupation by probability and intensity of exposure to 17 specific agents including formaldehyde (9.4% of controls were exposed to formaldehyde). For formaldehyde, three primary measures of exposure were estimated: ever/never exposed, duration of exposure, and cumulative exposure.

Statistical methods and results. Unconditional logistic regression was used to estimate ORs and 95% CIs. Formaldehyde effect estimates were adjusted for region, age, alcohol, and smoking. Elevated estimates were observed for most cancer sites, though no estimates achieved statistical significance. For cancers in all sites combined, the adjusted OR comparing subjects ever exposed to formaldehyde with those unexposed was 1.42 (95% CI = 0.94 to 2.15, 69 exposed cases). Adjusted odds ratios for individual sites were as follows: 1.01 (95% CI = 0.49 to 2.07, 13 exposed cases) for pharyngeal cancer, 1.45 (95% CI = 0.83 to 2.51, 23 exposed cases) for laryngeal cancer, 1.90 (95% CI = 0.99 to 3.63, 19 exposed cases) for esophageal cancer, and 1.28 (95% CI = 0.64 to 2.54, 14 exposed cases) for cancers of the oral cavity. The authors reported that no dose-response trend based on cumulative exposure or duration exposed was observed for any cancer site (data not presented). [It is not clear whether other occupational exposures were considered as confounders; reported effect estimates were not adjusted for other known occupational exposures.]

3.5.3.2 Salivary glands: United States, Wilson et al. *(2004)*

Study population. Wilson *et al.* (2004) reported on a case-control investigation of occupational risk factors for salivary gland cancer mortality using mortality records collected between 1984 and 1989 in 24 U.S. states. In this analysis, 2,505 cases aged 20 years or older whose death certificate listed cancer of the salivary gland as the underlying cause of death (60% men, 7% black) were included. Controls (N = 9,420) were randomly selected from all deaths unrelated to infectious disease and frequency matched by age (within 5 years), race, sex, and region (case to control ratio = 1:4).

Exposure assessment. Usual occupation and industry was obtained from death certificates for 95% of white and 87% of black men, and for 45% of white and 31% of black women. Jobs were coded according to the 1980 U.S. Census occupational classification scheme and entered into a job-exposure matrix developed by the study industrial hygienist to estimate the probability and intensity of exposure to several occupational substances

including formaldehyde. Subjects whose occupation was recorded as homemaker or retired were excluded from the job-exposure matrix.

Statistical methods and results. Multiple logistic regression was used to calculate ORs adjusted for age, marital status, and socioeconomic status based on occupation. A statistically significant exposure-response trend was observed for formaldehyde exposure probability combined with intensity among white men ($P < 0.001$) but not women. Compared with unexposed subjects, the adjusted OR for white men with a mid-high probability/low intensity of exposure was 2.4 (95% CI = 0.86 to 6.75, 6 exposed cases), and 1.6 (1.30 to 2.00, 31 exposed cases) for mid-high probability/mid-high intensity. No statistically significant ORs were observed for formaldehyde exposure and salivary gland cancer among black subjects, though elevated ORs were observed among black women.

3.5.3.3 Oral cavity and oropharynx: Italy, Merletti et al. *(1991)*

Study population. All incident cases of oral (N = 74) and oropharyngeal carcinoma (N = 12) diagnosed from July 1982 to December 1984 among male residents of Turin, Italy were assembled for a population-based case-control study to investigate whether occupational factors have an etiologic role in these cancers (Merletti *et al.* 1991). Of 103 eligible cases, 86 (83%) agreed to participate. Of 689 eligible controls selected from a stratified random sample of male Turin residents by age, 373 (55%) were enrolled.

Exposure assessment. Detailed occupational histories as well as history of smoking, alcohol intake, and diet were obtained from standardized questionnaires conducted by non-blinded, trained interviewers. For each job held since 1945 for at least six months, subjects reported job title, activity of the plant, and type of production. The 1,150 reported jobs were classified by two industrial hygienists blinded to case status into 771 unique categories based on the International Standard Classification of Occupations of the International Labor Office and the International Standard Industrial Classification. A job-exposure matrix constructed by IARC for a study of laryngeal cancer was applied to estimate the probability and intensity of exposure to 16 occupational substances including formaldehyde and non-specific exposures (e.g., dust).

Results. Odds ratios for oral and oropharyngeal carcinoma combined were estimated using unconditional logistic regression adjusting for age, education, birthplace, smoking, and alcohol consumption. Compared with subjects whose occupational exposure to formaldehyde did not exceed that of the general population, the adjusted OR for subjects with any excess exposure was 1.6 (95% CI = 0.9 to 2.8, 25 exposed cases) and the OR for subjects with probable or definite exposure was 1.8 (95% CI = 0.6 to 5.5, 6 exposed cases). The authors reported that inconsistent relationships were observed for duration of exposure to formaldehyde, though effect estimates ranged from 1.4 to 2.1 (95% CIs not reported). Separate results for oropharyngeal cancer (N = 12 cases) were not presented.

3.5.3.4 Oro- and hypopharynx: Washington State, Vaughan et al. *(1986a)*

The association between oro- and hypopharyngeal cancer (OHPC) (N = 205) and occupational formaldehyde exposure was also examined by Vaughan *et al.* (1986a) in the population-based case-control study (552 controls) in Washington state (see Section 3.5.1

for complete study description and results on sinonasal cancers; see Section 3.5.2 for results on nasopharyngeal cancers). Approximately 72% of OHPC cases occurred among subjects classified as unexposed. Odds ratios adjusted for age, sex, smoking, and alcohol showed no association between maximum lifetime exposure to formaldehyde and OHPC. Effect estimates for total number of years exposed and cumulative exposure scores showed a modestly increased risk only for the longest exposure period or highest cumulative exposure categories: OR = 1.3 (95% CI = 0.7 to 2.5, 26 exposed cases) for ≥ 10 years exposure, and OR = 1.5 (95% CI = 0.7 to 3.0, 21 exposed cases) for a cumulative exposure score of ≥ 20. These estimates were higher when the analysis excluded occupational data obtained from proxy interviews.

3.5.3.5 Hypopharynx and larynx: France, Laforest et al. *(2000)*

Study population. A hospital-based case-control study was conducted in France to assess possible associations between occupational exposures including formaldehyde and histologically confirmed squamous-cell carcinomas of the hypopharynx and larynx among men (Laforest *et al.* 2000). Cases were diagnosed at one of 15 French hospitals between January 1989 and April 1991. Of 664 eligible living cases, 201 cases of hypopharyngeal cancer and 296 cases of laryngeal cancer were included. Controls were identified from the same medical catchment area as cases and were frequency matched to cases by age and hospital. Controls were diagnosed between 1987 and 1991 with primary cancers at other sites including colon/rectum, liver/gall bladder, pancreas, hematopoietic system, bones/cartilage, skin, soft tissue, prostate/testis, bladder/urinary organs, brain/nervous system, thyroid, and stomach. Of 355 eligible living controls, 296 (83%) were enrolled.

Exposure assessment. Trained occupational physicians, who were not blinded to case status, conducted interviews with subjects to collect information about demographic characteristics, smoking and alcohol consumption, and lifetime occupational history. Jobs were first coded by occupation and industry, and then occupational exposure to formaldehyde and other agents and were evaluated using a job-exposure matrix. The matrix estimated the probability and intensity of exposure for each job as well as lifetime duration for each subject; subjects with an estimated probability of exposure to formaldehyde less than 1% were considered unexposed. Three summary exposure indices were constructed: maximum probability of exposure (3 levels), total duration of exposure, and cumulative level of exposure (< 0.25 ppm, 0.25 to 1.00 ppm, > 1.00 ppm).

Statistical methods and results. Multivariate unconditional logistic regression was used to estimate ORs and 95% CIs adjusting for age, alcohol, and smoking. Other occupational exposures as well as education were considered as potential confounders. Subjects who were missing data on alcohol use or reported being non-drinkers (N = 33) were excluded from analysis. Further analyses were conducted excluding subjects with probability of exposure less than 10%, and excluding the 5, 10, and 15 years of exposure immediately preceding diagnosis to allow for a possible induction period. The adjusted (age, alcohol, smoking, and exposure to coal dust and asbestos) OR for hypopharyngeal cancers for men ever exposed to formaldehyde was 1.35 (95% CI = 0.86 to 2.14, 83 exposed cases). This estimate was 1.74 (95% CI = 0.91 to 3.34, 41 exposed cases) after excluding subjects with less than 10% probability of exposure. The OR comparing subjects with the

highest probability of exposure (> 50% probability) to those unexposed was 3.78 (95% CI = 1.50 to 9.49, 26 exposed cases); increasing probability of exposure was significantly associated with increasing risk of hypopharyngeal cancers ($P_{trend} < 0.005$). Excluding subjects with probability of exposure less than 10%, the OR for subjects with the highest duration of exposure (> 20 years) was 2.70 (95% CI = 1.08 to 6.73, 16 exposed subjects). The corresponding OR for subjects with the highest cumulative level of exposure was 1.92 (95% CI = 0.86 to 4.32, 25 exposed subjects). Evidence of a trend of increasing ORs for hypopharyngeal cancers with increasing duration ($P_{trend} < 0.04$) and cumulative level of exposure ($P_{trend} < 0.14$) to formaldehyde was observed.

Compared with unexposed subjects, the OR for laryngeal cancer among men ever exposed to formaldehyde was 1.14 (95% CI = 0.76 to 1.70, 102 exposed cases) after adjustment for age, alcohol, smoking, and exposure to coal dust and asbestos. This estimate did not change markedly after excluding subjects with probability of exposure less than 10%. The authors noted that no indication of an exposure-response trend was observed for any exposure index (data not presented). Among heavy drinkers (at least 5 glasses per day), the OR for laryngeal cancer associated with ever being exposed to formaldehyde was 1.68 (95% CI = 0.97 to 2.89, number of cases not specified). (No OR was reported for the association between alcohol consumption and laryngeal cancer independent of formaldehyde exposure.) Elevated but statistically nonsignificant associations were observed when cases were further stratified into laryngeal sub-sites. The authors noted that introducing an induction time did not substantially change the results for either hypopharyngeal cancer or laryngeal cancer (data not presented). [Controls included subjects with primary cancers at sites that have suspected associations with formaldehyde exposure (e.g., lymphohematopoietic malignancies). Such inclusion could have biased the observed effect estimates toward the null.]

3.5.3.6 Hypopharynx and larynx: Europe, Berrino et al. *(2003)*

Study population. Berrino *et al.* (2003) used occupational data obtained from a previously conducted case-control study by IARC of hypopharyngeal cancer and laryngeal carcinoma to investigate the association between occupational exposure to formaldehyde and cancer at these two sites. Cases of non-*in situ* cancer of the hypopharynx (N = 100) and larynx (N = 213) were identified between 1979 and 1982 at six centers in four southern European countries (France, Italy, Spain, and Switzerland). An age-stratified random sample of controls (N = 819) was selected by each center.

Exposure assessment. Occupational histories and information on diet, alcohol, and smoking were collected by interview in the hospital for cases and at home for controls. Some interviews were conducted with next of kin (details not provided). The occupational history questionnaire covered each job held at least one year after 1944 and collected information about title, task, industry, calendar time of employment, and potential exposure. A panel of occupational physicians, industrial hygienists, and chemical engineers blinded to case status assessed the probability of exposure for each job to 16 industrial chemicals including formaldehyde. A job-exposure matrix was then created to estimate intensity and probability of exposure for each job as well as a cumulative exposure index for each subject. Independent validations of the exposure

classification used in this analysis found that 14% of jobs classified by the job-exposure matrix as unexposed were considered to be definitely exposed, however.

Statistical methods and results. Odds ratios and 95% confidence intervals were estimated using unconditional logistic regression and adjusted for study center, age, smoking, alcohol, socioeconomic status, diet, and other occupational exposures. Results for formaldehyde were presented from analyses restricted to subjects less than 55 years of age in order to better estimate lifetime exposures, since occupational histories were only collected since 1945 (123 exposed cases and 196 exposed controls for hypopharyngeal and laryngeal carcinomas combined). No association between the probability of exposure to formaldehyde and hypopharyngeal/laryngeal cancer or in cancers originating from the endolarynx or hypopharynx was observed. Individuals with 10 to 19 years of exposure had an increased risk of hypopharyngeal/laryngeal cancer (OR for 10 to 19 years = 2.2, 95% CI = 1.2 to 4.2, number of exposed cases not reported), though a clear exposure-response trend was not evident.

3.5.3.7 Larynx: Washington state, Wortley et al. *(1992)*

Study population. Incident cases of laryngeal cancer identified by a population-based cancer registry in Seattle, Washington and diagnosed between September 1983 and February 1987 among residents of three large counties in western Washington state aged 20 to 70 years were included in a population-based case-control study of occupational risk factors for laryngeal cancer (Wortley *et al.* 1992). Of 291 eligible cases, 235 (81%) participated in the study (79% males). Controls were identified by random-digit dialing and frequency matched to cases by age and sex; the participation rate among eligible controls was 8%, yielding 547 controls (65% males).

Exposure assessment. In-person interviews were conducted (7% of case interviews with next-of-kin) to obtain information about lifetime occupational history, smoking, and alcohol intake. Occupational questions related to job titles, tasks, and industry for each job held at least six months; job title and industry were then coded according to the 1980 U.S. Census occupational codes. Exposure to six agents including formaldehyde was assessed in greater detail by a panel of four industrial hygienists who constructed a job-exposure matrix for each agent; jobs were then classified into four levels of exposure based on probability and intensity of exposure.

Statistical methods and results. Multivariate logistic regression was applied and a latency effect was considered by excluding all exposures within 10 years of case diagnosis or control selection. Fifty-eight cases (25%) and 124 controls (23%) were considered ever exposed to formaldehyde. No statistically significant effect estimates were observed between laryngeal cancer and exposure to formaldehyde estimated by peak exposure or duration of exposure, adjusted for age, smoking, alcohol, and education. When low-level exposures were excluded, the OR among workers with medium or high exposure for at least 10 years duration compared with unexposed workers was 4.2 (95% CI = 0.9 to 19.4, number of. exposed cases not reported); the corresponding OR among workers with high exposure was 4.3 (95% CI = 1.0 to 18.7). The authors noted that these estimates increased slightly when the 10-year exposure lag was applied to account for a latency period (data not presented).

3.5.3.8 Larynx: Turkey, Elci et al. *(2003) and Elci and Akpinar-Elci (2009)*

Study population. A hospital-based incident case-control study was conducted to investigate occupational risk factors for laryngeal cancer among men in Turkey (andElci *et al.* 2003, Elci and Akpinar-Elci 2009). The original case group included 951 confirmed cases of laryngeal cancer among men presenting at an oncology treatment center at a hospital in Istanbul between 1979 and 1984. Controls (N = 1,519) were selected from hospital patients with other cancers thought not to share similar etiologic factors with laryngeal cancer (including Hodgkin's lymphoma, soft tissue sarcoma, and testicular cancer) and non-cancer diagnoses. [The use of subjects with other cancers might bias the findings towards the null if formaldehyde exposure is a risk factor for those cancers.]

Exposure assessment. Upon admission to the hospital, all patients responded to a questionnaire about occupational history, and tobacco and alcohol use; questionnaire data was complete for 99% of cases and all controls. A job-exposure matrix was constructed by an industrial hygienist blinded to case/control status and used to estimate for each reported occupation and industry the probability and intensity of exposure to five occupational substances, including formaldehyde.

Statistical methods and results. In the 2003 study, unconditional logistic regression was applied to estimate ORs adjusted by age, smoking, and alcohol use. The OR for laryngeal cancer among men considered ever exposed to formaldehyde was 1.0 (95% CI = 0.8 to 1.3, 89 exposed cases). No association by either intensity or probability of exposure to formaldehyde and laryngeal cancer was observed: ORs were 1.1 (95% CI = 0.8 to 1.5, 82 exposed cases) for low-intensity of exposure, 0.5 (95% CI = 0.2 to 1.3, 6 exposed cases) for medium intensity, and 0.7 (95% CI = 0.1 to 7.1, 1 exposed case) for high intensity, and from 1.0 (95% CI = 0.7 to 1.4, 72 exposed cases), 1.1 (95% CI = 0.6 to 2.2, 16 exposed cases) to 1.0 (95% CI = 0.1 to 11.2, 1 exposed case) for low, medium and high probability of exposure, respectively.

A subsequent analysis of never-smoking and never-drinking cases (N =189) and controls (N= 536) from the population described by Elci *et al.* (2003) was conducted (Elci and Akpinar-Elci 2009). A statistically nonsignificant increase in laryngeal cancer was observed among formaldehyde-exposed cases (OR = 1.2, 95% CI = 0.7 to 2.0; 27 exposed cases), consisting primarily of an increase in the risk of glottal cancers (OR = 1.6, 95% CI = 0.7 to 3.7, 6 exposed cases).

3.5.3.9 Larynx: Shangina et al. *(2006)*

Study population. A multi-center case-control study of laryngeal and hypopharyngeal cancers was conducted using all incident cases diagnosed between 1999 and 2002 among men and women 15 to 79 years of age and identified in study centers in four central and Eastern European countries. Hospital-based controls, recruited within 6 months of the recruitment period for cases, were frequency matched to cases by age and excluded diagnoses of cancer or diseases associated with tobacco or alcohol. Thirty-four men with hypopharyngeal cancer and 316 men with laryngeal cancer and 728 male controls were included in the analysis (there were insufficient cases among women to warrant analysis).

Exposure assessment. Occupational histories and demographic and lifestyle data were obtained by personal interview. Job-exposure matrices were constructed for selected occupations or industries by industrial hygienists. Exposures were classified by intensity, frequency, and probability.

Statistical methods and results. Unconditional logistic regression analysis was used to analyze associations with 73 occupational agents (ever vs. never exposed, duration and cumulative exposure). Linear trends were calculated by fitting categorical variables as continuous variables in the models. Risk estimates were adjusted for age, smoking, and lifetime alcohol consumption. Exposure to formaldehyde was associated with a statistically nonsignificant increase in laryngeal cancer (OR = 1.68, 95% CI = 0.85 to 3.31, 18 cases); the OR increased with duration of exposure ($P = 0.06$) and cumulative exposure ($P = 0.07$). The OR for the highest level of cumulative exposure (> 22,700 mg/m^3-hours) was 3.12 (95% CI = 1.23 to 7.91, number of cases not reported). There were less than ten cases of hypopharyngeal cancer associated with formaldehyde exposure and no risk estimates were presented.

3.5.4 Lung cancer

Section 3.5.4 reviews case-control studies that examined the association between formaldehyde and lung cancer. These studies were conducted in Denmark (Jensen and Anderson (1982), the United Kingdom (Coggon *et al.* 1984), Canada (Gérin *et al.* 1989), the United States (Brownson *et al.* 1993), and Uruguay (De Stefani *et al.* 2005). Four nested case-control studies of respiratory cancer were described in Sections 3.2.4 (Chiazze *et al.* 1997, Marsh *et al.* 2001), 3.2.5 (Partanen *et al.* 1990), 3.2.6 (Andjelkovich *et al.* 1994) and 3.2.7 (Bond *et al.* 1986). Note that Coggon *et al.* (1984) included cancer of the trachea in their analysis of respiratory cancers.

3.5.4.1 Denmark: Jensen and Anderson (1982)

Jensen and Andersen (1982) reported on a small case-control series of 84 lung cancers (79 male, 5 female) among Danish physicians, identified from the Danish Cancer Registry between 1943 and 1976 and 252 physician controls matched on age, sex, and survival (no details on the selection of controls or cases was given). No association with potential sources of formaldehyde exposure were reported. 8 cases and 23 controls had ever worked in anatomy, pathology, or forensic medicine (RR = 1.0, 95% CI = 0.4 to 2.4).

3.5.4.2 United Kingdom: Coggon et al. *(1984)*

Study population. Coggon *et al.* (1984) conducted a population-based case-control study using death certificates to obtain information about the occupations of all males under the age of 40 years who died in England or Wales between 1975 and 1979 of epithelial cancers of the lung, trachea, or bladder (see Section 3.5.7 for results on bladder cancer). Cases of lung and tracheal carcinoma were combined and considered cancer of the bronchus (N = 598). Controls (N = 1,180) that had died from any other cause during the same time period were individually matched to each case by sex, year of death (within 5 years), year of birth, and residential district. Of 598 cases, 582 (97%) were matched with two controls; the remaining cases were matched with one control.

Exposure assessment. Occupations noted on the death certificates were coded using the 1970 Office of Population Census and Surveys Classification of Occupations scheme and entered into a job-exposure matrix by a trained occupational hygienist. Using this matrix, each of the 233 uniquely classified occupations was then assigned an exposure score (high/low/none) to nine known or suspected carcinogens, including formaldehyde. Among workers with carcinoma of the bronchus, 296 cases (50%) were considered exposed to formaldehyde; 472 controls (40%) were considered exposed.

Statistical methods and results. Matched tabular analysis was used to calculate estimates of the association between each carcinogen and carcinoma of the bronchus. For all exposed occupations, the OR for formaldehyde was 1.5 (95% CI = 1.2 to 1.8, 296 exposed cases, $P < 0.01$). Among occupations considered to have high exposure to formaldehyde, the OR was 0.9 (95% CI = 0.6 to 1.4, 44 exposed cases). [The ability to detect an effect in this study was limited by (1) the use of death certificates for occupational information, thus limiting the construction of a complete job-exposure matrix and resulting in potential non-differential exposure misclassification, (2) matching by pay class, which is likely to be correlated with occupation, and (3) insufficient capture of long-term exposures and insufficient follow-up to account for the relevant latency period of lung cancer, since subjects in this study had died before 40 years of age.]

3.5.4.3 Canada: Gérin et al. (1989)

Study population. Gérin *et al.* (1989) investigated the association between exposure to formaldehyde and subsequent risk of cancer at 14 primary sites of interest among males aged 35 to 70 years, using data from a large multi-site case-control study in Montreal, Canada of occupational exposures and cancer. Histologically confirmed primary incident cases of cancer (N = 4,510) diagnosed between September 1979 and December 1985 were ascertained from all hospitals in the Montreal area. This analysis included 857 cases of lung cancer (see Section 3.6.5 for results on lymphohematopoietic malignancies, and 3.6.6 for results on other cancer sites). Sub-types of lung cancer were also examined including oat-cell (N = 159) and squamous-cell cancers (N = 359), adenocarcinomas (N = 162), and other histologic sub-types (N = 177). For each case series, a cancer control group was selected from the case series that included patients with tumors at any other site (some exceptions noted). In addition to the internal cancer control series, 740 population-based controls frequency matched by age were selected from electoral lists; 533 (72%) agreed to participate.

Exposure assessment. Trained interviewers collected information from each patient or next-of-kin on demographic characteristics, medical history, diet, and a complete occupational history including a semi-structured probing section designed to elicit detailed descriptions of each job ever held in a working lifetime. Jobs were coded according to standard Canadian classifications and then further classified by a team of chemists and hygienists by probability, frequency, and concentration of exposure to 300 occupational exposures including formaldehyde. Of 4,259 interviewed subjects, 971 (23%) subjects ever held at least one job classified as exposed to formaldehyde.

Statistical methods and results. Odds ratios and 95% CIs were estimated using logistic regression. Both occupational and non-occupational factors were evaluated as potential

confounders using change-in-estimate methods whereby any factor that changes the estimate of formaldehyde for the cancer site of interest by more than 10% is considered a confounder. Models were further adjusted by five *a priori* variables including age, ethnicity, income, smoking, and "dirtiness" (a semi-quantitative measure constructed by the study chemists) of the jobs held. The OR for all lung cancer and any formaldehyde exposure was 0.8 (95% CI = 0.6 to 1.0, 180 exposed cases) using the cancer control series. Results using the population control series were not markedly different. [Some controls had types of cancer potentially associated with formaldehyde; inclusion of these controls could potentially attenuate true effects.] The OR for the highest exposure category (i.e., greater than 10-years duration of exposure at high concentrations) was 1.5 (95% CI = 0.8 to 2.8, 24 exposed cases). In the analysis by histologic subtype, the largest estimates in magnitude were observed for adenocarcinomas: the OR for subjects classified into the highest exposure category was 2.3 (95% CI = 0.9 to 6.0, 7 exposed cases) using the cancer control series.

3.5.4.4 Missouri: Brownson et al. *(1993)*

Study population. Brownson *et al.* (1993) conducted a population-based case-control study to investigate occupational risk factors for incident lung cancer among non-smoking women. Eligible cases included cases of primary lung cancer (N = 429) identified by the Missouri Cancer Registry and diagnosed between 1986 and 1991 among white women aged 30 to 84 years who were Missouri residents and either lifetime non-smokers or ex-smokers who had stopped smoking at least 15 years prior to diagnosis or had smoked less than one pack-year. Controls (N = 1,021) were selected from state driver's license files (for women less than 65 years of age) and from Medicare recipient rosters (for women aged 65 or older); controls were frequency matched by age (case to control ratio = 1:2).

Exposure assessment. In-person occupational history interviews were conducted with 429 cases (66% of eligible cases; 58% case interviews with next-of-kin) and 1,021 controls (67% of eligible controls) to obtain information about job titles, calendar duration of employment, and exposure to specific substances.

Statistical methods and results. Odds ratios were estimated using multivariate logistic regression. All subjects who reported exposure to formaldehyde were also lifetime non-smokers. The OR for lung cancer among all subjects ever exposed to formaldehyde was 0.9 (95% CI = 0.2 to 3.3, 3 exposed cases), adjusted for age and history of previous lung disease.

3.5.4.5 Uruguay: De Stefani et al. *2005*

Study population. De Stefani *et al.* (2005) conducted a hospital-based case-control study of 338 incident cases of lung adenocarcinoma, identified among men in four hospitals between 1994 and 2000, in relation to occupations and occupational exposures. Hospital control subjects (N = 1,014) were frequency matched to cases on age, residence, and urban/rural status; patients with tobacco-related diseases or recent changes in diet were excluded.

Exposure assessment. Occupational histories, based on job titles and self-reported exposures to known or suspected occupational agents, plus demographic data, lifestyle and medical variables, were ascertained by in-person administration of a standardized questionnaire.

Statistical methods and results. Unconditional logistic regression analysis was used to calculate odds ratios for employment in selected occupations (for which at least 15 cases or controls reported employment) and selected exposures. Analyses were stratified by duration of employment (1 to 20 and > 20 years) and smoking. Ever exposure to formaldehyde was associated with a statistically significant increase in lung adenocarcinoma (OR = 1.7, 95% CI = 1.1 to 2.8, 32 cases, adjusted for age, residence, urban/rural status, education, body mass index, family history of lung cancer, smoking status, including age at first smoking, average number of cigarettes per day, and years since quitting). Most of the risk associated with formaldehyde exposure was observed among those with the longest duration of employment (1 to 20 years: OR = 0.9, 95% CI = 0.4 to 1.9, 10 cases, and > 20 years: OR = 3.0, 95% CI = 1.6 to 5.8, 22 cases, P_{trend} = 0.004). Subjects reporting exposure to formaldehyde were employed primarily as agricultural workers, histology technicians, medical personnel, and foundry workers. Exclusion of foundry workers did not substantially alter the results.

3.5.5 Lymphohematopoietic malignancies

Section 3.6.5 reviews case-control studies that examined the association between formaldehyde and lymphohematopoietic malignancies (ICD codes 200-209) including non-Hodgkin's and Hodgkin's lymphoma (Blair *et al.* 1993, Gérin *et al.* 1989, Richardson *et al.* 2008, Tatham *et al.* 1997, Wang *et al.* 2009a), leukemia (Blair *et al.* 2001), multiple myeloma (Heineman *et al.* 1992, Pottern *et al.* 1992) and myelodysplastic syndrome (West *et al.* 1995). One study was conducted in Canada (Gérin *et al.* 1989), four in Europe (Heineman *et al.* 1992, Pottern *et al.* 1992, West *et al.* 1995, Richardson *et al.* 2008), and five in the United States (Boffetta *et al.* 1989, Blair *et al.* 1993, Tatham *et al.* 1997, Blair *et al.* 2001, Wang *et al.* 2009a). Gérin *et al.* (1989) was described previously in Section 3.5.4. Four nested case-control studies of lymphohematopoietic malignancies were described in Sections 3.2 (Partanen *et al.* 1993), 3.2.7 (Ott *et al.* 1989), 3.3 (Hauptmann *et al.* 2009), and 3.4 (Boffetta *et al.* 1989).

3.5.5.1 Canada: Gérin et al. *(1989)*

Gérin *et al.* (1989) investigated the association between exposure to formaldehyde and Hodgkin's (N = 53) and non-Hodgkin's lymphoma (N = 206) among males aged 35 to 70 years, using data from a large multi-site case-control study in Montreal, Canada (see Section 3.5.4 for complete study description and results on cancer of the bronchus). Controls consisted of various internal control groups selected from the case series, and 740 population controls. Using the cancer control series, the ORs (adjusted for age, ethnicity, socioeconomic status, smoking, and "dirtiness" of jobs held) for non-Hodgkin's and Hodgkin's lymphoma comparing ever exposed with never exposed was 0.9 (95% CI = 0.6 to 1.3, 47 exposed cases), and 0.5 (95% CI = 0.2 to 1.2, 8 exposed cases), respectively. (Effect estimates did not change markedly using the population-based control series.) Non-Hodgkin's lymphoma was further evaluated by exposure duration

and concentration; effect estimates ranged from 0.7 to 1.3 (e.g., OR = 1.3, 95% CI = 0.7 to 2.4, for 15 cases exposed at low cumulative concentration for greater than 10 years).

3.5.5.2 Denmark: Heineman et al. *(1992) and Pottern* et al. (*1992)*

Study population. Heineman *et al.* (1992) and Pottern *et al.* (1992) conducted a population-based case-control study of the association between multiple myeloma incidence in Danish men (Heineman *et al.* 1992) and women (Pottern *et al.* 1992) in relation to their occupation. The analysis of men was conducted based on 1,098 incident cases for whom industrial occupational histories could be constructed and diagnosed between 1970 and 1984. Cases were identified via the Danish Cancer Registry and matched with age- and sex-matched controls. The analysis of women was based on 363 cases and 1,517 controls diagnosed over the same period who had a history of industrial employment and for whom exposure to one or more of 47 chemical agents could be evaluated.

Exposure assessment. A job-exposure matrix was constructed by industrial hygienists based on pension and tax records of employment history by industrial employment history and most recent occupations. Among men, those recorded with more than 5 years of employment (791 cases and 3,070 controls), potential exposure to one or more of 47 chemicals was evaluated. (The numbers of cases and controls for whom historical industrial exposures could be established is not clearly stated.)

Statistical methods and results. Maximum likelihood odds ratios were calculated for each occupation vs. all occupations combined. For analyses of specific exposures, comparison between estimated exposed and never exposed subjects was conducted. Neither possible (OR = 1.0, 95% CI = 0.8 to 1.3, 144 cases) nor probable (OR = 1.1, 95% CI = 0.7 to 1.6, 41 cases) exposure to formaldehyde was associated with an increased risk of multiple myeloma among men in this study. Fifty-six (56) women with multiple myeloma were considered to have possible exposure to formaldehyde and 4 probable exposure; in neither case were the odds ratios significantly elevated in comparison with controls (ORs = 1.1, 95% CI = 0.8 to 1.6, and 1.6, 95% CI = 0.4 to 5.3, respectively).

3.5.5.3 United Kingdom: West et al. *(1995)*

Study population. West *et al.* (1995) conducted a population-based case-control study of incident cases of myelodysplastic syndrome (MDS) in residents over 15 years of age in Southeast Wales, Wessex, and West Yorkshire to identify occupational and environmental exposures potentially associated with myelodysplasia in the United Kingdom. Of 635 eligible cases, 400 (63%) were available for analysis; 46% of the cases were women. Non-cancer controls (approximately 400, actual number not reported) were selected from hospitals and outpatient clinics and individually matched to cases by age (within 3 years), sex, area of residence, hospital, and year of diagnosis (within 2 years).

Exposure assessment. Lifetime exposure to over 70 potential risk factors for MDS including formaldehyde was estimated using in-depth interviews that probed subjects about duration and intensity of exposure from jobs held six months or more, relevant hobbies, and medical therapies. Occupational exposure was estimated in consultation

with industrial chemists and occupational hygienists using the self-reported job histories and then categorized by duration and intensity (low/medium/high).

Statistical methods and results. Odds ratios were obtained using matched-pair analysis. Confidence intervals were only reported if the lower 95% limit was greater than 0.80. The ORs for formaldehyde were 1.17 (15 exposed cases, 13 exposed controls) for subjects with at least 10 hours of lifetime exposure at any intensity, 2.33 (number of exposed cases and controls not reported) for subjects with at least 50 hours of lifetime exposure at medium or high intensity, and 2.00 for subjects with at least 2,500 hours of lifetime exposure at medium or high intensity.

3.5.5.4 United States: Tatham et al. *(1997)*

Study population. Occupational risk factors for subgroups of non-Hodgkin's lymphoma were investigated in a population-based case-control study of male cases born between 1929 and 1953, diagnosed between 1984 and 1988, and identified by population-based cancer registries in Atlanta, Connecticut, Iowa, Kansas, Miami, San Francisco, Detroit, and Seattle (Tatham *et al.* 1997). Only living cases were eligible, and diagnoses were confirmed by a panel of pathologists. Living controls were identified using random-digit dialing and frequency matched to cases by registry and date of birth (within 5 years). Of 2,354 identified cases and 1,910 controls, the final numbers of subjects available for analysis were 1,048 cases (45%) and 1,659 controls (87%) after exclusions for a variety of reasons including unconfirmed diagnosis and presence of comorbid medical conditions. Three subgroups of non-Hodgkin's lymphoma were identified: small-cell diffuse lymphoma (N = 185), follicular lymphoma (N = 268), and large-cell diffuse lymphoma (N = 526).

Exposure assessment. All study subjects were interviewed by telephone to collect information about demographic and lifestyle characteristics, medical and military histories, and occupational history covering all jobs held for at least one year. The job history included questions about job title, tasks, type of industry, and calendar duration as well as information about exposure to specific substances including formaldehyde. Study investigators classified exposure to formaldehyde and other substances using data from the self-reported occupational histories.

Statistical methods and results. Conditional logistic regression was used to estimate ORs and 95% CIs. Covariates considered potential confounders included age at diagnosis, education, ethnicity, year of entry into the study, being Jewish, marital status, risk factors for AIDS, military service, and smoking. Among all cases of non-Hodgkin's lymphoma combined, 93 (8.9%) cases were exposed to formaldehyde; 130 (7.8%) controls were considered exposed. The adjusted OR for all lymphomas combined associated with ever being exposed to formaldehyde was 1.20 (95% CI = 0.86 to 1.50, 93 exposed cases). For the specific subgroups, the corresponding ORs were 1.4 (95% CI = 0.87 to 2.40, 21 exposed cases) for small-cell diffuse lymphomas, 0.71 (95% CI = 0.41 to 1.20, 17 exposed cases) for follicular lymphomas, and 1.10 (95% CI = 0.79 to 1.70, 46 exposed cases) for large-cell diffuse lymphomas.

3.5.5.5 Iowa and Minnesota: Blair et al. *(1993, 2001)*

Study population. Blair *et al.* (1993, 2001) conducted a population-based case-control study of occupation, leukemia (Blair *et al.* 2001) and non-Hodgkin's lymphoma (Blair *et al.* 1993) in Iowa and Minnesota. All cases of histologically-confirmed leukemia and non-Hodgkin's lymphoma diagnosed among white men at least 30 years of age were identified from the Iowa State Cancer Registry between 1981 and 1983 together with all such cases from a surveillance network of hospitals in Minnesota (97% coverage) between 1980 and 1982. Because the primary purpose of the study was to evaluate agricultural risk factors, cases and controls residing in the urban areas of Minneapolis, St. Paul, Duluth, and Rochester were excluded. For the analysis of leukemia, 669 eligible cases were identified, 578 (86%) of whom participated in the study; interviews were conducted with 340 living cases and 238 surrogates for deceased or severely ill cases. Population-based controls (N = 1,245) were identified using random-digit dialing to obtain controls under 65 years of age (N = 474, 77% participation rate), from Health Care Financing Administration records to obtain controls over 65 years of age (N = 519, 79% participation rate), and from state death certificate records to obtain surrogate respondents for deceased subjects (N = 550, 77% participation rate). Controls were frequency matched by 5-year age group, vital status at time of interview, and state of residence. Five hundred thirteen (513) cases and 1,087 controls were used for analysis after excluding subjects whose sole occupation was farming since the incidence of leukemia was previously found to be significantly elevated among farmers in this study population. Histologic subtypes included in this analysis were: chronic lymphocytic leukemia (N = 214), acute myeloid leukemia (N = 132), chronic myeloid leukemia (N = 46), acute lymphocytic leukemia (N = 13), myelodysplasia (N = 58), and other miscellaneous leukemia types (N = 50).

For the analysis of non-Hodgkin's lymphoma (histologic subtypes of non-Hodgkin's lymphoma included follicular, diffuse and other subtypes) 715 eligible cases were identified, of whom 622 (87%) were interviewed. Population-based controls (N = 1,245) without lymphohematopoietic cancers and frequency-matched on 5-year age group, vital status, and residence were identified.

Exposure assessment. Structured interviews were conducted between 1981 and 1984 to collect information about occupational history for each job held for at least one year, demographic characteristics, residential history, medical history, and family history of cancer, as well as smoking and alcohol use. The majority of in-person interviews were conducted directly with cases or control participants; approximately one-third were conducted in person with next-of-kin surrogate respondents. The occupational history included questions about job title, industry, and calendar duration of employment. A job-exposure matrix was constructed for selected occupational exposures including formaldehyde, and exposure assignment was made without knowledge of case status. Probability of exposure for each industry/job combination was categorized on a three-point scale, and intensity of exposure was categorized on a four-point scale, considering known changes in potential exposure probabilities by industry and calendar decade.

Statistical methods and results. Unconditional logistic regression was used to estimate ORs and 95% CIs for all leukemias or all non-Hodgkin's lymphoma and for individual

histological subtypes, adjusting for the matching factors as well as pesticide use, education, hair-dye use, family history of cancer, and smoking. In the analysis of leukemias, effect estimates for potential exposure to formaldehyde were generally close to the null for all leukemias combined (low exposure: OR = 1.0, 95% CI = 0.7 to 1.4, 61 exposed cases; high exposure: OR = 0.7, 95% CI = 0.2 to 2.6, 3 exposed cases) and by histologic subtype. Elevated effect estimates were based on small sample sizes (e.g., the OR for chronic myeloid leukemia was 2.9 (95% CI = 0.3 to 24.5, 1 exposed case among individuals with high exposure). [Small numbers of exposed cases and controls (i.e., 3 highly exposed cases total and 9 highly exposed controls) limited the ability of this study to detect an effect.]

In the analysis of non-Hodgkin's lymphoma, the adjusted overall OR for potential exposure to formaldehyde was 1.2 (95% CI = 0.9 to 1.4, 84 exposed cases). The OR was similar among those with a high intensity of exposure (OR = 1.3 (95% CI = 0.5 to 3.8, 6 exposed cases) than among those with low intensity (OR = 1.2, 95% CI = 0.9 to 1.7, 78 exposed cases). Although a 2-fold increase in risk for diffuse non-Hodgkin's lymphoma was observed among men with high intensity of exposure, there was no consistent difference between effect estimates for subtypes according to intensity of exposure and none of the estimates were significantly elevated.

3.5.5.6 Germany: Richardson et al. *(2008)*

Study population. A population-based case-control study of non-Hodgkin's lymphoma and chronic lymphocytic leukemia in association with occupational histories was conducted using 858 incident cases diagnosed between 1986 and 1998 among men and women 15 to 75 years of age and identified via hospitals and general practices in six counties in northern Germany. Controls (N = 1,821) were drawn from population registries and individually matched to case (at least two controls per case) on sex, year of birth, and region within the study counties; controls had to be leukemia or lymphoma free by the end of the study period.

Exposure assessment. Occupational histories were ascertained by personal interview with respondents and formed the basis of job-exposure matrices that were constructed by industrial hygienists for the longest held occupations. Smoking histories and socioeconomic data were also collected.

Statistical methods and results. Conditional logistic regression analysis was used to examine associations with longest held occupations and with potential exposure (ever vs. never and cumulative exposure, lagged for two years) to 50 agents of interest. Models were adjusted for smoking (never-, ex- and current smokers). A total of 27 high malignancy cases of non-Hodgkin's lymphoma were estimated to be potentially ever exposed to formaldehyde (OR = 1.52, 95% CI = 0.88 to 2.63, 27 cases); for low malignancy non-Hodgkin's lymphoma, the OR was 1.18 (95% CI = 0.79 to 1.75, 45 cases), and for chronic lymphocytic leukemia, the OR was 1.16 (95% CI = 0.71 to 1.89, 29 cases). No analyses by cumulative exposure to formaldehyde were conducted.

3.5.6 Connecticut: Wang et al. (2009a)

Study population. Wang *et al.* (2009a) conducted a population-based case-control study of non-Hodgkin's lymphoma incidence among women residents aged 21 to 84 years old in Connecticut. Seventy-two percent (72%) of the women (N = 601) were available for in-person interviews and were included in the study, together with 717 controls identified through random-digit dialing (69% participation rate) or Medicare or Medicare files (47% participation rate).

Exposure assessment. A job-exposure matrix developed by the National Cancer Institute was used to construct exposure histories from occupation and industry histories provided by respondents, who were assigned semi-quantitative estimates of solvent and formaldehyde exposure by intensity and probability (low, medium, and high) according to combinations of industry and occupation.

Statistical methods and results. Unconditional logistic regression models, adjusting for age, family history of hematopoietic cancers, alcohol consumption, and race were used to estimate odds ratios of the association between cumulative formaldehyde exposures and risk of non-Hodgkin's lymphoma. (Adjustment for other variables including income, education, smoking, and immune disease history did not affect observed associations and were excluded from final models.) Polytomous logistic regression models were used to evaluate the association between histological subtypes of non-Hodgkin's lymphoma and formaldehyde exposure. Ever exposure was associated with a borderline statistically significant increase in risk of non-Hodgkin's lymphoma (OR = 1.3, 95% CI = 1.0 to 1.7, 203 exposed cases; adjusted for age, family history of hematopoietic disease, race, and alcohol use). However, results by level of intensity of estimated exposure and level of probability of exposure were somewhat inconsistent: borderline statistically significant associations were observed for low average intensity (OR = 1.4, 95% CI = 1.0 to 1.8, 129 exposed cases) and low average probability (OR = 1.3, 95% CI = 1.0 to 1.7, 165 exposed cases) but not medium or high intensities (OR = 1.2, 95% CI = 0.8 to 1.7, 74 exposed cases) or probabilities (OR = 1.4, 95% CI = 0.9 to 2.3, 38 exposed cases) (P_{trend} = 0.21 and 0.11, respectively). The risk of non-Hodgkin's lymphoma appeared to be confined to large B-cell lymphomas, which were associated with an OR of 1.9 (95% CI = 1.3 to 2.6, 80 exposed cases) among ever vs. never exposed. A statistically significantly increased risk of this subtype was observed for formaldehyde exposure at low average intensity (OR = 2.1, 95% CI = 1.4 to 3.1, 54 exposed cases), but medium to high average intensity of exposure was associated with a lower risk (OR = 1.5, 95% CI = 0.9 to 2.4, 26 exposed cases). When exposure probabilities were analyzed, a medium-high probability of formaldehyde exposure yielded a risk of 2.6 (95% CI = 1.5 to 4.7, 20 exposed cases) for large B-cell lymphomas ($P_{trend} < 0.01$). No association with follicular lymphoma, chronic lymphocytic lymphoma/small lymphocytic lymphomas and formaldehyde were observed.

3.5.7 Cancers at other sites

Section 3.5.7 reviews case-control studies that examined the association between formaldehyde and several other tumor sites not reviewed in previous sections. Gérin *et al.* (1989) (described previously in Section 3.5.4) reported results for various cancers. Tumor sites examined in other investigations include bladder (Coggon *et al.* 1984, Siemiatycki *et al.* 1994), breast (Cantor *et al.* 1995), pancreas (Kernan *et al.* 1999), rectum (Dumas *et al.*

2000), and eye (Holly *et al.* 1996). Nested case-cohort studies of breast cancer (Ray *et al.* 2007) and thyroid cancer (Wong *et al.* 2006) among Chinese textile workers are discussed in Section 3.2, and a nested case-control study of brain cancer (Hauptman *et al.* 2009) among embalmers was discussed in Section 3.3. The studies in this section are organized by site.

3.5.7.1 Multiple tissue sites: Canada, Gérin et al. *(1989)*

Gérin *et al.* (1989) evaluated potential associations between occupational exposure among men to formaldehyde and cancers of the esophagus (N = 107), stomach (N = 250), colorectum (N = 787), liver (N = 50), pancreas (N = 117), prostate (N = 452), bladder (N = 486), kidney (N = 181), and melanoma of the skin (N = 121) in a large multi-site case-control study in Montreal (see Section 3.5.4 for complete study description and results for respiratory cancer; see Section 3.5.5 for results for lymphohematopoietic malignancies). Controls consisted of various internal control groups selected from the case series and 740 population controls. No elevated ORs were observed for any of these cancers.

3.5.7.2 Bladder cancer: United Kingdom, Coggon et al. *(1984)*

Coggon *et al.* (1984) used death certificates in this population-based case-control study to obtain information about the occupations of all males under the age of 40 years who died in England or Wales during 1975 to 1979 of epithelial bladder cancer (see Section 3.5.4 for complete study description and results for cancer of the bronchus). Two hundred ninety-one (291) cases and 578 controls were included in the analysis. Exposure to formaldehyde was determined using a job-exposure matrix. Among subjects with bladder cancer, 132 cases (45%) were considered exposed to formaldehyde; 472 controls (40%) were considered exposed. For all exposed occupations, the OR for formaldehyde was 1.0 (95% CI = 0.7 to 1.3, 132 exposed cases). Among occupations considered to have high exposure to formaldehyde, the OR increased in magnitude to 1.5 (95% CI = 0.9 to 2.5, 30 exposed cases).

3.5.7.3 Bladder cancer: Canada, Siemiatycki et al. *(1994)*

Siemiatycki *et al.* (1994) investigated the association between exposure to formaldehyde and bladder cancer using data from the large multi-site case-control study in Montreal, Canada studied by Gérin *et al.* (1989) (see Section 3.5.4 for complete study description). Included in this analysis were 484 men (ages 35 to 70 years) with primary, incident, histologically confirmed bladder cancer (575 eligible cases, 84% participation rate). From the parent study, 1,879 controls with cancer at other sites (excluding lung and kidney) and 533 community controls (72% participation rate) were selected; control groups were pooled for analysis. Adjusting for age, ethnicity, socioeconomic status, smoking, coffee consumption, and interview type (self/proxy), the OR for bladder cancer was 1.2 (95% CI = 0.9 to 1.6, 67 exposed cases) among men with non-substantial exposure to formaldehyde and 1.2 (95% CI = 0.7 to 2.0, 17 exposed cases) among men with substantial exposure. Adjusting for additional exposure to several occupational substances reduced effect estimates for men considered to have substantial formaldehyde exposure (OR = 0.9, 95% CI = 0.5 to 1.7), but did not alter the estimate for nonsubstantial exposure.

3.5.7.4 Breast cancer: United States, Cantor et al. *(1995)*

Study population. A database of mortality records from 1984 to 1989 in 24 states in the United States was assembled for a series of case-control studies designed to investigate associations between occupational factors and cancer mortality. Cantor *et al*. (1995) reported on their investigation of occupational risk factors for breast cancer mortality among women. For this analysis, cases (N = 59,515) included white and black women (10% black) whose death certificate listed breast cancer as the underlying cause of death. Controls were randomly selected from all non-cancer deaths and frequency matched by age (within 5 years) and race (case to control ratio = 1:4).

Exposure assessment. Usual occupation and industry were obtained from death certificates and coded according to the 1980 U.S. Census occupational classification scheme. Homemakers were excluded, leaving 29,387 white and 4,112 black breast cancer cases, and 102,955 white and 14,839 black controls. The remaining occupational and industry codes were then entered into a job-exposure matrix to estimate the probability and level of exposure to 31 occupational exposures, including formaldehyde.

Statistical methods and results. Odds ratios were stratified by race and adjusted for age at death and socioeconomic status (based on occupation). The risk estimate for breast cancer was elevated among black women with the highest category of exposure probability (OR = 1.45, 95% CI = 1.2 to 1.7, 311 exposed cases) and with the highest exposure level (OR = 1.26, 95% CI = 1.0 to 1.5, 192 exposed cases). However, these trends were not observed among white women: ORs ranged from 0.93 to 1.19 (e.g., 1.19, 95% CI = 1.1 to 1.3 for 1,815 cases exposed at the highest level). Further analysis excluded women considered to have a low probability of exposure. Among white women, the ORs were 1.14 ($P < 0.05$), 0.93, and 1.20 ($P < 0.05$) for low, moderate, and high intensity of exposure, respectively; among black women, the corresponding ORs were 1.38 ($P < 0.05$), 1.30 ($P < 0.05$), and 1.36 ($P < 0.05$). Confidence intervals were not reported.

3.5.7.5 Pancreatic cancer: United States, Kernan et al. *(1999)*

Study population. Kernan *et al.* (1999) reported on a case-control investigation of occupational risk factors for pancreatic cancer mortality using the mortality records collected between 1984 and 1993 in 24 U.S. states (Cantor *et al.* 1995, reviewed in this section, also used this database, though the study period was earlier). In this analysis, 63,097 cases were included whose death certificate listed pancreatic cancer as the underlying cause of death. Controls (N = 252,368) were randomly selected from all non-cancer deaths (excluding pancreatitis and other pancreatic diseases) and frequency matched by age (within 5 years), race, sex, and state (case to control ratio = 1:4).

Exposure assessment. Usual occupation and industry were obtained from death certificates, coded according to the 1980 U.S. Census occupational classification scheme, and entered into a job-exposure matrix developed by industrial hygienists to estimate the probability and intensity of exposure to formaldehyde, 11 chlorinated hydrocarbons, and 2 groups of solvents. Forty-eight percent (48%) of male cases (N = 30,389) and 51% of female cases (N = 31,962) were considered exposed to formaldehyde.

Statistical methods and results. Logistic regression was applied to estimate ORs and 95% CIs, stratified by race (black/white) and sex and adjusted for age at death, metropolitan status, region of residence, and marital status. Analysis by exposure intensity yielded ORs ranging from 1.0 to 1.4 for each race-sex combination, with some estimates achieving statistical significance. [The large number of exposed cases in this study increased the power to detect an effect.] Analysis by exposure probability yielded ORs ranging from 0.8 to 1.5; again, some estimates were statistically significant. Analysis by exposure intensity and probability combined showed that among the entire study sample, the OR for those with both high exposure intensity and high exposure probability was 1.4 (95% CI = 1.0 to 1.8, 56 exposed cases). Among all subjects with high exposure probability, the ORs were 2.8 (95% CI = 0.7 to 1.8, 3 exposed cases) for those with low exposure intensity, and 1.4 (95% CI = 1.2 to 1.6, 546 exposed cases) for those with medium intensity. Among all subjects with high exposure intensity, the ORs were 1.0 (95% CI = 0.9 to 1.3, 171 exposed cases) for those with low exposure probability and 1.2 (95% CI = 0.8 to 1.6, 47 exposed cases) for those with medium probability. Though an exposure-response relationship was not observed with intensity of exposure, exposure-response relationships by probability of exposure were consistent for each level of exposure intensity.

3.5.7.6 Rectal cancer: Canada, Dumas et al. *(2000)*

Study population. Dumas *et al.* (2000) evaluated the association between exposure to formaldehyde and incident cases of rectal cancer among males aged 35 to 70 years, using data from the large multi-site case-control study in Montreal, Canada studied by Gérin *et al.* (1989) (see Section 3.5.4 for complete study description and exposure assessment). For this analysis, 257 cases of primary rectal cancer (304 eligible cases; 85% participation rate), 1,295 cancer controls (excluding lung and intestinal site cancers), and 533 community controls (72% participation rate) were enrolled.

Statistical methods and results. Odds ratios were adjusted for age, education, interview status (self/proxy), smoking, beer consumption, and body mass index, but not for other occupational exposures. Results were presented using the cancer control series as the referent group. Among men considered to have any occupational exposure to formaldehyde, the OR for rectal cancer was 1.2 (95% CI = 0.8 to 1.9, 36 exposed cases). Among men with substantial exposure, the OR increased to 2.4 (95% CI = 1.2 to 4.7, 13 exposed cases). The authors noted that the overall exposure-response pattern reflected an increase in risk with increasing duration and concentration of exposure (data not shown). [Use of a control group including subjects with cancers that other studies have suggested are potentially associated with formaldehyde exposure (such as esophageal carcinoma, bladder cancer, and lymphomas) might have attenuated the observed effect estimate.]

3.5.7.7 Uveal cancer: United States, Holly et al. *(1996)*

Study population. Holly *et al.* (1996) conducted a case-control study to evaluate whether certain occupational exposures were associated with incident cases of uveal cancer (also known as intraocular melanoma) among white males aged 20 to 74 years living in the western United States. The case group (N = 121, 95% participation rate) comprised all histologically confirmed cases of uveal carcinoma either diagnosed or treated between

January 1978 and February 1987 at the Ocular Oncology Unit of the University of San Francisco. For each case, two controls were selected using random-digit dialing and individually matched by area of residence and age (within 5 years); 447 controls were enrolled (77% participation rate).

Exposure assessment. Telephone interviews were conducted to elicit information about demographic, medical, and phenotypic characteristics (i.e., eye color), occupational history and exposure to chemicals, and history of smoking, diet, residence, and sun exposure. Exposure to chemicals of interest including formaldehyde was determined by asking each participant whether they had ever worked with or been regularly exposed (at least three hours per week for at least six months) to each chemical at a job or while engaging in hobbies, recreational activities, or home maintenance.

Statistical methods and results. Odds ratios were estimated using unconditional logistic regression adjusting for age, eye characteristics, and response type to sun exposure. The OR for uveal carcinoma among men who reported ever being exposed to formaldehyde either occupationally or recreationally was 2.9 (95% CI = 1.2 to 7.0, 13 exposed cases). [Results of this study might be affected by recall bias since exposure assessment was based entirely on a subject's personal recollection of formaldehyde exposure.]

3.6 Summary by tumor site

This section summarizes the findings for the cohort and case-control studies for each of the major cancer sites. A number of the cohort studies, the majority of which have studied workers in a variety of industries, relied on external (SMR and PMR) analyses; relatively few conducted internal analyses of exposed and unexposed workers. [All studies of occupational groups are potentially subject to biases introduced by selection of healthy persons into the working population. Few studies have either sufficient numbers of exposed individuals to enable exposure-response relationships to be assessed or have quantitative exposure measurements on which to base the assignment of exposure categories. Since some of the tumor types potentially related to formaldehyde exposure are rare (e.g., sinonasal and nasopharyngeal cancers) most of the cohort studies have limited statistical power to detect statistically significant increases in risk in association with exposure to formaldehyde. The case-control studies of these and other cancer endpoints often lack adequate data on exposure to formaldehyde. In addition, relatively few cohort or case-control studies have attempted to control for potentially confounding exposures or lifestyle factors; however, many of the cohort studies were conducted in several different industries, and thus it is unlikely that workers were exposed to the same confounders in the various studies.]

[Four studies of occupational populations were available that had relatively large numbers of formaldehyde-exposed workers: (1) the NCI cohort of mixed industry workers (Hauptmann *et al.* 2003, 2004, Beane Freeman *et al.* 2009), (2) the cohort of British chemical workers (Coggon *et al.* 2003), (3) the NIOSH cohort of garment workers (Pinkerton *et al.* 2004), and (4) the NCI study of workers in the funeral industry (Hauptmann *et al.* 2009).] Detailed exposure-response relationships according to peak, average, duration, and cumulative exposure were examined only in the NCI studies (Hauptmann *et al.* 2004, 2009, Beane Freeman *et al.* 2009). The other large cohort study,

of British chemical workers, also examined exposure-response relationships by exposure level, and by duration of employment and time since first employment in jobs with high exposure, using external SMR analyses for selected cancer sites. The NIOSH cohort of garment workers (Pinkerton *et al.* 2004) evaluated mortality for selected cancer sites by duration of exposure, time since first exposure, and time of first exposure (exposure was higher for earlier time periods). The other cohorts (of both industrial and health professional workers) were smaller, and in general only reported mortality for ever-exposed workers. (Note that not all cohort studies reported findings for each cancer site.) Where findings were reported but no deaths or cases were observed, as specifically noted by the authors, the annotation "0 deaths" is used in the accompanying tables. Studies in which no findings for a given site were specifically reported are noted in the footnotes for that table.

3.6.1 Cancers of the paranasal sinuses and nasal cavity

Sinonasal carcinoma is a rare cancer (the annual incidence is approximately 1 case per 100,000 in most countries), [which limits the ability of even large occupational cohort studies to achieve enough statistical power to detect significant associations. Further, sinonasal carcinoma is thought to have a long latency period (at least 10 years, with some estimates as high as 40 years), meaning that study designs must have a long enough follow-up to capture exposed cases]. Approximately 70% to 80% of primary sinonasal carcinoma occurs in the paranasal sinuses rather than the nasal cavity, but most of the available studies do not distinguish between sites when identifying cases of sinonasal cancers; Hauptmann *et al.* (2004) is one exception.

The relationship between sinonasal cancers and occupational exposure to formaldehyde has been investigated in cohort, nested case-control and population-based case-control studies. The key findings are summarized in Table 3-4a and b. (See Section 3.1 for a description of sinonasal cancers, and Section 3.5.1 for a detailed summary of case-control studies that investigated sinonasal cancers.) [The cohort studies have low statistical power to detect sinonasal cancers, and case-control studies are more informative.]

3.6.1.1 Cohort studies

Increases in the risk of sinonasal cancers were reported in two cohort studies of formaldehyde-exposed workers: (1) a statistically significant increased risk of sinonasal cancers was observed among male Danish workers exposed to formaldehyde (SPIR = 2.3, 95% CI = 1.3 to 4.0, 13 exposed cases and SPIR = 3.0, 95% CI = 1.4 to 5.7, 9 exposed cases for exposed male workers without exposure to wood dust); risks, although not statistically significant, were also increased among women (SPIR = 2.4, 95% CI = 0.6 to 6.0; 4 exposed cases) (Hansen and Olsen 1995, 1996), and (2) a nonsignificant increased risk in sinonasal cancer mortality among formaldehyde-exposed workers was observed in the NCI cohort (SMR = 1.19, 95% CI = 0.38 to 3.68, 3 deaths) (Hauptmann *et al.* 2004). In the latter study, statistically nonsignificant elevated relative risks were observed for some categories of average, peak, and cumulative exposure. [However, the small number of exposed cases limits the ability to evaluate exposure-response relationships.] In an industrial cohort study of tannery workers, one death from squamous-cell sinonasal cancer was reported among formaldehyde-exposed workers in the finishing department

(Stern *et al* 1987). No association with formaldehyde exposure was found in a standardized mortality analysis among British chemical workers (2 observed deaths vs. 2.3 expected) (Coggon *et al.* 2003), which was one of the larger cohort studies. No cases of sinonasal cancers were identified in the NIOSH cohort (Pinkerton *et al.* 2004) or in the small industrial cohorts of Dell and Teta (1995) and Andjelkovich *et al.* (1995). No findings were specifically reported for this site by Bertazzi *et al*. (1989), Edling *et al.* (1987b), and Stellman *et al.* (1998). Among the studies of health professionals, embalmers, anatomists, and pathologists, no cases of sinonasal cancers were observed by Hayes *et al.* (1990), Levine *et al.* (1984), Stroup *et al.* (1986), and Walrath and Fraumeni (1983, 1984). [However, these were small cohorts with limited power to detect rare cancers. No findings were specifically reported by Hall *et al.* (1991).] (See Table 3-4a.)

3.6.1.2 Case-control studies

Six case-control studies and one pooled case-control analysis on sinonasal cancers were identified. Statistically significant increased risks for (1) all sinonasal cancers were found in studies by Olsen *et al*. (1984) (OR = 2.8, 95% CI = 1.8 to 4.3, 33 exposed cases) and Hayes *et al.* (1986) (OR = 2.5, 95% CI = 1.2 to 5.0, 15 exposed cases), (2) adenocarcinoma in the study by Luce *et al.* (1993) (for the highest categories of different exposure metrics) and in the pooled analysis by Luce *et al.* (2002) (ORs = 3.0, 95% CI =1.5 to 5.7, 91 cases among men with the highest exposure and 6.2, 95% CI = 2.0 to 19.7, 5 cases among women with the highest exposure), and (3) squamous-cell carcinomas in the study by Hayes *et al.* (1986) (OR = 2.4, 95% CI = 1.1 to 5.1, 13 exposed cases).

Several studies reported that risk estimates increased with increasing exposure or were the highest among subjects in the highest category of exposure. Luce *et al.* (1993) reported that among males with probable exposure to formaldehyde, risks for adenocarcinoma increased with increasing exposure duration (OR = 6.86, 95% CI = 1.69 to 27.80, 57 exposed cases among workers with > 20 years of exposure) and cumulative exposure (OR = 6.91, 95% CI = 1.69 to 28.23, 52 exposed cases among workers with the highest cumulative exposure). Hayes *et al.* (1986) reported higher ORs for SNC among subjects with high exposure (see Table 3.4b) compared with any exposure. ORs were also higher for adenocarcinoma among men and women with the highest exposure in the pooled analysis by Luce et al. (2002). Roush *et al.* (1987) observed a statistically nonsignificant increase in risk only among cases with a high probability of exposure and 20-year lag time since first exposure (OR = 1.5, 95% CI = 0.6 to 3.9, 7 exposed cases); no increased risk was found for any exposure or high exposure with no lag time.

No association between formaldehyde exposure and sinonasal cancer was observed in a small cancer registry study (12 exposed cases) by Vaughan *et al.* 1986a, and in an industry study of woodworkers identified by insurance records (Pesch *et al.* 2008).

The pooled analysis by Luce *et al*. (2002) and the study by Luce *et al*. (1993) reported increased risks for adenocarcinoma type cancers, but not for squamous-cell carcinoma. Similar risk estimates were found for both histological subtypes in the study by Olsen and Asnaes (1986) (except among workers not exposed to wood dust). Hayes *et al*. (1986)

found similar ORs for all SNC and for squamous-cell carcinoma, but risk estimates for adenocarcinoma could not be calculated because of small numbers of exposed workers.

[Known risk factors for sinonasal cancers include the human carcinogens nickel dust (NTP 2005a) and wood dust, particularly, in the latter case, for adenocarcinoma (IARC 1995, NTP 2005a). In some studies, e.g., among workers in the woodworking and lamination industries, there may be a high degree of collinearity between formaldehyde and wood dust exposure]; for example, 97% of subjects considered to be probably or definitely exposed to formaldehyde were also jointly exposed to wood dusts in a case-control study by Luce *et al.* (1993). Some studies calculated risk among workers not exposed to wood dust or evaluated combined effects from exposure to wood dust and formaldehyde. Olsen and colleagues (1984, 1986) reported that when only those cases with no wood dust exposure were considered, the observed risk for squamous-cell carcinoma, and all sinonasal cancer was not altered, but a statistically significant increase in the risk of formaldehyde exposure was observed among adenocarcinoma cases (RR = 7.0, 95% CI = 1.1 to 43.9) based on only one exposed case, however. Among all cases of sinonasal cancer with both wood dust and formaldehyde exposure, the RR was 3.5 (95% CI = 2.2 to 5.6, 28 exposed cases). The increased risk estimates for sinonasal cancer reported in the study by Hayes *et al.* (1986) were for workers with little or no exposure to wood dust. Effect modification by wood dust has also been observed, whereby concurrent exposure to wood dust increased the independent risk of sinonasal cancers associated with exposure to formaldehyde or wood dust alone (Olsen *et al.* 1984, Luce *et al.* 1993, 2002).]

3.6.1.3 Meta-analyses

Bosetti *et al.* (2008) conducted a meta-analysis of occupational cohort mortality studies of formaldehyde exposure that included sinonasal cancers, and reported a nonsignificantly elevated estimated RR (using weighted average SMRs) of 1.01 (95% CI = 0.33 to 2.35, 5 deaths) among 8 cohorts of industrial workers (no deaths were reported among 5 cohorts of health professional workers). (See Table 3-10 for a list of studies included in the meta-analysis; note that not all studies were included in analyses for specific cancer sites.)

Collins *et al.* (1997) conducted a meta-analysis to evaluate the association between formaldehyde exposure and upper respiratory cancers, including sinonasal cancers. Nine cohort and 11 case-control mortality studies that reported findings on sinonasal cancers and in which formaldehyde exposure was analyzed separately were included. (See Table 3-10 for a list of studies included in the meta-analysis.) A total of 933 observed vs. 807.7 deaths were included. The estimated meta relative risk (mRR) for the 9 cohort studies was 0.3 (95% CI = 0.1 to 0.9, 3 deaths); each of the 3 deaths occurred in the 3 industrial cohorts (with none reported in six other cohorts) and yielded a mRR of 0.6 (95% CI = 0.1 to 1.7). Among the 11 case-control studies, the estimated mRR was 1.8 (95% CI = 1.4 to 2.3, 933 deaths); there was substantial variation between the five U.S. studies (mRR = 1.0, 95% CI = 0.7 to 1.5, 351 deaths) and the six European studies (mRR = 2.9, 95% CI = 2.2 to 4.0, 582 deaths), which the authors suggested might be due in part to wood dust exposure in some of the latter studies.

Table 3-4a. Summary of cohort studies of formaldehyde exposure and cancer of the sinus and nasal cavities (SNC)[a]

Reference	Study population and follow up	Risk estimate, 95% CI; number of observed cases or deaths	Comments
Studies of industrial workers			
Andjelkovich *et al.* 1995	Iron foundry workers, Michigan, USA N = 3,929 1960–89	0 deaths, expected NR	SMR for formaldehyde exposed subcohort
Coggon *et al.* 2003	British Chemical Workers Study, UK N = 14,014 1941–2000	SMR All 0.87 (0.11–3.14); 2 High exp. 0 (0–4.64); 0	
Dell and Teta 1995	Workers employed at a Union Carbide plastics manufacturing plant in New Jersey, USA 111 formaldehyde exposed workers 1946–88	0 deaths, expected NR	Small numbers of formaldehyde exposed workers
Hansen and Olsen 1995, 1996	Denmark N = 2,041 men, 1,263 women 1970–84	SPIR Men 2.3 (1.3–4.0); 13 Women 2.4 (0.6–6.0); 4 *No exposure to wood dust* Men 3.0 (1.4–5.7); 9 Women NR	SPIR adjusted for age and calendar time
Hauptmann *et al.* 2004	NCI cohort, USA N = 25,619 1966–94	SMR 1.19 (0.38–3.68); 3 *Exposure-response analysis* *RR; number of exposed deaths* Mean intensity (ppm) > 0–< 0.5 1.00 (Ref.) 0.5–< 1.0 1.48; 1 ≥ 1.0 NA; 0 P_{trend}[b] 0.802[d] P_{trend}[c] 0.562[d] Peak exposure (ppm) > 0–< 2.0 1.00 (Ref.) 2.0–< 4.0 1.55; 1 ≥ 4.0 1.47; 1 P_{trend}[b] 0.414 P_{trend}[c] 0.779 Cumulative exposure (ppm-yr) > 0–< 1.5 1.00 (Ref.) 1.5–< 5.5 1.32; 1 ≥ 5.5 NA; 0	Endpoint cannot be defined as SNC since paranasal sinuses were excluded Adjusted by calendar year, age, sex, race, and pay category; exposure was calculated with a 15-year lag interval

Reference	Study population and follow up	Risk estimate, 95% CI; number of observed cases or deaths	Comments
		P_{trend}[b] –0.855[d] P_{trend}[c] –0.715[d]	
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98	0 deaths; 0.16 expected	
Stern 2003	Workers employed in two chrome leather tannery plants, USA N = 9,365 1940–93 Formaldehyde exposed workers in the finishing department N = NR (1,050 deaths from all causes)	1 death, expected NR	Findings reported for formaldehyde-exposed worker
Studies of health professional workers			
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046 1975–85	0 deaths; 1.7 expected	Small cohort
Levine *et al.* 1984	Licensed embalmers in Ontario, Canada N = 1,413 First licensed 1928-57 Follow-up through 1977	0 deaths; 0.2 expected	Small cohort
Stroup *et al.* 1986	Anatomists who were members of the American Association of Anatomists, USA N = 2,317 1888–1979	0 deaths; 0.5 expected	Small cohort

Reference	Study population and follow up	Risk estimate, 95% CI; number of observed cases or deaths	Comments
Walrath and Fraumeni 1983	All licensed embalmers in New York, USA N = 1,263 1902–80	0 deaths; 0.5 expected	Small cohort
Walrath and Fraumeni 1984	All licensed embalmers in California, USA N = 1,109 1916–80	0 deaths; 0.6 expected	Small cohort

NR = not reported; Ref. = referent group; RR = relative risk ratio; SMR = standardized mortality ratio; SPIR = standardized proportionate incidence cancer ratios.
[a]Findings for SNC cancers were not reported by Bertazzi *et al.* (1989), Stellman *et al.* (1998), Hall *et al.* 1991, and Edling *et al.* (1987b)
[b]P_{trend} across exposed.
[c]P_{trend} across exposed and non-exposed.
[d][The P_{trend} value reported was based on only 2 values.]

Table 3-4b. Summary of case-control studies of formaldehyde exposure and sinonasal cancer

Reference/Study geographic location	Study population	Exposure assessment	OR or RR (95% CI); exposed cases	Comments
Olsen and Asnaes 1986, Olsen *et al.* 1984 Denmark	*Population-based study* 1970–82 *Cases:* 488 (67% men) identified by Danish Cancer Registry (1984) (466 cases reported in 1986 study due to recoding) *Controls*: 2,465 men and women identified from registry with cancer of the colon, rectum, breast, or prostate and matched to cases for age, sex and year of diagnosis	Employment histories obtained from national pension and population registries and exposure classified by job description and industry	Analysis only on men[a] *Certainly exposed (not adjusted)* SNC 2.8 (1.8–4.3); 33 *Ever exposed (adj. for wood dust exposure)* ADC 2.2 (0.7–7.2); 17 SCC 2.3 (0.9–5.8); 13 SNC 1.6 (NR) *Ever exposed, not exposed to wood dust* ADC 7.0 (1.1–43.9); 1 SCC 2.0 (0.7–5.9); 4 SNC 1.8 (0.7–3.9); 5 *Exposed to both formaldehyde and wood dust* SNC 3.5 (2.2–5.6); 28 With 10-yr lag 4.1 (2.3–7.3); 20	80% power to detect an OR of 2.0 for SNC Lagging exposure by 10 years did not alter results
Hayes *et al.* 1986 The Netherlands	*Population-based study* 1978–81 *Cases:* 91 men (deceased and alive) with confirmed SNC, identified from cancer treatment center records *Controls:* 195 age-matched (frequency) men randomly selected from the population (both living and deceased)	Occupational histories obtained by interview and exposure classified by job description and industry by two independent industrial hygienists (IH_A and IH_B)	Subjects with little or no exposure to wood dust[b] *All SNC* Any exposure/IH_A 2.5 (1.2–5.0); 15 Any exposure/IH_B 1.6 (0.9–2.8); 24 High exposure/IH_A 3.0 (1.0–8.7); 7 High exposure/IH_B 2.1 (1.1–4.1); 17 *SCC* Any exposure/IH_A 3.0 (1.3–6.4); 12 Any exposure/IH_B 1.9 (1.0–3.6); 19 High exposure/IH_A 3.1 (0.9–10.0); 5 High exposure/IH_B 2.4 (1.1–5.1); 13	No adjustment, but effect estimates did not change after adjustment for smoking or alcohol use

Reference/Study geographic location	Study population	Exposure assessment	OR or RR (95% CI); exposed cases	Comments
Vaughan *et al.* 1986b Washington, United States	*Population-based study* 1979–83 *Cases*: 53 incident cases identified using the SEER registry *Controls*: 552 frequency matched, and identified from random-digit dialing	Occupational histories and other information obtained by interview (present and proxy) and exposure classified using a JEM	12 exposed cases at any level, 3 exposed for at least 10 years *ORs ≤ 1.0 (all CIs included 1.0) for all exposure estimates including:* Maximum exposure level (low and medium or high) Number of years exposed (1–9, 10+) Exposure scores (5–19 and 20+)	Adjusted for sex, age, smoking, and alcohol Only 12 exposed cases at any level Recall error due to next of kin interviews for the deceased subjects
Roush *et al.* 1987 Connecticut, United States	*Population-based study* 1935–75 *Cases:* 198 men who died with SNC identified using the Connecticut Tumor Registry *Controls:* 605 randomly selected men who died during the same time period	Occupational histories obtained from death certificates and city directories, and exposure classified by job title and industry High exposure ≥ 1 ppm	Probably exposed: level/lag time Any/none 0.8 (0.5–1.3); 21 Any/20-yr 1.0 (0.5–1.8); 16 High[c] 1.0 (0.5–2.2); 9 High[c]/20 yr 1.5 (0.6–3.9); 7	Adjusted for age and calendar period
Luce *et al.* 1993 France	*Hospital-based study* 1986–98 *Cases:* 207 cases (167 males and 40 females) identified from area hospital records. Analysis on 166 male cases - 82 ADC (7 unexposed, 6 with possible exposure, 69 with probable or definite exposure), 59 SCC (36 unexposed, 7 with possible exposure, 16 with probably or definite exposure;) and 25 with other histological types) *Controls:* (1) Hospital-based series – 323 patients with cancers other than SNC and frequency matched by age and sex; (2) population-based series	Occupational histories and other information obtained by interview and exposure classified by job title and industry	*Possible exposure among men* SCC 0.96 (0.38–2.42); 7 *SCC: Probable or definite exposure to formaldehyde among men* Cases/controls 27.1%/25.3% Average level < 2 0.70 (0.28–1.73); 7 > 2 1.32 (0.54–3.24); 9 Date of first exposure ≤ 1944 1.47 (0.58–3.71); NR ≥ 1945 0.66 (0.27–1.64); NR No relationship[d] between SCC risk and cumulative exposure, duration of exposure, age of first exposure *Men with medium or high exposure to wood dust among men*	Adjusted for age and exposure to wood dust (squamous-cell type only), glues, and adhesives; 97% of ADC cases were also exposed to wood dust (which is a risk factor for ADC)

Reference/Study geographic location	Study population	Exposure assessment	OR or RR (95% CI); exposed cases	Comments
	sex; (2) population-based series (N = 86) – lists of friends and family provided by cases and matched by sex, age, and residence		*ADC – exposure to formaldehyde* Possible exposure 1.28 (0.16–10.42); 4 *Probable or definite exposure* Average level ≤ 2 4.15 (0.96–17.84); 24 > 2 5.33 (1.28–22.20); 43 Duration (yr) ≤ 20 1.03 (0.18–5.77); 10 > 20 6.86 (1.69–27.80); 57 Cumulative level ≤ 30 1.13 (0.19–6.90); 8 30–60 2.66 (0.38–18.70); 7 > 60 6.91 (1.69–28.23); 52 Date of first exposure ≤ 1944 6.02 (1.18–30.69); 26 ≥ 1945 4.26 (1.06–17.20); 41 ADC: Combined effects with wood dust among men Formaldehyde only 8.1 (0.9–72.9); 4 Wood dust only 130 (14.2–1,191); 6 Both exposures 692 (91.9–5,210); 71	

Reference/Study geographic location	Study population	Exposure assessment	OR or RR (95% CI); exposed cases	Comments
Luce *et al.* 2002	*Pooled analysis (12 case-control studies)* *Cases:* 195 ADC (169 men, 26 women); 432 SCC (330 men, 102 women) *Controls:* 3,136 (2,349 men, 787 women)	Occupational history information was used to develop a JEM Cumulative exposure: products of probability, level and duration of exposure for total work history	Cumulative exposure to formaldehyde *Men* SCC Low 1.2 (0.8–1.8); 43 Medium 1.1 (0.8–1.6); 40 High 1.2 (0.8–1.8); 30 ADC Low 0.7 (0.3–1.9); 6 Medium 2.4 (1.3–4.5); 31 High 3.0 (1.5–5.7); 91 *Women* SCC Low 0.6 (0.2–1.4); 6 Medium 1.3 (0.6–3.2); 7 High 1.5 (0.6–3.8); 6 ADC Low 0.9 (0.2–4.1); 2 Medium 0 cases High 6.2 (2.0–19.7); 5 *ADC in men: OR for cumulative exposure to formaldehyde* No or low exposure to wood dust No/low 1.0 (ref.) Medium 1.3 (0.5–3.3) High 2.2 (0.8–6.3) Medium or high exposure to wood dust No/low 1.0 (ref.) Medium 7.7 (2.6–22.8) High 17.0 (6.3–45.6)	SCC: OR adjusted for age and study ADC: OR adjusted for age, study, cumulative exposure to wood dust and leather dust Includes some studies described above: Hayes *et al*. (1986), Vaughan *et al.* (1986), Luce *et al.* (1993),
Pesch *et al.* 2008 Germany	*Industry-wide case-control study woodworking industry* 2003–05 *Cases:* 129 men (86 [57 living plus 29 next of kin] participated)	Occupational exposure assessed by interview and JEM	*Formaldehyde exposure* Never 1.0; 39/92 (ref.) < 1985 0.46 (0.14–1.54); 8 ≥ 1985 0.94 (0.47–1.90); 39	Adjusted for age, region, smoking, interview status and average exposure to wood dust. Wood dust exposure

Reference/Study geographic location	Study population	Exposure assessment	OR or RR (95% CI); exposed cases	Comments
	identified from an industry insurance database of occupational diseases with ADC *Controls:* frequency matched (4 accident cases per case) 204 participants, including 69 next of kin, identified from a database of accidents occurring between home and the workplace, and fall accidents occurring during shift			associated with highly significant elevations of risk in this population

ADC = adenocarcinoma; IH = industrial hygienist; JEM = job exposure matrix; NR = not reported; OR = odds ratio; PMR = proportionate mortality ratio; RR = risk ratio; SMR = standardized mortality ratio; SNC = sinonasal cancer; SCC = squamous-cell carcinoma.

[a]Women excluded from analysis since only 0.1% of controls were exposed; 4.2% of control men were exposed.

[b]Confidence intervals are 90% instead of 95%.

[c]High exposure in some year of working life; only 10 individuals were exposed to high exposure for most of their working lives.

[d]ORs for all categories below 1.1 (except cumulative exposure < 30, OR = 1.26), and 95% CIs included 1.0.

3.6.2 Cancer of the nasopharynx

Nasopharyngeal carcinoma is a rare cancer, with an annual incidence rate less than 1 per 100,000 in most populations. WHO has classified nasopharyngeal cancers into three major types: (I) squamous-cell carcinomas with keratinizing potential, (II) squamous-cell carcinomas without keratinizing potential, and (III) undifferentiated carcinomas or lymphoepitheliomas (Barnes *et al.* 2005). The etiology of these subtypes appears to be distinct, and appears to have viral, genetic, and environmental etiology. Only Type I nasopharyngeal carcinomas have been associated with potential exposure to chemical agents including formaldehyde, alcohol, or smoking (Bray *et al.* 2008). The majority of cohort studies have low statistical power to detect nasopharyngeal cancers. As in the case of sinonasal cancers, findings for this site are not specifically reported in a number of studies; these are noted in a footnote to the table. In other studies, the authors reported specifically that no deaths from this site were observed, indicated by the note "0 deaths observed" in the tables.

The relationship between nasopharyngeal cancers and occupational exposure to formaldehyde has been investigated in cohort, nested case-control and population-based case-control studies, and the key findings are summarized in Table 3-5a and b. (See Section 3.1 for a description of nasopharyngeal cancers, and Section 3.5.2 for a detailed summary of case-control studies investigating nasopharyngeal cancers.) Note that in several studies, findings for nasopharyngeal cancers have not been reported separately, and only pharyngeal cancers combined or buccal cavity and pharyngeal cancers combined are reported. Findings for these sites are reported in Section 3.6.3.

3.6.2.1 Cohort studies

Increased risks of nasopharyngeal cancers among formaldehyde-exposed workers were reported in three cohort studies: (1) a statistically significant increase in the risk of nasopharyngeal cancers mortality in the NCI cohort (SMR = 2.10, 95% CI = 1.05 to 4.21, 8 exposed cases) (Hauptmann *et al.* 2004), (2) statistically nonsignificant increases in mortality among white (PMR = 1.89, 95% CI = 0.39 to 5.48; 3 deaths) and non-white embalmers (PMR = 4.00, 95% CI = 0.10 to 22.29, 1 death) from the United States (Hayes *et al.* 1990), and (3) a statistically nonsignificant increased incidence of nasopharyngeal cancers among male Danish workers exposed to formaldehyde (SPIR = 1.3, 95% CI = 0.3 to 3.2. 4 exposed cases) (Hansen and Olsen 1995, 1996). Edling *et al.* (1987b) reported one incident case among formaldehyde-exposed workers in the abrasive material industry, and Coggon *et al.* (2003) reported one death from nasopharyngeal cancer (vs. 2.0 expected) among exposed British chemical workers. No deaths from nasopharyngeal cancers were reported in a very small study of formaldehyde-exposed plastics manufacturing workers (Dell and Teta 1995), among women in the Danish cohort (Hansen and Olsen 1996), in a study of formaldehyde-exposed iron foundry workers (Andjelkovich *et al.* 1995), in the NIOSH cohort (0 observed vs. 0.96 expected deaths; Pinkerton *et al.* 2004), and in two studies of professionals (Stroup *et al.* 1986, Walrath and Fraumeni 1983). (Six studies did not report findings for nasopharyngeal cancers; see Table 3-5a.)

Exposure-response relationships between formaldehyde exposure and nasopharyngeal cancer risk were evaluated in the large NCI-sponsored historical cohort study in mixed industries (Hauptmann *et al.* 2004) using internal analyses. (The lowest exposure group was used as the referent group for analyses of cumulative exposure and duration of exposure analyses, but the non-exposed group was the referent group for analyses of average exposure and peak exposure because there were no cases in the lowest exposure groups.) Two exposure trends were reported; one among the exposed group only and one for the combined exposed and unexposed groups. Relative risks of nasopharyngeal cancers increased with peak exposure ($P_{trend} < 0.001$ among exposed and $P_{trend} = 0.044$ for combined exposed and unexposed workers), average exposure ($P_{trend} = 0.066$ among exposed and $P_{trend} = 0.126$ among combined exposed and non-exposed workers), cumulative exposure ($P_{trend} = 0.025$ among exposed and $P_{trend} = 0.029$ among combined exposed and unexposed workers). The trends for duration of exposure were $P_{trend} = 0.147$ for exposed and 0.206 for unexposed workers. All seven of the exposed deaths occurred among workers with the highest peak exposure (> 4 ppm), and six of the exposed deaths were among workers with average exposures of > 1.0 ppm. Because five of the nine nasopharyngeal cancer cases occurred in one plant (Wallingford, Connecticut), the authors conducted analyses adjusting for plant and found similar exposure-response relationships with peak (adjusted P_{trend} among exposed = 0.008), average (adjusted P_{trend} among exposed = 0.404), and cumulative exposure (P_{trend} among exposed = 0.007), and also found a significant trend for exposure duration (P_{trend} among exposed = 0.043). [As mentioned in Section 3.2.1, Plant 1 (the Wallingford plant) had the largest numbers of workers exposed to formaldehyde levels greater 0.5 ppm of all the 10 plants in their first jobs, although it is not clear whether this pattern was observed for all jobs held by these workers.] Marsh *et al.* (2002, 2007a) reported findings on the Wallingford cohort (follow-up was to 1998 in the 2002 report and 2003 in the 2007 report), and found a significant excess of nasopharyngeal cancers in both (SMR = 4.23, 95% CI = 1.78 to 9.13, 7 deaths for the 2007 follow-up). The authors reported that for five of the seven formaldehyde-exposed nasopharyngeal cancer deaths, external employment in metal working occupations was observed. In a case-control analysis of these deaths, and after adjustment for metal-working and smoking, the OR for exposure to formaldehyde was 2.87 but no longer robust (95% CI = 0.21 to ∞). A trend toward increasing risk with increasing duration and cumulative, but not average, exposure to formaldehyde was still observed. When interaction modeling was applied, the OR for the five cases with both formaldehyde exposure and metal-working employment and 12 controls was 9.20 (95% CI = 0.91 to 436.5, adjusted for smoking).

3.6.2.2 Case-control studies

The relationship between formaldehyde exposure and nasopharyngeal cancer risk was evaluated in nine case-control studies (see Table 3-5b), six of which reported elevated risks for nasopharyngeal cancers among the formaldehyde-exposed subgroup of workers. Olsen *et al.* (1984) reported no increase in nasopharyngeal cancers among men ever exposed to formaldehyde (RR = 0.7, 95% CI = 0.3 to 1.7, number of exposed cases not reported), although a statistically nonsignificant increase was observed among women (RR = 2.6, 95% CI = 0.3 to 21.9; number of exposed cases not reported).

Hildesheim *et al.* (2001) and Vaughan *et al.* (2000) reported exposure-response trends in their analyses. The risk of nasopharyngeal cancers was found to increase linearly in both studies with duration of exposure to formaldehyde (P_{trend} = 0.08, P_{trend} = 0.01, respectively) and cumulative exposure (P_{trend} = 0.10, P_{trend} = 0.03, respectively). In addition to these two studies with larger sample sizes (Hildesheim *et al.* 2001, Vaughan *et al.* 2000), three other case-control studies examined semi-quantitative exposure indices and found elevated odds ratios among workers with longer latencies, duration of exposure or exposure categories (Table 3-5b). For example, West *et al.* (1993) reported higher risks among workers first exposed before the age of 25 (OR = 2.7, 95% CI = 1.1 to 6.6, 16 exposed cases) or with greater than 25 years since first exposure (OR = 2.9, 95% CI = 1.1 to 7.6, 14 exposed cases) in models adjusted for exposure to wood dust and exhaust fumes; Roush *et al.* (1987) reported an OR of 2.3 (95% CI = 0.9 to 6.0, 7 exposed cases) for subjects with probable exposure and 20 years lag time; and Vaughan *et al.* (1986a) reported an OR of 2.1 (95% CI = 0.6 to 7.8, 3 exposed cases) for their highest exposure category.

Three studies did not find an association between exposure to formaldehyde and nasopharyngeal cancer. Armstrong *et al.* (2000) reported an OR of 0.71 (95% CI = 0.34 to 1.43, number of cases not reported) for ever exposure after adjustment for smoking and diet; no exposure-response relationship was observed for a 10-fold increase in ratio of hours exposed (quantitative data not presented). No cases of nasopharyngeal cancer were observed among formaldehyde-exposed workers (compared with 10 non-cases exposed to formaldehyde) in a case-cohort study of nasopharyngeal and sinonasal cancers among female textile workers in Shanghai, China (Li *et al.* 2006). No association (OR = 0.1, 95% CI = 0.01 to 1.2; 2 exposed deaths) between formaldehyde exposure and nasopharyngeal cancer was found in the nested case-control mortality study among embalmers and funeral directors (Hauptmann *et al.* 2009). Average exposure levels of the exposed cases were equal to or higher than that observed among exposed controls for most metrics, according to the authors.

Risk factors for nasopharyngeal cancers include wood dust, Epstein-Barr virus (EBV) seroprevalence, and some dietary factors. Smoking might also be a confounder (for example, Armstrong *et al.* [2000] reported, for subjects with nasopharyngeal cancers, a statistically significant 2 to 3-fold increase in risk associated with > 6 months of active smoking, and also for parental smoking among nonsmokers). Increased risks of nasopharyngeal cancers associated with exposure to formaldehyde were still observed in several studies after controlling for smoking (Vaughan *et al.* 1986a, West *et al.* 1993, Vaughan *et al.* 2000), but an additional study (Hildesheim *et al.* 2001) did not observe a confounding effect of smoking in their study. Three of the studies that reported elevated risks for nasopharyngeal cancer and formaldehyde exposure evaluated concurrent exposure to wood dust as a potential confounder: West *et al* (1993) observed an increase in NPC after adjusting for exposure to wood dust, and Vaughan *et al.* (2000) and Hildesheim *et al.* (2001) reported that adjusting for wood dust exposure did not change their findings. EBV seroprevalence was investigated as a potential confounder in the study by Hildesheim *et al.*; the risk of nasopharyngeal cancers and ever exposure to formaldehyde was higher among EBV-seropositive subjects (OR = 2.7, 95% CI = 1.2 to 6.2) than among the total population (OR = 1.4, 95% CI = 0.93 to 2.2); however, in

contrast to the total population, the RR (among the subpopulation) did not increase with increasing exposure duration or increasing cumulative exposure

3.6.2.3 Meta-analyses

Bosetti *et al.* (2008) conducted a meta-analysis of three cohort mortality studies of formaldehyde exposure among industrial workers that included nasopharyngeal cancers (Hauptmann *et al.* 2004, Coggon *et al.* 2003, and Pinkerton *et al.* 2004; see also Table 3-10), and reported a nonsignificantly elevated estimated SMR for nasopharyngeal cancers of 1.33 (95% CI = 0.69 to 2.56, 9 deaths). (Note that studies by Bertazzi *et al.* (1986), Edling *et al.* (1987a), and Andjelkovich *et al.* (1995) were excluded as they did not report expected deaths.)

Collins *et al.* (1997) conducted a meta-analysis to evaluate the association between formaldehyde exposure and upper respiratory tract cancers, including nasopharyngeal cancers. Fourteen cohort studies (6 of industrial workers, 4 of pathologists, and 4 of embalmers), together with 4 nested and 11 non-nested case-control studies, were included in the meta-analysis (Table 3-10). A statistically significant increase in the risk of nasopharyngeal cancers across all studies combined was observed (mRR = 1.3, 95% CI = 1.2 to 1.5, 455 deaths). The mRR for the cohort studies alone was not elevated, however (mRR = 1.0; 95% CI = 0.5 to 1.8, 10 deaths), and the mRRs for the case-control studies was elevated but not statistically significant (mRR = 1.3, 95% CI = 0.9 to 2.1, 445 deaths).

Bachand *et al.* (2010) conducted a meta-analysis of cohort and case-control studies on formaldehyde exposure and the risk of nasopharyngeal cancers (Table 3-10). Eight cohort studies (one a re-analysis of the NCI cohort by Marsh and Youk [2005] and one of a component plant (Plant 1) from the NCI cohort by Marsh *et al.* [2007a]) and seven case-control studies were considered for inclusion in the meta-analysis. The authors excluded proportionate mortality studies and conducted analyses that both included and excluded results from Plant 1 of the NCI cohort study. The meta-analysis also took into account the potential confounding effect of smoking in the case-control studies. Quantile plots and regression modeling were used to estimate summary relative risk estimates and evaluate heterogeneity and publication bias. The authors suggested the possibility of publication bias with respect to the cohort studies. For cohort studies, relative risks for the individual studies ranged from 0.2 to 10.32 (the latter from the Wallingford plant in the NCI cohort). Excluding findings from the Wallingford plant in the Hauptmann *et al.* (2004) and Marsh *et al.* (2007a) studies, the overall estimated summary risk estimate for nasopharyngeal cancers, using the SMR for Plants 2-10 calculated in the re-analysis of Marsh and Youk (2005) [SMR = 0.65 compared with local rates or 0.64 compared with national rates] was 0.72 (95% CI = 0.40 to 1.29). When the SMR calculated for the Wallingford plant (Plant 1) by Marsh and Youk (2005) was included [SMR = 10.32], the summary risk estimate increased from 0.72 to 1.60, however. This compared with a summary risk estimate of 1.17 (95% CI = 0.73 to 1.86) when the SMR of 2.10 observed in the NCI cohort analysis of all ten plants by Hauptmann *et al.* (2004) was used. The authors stated that inclusion of the risk estimate from Wallingford plant led to significant heterogeneity among studies (Q test P value < 0.0001).

For case-control studies, excluding the Marsh study (Marsh *et al.* 2007a), the overall mRR was 1.22 (95% CI = 1.00 to 1.50). Results for four case-control studies that adjusted for smoking were slightly lower (mOR = 1.10, 95% CI = 0.80 to 1.51) than for the two studies that did not (mOR = 1.32, 95% CI = 1.01 to 1.71). No effect of socioeconomic status or region was observed.

[The meta-analyses for the cohort studies included observed and expected numbers (1) specific for nasophargyneal cancer for the studies by Coggon *et al.* (2003) and the Marsh *et al.* (2007a) reanalysis of the NCI cohort (excluding the Wallingford plant), (2) all buccal cavity and pharyngeal cancers combined (ICD 140–149) for the studies of Levine *et al.* (1984), Stroup *et al*. (1986) and Stern *et al.* (1987), and (3) all pharyngeal cancers (ICD 146–149) for the Pinkerton *et al*. (2004) study. (Stroup *et al*. noted that the one observed death of buccal cavity/pharyngeal cancer was a salivary gland tumor and Pinkerton *et al*. note that there were no observed deaths from nasopharyngeal cancer). In addition, findings for the whole workforce in the two cohorts of tannery workers studied by Stern *et al.* (1987) were included, although the authors listed formaldehyde exposure only for a small subgroup of finishing workers, in which one observed death from buccal and pharyngeal cancer combined was noted among finishing workers (expected numbers and data specific for nasopharyngeal cancer were not provided). Bachand *et al.* stated that restricting the meta-analysis to studies focusing only on nasopharyngeal cancer produced similar findings (data not reported). The meta-analyses for nasopharyngeal cancer from case-control studies included findings specific for nasopharyngeal cancers except for the study of Gustavsson *et al.* (1998), which used risk estimates for pharyngeal cancer (oropharynx and hypopharynx) and which excluded the ICD code for NPC (147). In addition, the study of NPC by West *et al.* (1993) was not included in the analysis.]

Table 3-5a. Summary of cohort studies of formaldehyde exposure and nasopharyngeal cancers[a]

Reference	Study population and follow up	Risk estimate, 95% CI; number of observed cases or deaths	Comments
Studies of industrial workers			
Andjelkovich *et al.* 1995	Iron foundry workers, Michigan, USA N = 3,929 1960–89	0 deaths, expected NR	SMR for formaldehyde exposed subcohort
Coggon *et al.* 2003	British Chemical Workers Study, UK N = 14,014 1941–2000	1 death, 2 expected	

Reference	Study population and follow up	Risk estimate, 95% CI; number of observed cases or deaths	Comments
Dell and Teta 1995	5,923 workers employed at a Union Carbide plastics manufacturing plant in New Jersey, USA 1946–67 111 formaldehyde-exposed workers 1946–88	0 deaths, expected NR	Small numbers of formaldehyde exposed workers
Edling *et al.* 1987b	Swedish abrasive materials industry N = 506 male blue collar workers Mortality 1958–83 Incidence 1958–81	1 incident case, expected NR	Small cohort Case had exposure < 0.1 mg/m^3 [<0.08 ppm] and < 5 yr exposure to formaldehyde
Hansen and Olsen 1995, 1996	Denmark N = 2,041 men, 1,263 women 1970–84	SPIR Men 1.3 (0.3–3.2); 4 Women NR; 0, 0.8 expected	SPIR adjusted for age and calendar time
Hauptmann *et al.* 2004	NCI cohort, USA N = 25,619 1966–94	SMR 2.10 (1.05–4.21); 8 *Exposure-response analyses (RR, number of exposed deaths)* Average intensity (ppm) 0 1.00; 2 (Ref.) > 0–< 0.5 NA; 0 0.5–< 1.0 0.38; 1 ≥ 1.0 1.67; 6 P_{trend}[b] 0.066 P_{trend}[c] 0.126 Peak exposure (ppm) 0 ppm 1.00; 2 (Ref.) > 0–< 2.0 NA; 0 2.0–< 4.0 NA; 0 ≥ 4.0 1.83; 7 P_{trend}[b] < 0.001 P_{trend}[c] 0.044[d] Cumulative exposure (ppm-yr) 0 ppm 2.40; 2 > 0–< 1.5 1.00; 3 (Ref.) 1.5–< 5.5 1.19; 1 ≥ 5.5 4.14; 3 P_{trenb} 0.025 P_{trend}[c] 0.029	Adjusted by calendar year, age, sex, race, and pay category; exposure was calculated with a 15-year lag interval 10 total deaths (8 exposed) from cancer of the nasopharynx; one death subsequently re-classified as oropharynx and excluded from internal analysis (6 of the 10 deaths occurred in Wallingford plant) See Section 3.2 for reanalysis by Marsh *et al.* (2004), and nested case-control study of Wallingford plant (Marsh 2007a)

Reference	Study population and follow up	Risk estimate, 95% CI; number of observed cases or deaths	Comments
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98	0 deaths, 0.96 expected	
Studies of health professionals workers			
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046 1975–85	PMR Whites 1.89 (0.39–5.48); 3 Non-whites 4.00 (0.10–22.29); 1	Small cohort
Stroup *et al.* 1986	Anatomists, members of the American Association of Anatomists, USA N = 2,317 1888–1979	0 deaths, expected NR	Small cohort
Walrath and Fraumeni 1983	All licensed embalmers in New York, USA N = 1,263 1902–80	0 deaths, expected NR	Small cohort

NR = not reported; PMR = proportionate mortality ratio; Ref. = referent group; RR = relative risk ratio; SMR = standardized mortality ratio; SPIR = standardized proportionate incidence cancer ratio.
[a]Results for NPC not reported individually by Bertazzi *et al.* (1989), Hall *et al.* (1991), Levine *et al.* (1984), Stellman *et al.* (1998), Stern (2003), Walrath and Fraumeni (1984).
[b]P_{trend} across exposed.
[c]P_{trend} across exposed and non-exposed.
[d][The P_{trend} value reported was based on only 2 values.]

Table 3-5b. Summary of case-control studies (including nested case-control studies) of formaldehyde exposure and nasopharyngeal cancer

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
Olsen *et al.* 1984 Denmark	*Population-based study* 1970–82 *Cases*: 293 men with NPC identified using Danish Cancer Registry; 266 used in analysis of NPC (excluding sarcomas) *Controls*: 2,465 men and women identified from registry with cancer of the colon, breast, or prostate and matched to cases for age, sex and year of diagnosis	Employment histories obtained from national pension and population registries and exposure classified by job title and industry	Ever exposed Men 0.7 (0.3–1.7); NR Women 2.6 (0.3–21.9); NR	No adjustment 4.2% of male and 0.1% of female controls considered exposed, number of cases not given
Vaughan *et al.* 1986a Washington, United States	*Population-based study* 1979–83 *Cases*: 27 incident cases identified using the SEER registry *Controls*: 552 frequency matched, and identified from random-digit dialing	Occupational histories and other information obtained by interview and exposure classified using a JEM	*Maximum exposure level* Low 1.2 (0.5–3.3); 7/121 Med. or high 1.4 (0.4–4.7); 4/50 *Exposure duration (yr)* 1–9 1.2 (0.5–3.1); 8/127 10+ 1.6 (0.4–5.8); 3/44 *Exposure score (weighted sum of duration and exposure level)* Low 0.9 (0.2–3.2); 3/59 High 2.1 (0.6–7.8); 3/29	Adjusted for smoking and race Low = exposure score of 5–19 High = exposure score of 20+

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
Roush *et al.* 1987	*Population-based study*	Occupational histories obtained from death certificates and city directories, and exposure classified by job title and industry	*Probably exposed: level/lag time*	Adjusted for age and calendar period
West *et al.* 1993 The Philippines	*Hospital-based study* (period of case ascertainment is unclear) *Cases:* 104 incident cases of NPC identified at Philippines General Hospital *Controls*: (1) 104 matched (sex, age, and ward type) hospital controls; and (2) 101 matched (sex, age, and neighborhood) community controls	Occupational histories and other information obtained by interview and exposure classified by job description and industry	Adjusted for wood and exhaust fumes *Duration of exposure (yr)/lag (yr)* < 15/0 2.7 (1.1–6.6); 19/8 ≥ 15/0 1.2 (0.48–3.2); 8/14 < 15/10 1.6 (0.65–3.8); 11/11 ≥ 15/10 2.1 (0.70–6.2); 8/8 *Years since 1st exposure* < 25 1.3 (0.55–3.2); 12/12 ≥ 25 2.9 (1.1–7.6); 14/10 *Age at 1st exposure* ≥ 25 1.2 (0.47–3.3); 11/10 < 25 2.7 (1.1–6.6); 16/12 *Final model: years since 1st exposure* < 25 1.2 (0.41–3.6); 12/12 ≥ 25 4.0 (1.3–12.3); 14/10	Risk estimate calculated using all controls Two models: (1) adjusted for years since first exposure to wood and exhaust fumes; analysis of years since first exposure (2) final model - further adjusted for education, consumption of processed meats and fresh fish, smoking, and use of mosquito coils and herbal medicines
Armstrong *et al.* 2000 Malaysia	*Population-based study* 1987–92 *Cases:* 282 NPC cases identified from health center records in Kuala Lumpur and Selangor among Malaysian Chinese *Controls:* 282 matched	Occupational histories and other information obtained by interview and classified by job description and industry Range of exposures: TWA = 0.16–0.35 mg/m^3 [0.13–0.28 ppm] (except	Ever exposed 0.71 (0.34–1.43)[a] No exposure-response relation with increasing duration, lag time, or intensity No. of exposed cases not specified; 9.9% of total cases exposed to formaldehyde and 49 pairs (at least one exposed to formaldehyde) included in analyses	Adjusted for smoking and diet Controls selected by house to house sampling

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
	(sex and age) controls	adhesives industry, ≥ 0.37 mg/m^3 [≥ 0.30 ppm])		
Vaughan *et al.* 2000 United States (Connecticut, Iowa, Utah, Washington, and Detroit)	*Population-based study* 1987–93 *Cases*: 196 NPC identified from SEER registries *Controls*: 244 frequency matched (age, sex, and registry) controls in the same locations identified from random digit dialing	Occupational histories and other information obtained by interview (participant and proxy) and classified by job description and industry *Exposure group:8-h TWA (ppm)* Low < 0.10 Moderate ≥ 0.10–< 0.50 High ≥ 50	Histological type *Ever exposed* All epithelial 1.3 (0.8–2.1); 79/79 Undifferentiated and non-keratinizing 0.9 (0.4–2.0); 18/79 Differentiated squamous cell 1.5 (0.8–2.7); 49/79 Epithelial (NOS) 3.1 (1.0–9.6); 12/79 *Exposure duration (P_{trend})* All epithelial 0.07 Undifferentiated and non-keratinizing 0.82 Differentiated squamous cell 0.03 Epithelial NOS 0.04 *Maximum exposure* P_{trend} > 0.05 for all histological types Analysis excluding undifferentiated and non-keratinizing histologies *Possible, probable, or definite exposure* Ever exposed 1.6 (1.0–2.8); 61/79 Duration (yr) 1–5 0.9 (0.4–2.1); 16/41 6–17 1.9 (0.9–4.4); 20/19 ≥ 18 2.7 (1.2–6.0); 25/19 P_{trend} 0.014 Cumulative exposure (ppm-yr) 0.05–0.40 0.9 (0.4–2.0); 15/40 > 0.4–1.10 1.8 (0.8–4.1); 22/20 > 1.10 3.0 (1.3–6.6); 24/19	Adjusted for age, sex, region, smoking, proxy status, and education Exposure to wood dust did not increase the risk of NPC in this study

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
			P_{trend} 0.033 *Probable or definite exposure* Ever 2.1 (1.1–4.2); 27/30 Duration, P_{trend} 0.069 Cumulative, P_{trend} 0.13 *Definite exposure* Ever exposed 13.3 (2.5–70); 10/2 Duration, P_{trend} < 0.001 Cumulative, P_{trend} < 0.001	
Hildesheim *et al.* 2001 Taipei, Taiwan	*Population-based study* 1991–94 *Cases*: 375 NPC cases identified at 2 tertiary care hospitals *Controls*: 325 individually matched (sex, age, residence) controls with no history of NPC identified using a National Household Registration system	Occupational histories and other information obtained by interview and classified by job title and industry	Ever 1.4 (0.93–2.2); 74/41 *Cumulative exposure (ppm-yr)* < 25 1.3 (0.70–2.4); 29/19 ≥ 25 1.5 (0.88–2.7); 45/22 P_{trend} 0.10 *Exposure duration (yr)* All subjects ≤ 10 1.3 (0.69–2.3); 31/21 > 10 1.6 (0.91–2.9); 43/ 20 P_{trend} 0.08 No association with years since first exposure or age at first exposure Subjects without exposure to wood (yr) ≤ 10 1.3 (NR); 23/16 > 10 1.7 (NR); 28/13 P_{trend} 0.09 Risk estimates (~2) increased in individuals with high average intensity or probability of exposure but no exposure-response relationships with duration or cumulative exposure were observed *Joint effects of exposure (years) to wood dust and formaldehyde*	Adjusted for age, sex, ethnicity, and education Exposure to wood dust was associated with an increased risk of NPC in this study Correlation between wood and formaldehyde exposure in the control population ranged from 0.26 to 0.35

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
			Wood dust / Formaldehyde (yr) Yr: 0 / ≤ 10 / > 10 None: 1.0 / 1.3 / 1.7 ≤ 10 yr: 1.4 / 1.0 / 1.8 > 10 yr: 2.6 / (3/0)[b] / 1.8	
Li *et al.* 2006 Shanghai, China	*Case-cohort study* 1989–98 *Cohort:* 267,400 women textile workers in 526 factories from 1925 to 1958 *Cases*: 67 NPC cases with occupational history information *Controls:* 3,188 women randomly selected from cohort and matched by age distribution to cases	Occupational histories obtained from employment records or interviews with supervisors or co-workers, or the subject themselves (10% of subjects) JEM developed based on knowledge of process and frequency of exposures in a process	No cases and 10 non-cases were exposed to formaldehyde	Very few subjects were classified as being exposed to formaldehyde No measurement of exposure; exposure misclassification likely
Hauptmann *et al.* 2009	*Nested case-control study* *Cohort:* 6,808 death certificates from 1960 to 1986. Identified from registries of the National Funeral Director Association, licensing board and state funeral director's associations, NY State Bureau of Funeral Directors and CA Funeral Directors and Embalmers *Cases:* 4 NPC cases *Controls:* 265 randomly selected with deaths attributed to other causes	Occupational history obtained by interviews with next of kin and co-workers (multiple) using detailed questionnaires. Exposure was assessed by linking questionnaire responses to an exposure assessment experiment Exposure (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure response data	Ever embalming 0.1 (0.01–1.2); 2 Average exposure levels of 2 exposed cases were equal or higher than the corresponding levels among exposed controls for most exposure metrics.	Cohorts include Hayes *et al.* 1990, Walrath *et al.* 1983, 1984

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
	excluding cancer of the buccal cavity and pharynx, respiratory system, and eye, brain or other parts of the nervous system.			

8-h TWA = 8-hour time-weighted average; JEM = job exposure matrix; NOS = not otherwise specified; OR = odds ratio; RR = relative risk ratio; SEER = Surveillance, Epidemiology and End Results Program (NCI).
[a]Only 8 individuals were exposed for > 10 years outside the 10-year latency period.
[b]Number of cases and controls.

3.6.3 Other head and neck cancers

This section summarizes studies of head and neck cancers other than sinonasal cancers and nasopharyngeal cancers, including combined cancers of the upper respiratory system, and cancers of the oral or buccal cavity, pharynx, the oro- and/or hypopharynx (OHPC), salivary glands, and larynx. See Section 3.1 for a description of these head and neck cancers, and Section 3.5.3 for a detailed summary of corresponding case-control studies and Tables 3-6a and 3-6b for a summary of the site-specific risk estimates. Note that no results were reported for other head and neck cancers in cohort studies conducted by Bertazzi *et al.* (1989), Dell and Teta (1995), Edling *et al.* (1987b), Hall *et al.* (1991), Stellman *et al.* (1998).

Known risk factors for cancers of the upper respiratory system include smoking and alcohol use, although these factors contribute more heavily to some cancer sites than others. All of the case-control studies reviewed in this section adjusted for smoking, with the exception of Wilson *et al.* (2004).

3.6.3.1 Upper respiratory cancer

One large nested case-control study (Partanen *et al.* 1990) (see Table 3-6b) and the NCI cohort of mixed industries (Hauptmann *et al.* 2004) (see Table 3-6a) examined all upper respiratory tract cancers combined. Partanen *et al.* (1990) found an increase in cancer risk in relation to formaldehyde exposure (OR = 2.38, 95% CI = 0.43 to 13.2, deaths adjusted for vital status), but this was based on only 2 deaths. Hauptmann *et al.* (2004) reported higher RRs for the highest categories of peak and average exposure (compared with the lowest categories of exposure), although no statistically significant trends were observed (see Table 3-6b). Hauptmann *et al.* (2004) did not control for smoking in the cohort because, according to the authors, the prevalence of smoking did not differ by formaldehyde exposure.

3.6.3.2 Buccal cavity and pharyngeal cancer

Elevated (although not statistically significant) risks for cancers of the mouth, buccal cavity, or buccal cavity combined with the pharynx were observed in several cohort studies, including iron foundry workers exposed to formaldehyde (SMR = 1.31, 95% CI = 0.48 to 2.86, 6 deaths) (Andjelkovich *et al.* 1995), male and female garment workers with potential exposure to formaldehyde (SMR = 1.33, 95% CI = 0.36 to 3.41, 4 deaths) (Pinkerton *et al.* 2004), British chemical workers (SMR for mouth = 1.28, 95% CI = 0.47 to 2.78; 6 deaths, SMR for pharynx = 1.55, 95% CI = 0.87 to 2.56; 15 deaths) (Coggon *et al.* 2003), and embalmers from the United States (PMR for whites = 1.19 (95% CI = 0.78 to 1.74, 26 deaths, and PMR for non-whites = 1.25 (95% CI = 0.34 to 3.2, 4 deaths) (Hayes *et al*. 1990), New York (PMR = 1.13, 8 deaths among all white males, and 2.01, 7 deaths among men licensed only as embalmers) (Walrath and Fraumeni 1983), and California (PMR = 1.3, 8 deaths) (Walrath and Fraumeni 1984). Hansen and Olsen (1996) reported a SPIR of 1.1 (95% CI = 0.7 to 1.7; 23 cases) among male Danish workers, and one death from buccal cavity and pharynx cancer was reported among formaldehyde-exposed tannery workers (Stern *et al.* 1987) (findings were not reported in the 2003 follow-up). No association with formaldehyde exposure and cancer of the

buccal cavity or buccal cavity and pharynx cancers (combined) was found in the NCI cohort study (Hauptmann *et al.* 2004), the Danish cohort (women) (Hansen and Olsen 1996), and in two studies of health professionals (Levine *et al.* 1984 and Stroup *et al.* 1986) (see Tables 3-6a and 3-6b), or in a cancer registry study among Finnish men and women by Tarvainen *et al.* (2008) (SIRs ranged from 0.73 to 1.01 for low, medium, and high exposure).

Two population-based case-control studies found nonsignificant increases for cancer of the oral cavity or oral cavity and pharynx combined and any exposure to formaldehyde: OR for oral cavity and oropharynx combined = 1.6 (95% CI = 0.9 to 2.8, 25 cases) (Merletti *et al.* 1991) and OR for oral cavity = 1.28 (95% CI = 0.64 to 2.54, 14 cases) (Gustavsson *et al.* 1998) (Table 3-6b). In the only study of salivary gland cancer, Wilson *et al.* (2004) found that risks increased with increasing probability of exposure, and intensity of exposure (combined) was associated with cancer ($P_{trend} < 0.001$, in analyses including low-level exposures). Though this case-control study was quite large, no adjustment was made for smoking status.

No increased risks were found for pharyngeal cancer in the Swedish case-control study (Gustavsson *et al.* 1998). Laforest *et al.* (2000) found a positive association between formaldehyde and hypopharyngeal squamous-cell carcinoma in a hospital-based case-control study in France; this study also noted a strong exposure-response trend with increasing probability ($P_{trend} < 0.005$), duration ($P_{trend} < 0.04$), and cumulative exposure ($P_{trend} < 0.14$) to formaldehyde. Berrino *et al.* (2003) reported increased risks of hypopharyngeal cancer among workers with > 10 years duration of exposure, although risk estimates did not increase with increasing duration of exposure or probability of exposure; this study included a validation analysis which suggested that the exposure assessment was not sensitive to formaldehyde. Vaughan *et al.* (1986a) found a statistically nonsignificant increased risk for oro-and hypopharynx cancers (combined) among subjects with high exposure scores or longer exposure duration.

3.6.3.3 Laryngeal cancer

With respect to laryngeal cancer, none of the cohort studies reported an association with laryngeal cancer except for a statistically nonsignificant increase among highly exposed British chemical workers (SMR = 1.56, 95% CI = 0.63 to 3.22; 7 deaths) (Coggon *et al.* 2003) (see Table 3-6a). In internal analyses, Hauptmann *et al.* (2004) observed an increased risk (OR = 2.02, 95% CI not reported) for the highest category of exposure intensity only.

Among five case-control studies that focused on cancer of the larynx, Wortley *et al.* (1992) found elevated risks at the highest levels of peak exposure with greater than 10 years of exposure (OR = 4.3, 95% CI = 1.0 to 18.7, number of cases not reported), but no exposure-response relationship was observed with duration, peak, or level of exposure. Gustavsson *et al.* (1998) observed an elevated though statistically nonsignificant risk ratio for any exposure and squamous-cell type laryngeal cancer (OR = 1.45, 95% CI = 0.83 to 2.51, 23 cases). In a case-control study of 316 laryngeal cancers in a hospital-based multi-center European study, Shangina *et al.* (2006) reported a statistically nonsignificant increase in laryngeal cancer in association with formaldehyde exposure

(OR = 1.68, 95% CI = 0.85 to 3.31, 18 exposed cases); risks increased with increasing duration (P_{trend} = 0.06) and cumulative exposure (P_{trend} = 0.07). However, in other studies, effect estimates were generally close to the null. Laforest *et al*. (2000) found no association between probability of exposure, exposure duration, and cumulative exposure to formaldehyde and laryngeal cancer. Similarly, no evidence of an exposure-response relationship or no increase in risk of laryngeal cancer (OR = 1.0, 95% CI = 0.8 to 1.3, 89 exposed cases) was found in a hospital-based case-control study by Elci *et al.* (2003). In a subsequent analysis of only those subjects who had no history of alcohol use or smoking (Elci and Akpinar-Elci 2009), a small but nonsignificant increase in laryngeal cancer was observed in association with formaldehyde exposure (OR = 1.2, 95% CI = 0.7 to 2.0, 27 exposed cases).

3.6.3.4 Meta-analysis

In a meta-analysis of 10 occupational cohort mortality studies that included analyses of oral cavity and pharyngeal cancers (Table 3-10), Bosetti *et al.* (2008) calculated a combined estimated RR (using a weighted average of SMRs and/or PMRs) of 1.09 (95% CI = 0.88 to 1.34, 88 deaths) among industrial workers and 0.96 (95% CI = 0.75 to 1.24, 61 deaths) among medical workers exposed to formaldehyde.

Table 3-6a. Summary of cohort studies of formaldehyde exposure and cancers of the oral cavity, pharynx, and larynx[a]

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
Studies of industrial workers			
Andjelkovich *et al.* 1995	Iron foundry workers, MI USA N = 3,929 1960–89	*Buccal cavity/pharynx* SMR 1.31 (0.48–2.86); 6 Internal analysis quartiles of cumulative exposure compared with never): 6 exposed, 5 unexposed Ever 0.59 (0.14–2.93) Q3+Q4 1.16 (0.20–6.51) *Larynx* SMR 0.98 (0.11–3.53); 2	SMR for formaldehyde-exposed subcohort Internal analyses using unexposed workers as referent were adjusted for race, smoking, and exposure to silica
Coggon *et al.* 2003	British Chemical Workers Study, UK N = 14,014 1941–2000	SMR Mouth 1.28 (0.47–2.78); 6 Pharynx 1.55 (0.87–2.56); 15 Larynx 1.07 (0.58–1.79); 14 *High-exposed workers* Mouth 1.32 (0.16–4.75); 2 Pharynx 1.91 (0.70–4.17); 6 Larynx 1.56 (0.63–3.22); 7	
Hansen and Olsen 1995, 1996	Denmark N = 2,041 men 1,263 women 1970–84	SPIR *Buccal cavity/pharynx*[#] Men 1.1 (0.7–1.7); 23 Women 0.8 (0.3–1.7); 6 *Larynx* Men 0.9 (0.6–1.2); 32 Women 0.6 (0.1–1.7); 3	SPIR adjusted for age and calendar time Workers had 10 or more years of formaldehyde exposure before diagnosis
Hauptmann *et al.* 2004	NCI cohort, USA N = 25,619 1966–94	SMR Buccal cavity 1.01 (0.77–1.34); 49 Larynx 0.95 (0.63–1.43); 23 Internal analysis RR, cases *Upper respiratory tract* Mean intensity (ppm) 0 1.47; 11 > 0–< 0.5 1.00; 18 (Ref.) 0.5–< 1.0 1.69; 11 ≥ 1.0 2.21*; 15 P_{trend}[b] 0.122 P_{trend}[c] 0.158 Peak exposure (ppm) 0 1.32; 11 > 0–< 2.0 1.00; 14 (Ref.)	Adjusted by calendar year, age, sex, race, and pay category; exposure was calculated with a 15-year lag interval

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
		2.0–< 4.0 1.24; 12 ≥ 4.0 1.65; 18 P_{trend}[b] 0.142 P_{trend}[c] 0.302 Cumulative exposure (ppm-yr) 0 1.24; 11 > 0–< 1.5 1.00; 23 (Ref.) 1.5–< 5.5 1.92; 15 ≥ 5.5 0.86; 6 P_{trend}[b] 0.765 P_{trend}[c] 0.744 *Buccal cavity* Mean intensity (ppm) 0 2.42*; 13 > 0–< 0.5 1.00; 18 (Ref.) 0.5–< 1.0 2.41; 16 ≥ 1.0 1.89; 15 P_{trend}[b] 0.504 P_{trend}[c] 0.791 Peak exposure (ppm) 0 2.08; 13 > 0–< 2.0 1.00; 15 (Ref.) 2.0–< 4.0 1.07; 11 ≥ 4.0 1.83; 23 P_{trend}[b] 0.072 P_{trend}[c] 0.433 Cumulative exposure (ppm-yr) 0 1.98; 13 > 0–< 1.5 1.00; 25 (Ref.) 1.5–< 5.5 1.59; 12 ≥ 5.5 1.74; 12 P_{trend}[b] 0.365 P_{trend}[c] 0.422 *Larynx* Mean intensity (ppm) 0 1.09; 6 > 0–< 0.5 1.00; 11 (Ref.) 0.5–< 1.0 1.00; 4 ≥ 1.0 2.02; 8 P_{trend}[b] 0.263 P_{trend}[c] 0.284 Peak exposure (ppm) 0 0.86; 6 > 0–< 2.0 1.00; 10 (Ref.) 2.0–< 4.0 1.19; 8 ≥ 4.0 0.64; 5 P_{trend}[b] -0.572 P_{trend}[c] -0.645 Cumulative exposure (ppm-yr)	

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
		0 0.97; 6 > 0–< 1.5 1.00; 13 (ref) 1.5–< 5.5 1.81; 9 ≥ 5.5 0.23; 1 P_{trend}[b] -0.027 P_{trend}[c] 0.043	
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98	SMR Buccal cavity 1.33 (0.36–3.41); 4 Pharynx 0.64 (0.13–1.86); 3 Larynx 0.88 (0.18–2.59); 3	
Stern *et al.* 1987 (data for this site not reported in 2003 update)	Workers employed in two chrome leather tannery plants, USA N = 9,365 1940–82 Formaldehyde-exposed workers in the finishing department N = NR (1,050 deaths from all causes)	SMR or observed deaths Buccal cavity/ Pharynx 1 death Larynx NR	SMR reported for formaldehyde-xposed workers
General population study			
Tarvainen *et al.* 2008 Finland	Male and females born 1906–45 from the Finnish Cancer Registry with oral cavity, tongue,and pharyngeal cancers (excluding nasopharynx) N = 2,708 1971–95	SIR *Formaldehyde, estimated cumulative exposure, ppm-yr:* Low 0.79 (0.6–1.03); 59 Medium 1.01 (0.43–1.98); 8 High 0.73 (0.27–1.59); 6	Cancer registry-based standardized incidence study Adjusted for age, calendar period and socioeconomic status Exposures lagged for ten years
Studies of health professional workers			
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046	PMR *Buccal cavity/pharynx* Whites 1.19 (0.78–1.74); 26 Non-whites 1.25 (0.34–3.2); 4 *Larynx* Whites 0.64 (0.26–1.33); 7 Non-whites 0 death vs. 1.6 exp.	Small cohort

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
	1975–85		
Levine *et al.* 1984	Licensed embalmers in Ontario, Canada N = 1,413 First licensed 1928–57 Follow-up through 1977	Observed deaths Buccal cavity/ pharynx 1 death, 2.1 expected Larynx 1 death, 1 expected	Small cohort
Stroup *et al.* 1986	Anatomists, members of the American Association of Anatomists, USA N = 2,317 1888–1979	SMR Buccal cavity/ pharynx 0.2 (0.0–0.8); 1 Larynx 0.4 (0.0–2.0); 1	Small cohort
Walrath and Fraumeni 1983	All licensed embalmers and funeral directors in New York, USA N = 1,263 1902–80	PMR (men) or observed deaths *Buccal cavity and pharynx* All whites 1.13 (NR); 8, $P > 0.05$ Embalmers only 2.01 (NR); 7, P > 0.05 Larynx All whites 2 deaths, 3.4 expected All non-whites 2 deaths*	Small cohort
Walrath and Fraumeni 1984	All white male licensed embalmers in California, USA N = 1,109 1916–80	PMR (white males) Buccal cavity/ pharynx 1.31 (NR); 8, $P > 0.05$ Larynx 2, 2.6 expected	Small cohort

*$P < 0.05$.
NPC = nasopharyngeal cancer; NR = not reported; PCMR = proportionate cancer mortality ratio; PMR = proportionate mortality ratio; Q = quartile; Ref. = referent group; RR = relative risk ratio, SMR = standardized mortality ratio; SPIR = standardized proportionate incidence cancer ratio.
[a]Results for oral cavity, pharynx and larynx cancers were not reported by Edling *et al.* 1987b, Dell and Teta, 1995, Bertazzi *et al.* 1989, Stellman *et al.* 1998, and Hall *et al.* 1991.
[b]P_{trend} across exposed.
[c]P_{trend} across exposed and non-exposed.

Table 3-6b. Summary of case-control studies (including nested case-control studies) and cancer registry studies of formaldehyde exposure and cancers of the oral cavity, pharynx, and larynx

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
Partanen *et al.* 1990; (update of Partanen *et al.* 1985) Finland	*Nested case-control study* Cohort: particleboard, plywood, or formaldehyde glue factory workers, 1957–80 *Cases:*136 cases of all respiratory system cancer including tongue, pharynx, larynx, epiglottis, trachea, and lung *Controls:* 408 controls randomly selected from cohort; 3:1 ratio, matched on year of birth and alive at date of case diagnosis	Occupational histories obtained using plant records and classified using factory-specific JEMs	Upper respiratory only ≥ 3 ppm-months 2.38 (0.43–13.2); 2 With 10-yr lag 2.40 (0.31–18.6); 2 Referent group < 3 ppm-months	Adjusted for vital status and smoking
Wilson *et al.* 2004 United States (24 states)	*Death certificate-based study* 1984–89 *Cases*: 2,505 cases of salivary gland carcinoma (60% men, 7% black) identified by mortality records *Controls*: 9,420 frequency matched (age, race, sex and region) randomly selected from deaths not related to infectious disease	Occupational histories were obtained from death certificates and classified using a JEM	White men: Salivary gland *Probability/intensity of exposure* Low/low 0.9 (0.70–1.15) Low/mid-high 0.7 (0.35–1.26) Mid-high/low 2.4 (0.86–6.75) Mid-high/mid-high 1.6 (1.30–2.0) P_{trend} < 0.001	Adjusted for age, marital status, and socioeconomic status
Vaughan *et al.*	*Population-based study,*	Occupational histories	Oro- and hypopharynx	Adjusted for sex, age, smoking,

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
1986a Washington, United States	1980–83 Cases: 205 cases of oro- and hypopharyngeal cancer identified by SEER registry *Controls*: 552 frequency matched, and identified by random-digit dialing	obtained by interview and classified using a JEM	*Exposure scores* Low 0.6 (0.3–1.2); 14/59 High 1.5 (0.7–3.0); 21/29 *Exposure Duration (yr)* 1–9 0.6 (0.3–1.0); 32/127 > 10 1.3 (0.7–2.5); 26/44 *Maximum exposure level* OR < 1.0 for all groups and CIs included 1.0	and alcohol For exposure scores: Low = 5–19 and High = 20+
Merletti *et al.* 1991 Turin, Italy	*Population-based study* Jul. 1982–Sep. 1984 *Cases:* All male Turin residents diagnosed with cancer of the oral cavity and oropharynx (103 eligible cases), 86 agreed to interview *Controls:* random sample of 679 age- and sex-matched controls: 373 were enrolled (agreed to interview and had complete occupational history)	Occupational histories obtained by interview and classified using a JEM	Oral cavity and oropharynx combined *Exposure to formaldehyde* Any 1.6 (0.9–2.8); 25/79 Probable or definite 1.8 (0.6–5.5); 6/13 No exposure-response relationships observed, but elevated ORs observed for most exposure categories	Adjusted for age, education, area of birth, smoking, and alcohol

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
Laforest *et al.* 2000 France	*Hospital-based study* Jan. 1989–Apr. 1991 *Cases*: 201 men with confirmed SCC of the hypopharynx identified from 15 French hospitals (from 644 eligible cases of laryngeal and pharyngeal cancers and 80% participation rate) *Controls*: 355 controls matched (frequency) by age and hospital with primary cancer at other sites; 296 interviewed and included in analyses	Occupational histories and other information obtained by interview and exposure to formaldehyde classified using a JEM	Hypopharynx - SCC *Probability of exposure (%)* < 10 1.08 (0.62–1.88); 42/50 10–50 1.01 (0.44–2.31); 15/20 > 50 3.78 (1.50–9.49); 26/15 P_{trend} < 0.005 *For probability of exposure ≥ 10%:* Ever exposed 1.74 (0.91–3.34); 41/35 Exposure duration (yr) < 7 0.74 (0.20–2.68); 3/2 7–20 1.65 (0.67–4.08); 13/11 20+ 2.70 (1.08–6.73); 16/16 P_{trend} < 0.04 Cumulative level < 0.02 0.78 (0.11–5.45); 3/2 0.02–0.09 1.77 (0.65–4.78); 13/11 > 0.09 1.92 (0.86–4.32); 25/22 P_{Prend} < 0.14	Adjusted for age, smoking, alcohol, and exposure to coal dust and asbestos; subjects matched by age Controls included subjects with primary cancers at sites that have suspected associations with formaldehyde exposure Also studied laryngeal cancer (see below)
Berrino *et al.* 2003 Europe: France, Italy, Spain, Switzerland	*Population-based study* 1979–82 *Cases:* 315[a] men under 55 with hypopharyngeal/ laryngeal cancer (213 endolarynx and 100 HPC + epilarynx) identified from 6 health care centers *Controls:* 819 men under 55 identified from a random sample (age and sex stratified) of the population from each center 113 exposed cases and 192 unexposed cases;	Occupational histories and other information obtained by interview and exposure to formaldehyde were classified using a JEM. Some interviews with next of kin	Individuals less than 55 Hypopharynx/larynx Ever exposed 1.3 (0.8–2.0); 113/192 *Probability of exposure:* Possible 1.5 (0.9–2.4); 90/146 Probable 0.9 (0.4–1.9); 23/50 *Exposure duration (yr)* < 10 1.1 (0.5–2.1) 10–19 2.2 (1.2–4.2) 20+ 1.3 (0.6–2.8) 10+ (20-yr lag) 1.7 (0.9–3.3) *Anatomical origin of tumor* Endolarynx Possible 1.4 (0.8–2.7)	Adjusted for age, sex, smoking, alcohol, diet, SES, center, and exposure to asbestos, PAH, Cr, As, wood dust, solvents, and other dusts and gases Independent validation of JEM classified 14% of the unexposed jobs as definitely exposed No significant associations found in analysis of individuals (695 cases and 1,357 controls) over 55 (numbers for formaldehyde not given)

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
	196 exposed controls and 623 unexposed controls		Probable 1.0 (0.4–2.3) *Hypopharnx (includes epilarynx)* Possible 1.3 (0.6–2.6) Probable 0.5 (0.1–1.8)	
Gustavsson *et al.* 1998 Sweden	*Population-based case-control studies various cancers* Jan. 1988–Jan. 1991 *Cases:* identified from health care records and cancer registries Oral cavity (N = 128) Pharynx (N = 138) Larynx (N = 157) *Controls:* 641 selected from population registries and matched by region and age	Occupational histories, lifestyle and environmental information obtained by interview and exposure classified by job title and industry	*Ever exposed* Oral cavity 1.28 (0.64–2.54); 14 Pharynx 1.01 (0.49–2.07); 13 Larynx squamous-cell type 1.45 (0.83–2.51); 23 No exposure relationship with cumulative exposure or duration	Adjusted for age, region, smoking, and alcohol
Wortley *et al.* 1992 Washington,	*Population-based case-control study* Sep. 1983–Feb. 1987 *Cases:* 235 cases of larynx cancer identified from population-based cancer registry in Seattle (with phones) *Controls:* 547 identified by random-digit dialing, matched 2:1 with cases on age and sex 58 exposed cases and 124 exposed controls	Occupational histories and other information obtained by phone interview and exposure to formaldehyde classified using a JEM 7% of case interviews with next of kin	Larynx *Analyses excluding low-level exposure* Exposure category scores, > 10-yr exposure Medium or high 4.2 (0.9–19.4); NR High 4.3 (1.0–18.7); NR *Analyses including low-level exposure* No exposure-response relationship was seen with duration, peak, or level of exposure	Adjusted for age, smoking, alcohol, and education; subjects matched by age and sex
Laforest *et al.* 2000	*Hospital-based study*, 1989–91	Occupational histories and other information	Larynx	Adjusted for age, smoking, alcohol, and exposure to coal

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
France	1989–91 *Cases*: 296 men with confirmed cancer of the larynx identified from 15 French hospitals *Controls*: 296 men matched (frequency) by age and hospital with primary cancer at other sites	obtained by interview and exposure to formaldehyde classified using a JEM	*Probability of exposure (%)* < 10 1.16 (0.73–1.86); 58/50 10–50 1.12 (0.55–2.30); 23/20 > 50 1.04 (0.44–2.47); 21/15 *For probability of exposure ≥ 10%:* Ever exposed 1.17 (0.63–2.17); 44/35 Duration of exposure (yr) ≤ 7 1.68 (0.60–4.72); 15/7 7–20 0.86 (0.33–2.24); 14/12 20+ 1.14 (0.47–2.74); 15/16 Cumulative level (ppm-yr) <0.02) 0.68 (0.12–3.90); 4/2 0.02–0.09 1.86 (0.76–4.55); 17/11 > 0.09 0.91 (0.42–1.99); 23/22 *Larynx subtypes/ever exposed* Endolarynx 1.07 (0.69–1.66); 65 Epilarynx 1.25 (0.71–2.19); 37	dust and asbestos; subjects matched by age Controls included subjects with primary cancers at sites that have suspected associations with formaldehyde exposure
Elci and Akpinar-Elci 2009, Elci *et al.* 2003 Turkey	*Hospital-based case-control study* 1979–84 *Cases:* 951 men with confirmed cases of laryngeal cancer, 189 non-smoking and non-drinking cases *Controls:* 1,519 hospital patients, 536 non-smoking and non-drinking controls	Occupational histories and lifestyle information obtained by interview and exposure classified using a JEM	Larynx *Total population* Ever 1.0 (0.8–1.3); 89 Exposure intensity Low 1.1 (0.8–1.5); 82 Medium 0.5 (0.2–1.3); 6 High 0.7 (0.1–7.1); 1 Exposure probability Low 1.0 (0.7–1.4); 72 Medium 1.1 (0.6–2.2); 16 High 1.0 (0.1–11.2); 1 *Non-smoking and non-drinking analysis – ever exposure* All larynx 1.2 (0.7–2.0); 27	Adjusted for age, smoking, and alcohol Hospital controls included Hodgkin's lymphoma, soft tissue sarcoma, testicular cancer and non-cancer

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases and controls	Comments
			Supraglottic 1.0 (0.5–2.2); 11 Glottic 1.6 (0.7–3.7); 8 Other 1.1 (0.5–2.7); 8	
Shangina *et al.* 2006 Central and Eastern Europe	*Multi-center case-control study* 1999–2002 *Cases:* 316 males with incident laryngeal cancer (histologically or cytologically confirmed), ages 15–79, with occupational data *Controls:* 728 male hospital controls with occupational data, recruited within 6 month of recruitment period of case, and matched to case by age	Occupational history obtained by interviews and evaluated by industrial hygienists	*Larynx* Ever exposed 1.68 (0.85–3.31); 18 Cumulative exposure (mg/m^3-hours) ≥22,700 3.12 (1.23–7.91); NR *Exposure response (P_{trend})* Duration of exposure 0.06 Cumulative exposure 0.07	OR only reported for highest level of cumulative exposure. Hospital controls excluded diseases and cancer related to tobacco or alcohol. Risk estimates for formaldehyde exposure and hypopharyngeal cancer not reported (less than 10 exposed cases).

HPC = hypopharyngeal cancer; JEM = job exposure matrix; OR = odds ratio; RR = relative risk ratio; SCC = squamous-cell carcinoma; SEER = Surveillance, Epidemiology and End Results Program (NCI).

[a]Original study included 1,010 cases and 2,176 controls. Complete lifetime occupational histories were only available for subjects under 55, so analysis was restricted to this age group.

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3.6.4 Respiratory cancers or lung cancer

The relationship between occupational exposure to formaldehyde and lung or respiratory system cancers has been investigated in a large number of cohort, nested case-control, and population-based case-control studies. The key findings are summarized in Table 3-7a and 7b. (See Section 3.5.4 for a detailed summary of case-control studies investigating lung cancer.)

3.6.4.1 Cohort studies

Increased risks for lung or respiratory cancer were reported in five of the industrial cohorts, two of which were statistically significant or borderline significant (Andjelkovich *et al.* 1995, Dell and Teta 1995, Hansen and Olsen 1995, 1996 [women only], Coggon *et al.* 2003). (See below for a discussion of the nested case-control study of the iron foundry workers reported by Andjelkovich *et al*. [1994].) Coggon *et al.* (2003) reported a statistically significant increase in the risk of lung cancer among highly exposed (> 2 ppm) British chemical workers (SMR = 1.58, 95% CI = 1.40 to 1.78, 272 deaths). Risks increased with increasing exposure level (low, medium, high, $P_{trend} < 0.001$), but not with duration of exposure. In the NCI cohort (Hauptmann *et al.* 2004), no increased risk of lung cancer was observed in external analysis, and no clear trends with average, peak, or cumulative exposure were observed in internal analyses, although elevated RRs were found in some exposure categories. No increases were observed in the NIOSH garment workers cohort (Pinkerton *et al.* 2004), the Danish mixed industry cohort (men) (Hansen and Olsen 1995, 1996), or the abrasive material industry (Edling *et al.* 1987b); or among formaldehyde resin producers (Bertazzi *et al.* 1989), tannery workers exposed to formaldehyde (Stern *et al.* 2003), or most of the studies of health professional workers (see Table 3-7a). Stellman *et al*. (1998) reported a significant risk for woodworkers exposed to formaldehyde (SMR = 2.63 (95% CI = 1.25 to 5.51, 7 deaths) but not among non-woodworkers exposed to formaldehyde (SMR = 0.93, 95% CI = 0.73 to 1.18, 104 deaths).

3.6.4.2 Case-control studies

Ten case-control (including nested case-control) studies have evaluated the relationship between exposure to formaldehyde and lung or respiratory cancer; two studies reported on respiratory system cancers and eight studies on lung cancer independently (see Table 3-7b). Marsh *et al.* (2001) and Stone *et al*. (2004) reported increased risks of respiratory (lung and larynx) cancers associated with formaldehyde exposure in their nested case-control study within an industrial cohort of glass wool manufacturing workers (OR = 1.61, 95% CI = 1.02 to 2.57, 591 ever-exposed cases, adjusted for smoking but not other exposures among men and OR = 1.24, 95% CI = 0.74 to 2.09 for cumulative exposure among women). Partanen *et al.* (1985, 1990) noted elevated but statistically nonsignificant risks in combined mouth, tongue, nose and sinuses, pharynx, larynx, trachea, epiglottis, and lung cancer associated with formaldehyde exposure; in their updated analysis (Partanen *et al.* 1990), the OR for cumulative exposure of at least 3 ppm-months with a 10-year lag was 1.39 (95% CI = 0.40 to 4.10). Risk estimates were higher for cancers of the upper respiratory system only (see Table 3-6b and Section 3.6.3).

Several studies reported increased risks (both statistically significant and nonsignificant risk) for lung cancer. Increased risks were found among glass wool workers with 100 to 999 cumulative days of exposure to formaldehyde (RR = 1.27, 95% CI = 0.50 to 3.21, 15 deaths) (Chiazze *et al.* 1997), and iron foundry workers exposed to formaldehyde (OR = 1.31. 95% CI = 0.83 to 2.07, unlagged exposure, number of deaths not reported) (Andjelkovich *et al*. 1994); however, risks decreased in exposure-response analyses by lag or duration of exposure. Increased risks were also observed in two population-based case-control studies and one hospital-based case-control study. Gérin *et al.* (1989) reported an OR of 1.5 (95% CI = 0.8 to 2.8) for high-level formaldehyde exposure only with at least 10-years duration, but no adjustment was made for smoking. Coggon *et al.* (1984) found a statistically significant increased risk for lung cancer cases among men ever exposed to formaldehyde (OR = 1.5, 95% CI = 1.2 to 1.8, 296 cases), but no risk was observed among men in occupations with high exposure (OR = 0.9, 95% CI = 0.6 to 1.4, 44 exposed cases). The hospital-based case-control study evaluated risks for lung adenocarcinoma; a statistically significant risk was observed for ever exposure to formaldehyde (OR = 1.7, 95% CI to 1.1 to 2.8, 32 exposed cases), and the risk increased with increasing duration of exposure (P_{trend} = 0.004) (De Stefani *et al.* 2005). However, no increased risks of lung cancer were reported in a nested case-control study of Dow Chemical workers (Bond *et al.* 1986), a small cancer registry study of physicians (Jensen and Andersen 1982), or a population-based case-control study of women (Brownson *et al.* 1993).

For lung cancer and any respiratory system cancer, smoking is the principal potential confounder; occupational exposure to dusts, synthetic vitreous fibers and other ambient exposures may also be of concern. Several studies have attempted to make some adjustment for smoking status (exceptions include Coggon *et al.* 1984, Bond *et al.* 1986, Gérin *et al.* 1989, Chiazze *et al.* 1997, and Hauptmann *et al.* 2004), although in most cases, estimates of smoking are limited to a sample of subjects, to proxy data, or to ever-never smoking status.

3.6.4.3 Meta- analysis

In a meta-analysis of 14 occupational cohort mortality studies, which included deaths from lung cancer (Table 3-10), Bosetti *et al*. (2008) calculated combined estimated RRs (using weighted SMRs and/or PMRs) of 1.06 (95% CI = 0.92 to 1.23, 1,459 deaths) among industrial workers and 0.63 (95% CI = 0.47 to 0.84, 562 deaths) among medical workers in association with formaldehyde exposure.

Table 3-7a. Summary of cohort studies of formaldehyde exposure and cancers of the lung

Reference	Study population and follow up	Risk estimate (95% CI), number of exposed cases or deaths	Comments
Studies of industrial workers			
Andjelkovich *et al.* 1995	Iron foundry workers, MI USA N = 3,929 1960–89	Lung cancer SMR 1.20 (0.89–1.58); 51 RR 1.13, NR; $P > 0.05$ Internal analysis (quartiles of cumulative exposure compared with never): 41 exposed, 24 unexposed Ever 0.71 (0.43–1.21); NR Q3 + Q4 0.59 (0.28–1.20); NR	SMR – formaldehyde-exposed subcohort See Table 3-6b for related nested case-control of larger cohort Internal analyses using unexposed workers as referent were adjusted for race, smoking, and exposure to silica
Bertazzi *et al.* 1989 (update of Bertazzi *et al.* 1986)	Resin manufacturing workers, Italy N = 1,330 men 1959–86	Lung cancer among formaldehyde-exposed workers SMR 0.69 (NR); 6 Entire plant analysis: No increased risk with increasing years of exposure, or years since first exposure, and no pattern with age at initial risk or calendar time-period of initial exposure	No quantitative exposure assessment; 28% person-years assigned to definite exposure to formaldehyde
Coggon *et al.* 2003	British Chemical Workers Study, UK N = 14,014 1941–2000	SMR for lung cancer All 1.22 (1.12–1.32); 594 high exposed 1.58 (1.40–1.78); 272 *Exposure response for lung cancer* Increasing risk with increasing exposure level (low, medium, high), $P_{trend} < 0.001$ Inverse trend with duration of high exposure	
Dell and Teta 1995	Workers employed at a Union Carbide plastics manufacturing plant in New Jersey, USA 57 formaldehyde-exposed workers in hexamethylenetetramine production 111 workers (total) exposed to formaldehyde 1946–88	Lung cancer Hexamethylenetetramine production workers SMR 4 deaths vs. 1.1 exp. All formaldehyde-exposed workers NR	Small numbers of formaldehyde-exposed workers Lung cancer risk elevated in whole cohort

Reference	Study population and follow up	Risk estimate (95% CI), number of exposed cases or deaths	Comments
Edling *et al.* 1987b)	Abrasive materials industry, Sweden N = 506 male blue collar workers Mortality 1958–83 Incidence 1958–81	Lung cancer SMR NR Incidence Obs./Exp. 0.57 (0.1–2.1); 2	
Hansen and Olsen 1995, 1996	Danish formaldehyde-exposed worker N = 2,041 men, 1,263 women 1970–84	Lung cancer SPIR Men 1.0 (0.9–1.1); 410 Women 1.2 (0.96–1.4); 108 *No wood dust exposure* Men 1.0 (0.9–1.1); 250 Women NR	SPIR adjusted for age and calendar time Workers had 10 or more years exposure to formaldehyde before diagnosis
Hauptmann *et al.* 2004	NCI cohort, USA N = 25,619 1966–94	Lung cancer SMR 0.97 (0.90–1.05); 641 *Internal analysis (RR, number of cases)* Average exposure (ppm) > 0.0–< 0.5 1.0 ; 348 (Ref.) > 0.5–< 1.0 1.15; 141 ≥ 1.0 1.14; 152 P_{trend}[a] 0.843 P_{trend}[b] 0.760 Peak exposure (ppm) > 0.0–< 2.0 1.0; 237 (Ref.) 2.0–< 4.0 1.45; 227 ($P < 0.05$) ≥ 4.0 0.94; 177 P_{trend}[a] -0.669 P_{trend}[b] -0.874 All RRs for cumulative exposure < 1	Internal analysis adjusted by calendar year, age, sex, race, and pay category; exposure was calculated with a 15-year lag interval Average, cumulative, and peak exposures compared with lowest exposed category
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98	Lung cancer SMR 0.98 (0.82–1.15); 147 SMR did not increase with increasing duration, time since first exposure, or earlier start dates	Standardized mortality study
Stern 2003 (update of Stern *et al.* 1987)	Workers employed in two chrome leather tannery plants, USA (N = 9,365) 1940–93 Formaldehyde-exposed workers in the finishing department N = NR (1,050 death from all causes)	Respiratory cancers SMR 0.94 (NR); 71	Findings reported for formaldehyde-exposed workers in the finishing department

Reference	Study population and follow up	Risk estimate (95% CI), number of exposed cases or deaths	Comments
General population study			
Stellman *et al.* 1998 50 U.S. states, District of Columbia, Puerto Rico	Woodworkers: American Cancer Society Cancer Prevention Study N = 362,823 (total); 45,399 in woodworking occupations 1982–88	Lung cancer RR for formaldehyde exposure non wood-workers 0.93 (0.73–1.18); 104 woodworkers 2.63 (1.25–5.51); 7	Internal analysis using non-woodworkers or workers without exposure to wood dust Adjusted for age and smoking
Studies of health professional workers			
Hall *et al.* 1991	Pathologists, members of professional organizations in the UK N = 3,872 1974–87	Lung cancer (England & Wales) SMR 0.19 (0.09–0.36); 9	
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046 1975–85	Lung cancer PMR Whites 0.97 (0.86–1.09); 285 Non-whites 0.75 (0.47–1.13); 23	
Levine *et al.* 1984	Licensed embalmers in Ontario, Canada (N = 1,413) First licensed 1928–57 Follow-up through 1977	Lung cancer SMR 0.94 (NR); 19	
Stroup *et al.* 1986	Anatomists, members of the American Association of Anatomists, USA N = 2,317 1888–79	Lung cancer SMR 0.3 (0.1–0.5); 12	
Walrath and Fraumeni 1983	All licensed embalmers and funeral directors in NY, USA N = 1,263 1902–80	Lung cancer (white males) PCMR 1.11 (NR); 70 Lung and pleura PMR 1.08 (NR); 72	
Walrath and Fraumeni 1984	All licensed embalmers in CA, USA N = 1,109 1916–80	Lung and pleural cancer (white males) PMR 0.96 (NR); 41 PCMR 0.87 (NR); 41	

Exp. = expected; NR = not reported; PMR = proportionate mortality ratio; PCMR = proportionate cancer mortality ratio; Q = quartile; Obs. = observed; Ref. = referent group; RR = relative risk ratio; SMR = standardized mortality ratio; SPIR = standardized proportionate incidence cancer ratio.
[a] P_{trend} across exposed.
[b] P_{trend} across exposed and non-exposed

Table 3-7b. Summary of case-control studies (including nested case-control studies) investigating formaldehyde exposure and lung or respiratory cancer

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Jensen and Andersen 1982 Denmark	*Cancer registry-based case-control study of physicians* 1943–76 *Cases:* 84 incident lung cancers *Controls:* physicians matched on age, sex, and survival to date of diagnosis	Medical specialization and place of work for cases were compared with controls to assess the potential for increased relative exposure levels	RR for lung cancer ever worked in pathology, forensic medicine, anatomy 1.0 (0.4–2.4); 8/23	Small number of exposed cases No increase in risk among other physician specialties
Coggon *et al.* 1984 United Kingdom	*Population-based study* 1975–79 *Cases*: 598 men under 40 identified from death certificates with cancer of the trachea, bronchus, or lung *Controls:*1,180 men who died from other causes and matched to cases by sex, year of birth and death, and residence	Occupational histories obtained from death certificates, exposure classified by JEM	Lung cancer Ever-exposed 1.5 (1.2–1.8); 296/472 Occupations with high exposure 0.9 (0.6–1.4); 44/90	Matched tabular analysis, including matching for pay class
Bond *et al.* 1986 Texas, United States (update of Bond *et al.* 1985)	*Nested case-control of Dow Chemical workers (Bond* et al. *1985)* 1940–80 *Cases*: 308 men with lung cancer identified using death certificates *Controls*: matched by race, years of birth and hire	Occupational histories obtained from company employment records and classified by job task	Lung cancer Ever exposed 0.62 (0.29–1.34); 9/27 15-yr lag 0.31 (0.11–0.86); 4/24	Small numbers of exposed cases

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Gérin *et al.* 1989 Montreal, Canada	*Multi-site study* 1979–85 *Cases*: 857 men; incident cases identified from all hospitals *Controls*: (1) cancer controls, internal controls with tumors at other sites and (2) 740 population-based controls matched by age (533 participated)	Occupational histories obtained by interview; exposure classified by job description and industry *Estimated exposure index* Low < 0.1 ppm Med. 0.1–1 ppm High ≥ 1 ppm	Lung cancer (all) Any[a] 0.8 (0.6–1.0); 180 *Exposure duration (yr)/exposure index (cancer controls)*[a] < 10/any 0.8 (0.6–1.2); 62 ≥ 10/ low 0.5 (0.3–0.8); 33 med. 1.0 (0.7–1.4); 61 high 1.5 (0.8–2.8); 24 Adenocarcinoma ≥ 10/high 2.3 (0.9–6.0); 7/NR	Adjusted for (1) age, (2) ethnicity, (3) cigarette smoking, (4) self-reported income, (5) jobs held and other occupational factors; highest OR observed for adenocarcinoma with highest exposure, similar estimates were observed for other histologic subtypes
Partanen *et al.* 1990 (update of Partanen *et al.* 1985) Finland	*Nested case-control study of plywood, particleboard, and formaldehyde glue factory workers* (N = 7,303) 1957–82 *Cases*: 136 respiratory cancer cases including tongue, pharynx, larynx, trachea, epiglottis, and lung identified using the Finnish Cancer Registry *Controls*: 408 controls selected randomly from cohort and matched (3:1) by year of birth	Occupational histories obtained using plant records and classified using factory-specific JEMs	Workers with ≥ 3 ppm-mo vs. < 3 ppm-mo Lung 0.69 (0.21–2.24); 9 10-yr lag 0.89 (0.26–3.00); 7 Respiratory 1.11 (0.40–3.11); 11 10-yr lag 1.39 (0.40–4.10); 9 No association with level of exposure, cumulative exposure, and exposure duration	Small numbers of exposed cases Adjusted for vital status and smoking
Brownson *et al.* 1993 Missouri, United States	*Population-based study* 1986–91 *Cases*: 429 women with lung cancer identified from the Missouri Cancer Registry *Controls*: 1,021 age-matched, selected from Medicare records	Occupational histories obtained by interview; exposure classified by job description	Lung cancer Ever-exposed 0.9 (0.2–3.3); 3	Small numbers of exposed cases Adjusted for age, previous history of lung disease and smoking

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Andjelkovich *et al.* 1994 Michigan, United States	*Nested case-control study of iron foundry workers* (N = 8,147) (update of Andjelkovich *et al.* 1990) 1950–89 *Cases*: 220 lung cancer *Controls*: matched on race from cohort (10:1) using incidence density sampling	Occupational histories obtained from employment records and classified using a JEM	Lung cancer Ever-exposed 1.31 (0.83–2.07); NR Effects decreased with increasing lag periods	Adjusted for smoking, birth cohort, and exposure to silica Analysis using subset of controls with smoking information
Chiazze *et al.* 1997 South Carolina, United States	*Nested case-control study of fiberglass manufacturing plant workers* (N = 4,631) 1951–91 *Cases:* 47 white men with lung cancer *Controls:* 122 white men matched on year of birth and survival to end of follow-up or death	Occupational histories obtained by interview and a historical exposure reconstruction; exposure was classified by a committee of experts	Lung cancer *Cumulative days of exposure* 0.2 –< 100 0.94 (0.38–2.36); 14 100–999 1.27 (0.50–3.21); 15 1000+ 1.14 (0.11–12.1); 1	Small numbers of exposed cases Unadjusted
Marsh *et al.* 2001, Youk *et al.* 2001 Stone *et al.* 2004 United States	Marsh *et al.* 2001: *Nested case-control study of male and female fiberglass workers* (N = 32,110) 1970–92 *Cases:* 874 respiratory system cancers combined including larynx, bronchus, trachea, and lung *Controls*: alive when case died and matched by date of birth Stone *et al.* (2004): N = 4,008 women; 1970–92	Occupational histories obtained from company employment records and relevant industrial hygienic literature; exposure estimated using job location-weighted measures	RR for all respiratory system combined *Men* Ever-exposed 1.61 (1.02–2.57); 591 lag (yr) 5 1.62 (1.04–2.54); 588 10 1.46 (0.96–2.23); 581 20 1.17 (0.82–1.67); 537 No clear trends with cumulative or average exposure *Women: cumulative exposure to formaldehyde* RR 1.24 (0.74–2.09); 39	*Men* Adjusted for smoking Analysis on 516 pairs (631 cases and 570 controls) *Women* 37.6 person-years exposed to formaldehyde No adjustment for smoking; models with formaldehyde and glass wool were similar to univariate analysis

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
	3,563 included in analysis 53 respiratory-system cancer cases			
De Stefani *et al.* 2005 Uruguay	*Hospital-based study* 1994–2000 *Cases:* 338 men with lung adenocarcinoma (histologically confirmed) selected from 4 major hospitals; 97% response rate *Controls:* 1,014 hospital controls, men with conditions not related to tobacco smoking, frequency matched on age, residence and urban/rural status	Occupational history (job titles and self-reported exposure to known or suspected carcinogens) obtained and lifestyle information from questionnaire	OR for exposure to formaldehyde Ever 1.7 (1.1–2.8); 32 *Duration (yr)* 1–20 0.9 (0.4–1.9); 10 21 + 3.0 (1.6–5.8), 22 P_{trend} 0.004	Hospital controls excluded conditions related to tobacco smoking or recent changes in diet OR adjusted for age, residence, urban/rural status, education, BMI, smoking status, # cigarettes/day, years since quit, and years at start of smoking

BMI = body mass index; JEM = job exposure matrix; NR = not reported; OR = odds ratio; RR = relative risk ratio.
[a]ORs calculated using hospital controls with other cancers; similar estimates using population-based controls.

3.6.5 Lymphohematopoietic cancers

The relationship between occupational exposure to formaldehyde and lymphohematopoietic cancer has been investigated in several cohort, nested case-control, and population-based case-control studies. The key findings are summarized in Table 3-8a and b. (See Section 3.5.5 for a detailed summary of case-control studies investigating lymphohematopoietic cancer.)

3.6.5.1 Cohort studies

Eight cohort studies (including all six studies of health profession workers) have reported increased mortality of all lymphohematopoietic cancers combined, although most of the increases were not statistically significant (Walrath and Fraumeni 1983, 1984, Levine *et al.* 1984, Stroup *et al.* 1986, Stellman *et al.* 1988 [the increase was strongest among woodworkers exposed to formaldehyde], Bertazzi *et al.* 1989, Hayes *et al.* 1990, and Hall *et al*. 1991). (See Table 3-8a for risk estimates.) No increased risk of lymphohematopoietic cancers was observed among garment workers in the NIOSH cohort (Pinkerton *et al.* 2004), among formaldehyde-exposed workers in the iron foundry industry (Andjelkovich *et al.* 1995), or among formaldhyde-exposed workers in the tannery industry (Stern 2003). Risk estimates (or number of deaths) were not reported by Coggon *et al.* (2003), Edling *et al.* (1987b), Hansen and Olsen (1995, 1996), or Dell and Teta (1995). Although no increase in all lymphohematopoietic cancers combined (SMR = 0.94, 95% CI = 0.84 to 1.06, 286 cases) was observed in the external analysis in the large NCI cohort, a statistically significant trend for all lymphohematopoietic cancers was observed with peak (P_{trend} = 0.02 among exposed groups, and P_{trend} = 0.04 among exposed and unexposed), but not average or cumulative, exposure in the internal analysis (Beane Freeman *et al.* 2009). Peak exposures exceeding 4 ppm (compared with peaks of > 0.0 to 1.9 ppm) were associated with a statistically significant increase in all lymphohematopoietic cancers (RR = 1.37, 95% CI = 1.03 to 1.81, 108 deaths).

Most studies (except for Edling *et al.* 1987b, Bertazzi *et al.* 1989, and Dell and Teta 1995) reported results for leukemia. Similar to the findings for all lymphohematopoietic cancers, all six studies of health professionals reported increased risks (SMR or PMR) for leukemia, although most findings were not statistically significant. In general, most studies reported the highest risks for myeloid leukemia: statistically significant increased mortality for myeloid leukemia was found among embalmers (whites and non-whites) (PMR = 1.57, 95% CI = 1.01 to 2.34, 24 deaths) (Hayes *et al.* 1990) and U.S. anatomists (SMR = 8.8, 95% CI = 1.8 to 25.5, 3 deaths) (Stroup e*t al.* 1986). In the industrial cohort studies, statistically nonsignificantly increased risks for leukemia were found among garment workers in the NIOSH cohort (Pinkerton *et al*. 2004), and among Danish women (Hansen and Olsen 1995, 1996) (see Table 3.8a for risk estimates).

A few studies evaluated risk by exposure duration, date of first exposure, or time since first exposure. In the NIOSH cohort (Pinkerton *et al.* 2004), risks for leukemia, myeloid leukemia, and acute myeloid leukemia were higher among workers with longer duration of exposure (10+ years) (SMR = 2.19, CI not reported, 8 deaths), longer time since first exposure (20+ years) SMR = 1.91 (95% CI exceeds 1.0, 13 deaths), and who were exposed prior to 1963 (when formaldehyde exposure was thought to be higher) (SMR =

1.61, 95% CI not reported, 11 deaths). The SMR among workers with both 10 years or more of exposure and with 20 or more years since first exposure was 2.43 (95% CI = 0.98 to 5.01; 7 deaths). In multiple cause analyses, among workers with both10 or more years of exposure and 20 years or more since first exposure, mortality from leukemia was significantly increased (SMR = 1.92, 95% CI = 1.08 to 3.17, 15 deaths), as was multiple cause mortality from myeloid leukemia (SMR = 2.55, 95% CI = 1.10 to 5.03, 8 deaths).

The NCI cohort study provided the most extensive exposure-response relationship analyses (Beane Freeman *et al.* 2009). In internal analyses, statistically significant trends were observed for all leukemias (P_{trend} = 0.12 among exposed and P_{trend} = 0.02 among exposed and unexposed) with peak exposures ≥ 4.0 ppm compared with > 0.0 to 1.9 ppm (associated with a relative risk of 1.42, 95% CI = 0.92 to 2.18, 48 deaths). The corresponding trends for myeloid leukemia were 0.13 among exposed and 0.07 among exposed and unexposed (associated with a relative risk of 1.78, 95% CI = 0.87 to 3.64, 19 deaths). No statistically significant trends for leukemia were observed for average or cumulative exposure. In these primary analyses, exposure was considered to be zero after 1980, the last date for which exposure data were available. If the cohort follow-up was censored two years after the last job for the individuals who were still exposed in 1979 and alive two years later (instead of 2004); however, the association for myeloid leukemia with peak and average intensity of exposure was stronger than that observed in the primary analyses. A time series analysis found that cumulative risks for leukemia and myeloid leukemia for both peak and average exposure to formaldehyde reached their peak by 1980. In addition, the highest risks for all lymphohematopoietic cancers, all leukemias, myeloid leukemia, and Hodgkin's lymphoma occurred 15 to 25 years after first exposure.

In general, the 2004 update confirmed the findings of the earlier (1994) follow-up conducted by Hauptmann *et al.* (2003); however, the magnitude of the risk estimates for all leukemia and myeloid leukemia in the highest category of peak exposure were higher in the 1994 update compared with the 2004 update (RR = 1.60, 95% CI = 0.90 to 2.82, 29 deaths, P_{trend} = 0.09 among exposed and P_{trend} = 0.02 among exposed and unexposed; RR = 2.79, 95% CI = 1.08 to 7.21, 14 deaths, P_{trend} = 0.02 among exposed and P_{trend} = 0.008 among exposed and unexposed), and some of the exposure-response relationships were stronger in the earlier update. Leukemias observed in the early update by Hauptmann *et al.* (2003) were re-analyzed by Marsh and Youk (2004) using different exposure assessment methods; effect estimates and exposure-response trends were slightly reduced toward the null and were no longer statistically significant, though risk ratios remained elevated for both myeloid leukemia and all leukemias combined.

No increased risks for leukemia were reported in the large cohort of British chemical workers (Coggon *et al.* 2003), among formaldehyde-exposed workers in the American Cancer Society Cancer Prevention study (Stellman *et al.* 1998), in the subset of tannery workers exposed to formaldehyde (Stern 2003), or in iron foundry workers (Andjelkovich *et al.* 1995).

Fewer cohort studies reported findings for other types of lymphohematopoietic cancers. [The majority of studies were too small to be able to evaluate these cancers or did not

report findings by each subtype.] With respect to Hodgkin's lymphoma, Beane Freeman *et al.* (2009) reported an increased risk for Hodgkin's lymphoma in their external analysis (SMR = 1.42, 95% CI = 0.96 to 2.10, 25 deaths); in internal analyses, risks increased with increasing peak exposure (P_{trend} = 0.01 among exposed groups and P_{trend} = 0.004 among exposed and unexposed), and average exposure (P_{trend} = 0.05 among exposed groups and P_{trend} = 0.03), but not with cumulative exposure. Statistically significant risks were observed among workers with peak exposure of 2.0 to 3.9 ppm (RR = 3.30, 95% CI = 1.04 to 10.50; 8 deaths), peak exposures ≥ 4.0 ppm (RR = 3.96, 95% CI = 1.31 to 12.02, 11 deaths), and average exposure for 0.5 to 0.9 ppm (RR = 3.62, 95% CI = 1.41 to 9.31, 9 deaths). Hall *et al.* (1991) reported a SMR of 1.21 (95% CI = 0.03 to 6.71) based on one observed death among U.K. pathologists. One death was reported among the foundry workers (Andjelkovich *et al.* 1995). No excess in mortality from Hodgkin's lymphoma was found among the British Chemical workers (Coggon *et al*. 2003), U.S. garment workers (Pinkerton *et al.* 2004), Danish workers (Hansen and Olsen *et al.* 1995, 1996), or in most of the studies of professional workers (Walrath and Fraumeni 1983, 1984, Stroup *et al.* 1986, Hayes *et al.* 1990). [The numbers of exposed cases were small in these studies.]

For non-Hodgkin's lymphoma and other lymphomas, no excess risks were found in most studies (Walrath and Fraumeni 1983, 1984, Stroup *et al.* 1986, Andjelkovich *et al.* 1995, Hansen and Olsen 1995, 1996, Stellman *et al.* 1998, Coggon *et al.* 2003, Pinkerton *et al*. 2004, Beane Freeman *et al*. 2009), with the exception of Hayes *et al*. (1990), who reported a nonsignificantly increased PMR for non-Hodgkin's lymphoma (PMR = 1.26, 95% CI = 0.87 to 1.76, 34 deaths) and Edling *et al.* (1987b), who found 2 cases of lymphoma (vs. 1 expected) among workers in the abrasive material industry. Nonsignificantly increased risks for multiple myeloma were found among highly exposed British chemical workers (SMR = 1.18, 95% CI = 0.48 to 2.44, 7 deaths) (Coggon *et al.* 2003); abrasive material workers (4 observed vs. 2 expected, 95% CI = 0.5 to 14.4) (Edling *et al.* 1987b), and U.S. embalmers (PMR = 1.37, 95% CI = 0.84 to 2.12, 20 deaths) (Hayes *et al*. 1990). In the NCI cohort, statistically significantly increased risks for multiple myeloma were also found among workers with peak exposures ≥ 4.0 ppm compared with workers with peak exposures > 0 to < 2 ppm (RR = 2.04, 95% CI = 1.01 to 4.12, 48 cases, P_{trend} = 0.08 among exposed and > 0.5 among exposed and non-exposed; risks were also elevated in the non-exposed group compared with the lowest category of peak exposure. No increased risk was found in the American Cancer Society Cancer Prevention Study (Stellman *et al.* 1998) (see below for a discussion of the nested-case control study from this cohort conducted by Boffetta *et al.* 1989).

3.6.5.2 Case-control studies

Eleven case-control studies (including four nested case-control studies) were identified that evaluated exposure to formaldehyde and lymphohematopoietic cancers: two studies reported on all lymphohematopoietic cancers combined, four studies reported on leukemia, seven studies on non-Hodgkin's lymphoma, one study on Hodgkin's lymphoma, three studies on multiple myeloma, and two studies on myelodysplasia (see Table 3-8b). (Some studies evaluated more than one type of lymphohematopoietic cancer.)

Findings for leukemia were reported in three nested case-control studies and one population-based study. Two of the nested case-control studies also reported findings for all lymphohematopoietic cancers. (A study of chronic lymphocytic leukemia is discussed below since that type of leukemia is related to non-Hodgkin's lymphoma.) The only study on lymphohematopoietic cancers to report a detailed quantitative exposure-response analysis was the nested case-control study by Hauptmann *et al.* (2009) of embalmers and funeral directors, previously studied by Hayes *et al.* (1990) and Walrath and Fraumeni (1983, 1984). This was also the only study to include contributory as well as underlying causes of death in analyses. The authors reported findings for all lymphohematopoietic cancers and cancers of lymphoid and non-lymphoid origin, with a specific focus on myeloid leukemia. Elevated ORs for ever embalming were observed for all lymphohematopoietic cancers (OR = 1.4, 95% CI = 0.8 to 2.6, 144 exposed cases), and for cancers of non-lymphoid origin (OR = 3.0, 95% CI = 1.0 to 9.5, 44 exposed cases, $P = 0.059$). Significant increases for lymphohematopoietic cancers of nonlymphoid origin were observed among the highest categories of cumulative, average, and peak exposure to formaldehyde; the increases were primarily due to myeloid leukemia. Mortality from myeloid leukemia among men who had ever worked in embalming was significantly elevated (OR = 11.2, 95% CI = 1.3 to 95.6, 33 exposed cases) and increased significantly with the number of years of embalming ($P_{trend} = 0.020$) and with increasing peak exposure to formaldehyde ($P_{trend} = 0.036$). Compared with individuals who had performed fewer than 500 lifetime embalmings, statistically (or borderline) significant increased risks for myeloid leukemia were found for the highest categories of (1) duration of working in jobs with embalming (OR = 3.9, 95% CI = 1.2 to 12.5, $P = 0.024$), (2) number of embalmings (OR = 3.0, 95% CI = 1.0 to 9.2, $P = 0.057$), and (3) cumulative exposure to formaldehyde (OR = 3.1, 95% CI = 1.0 to 9.6, $P = 0.047$).

Findings for the other two nested case-control studies were based on small numbers of exposed cases: Partanen *et al.* (1993) found an increase in all lymphohematopoietic cancers (OR = 2.49, 95% CI = 0.81 to 7.59, 7 exposed cases) and leukemia (OR = 1.40, 95% CI = 0.25 to 7.91) among woodworking industry workers exposed to ≥ 3 ppm-month formaldehyde compared with < 3 ppm-month, and Ott *et al.* (1989) reported ORs in excess of 2.0 for leukemia (lymphocytic and nonlymphocytic) in association with 3 formaldehyde-exposed deaths. In a cancer registry-based study of leukemia, Blair *et al.* (2001) noted an elevated risk for chronic myeloid leukemia (OR = 2.9, 95% CI = 0.3 to 24.5), based on one highly exposed case, and for chronic myeloid leukemia and low/medium exposure to formaldehyde, but not for other histologic subtypes of leukemia and all leukemia; no increased risk for all leukemia was found among subjects with low (N = 128) or high (N = 9) exposure to formaldehyde.

Two of the nested case-control studies reported findings for all lymphomas or lymphohematopoietic cancers of lymphoid origin. No association was found between lymphohematopoietic cancers of lymphoid origin and ever embalming (OR = 1.1, 95% CI = 0.5 to 2.1, 81 exposed cases) and no exposure-response relationships were observed in the large nested case-control study of embalmers and funeral directors (Hauptmann *et al.* 2009). An elevated risk (OR = 4.02, 95% CI = 0.87 to 18.6, 5 exposed cases) was found for all lymphomas and exposure to formaldehyde (≥ 3 ppm-month compared with < 3 ppm-month) in the small nested case-control study of woodworkers (Partanen *et al.*

1993). In addition to these studies, other studies reported findings for specific lymphomas and exposure to formaldehyde (non-Hodgkin's lymphoma and Hodgkin's lymphoma). No quantitative measures of formaldehyde exposure were available in these studies, but several studies evaluated exposure-response relationships using semi-quantitative measures of exposure.

All but two of the studies on non-Hodgkin's lymphoma found small elevated risks for this cancer, although in most studies the estimates were statistically nonsignificant. An increase in risk (OR = 1.3, 95% CI = 1.0 to 1.7, 203 exposed cases) for non-Hodgkin's lymphoma and potential exposure to formaldehyde was observed in a case-control study of 601 incident non-Hodgkin's lymphoma cases among Connecticut women (Wang *et al*. 2009a). Risks increased with increasing combined probability and intensity (of exposure ($P_{trend} < 0.01$). Risks were highest and statistically significant for large B-cell type non-Hodgkin's lymphoma (OR = 1.9, 95% CI = 1.3 to 2.6, 80 exposed cases), and risks increased with average intensity ($P_{trend} = 0.03$) and average probability of exposure ($P_{trend} < 0.01$) (Wang *et al.* 2009a). In a cancer registry study, Blair *et al.* (1993) reported a small but nonsignificant increase in non-Hodgkin's lymphoma incidence and mortality in association with formaldehyde exposure (OR = 1.2, 95% CI = 0.9 to 1.4, 84 exposed cases), mainly for the diffuse non-Hodgkin's lymphoma subtype, but no relationship with intensity (low or high) of exposure was observed. An OR of 1.20 (95% CI = 0.86 to 1.50, 93 cases) was found for non-Hodgkin's lymphoma in a large case-control study using population-based cancer registries in the United States (Tatham *et al*. 1997). Richardson *et al.* (2008) reported nonsignificant increased risks for low-malignancy non-Hodgkin's lymphoma (OR = 1.18, 95% CI = 0.79 to 1.75, 45 exposed cases) and high-malignancy non-Hodgkin's lymphoma (OR = 1.52, 95% CI = 0.88 to 2.63, 27 exposed cases) and chronic lymphocytic leukemia (OR = 1.16, 95% CI = 0.71 to 1.89, 29 exposed cases) among a predominantly rural population in northern Germany. However, no association with ever exposure or with estimated duration of exposure to formaldehyde and non-Hodgkin's lymphoma was found in a Canadian population-based case-control study (Gérin *et al.* 1989) or among embalmers (OR = 0.9, 95% CI = 0.4 to 2.1) (Hauptman *et al.* 2009).

Increased risks for non-Hodgkin's lymphoma were found in two industry-based nested case-control studies, but they were based on small numbers of exposed cases. Ott *et al.* (1989) reported a 2-fold increase in non-Hodgkin's lymphoma among ever-exposed workers based on two cases, and Partanen *et al.* (1993) found a 4-fold increase in non-Hodgkin's lymphoma among workers exposed to ≥ 3 ppm-months of formaldehyde compared with < 3 ppm-months (OR = 4.24, 95% CI = 0.68 to 26.6, 4 exposed cases).

No association between ever exposure to formaldehyde and Hodgkin's lymphoma was observed in a Canadian population-based case-control study based on small numbers of exposed cases (OR = 0.5, 95% CI = 0.2 to 1.2, 8 exposed cases) (Gérin *et al.* 1989) or in the nested case-control study of embalmers (OR = 0.5, 95% CI = 0.1 to 2.6, 8 exposed cases).

Five studies reported findings for multiple myeloma and one study for myelodysplastic syndrome. Boffetta *et al.* (1989) reported an OR of 1.8 (95% CI = 0.6 to 5.7, 4 exposed

cases and 9 controls) for multiple myeloma incidence in a case-control study (N = 128) nested within a large prospective cohort assembled by the American Cancer Society (Stellman *et al.* 1998). Two parallel studies of cases of multiple myeloma were conducted among 835 men (Heineman *et al.* 1992) and 607 women (Pottern *et al.* 1992) drawn from all cases reported to the Danish Cancer Registry between 1970 and 1984 for whom occupational data were available from government records. ORs for probable exposure to formaldehyde were 1.1 (95% CI = 0.7 to 1.6, 41 exposed cases) among men and 1.6 (95% CI = 0.4 to 5.3, 4 exposed cases) among women. No association was observed in an industry-based case-control study based on one exposed case (OR =1.0, 95% CI not reported) (Ott *et al.* 1989). In the nested case-control study of embalmers, a statistically nonsignificant elevated risk was observed (OR = 1.4, 95% CI = 0.4 to 5.6) for ever embalming (vs. never embalming), but no association was observed for any of the exposure-response metrics (such as cumulative exposure) (Hauptman *et al.* 2009). West *et al.* (1995) noted elevated but statistically nonsignificant associations between myelodysplastic syndrome and formaldehyde exposure (ORs ranged from 1.17 to 2.33, 95% CIs not reported); effect estimates tended to increase with increasing cumulative exposure, but no clear exposure-response pattern was observed.

3.6.5.3 Meta-analyses

Four recent meta-analyses have been undertaken to summarize findings across studies of occupational exposure to formaldehyde and all lymphohematopoietic cancers combined or leukemia and are reviewed here (Collins and Lineker 2004, Bosetti *et al.* 2008, Zhang *et al.* 2009a, Bachand *et al.* 2010) (Table 3-10). One recent comprehensive review of available studies (Blair *et al.* 2007) is also briefly noted.

The meta-analysis conducted by Collins and Lineker (2004) included 12 cohort studies (including Hauptmann *et al.* 2003), four proportionate mortality studies, and two case-control studies. Fixed-effects models were used to obtain meta-relative risk values (mRR) and 95% confidence intervals, and random effects models were used to evaluate heterogeneity across studies as a potential indicator of bias, unmeasured confounding, effect modification, or different exposure levels across studies. The mRR across all studies was 1.1 (95% CI = 1.0 to 1.2) for leukemia, and estimates varied by type of study, country of study population, type of industry, year of publication, and study size. Generally, only weak or null mRRs were found for cohort studies (vs. case-control), industry-based studies (vs. embalmers and pathologists), studies published after 1995, and studies with at least 40 expected cases of leukemia.

Bosetti *et al.* (2008) conducted a meta-analysis of 12 cohort mortality studies that analyzed lymphohematopoietic cancers. With respect to all lymphohematopoietic cancers, the authors calculated a pooled estimated RR (computed as a weighted average of the SMRs and/or PMRs) of 0.85 (95% CI = 0.74 to 0.96, 234 deaths) for industrial workers and 1.31 (95% CI = 1.16 to 1.48, 263 deaths) for medical workers. The corresponding pooled RRs for leukemia were 0.90 (95% CI = 0.75 to 1.07, 122 deaths) and 1.39 (95% CI = 1.15 to 1.68, 106 deaths), respectively.

Zhang *et al.* (2009a) conducted a meta-analysis of 26 peer-reviewed cohort and/or case-control studies that provide data on relative risk estimates and confidence intervals for

lymphohematopoietic cancers and formaldehyde exposure, focusing on 15 studies of leukemia (Table 3-10). [Note that 6 studies included in either the Collins and Lineker (2004) or Bosetti *et al.* (2008) meta-analyses were excluded by Zhang *et al.* as they either did not include leukemia cases, had no clear exposed group, did not report relative risks and/or confidence intervals, or were not peer-reviewed publications]. The meta-analyses were confined to data from occupations known to have high formaldehyde exposure. In addition, results were grouped by subtype of leukemia where possible (six of the leukemia studies reviewed by the authors reported results by subtype). Summary risk estimates were calculated using both a fixed-effects inverse variance weighting method and a random-effects method; heterogeneity was assessed using a general variance-based method. The results below are reported for the fixed-effects models, which were applied to analyses of each of the types of lymphohematopoietic cancers. (Results for random-effects models (leukemia only) did not differ substantially from those for fixed-effects models.)

The calculated summary mRR for all lymphohematopoietic cancers (19 studies) was 1.25 (95% CI = 1.09 to 1.43, *P* value not stated), for Hodgkin's lymphoma (8 studies) the mRR = 1.23 (95% CI = 0.67 to 2.29, *P* not significant), for non-Hodgkin's lymphoma (11 studies) mRR = 1.08 (95% CI = 0.86 to 1.35, *P* not significant), and for multiple myeloma (9 studies) mRR = 1.31 (95% CI = 1.02 to 1.67, $P = 0.02$). With respect to leukemia in the 15 studies reviewed, the mRR was significantly elevated at 1.54 (95% CI = 1.18 to 2.00; $P < 0.001$). The highest risk was observed in association with myeloid leukemia in the 6 studies where subtypes were reported: mRR = 1.90 (95% CI = 1.31 to 2.76, $P = 0.001$) (all 6 studies reported RRs of 1.4 or higher). The authors noted that 51% of the leukemias observed in these studies of formaldehyde exposure were of the myeloid type, of which 64% were acute myeloid leukemia (AML), 19% are of the lymphocytic type, with others of unspecified type.

Bachand *et al.* (2010) conducted a meta-analysis of cohort and case-control studies on formaldehyde exposure and the risk of leukemia (Table 3-10). Fifteen cohort and two case-control studies were included in the meta-analysis (two of the cohort studies are of the same population). Note that of these studies, those of Robinson *et al.* 1987 and Matanoski 1991 are not reviewed in the present background document because they are not from peer-reviewed sources. The authors excluded proportionate mortality studies. Quantile plots and regression modeling were used to estimate summary relative risk estimates and evaluate heterogeneity and publication bias, of which no evidence was observed.

Relative risks for the individual studies ranged from 0.0 to 1.52; none was statistically significant. The estimated summary RR for all leukemias combined among the cohort studies (excluding the analysis by Marsh of the NCI cohort) was mRR = 1.05 (95% CI = 0.93 to 1.20); the summary OR for case-control studies was 0.99 (95% CI = 0.71 to 1.37). The results for the seven studies of professional/technical workers was mRR = 1.28 (95% CI = 0.98 to 1.66) and for the eight studies of industrial workers mRR = 0.99 (95% CI = 0.86 to 1.15). Findings for subtypes of leukemia, which were reported only by Beane Freeman *et al.* (2009), Pinkerton *et al.* (2004) and Stroup *et al.* (1986), were as follows: myeloid leukemia mRR = 1.09 (95% CI = 0.84 to 1.40), lymphatic or lymphocytic

leukemia mRR = 1.11 (95% CI = 0.81 to 1.52, and for other subtypes mRR = 0.97 (95% CI = 0.71 to 1.33). There was no substantial difference between studies conducted in the United States or Europe.

Table 3-8a. Summary of cohort studies of formaldehyde exposure and lymphohematopoietic cancers[a]

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
Studies of industrial workers			
Andjelkovich *et al.* 1995	Iron foundry workers, MI, USA N = 3,929 1960–89	SMR LHC 0.59 (0.23–1.21); 7 Leukemia 0.43 (0.05–1.57); 2 Reticulosarcoma/ lymphsarcoma 0.57 (0.01–3.15); 1 Hodgkin's lymphoma 0.72 (0.01–4.00); 1	SMR – formaldehyde-exposed subcohort based on national rates
Beane Freeman *et al.* 2009	NCI cohort, USA N = 25,619 1966-2004	SMR LHC 0.94 (0.84–1.06); 286 Hodgkin's lymphoma 1.42 (0.96–2.10); 25 NHL 0.85 (0.70–1.05); 94 All leukemia 1.02 (0.85–1.22); 116 Myeloid leukemia 0.90 (0.67–1.21); 44 Lymphatic leukemia 1.15 (0.83–1.59); 36 Internal analysis (RR) *All LH malignancies* Peak exposure 0.1–1.9 ppm 1.00; 103 (Ref.) 2.0–3.9 ppm 1.17 (0.86–1.59); 75 ≥ 4.0 ppm 1.37 (1.03–1.81); 108 P_{trend}[b] 0.02 P_{trend}[c] 0.04 Average intensity 0.1–0.4 ppm 1.00; 164 (Ref.) 0.5–0.9 ppm 1.29 (0.97–1.73); 67 ≥ 1.0 ppm 1.07 (0.78–1.47); 55 P_{trend}[b] > 0.50 P_{trend}[c] > 0.50 *Non-Hodgkin's lymphoma* No association with peak or average exp. *Hodgkin's lymphoma* Peak exposure 0.1–1.9 ppm 1.00; 6 (Ref.) 2.0–3.9 ppm 3.30 (1.04–10.50); 8 ≥ 4.0 ppm 3.96 (1.31–12.02); 11 P_{trend}[b] 0.01 P_{trend}[c] 0.004 Average intensity 0.1–0.4 ppm 1.00; 10 (Ref.) 0.5–0.9 ppm 3.62 (1.41–9.31); 9 ≥ 1.0 ppm 2.48 (0.84–7.32); 6	Internal analysis adjusted by calendar year, age, sex, race, and pay category; exposure was calculated with a 15-year lag interval No association with cumulative exposure Reanalysis of Hauptmann *et al.* (2003) data by Marsh and Youk (2004) found significant exposure-response relationship for all leukemia and myeloid leukemia for peak exposure, see Section 3.2

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
		P_{trend}[b] 0.05 P_{trend}[c] 0.03 *Multiple myeloma* <u>Peak exposure</u> 0.1–1.9 ppm 1.00; 14 2.0–3.9 ppm 1.65 (0.76–3.61); 13 ≥ 4.0 ppm 2.04 (1.01–4.12); 21 P_{trend}[b] 0.08 P_{trend}[c] > 0.50 <u>Average intensity</u> 0.1–0.4 ppm 1.00; 25 (Ref.) 0.5–0.9 ppm 1.40 (0.68–2.86); 11 ≥ 1.0 ppm 1.49 (0.73–3.04); 12 P_{trend}[b] > 0.50 P_{trend}[c] > 0.50 *All leukemia* <u>Peak exposure</u> 0.1–1.9 ppm 1.00; 41 (Ref.) 2.0–3.9 ppm 0.98 (0.60–1.62); 27 ≥ 4.0 ppm 1.42 (0.92–2.18); 48 P_{trend}[b] 0.12 P_{trend}[c] 0.02 <u>Average intensity</u> 0.1–0.4 ppm 1.00; 67 (Ref.) 0.5–0.9 ppm 1.13 (0.71–1.79); 25 ≥ 1.0 ppm 1.10 (0.68–1.78); 24 P_{trend}[b] 0.50 P_{trend}[c] > 0.50 *Myeloid leukemia* <u>Peak exposure</u> 0.1–1.9 ppm 1.00; 14 (Ref.) 2.0–3.9 ppm 1.30 (0.58–2.92); 11 ≥ 4.0 ppm 1.78 (0.87–3.64); 19 P_{trend}[a] 0.13 P_{trend}[b] 0.07 <u>Average intensity</u> 0.1–0.4 ppm 1.00; 24 (Ref.) 0.5–0.9 ppm 1.21 (0.56–2.62); 9 ≥ 1.0 ppm 1.61 (0.76–3.39); 11 P_{trend}[b] 0.43 P_{trend}[c] 0.40 *Lymphatic leukemia* No association with peak or average exposure	

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
Bertazzi *et al.* 1989	Resin manufacturing plant in Italy N = 1,330 1959-86	SMR (formaldehyde-exposed workers) LHC 1.73 (NR); 3 Leukemia NR Exposure-response relationships (duration, latency, age at risk, start time) evaluated for entire cohort, but numbers of LH cases were small (N = 7)	
Coggon *et al.* 2003	British Chemical Workers Study, UK N = 14,014 1941–2000	SMR *Entire cohort* LHC NR Multiple myeloma 0.86 (0.48–1.41); 15 Leukemia 0.91 (0.62–1.29); 31 Hodgkin's lymphoma 0.70 (0.26–1.53); 6 NHL 0.98 (0.67–1.39); 31 *Highly exposed* Multiple myeloma 1.18 (0.48–2.44); 7 Leukemia 0.71 (0.31–1.39); 8 Hodgkin's lymphoma 0.36 (0.01–2.01); 1 NHL 0.89 (0.41–1.70); 9	
Edling *et al.* 1987b	Swedish abrasive materials industry N = 506 male blue collar workers Mortality 1958–83 Incidence 1958–81	Observed/Expected: Incidence LHC NR Leukemia NR Lymphoma 2.0 (0.2–7.2); 2 Multiple myeloma 4.0 (0.5–14.4); 2 SMR not reported	Small cohort
Hansen and Olsen 1995, 1996	Danish formaldehyde exposed worker N = 2,041 men, 1,263 women 1970–84	SPIR LH NR Leukemia Men 0.8 (0.6–1.6); 39 Women 1.2 (0.7–1.8); 21 NHL Men 0.9 (0.6–1.2); 32 Women 1.0 (0.6–1.6); 20 Hodgkin's lymphoma Men 1.0 (0.5–1.7); 12 Women 1.1 (0.3–2.7); 4	SPIR adjusted for age and calendar time
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98 (Myeloid leukemia follow-up from 1960 and acute myeloid leukemia	SMR *Underlying cause of disease analysis* Entire cohort: LHC 0.97 (0.74–1.26); 59 Leukemia 1.09 (0.70–1.62); 24 Myeloid leukemia 1.44 (0.80–2.37); 15 Hodgkin's lymphoma 0.55 (0.07–1.98); 2 Reticulosarcoma/ lymphosarcoma 0.85 (0.28–1.99); 5 Other LH 0.97 (0.64–1.40); 28	Standardized mortality study 7 additional deaths from leukemia were identified in multiple cause of death analysis (5 deaths from lymphocytic leukemia and 2 from myeloid leukemia)

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
	myeloid leukemia from 1968)	Exposure variables Exposure duration: 10 + yr Leukemia 1.53 (NR); 12 Myeloid leukemia 2.19 (NR); 8 Acute myeloid leukemia 2.02 (NR); 5 Time since first exposure: 20+ yr Leukemia 1.31 (NR); 19 Myeloid leukemia 1.91* (NR); 13 Acute myeloid leukemia 1.93 (NR); 9 10+ yr duration, 20+ yr since first exposure Myeloid leukemia 2.43 (0.98–5.01); 7 Acute myeloid leukemia 2.51 (0.81–5.85); 5 Year of first exposure (< 1963) Leukemia 1.23 (NR); 19 Myeloid leukemia 1.61 (NR); 11 Acute myeloid leukemia 1.81 (NR); 8 *Multiple cause of death analysis* *Entire cohort* Leukemia 1.19 (0.81–1.68) Myeloid leukemia 1.38 (0.80–2.20) Lymphocytic leukemia 1.11 (0.48–2.19) > 10 yr of exposure Leukemia 1.78 (1.04–2.86); 17 Lymphocytic leukemia 2.12 (0.78–4.62); 6 Myeloid leukemia 2.24 (1.02–4.25); 9 Acute myeloid leukemia 1.91 (0.62–4.45); 5 ≥ 10 yr exposure + > 20 yr since first exp. Leukemia 1.92 (1.08–3.17); 15 Myeloid leukemia 2.55 (1.10–5.03); 8	
Stern 2003	Workers employed in two chrome leather tannery plants, USA (N = 9,365) 1940-93 Formaldehyde-exposed workers in the finishing department N = NR (1,050 deaths from all cause	SMR LHC 0.91 (NR); 22 Leukemia and aleukemia 0.93 (NR); 9	Findings reported for formaldehyde-exposed workers in the finishing department

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths	Comments
General population study			
Stellman *et al.* 1998	Woodworkers: American Cancer Society Cancer Prevention Study 50 U.S. states, District of Columbia, Puerto Rico N = 362,823 (total cohort); 45,399 in woodworking activities 1982–88	RR *Non-woodworkers exposed to formaldehyde* LHC 1.22 (0.84–1.77); 28 Leukemia 0.96 (0.54–1.71); 12 NHL 0.92 (0.50–1.68); 11 Multiple myeloma 0.74 (0.27–2.02); 4 *Woodworkers exposed to formaldehyde* LHC 3.44 (1.11–10.68); 3 Leukemia 5.79 (1.44–23.25); 2 NHL 2.88 (0.40–20.5); 1 Multiple myeloma 0	Internal analysis using non-woodworkers or workers without exposure to wood dust as controls Adjusted for age and smoking 387 woodworkers reported formaldehyde exposure; number of non-woodworkers exposed to formaldehyde not reported See Table 3.3b for nested case-control on multiple myeloma
Studies of health professional workers			
Hall *et al.* 1991	Pathologists, members of professional organizations in the UK N = 3,872 1974–87	SMR (male and female, England and Wales) LHC 1.44 (0.69–2.65); 10 Leukemia 1.52 (0.41–3.89); 4 Hodgkin's lymphoma 1.21 (0.03–6.71); 1	Small cohort
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046 1975–85	PMR LHC 1.39 (1.15–1.67); 115 Hodgkin's lymphoma 0.72 (0.15–2.10); 3 NHL 1.26 (0.87–1.76); 34 Multiple myeloma 1.37 (0.84–2.12); 20 Myeloid leukemia 1.57 (1.01–2.34); 24 Unspecified leukemia 2.28 (1.39–3.52); 20	Small cohort
Levine *et al.* 1984	Licensed embalmers in Ontario, Canada N = 1,413 First licensed 1928–57 Follow-up through 1977	SMR LHC 1.23 [0.53–2.43][d]; 8 Leukemia [1.60] [0.44–4.10][d]; 4	Small cohort
Stroup *et al.* 1986	Anatomists, members of the American Association of	SMR LHC 1.2 (0.7–2.0); 18 Lymphoma 0.7 (0.1–2.5); 2	Small cohort Chronic myeloid leukemia is for 1969–

Reference	Study population and follow up	Risk estimate (95% CI); number of exposed cases or deaths		Comments
	Association of Anatomists, USA N = 2,317 1888–1979	Hodgkin's disease Leukemia Chronic myeloid leukemia	0 deaths, 1.9 exp. 1.5 (0.7–2.7); 10 8.8 (1.8–25.5); 3	1979 when subtype data was available
Walrath and Fraumeni 1983	All licensed embalmers and funeral directors in NY, USA N = 1,263 1902–80	*PMR* *White males* LHC Lymphomas Hodgkin's disease Leukemia Myeloid leukemia *Non-white males* LHC	 1.21 (NR); 25 1.08 (NR); 5 2 vs. 2.3 exp. 1.40 (NR); 12 [1.5][d] (NR); 6 NR*; 3 cases	Small cohort
Walrath and Fraumeni 1984	All licensed embalmers in CA, USA N = 1,109 1916–80	PMR (white males) LHC Lymphomas Hodgkin's disease Leukemia Myeloid leukemia *Length of licensure and leukemia* < 20 yr ≥ 20 yr	 1.22 (NR); 19 [1.0][d] (NR); 3 0 vs. 2.5 exp. 1.75* (NR); 12 [1.5][d] (NR); 6 1.24 (NR); 4 2.21* (NR); 8	Small cohort

*$P < 0.05$.
exp. = expected number of cases or deaths; LHC = lymphohematopoietic cancer; NHL= non-Hodgkin's lymphoma; NR = not reported; PMR = proportionate mortality ratio; Ref. = referent group; RR = relative risk; SPIR = standardized proportionate incidence cancer ratio.
[a]Results not reported for Bertazzi *et al.* 1989, Dell and Teta 1995, Edling *et al.* 1987b, Stellman *et al.* 1998, and Stern *et al.* 2003.
[b]P_{trend} across exposed.
[c]P_{trend} across exposed and non-exposed.
[d]Calculated by IARC (2006).

Table 3-8b. Summary of case-control studies (including nested case-control studies) of formaldehyde exposure and lymphohematopoietic cancers

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Gérin *et al.* 1989 Montreal, Quebec	*Multi-site study* 1979–85 *Cases*: men, 206 NHL, 53 Hodgkin's disease, incident cases identified from all hospitals *Controls*: (1) cancer controls, internal controls with tumors at other sites and (2) 740 population-based controls (men) matched by age	Occupational histories and other information obtained by interview; exposure classified by job description and industry *Estimated exposure index* Low < 0.1 ppm Med. 0.1–1 ppm High ≥ 1 ppm	Non-Hodgkin's lymphoma Any[a] 0.9 (0.6–1.3); 47 *Exposure duration (yr)/exposure index (cancer controls)*[a] < 10 yr/any 0.8 (0.4–1.5); 13 ≥ 10 yr/ Low 1.3 (0.7–2.4); 15 Med. 0.8 (0.5–1.5); 14 High 0.7 (0.3–1.9); 5 Hodgkin's disease Ever exposed 0.5 (0.2–1.2); 8	Adjusted for age, ethnicity, self-reported income, jobs held, and other occupational factors
Ott *et al.* 1989 United States	*Nested case-control of workers chemical manufacturing workers* N = 29,139 1940–78 *Cases:* 129 LH (52 NHL, 20 multiple myeloma, 30 non-lymphocytic leukemia, and 18 lymphocytic leukemia) *Controls*: group matched incidence density sampling by decade first employed and survival	Occupational histories obtained from company employment records and classified using a job exposure matrix	*OR for ever exposed* NHL 2.0 (NR); 2 Lymphocytic leukemia 2.6 (NR); 1 Non-lymphocytic leukemia 2.6 (NR); 2 Multiple myeloma 1.0 (NR); 1	Unadjusted Very few workers exposed to formaldehyde

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Boffetta *et al.* 1989 United States	*Nested case-control study, American Cancer Society Cancer Prevention Study (1982 enrollment)* Follow-ups 1982–86 *Cases*: 128 incident cases of multiple myeloma *Controls*: 512 randomly selected incident controls matched on age, ACS region, sex, ethnicity(4:1)	Occupational exposures obtained by questionnaire	OR for history of exposure Multiple myeloma 1.8 (0.6–5.7); 4/9	
Heineman *et al.* 1992, Pottern *et al.* 1992 Denmark	*Population-based case-control study* 1970–84 *Eligible cases:* All 1,222 men and 1,010 women with multiple myeloma in Denmark reported to Danish Cancer Registry (1,098 men and 607 women included in study based on availability of occupational data) *Controls:* 4,888 age-matched men and 4,040 women from state pension fund records (4,169 men and 2,596 women included in study)	Exposures classified by JEM based on occupational and industry codes	*Possible exposure to formaldehyde vs. never exposed* Men 1.0 (0.8–1.3); 144/527 Women 1.1 (0.8–1.6); 56/235 *Probable exposure to formaldehyde vs. never exposed:* Men 1.1 (0.7–1.6); 41/142 Women 1.6 (0.4–5.3); 4/12	Adjusted for age

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Partanen *et al.* 1993 Finland	*Nested case-control study of plywood, particleboard, and formaldehyde glue factory workers* N = 7,303 1957–82 *Cases*: 204 LH cases (NHL, Hodgkin's disease, and leukemia) identified using the Finnish Cancer Registry *Controls*: 152 controls selected randomly from cohort and matched by year of birth and vital status in 1983	Occupational histories obtained from company employment records and classified using plant-specific JEMs	*All LH* < 3 ppm-mo 1.00 (Ref.) ≥ 3 ppm-mo 2.49 (0.81–7.59); 7 *All lymphomas* < 3 ppm-mo 1.00 (Ref.) ≥ 3 ppm-mo 4.02 (0.87–18.6); 5 *Non-Hodgkin's lymphoma* < 3 ppm-mo 1.00 (Ref.) ≥ 3 ppm-mo 4.24 (0.68–26.6); 4 *Leukemia* < 3 ppm-mo 1.00 (Ref.) ≥ 3 ppm-mo 1.40 (0.25–7.91); 2	Wood dust and solvents not found to be confounders OR for Hodgkin's disease could not be calculated due to small numbers
West *et al.* 1995 United Kingdom (South East Wales, Wessex, and West Yorkshire)	*Population-based study, case ascertainment is unclear* *Cases:* 400 cases of myelodysplastic syndrome (> 15 years old) identified from health care records *Controls*: 400 matched (age, sex, residence, hospital and yr of diagnosis) non-cancer controls selected from out- and inpatient clinics	Occupational histories and other information obtained by interview; exposure classified by job description, exposure to a list of specific chemicals, and industry	Hours of lifetime exposure/exposure intensity (low, med., high) *Myelodysplasia* ≥ 10/any 1.17 (NR); 15/13 ≥ 50/> med. 2.33 (NR); NR ≥ 2,500/> med. 2.00 (NR): NR	Matched pair analysis

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Tatham *et al.* 1997 United States (Atlanta, CT, IA, KS, Miami, San Francisco, Detroit, and Seattle)	*Population-based study* 1984–88 *Cases*: 1,048 living cases of NHL identified using population-based cancer registries *Controls:* 1,659 frequency matched (registry and date of birth) identified by random-digit dialing	Occupational histories and other information obtained by interview; exposure classified by job description and industry	Ever exposed All NHL 1.20 (0.86–1.50); 93 Small-cell diffuse 1.40 (0.87–2.40); 21 Follicular type 0.71 (0.41–1.20); 17 Large-cell diffuse 1.10 (0.79–1.70); 46	Adjusted for age at diagnosis, ethnicity, education, smoking, marital status, and other factors
Blair *et al.* 1993, Blair *et al.* 2001 Iowa, Minnesota, United States	*Population-based study* 1980–83 *Cases:* 513 leukemia cases (669 eligible) and 622 NHL (715 eligible) in white men > 30 yr old identified from the Iowa Cancer Registry and hospitals in Minnesota; men with farming as sole occupation excluded; 86% response rate) *Controls:* frequency-matched controls (age, vital status, and residence), identified by random-digit dialing, Health Care Financing Administration records, and death certificates*:* 1,087 for leukemia and 1,245 for NHL	Occupational histories and other data obtained by interview (present or proxy); exposure classified using a JEM	*NHL* Ever exposed 1.2 (0.9–1.7); 84 Exposure intensity *All NHL* Low 1.2 (0.9–1.7); 78 High 1.3 (0.5–3.8); 6 *Follicular NHL* Low 1.4 (0.9–2.2); 27 High 1.1 (0.4–22.7); 6 *Diffuse NHL* Low 1.3 (0.8–2.2);24 High 2.3 (0.6–8.6); 3 *Other NHL* Low 1.0 (0.6–1.6); 24 High 1.2 (0.3–5.8); 2 *All leukemia* Low 1.0 (0.7–1.4); 61/128 High 0.7 (0.2–2.6); 3/9 *Acute myeloid leukemia* Low 0.9 (0.5–1.6); 14/128 High NR *Chronic myeloid leukemia* Low 1.3 (0.6–3.1); 7/128	Adjusted for family history, education, smoking, and hair-dye use Urban residents excluded from selection of subjects and farmers excluded from analysis due to higher risk of leukemia

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
			High 2.9 (0.3–24.5); 1/9 *Chronic lymphocytic leukemia* Low 1.2 (0.7–1.8); 29/128 High 0.6 (0.1–5.3); 1/9 *Myelodysplasia* Low 0.8 (0.3–1.9); 6/128 High NR	
Richardson *et al.* 2008 Germany	*Population-based study* 1986–98 *Cases:* 858 incident cases of NHL (high and low malignancy) and CLL, men and women, ages 15–75, residing in specific counties in Germany *Controls:* 1,821 population controls (≥ 2/case), without lymphoma or leukemia, identified from population registries, and matched to each case on sex, year of birth, and region	Occupational history assessed by interviews and questionnaires; exposure to 50 chemicals assessed by JEM	Ever exposed NHL-high 1.52 (0.88–2.63); 27 NHL-low 1.18 (0.79–1.75); 45 CLL 1.16 (0.71–1.89); 29	Cumulative exposure to formaldehyde was not evaluated. (It was measured for other agents.) ORs adjusted for a three-level indicator (never, vs. ex.-, vs. current smoker) of smoking status

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
Wang *et al.* 2009a Connecticut, United States	*Population-based incident study* 1996–2000 *Cases:* 832 women with histologically confirmed non-Hodgkin's lymphoma diagnosed in Connecticut 21-84 years old, no previous cancer (601 participated) *Controls:* 717 frequency – matched random digit dialing plus Medicare/Medicaid record sample	Exposures classified using a JEM based on occupational and industry data obtained from in-person interviews	Ever exposed to formaldehyde (OR) All NHL 1.3 (1.0–1.7); 203 Large B cell type 1.9 (1.3–2.6); 80 Follicular type 1.1 (0.7–1.6); 41 Chronic lymphocytic leukemia/ small lymphocytic lymphoma 1.2 (0.7–2.0); 20 *All NHL* Intensity Low 1.4 (1.0–1.8); 129/120 Med-high 1.2 (0.8–1.7); 74/81 P_{trend} 0.21 Probability Low 1.3 (1.0–1.7); 165/166 Med-high 1.4 (0.9–2.3); 38/35 P_{trend} 0.11 Medium-high probability Low intensity 1.1 (0.5–2.4); 14 Med-high intensity 1.6 (0.9–3.1); 24 *No trend reported* *Large B cell-type NHL* Intensity Low 2.1 (1.4–3.1); 54 Medium-high 1.5 (0.9–2.4); 26 P_{trend} 0.03 Probability Low 1.7 (1.2–2.4); 60 Medium-high 2.6 (1.5–4.7); 20 P_{trend} < 0.01	69% of telephone controls and 47% of Medicare/Medicaid sample participated. Matched on age, sex, and Connecticut residence
Hauptmann *et al.* 2009	*Nested case-control study* *Cohort*: 6,808 death certificates from 1960 to 1986. Identified from registries of the National Funeral Director	Occupational history obtained by interviews with next of kin and co-workers (multiple) using detailed questionnaires. Exposure was assessed	*Embalming (referent never exposed)* *Ever exposed (OR)* LHC 1.4 (0.8–2.6); 144 Lymphoid 1.1 (0.5–2.1); 81 Nonlymphoid 3.0 (1.0–9.5); 44	Cohorts include Hayes *et al.* 1990, Walrath *et al.* 1983,1984 Only one case of myeloid leukemia was observed in reference of never exposed so analysis was repeated using

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
	Association, licensing board and state funeral director's associations, NY State Bureau of Funeral Directors and CA Funeral Directors and Embalmers *Cases:* 168 cases of LHC, including 99 cases of lymphoid leukemia, 48 cases of non-lymphoid leukemia, and 34 cases of myeloid leukemia *Controls:* 265 randomly selected with deaths attributed to other causes excluding cancer of the buccal cavity and pharynx, respiratory system, and eye, brain or other parts of the nervous system.	by linking questionnaire responses to an exposure assessment experiment. Exposure levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure data.	Myeloid leukemia 11.2 (1.3–95.6); 33 NHL 0.9 (0.4–2.1); NR Hodgkin's lymphoma 0.5 (0.1–2.6); 8 All lymphomas + CLL 1.0 (0.5–1.9); NR Multiple myeloma 1.4 (0.4–5.6); NR *Questionnaire-based metrics (P trend)* Duration of working in jobs with embalming LHC 0.058 Nonlymphoid 0.046 Myeloid leukemia 0.020 Number of embalmings LHC 0.477 Nonlymphoid 0.247 Myeloid leukemia 0.314 *Questionnaire and model based (P_{trend})* Cumulative exposure (ppm-h) LHC 0.422 Nonlymphoid 0.140 Myeloid leukemia 0.192 Average exposure (ppm) LHC 0.591 Nonlymphoid 0.096 Myeloid leukemia 0.058 8-h TWA (ppm) LHC 0.635 Nonlymphoid 0.256 Myeloid leukemia 0.396 Peak exposure (ppm) LHC 0.555 Nonlymphoid 0.089	embalmers with fewer than 500 lifetime embalmings as the referent group

Reference	Study population	Exposure assessment	OR or RR (95% CI); exposed cases or cases/controls	Comments
			Myeloid leukemia 0.036 No association of lymphoid origin LHC with any of the exposure metrics *Referent < 500 lifetime embalming: Myeloid leukemia* RR (highest category of exposure); *P* Duration (> 34 yr) 3.9 (1.2–12.5); 0.024 Number of embalmings (> 3,068) 3.0 (1.0–9.2); 0.057 Cumulative exposure (>9,253 ppm-yr) 3.1 (1.0–9.6) ; 0.047 Average exposure (> 1.9) 2.3 (0.7–7.5); NR 8-h TWA (> 0.18 ppm) 2.6 (0.8–8.3); NR Peak exposure (> 9.3 ppm) 2.9 (0.9–9.5); NR P_{trends} among the exposed group were the same as trends using non-embalmers as the referent group.	

8-h TWA = 8-hour time-weighted average; CLL = chronic lymphocytic leukemia; JEM = job exposure matrix; LHC = lymphohematopoietic cancer; NHL = non-Hodgkin's lymphoma; NR = not reported; OR = odds ratio; Ref. = referent group; RR = relative risk ratio.
[a]ORs calculated using hospital cancer controls; similar estimates using population-based controls.

3.6.6 Cancers of the brain and central nervous system

Several cohort mortality studies of health professionals including pathologists, anatomists, and embalmers have reported excess mortality from brain and central nervous system malignancies (Hall *et al.* 1991, Hayes *et al.* 1990, Levine *et al*. 1984, Stroup *et al.* 1986, Walrath and Fraumeni 1983, 1984) (see Section 3.3 and Table 3.9). Statistically significant increases were observed among anatomists in the United States (SMR = 2.7, 95% CI = 1.3 to 5.0, 10 deaths, compared with U.S. population, and 6.0, 95% CI = 2.3 to 15.6 using psychiatrists as a referent) (Stroup *et al.* 1983), and white male embalmers in New York (SMR = 2.34, 6 deaths) (Walrath and Fraumeni 1983) and California (PMR = 1.94, 9 deaths) (Walrath and Fraumeni 1984). Some studies of health professionals reported that longer exposure (as assessed by length of licensure or professional membership) might be associated with brain cancer mortality: higher risks were found among anatomists with longer professional membership (SMR = 7.0, 95% CI = 0.9 to 26.8 for 40 to 69 years vs. between 2 and 2.8 for 1 to 19, and 20 to 39 years) (Stroup *et al.* 1986). PMRs were also higher among New York embalmers who were > 30 years old (2.94, 5 deaths, $P < 0.05$ for > 30 years vs. 0.98, 4 deaths for < 30 years) at first licensure and who had only an embalmers license (PMR = 2.34, $P < 0.50$ for embalmer only vs. 0.93 for embalmer and funeral directors); embalmers are thought to have higher exposure to formaldehyde (Walrath and Fraumeni 1983). All of the brain cancers among anatomists occurred among subjects performing gross or microanatomy.

However, a nested case-control of brain cancer (N = 48 deaths) study among embalmers and funeral directors in the cohorts assembled by Hayes *et al.* (1990) and Walrath and Fraumeni (1983, 1984) found little evidence of consistent exposure-response relationships for duration of employment, number of embalmings, or estimated cumulative, average, 8-hour TWA, or peak exposure to formaldehyde (all trends nonsignificant) (Hauptmann *et al.* 2009). The OR for ever exposure to formaldehyde was 1.9 (95% CI = 0.7 to 5.3, 42 exposed cases).

In general, the industrial cohort studies found no increases for brain cancer, except small statistically nonsignificant increases were found in the NIOSH and Danish cohorts. In the NIOSH cohort, SMRs were higher (but not statistically significant) among workers exposed 20 or more years since first exposure (SMR = 1.20, 13 deaths) and workers whose first exposure was prior to 1963 (SMR = 1.17, 14 deaths), but not among workers with the longest duration of exposure (10+ years) (Pinkerton *et al*. 2004). Hauptmann *et al.* (2004) found no increase in brain and CNS cancers in their external SMR analysis of the NCI cohort; when these cancers were analyzed in internal analyses by average, peak, cumulative, and duration of exposure, no trends with exposure category were observed, and relative risks were generally at or below the referent category (in this study, the lowest exposure group). ORs for brain and CNS cancer were less than one in studies by Andjelkovich *et al.* (1995) and Coggon *et al.* (2003).

Bosetti *et al.* (2008) conducted a meta-analysis of data from a total of 11 cohorts that included deaths from brain cancer and calculated an estimated RR of 0.92 (95% CI = 0.75 to 1.13, 94 deaths) among industrial workers and 1.56 (95% CI = 1.24 to 1.96, 74 deaths) among health professional workers. Note that the findings for separate studies of health professional workers were significantly heterogeneous, according to the authors.

(See Table 3-10 for a list of studies included in their meta-analysis; note that not all studies were included in analyses for specific cancer sites.)

Table 3-9. Summary of studies of formaldehyde exposure and brain and CNS cancers[a]

Reference	Study population and follow up	Risk estimate for brain and CNS cancer, (95% CI); number of exposed cases or deaths	Comments
Studies of industrial workers			
Andjelkovich *et al.* 1995	Iron foundry workers, MI, USA N = 3,929 1960–89	SMR 0.62 (0.07–2.23); 2	Formaldehyde-exposed subcohort, comparison based on national rates
Coggon *et al.* 2003 (update of Acheson *et al.* 1984)	British Chemical Workers Study, UK N = 14,014 1941–2000	SMR Entire cohort 0.85 (0.57–1.21); 30 Jobs with high exposure 0.63 (0.25–1.29); 7	
Hansen and Olsen 1995, 1996	Danish formaldehyde-exposed workers N = 2,041 men, 1,263 women 1970–84	SPIR Men 1.1 (0.9–1.5); 54 Women 1.2 (0.8–1.6); 39 *No exposure to wood dust* Men 1.3 (0.8–1.8); 30 Women NR	SPIR adjusted for age and calendar time
Hauptmann *et al.* 2004	NCI cohort, USA N = 25,619 Entire cohort 1966–94	SMR 0.92 (0.68–1.23); 43 RR did not increase with increasing peak, average and cumulative exposure, and exposure duration	
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98	SMR All 1.09 (0.66–1.71); 19 Time since first exposure: 20 + yr 1.20 (NR); 13 Year of first exposure: prior to 1963 1.17 (NR); 14 No increased risk with increasing duration	Standardized mortality study
Studies of health professionals			
Hall *et al.* 1991	Pathologists, members of professional organizations in the UK N = 3,872 1974–87	SMR (males and females, England and Wales) Males and females 2.18 (0.80–4.75; 6 Males only 2.40 (0.88–5.22); 6	

Reference	Study population and follow up	Risk estimate for brain and CNS cancer, (95% CI); number of exposed cases or deaths	Comments
Hayes *et al.* 1990	Deceased embalmers and funeral directors identified using licensing board records, death certificates, and other sources, USA N = 4,046 1975–85	PMR White 1.23 (0.80–1.84); 24 Non-white NR; 0 (0.8 expected) PMRs were similar between embalmers and funeral directors	Small cohort
Levine *et al.* 1984	Licensed embalmers in Ontario, Canada N = 1,413 First licensed 1928–57 Follow-up through 1977	SMR [1.15] [0.24–3.37][b]; 3	Small cohort
Stroup *et al.* 1986	Anatomists, white male members of the American Association of Anatomists, USA N = 2,317 1988–79	SMR *AAA members vs. referent groups* USA 2.7 (1.3–5.0); 10 Psychiatrists 6.0 (2.3–15.6); 9 *Duration of membership (yr) (U.S. referent)* 1–19 2.0 (0.6–5.2); 4 20–39 2.8 (0.8–7.2); 4 40–69 yr 7.0 (0.9–26.8); 2	Small cohort All brain cancers were gliomas
Walrath and Fraumeni 1983	All licensed embalmers and funeral directors in NY, USA N = 1,263 1902–80	PMR (white males) All 1.56 (NR); 9 *Type of licensure* Embalmers 2.34* (NR); 6 Dual license[c] 0.93 (NR); 3 *Age at first license* < 30 yr 0.98 (NR); 4 > 30 yr 2.94* (NR); 5	Small cohort
Walrath and Fraumeni 1984	All licensed embalmers in CA, USA N = 1,109 1916–80	PMR (white males) All 1.94* (NR); 9 *Length of licensure and leukemia* < 20 1.98 (NR); 5 ≥ 20 1.89 (NR); 4	Small cohort
Hauptmann *et al.* 2009	*Nested case-control study* *Cohort*: 6,808 death certificates from 1960–86. Identified from registries of the	OR (referent never exposed) Ever 1.9 (0.7–5.3); 42 Exposure response – no significant trends for duration of exposure, no. of embalmings, cumulative exposure, average exposure, 8-h TWA exposure,	Cohorts include Hayes *et al.* (1990), Walrath *et al.* (1983, 1984) 38 of 42 brain tumors malignant)

Reference	Study population and follow up	Risk estimate for brain and CNS cancer, (95% CI); number of exposed cases or deaths	Comments
	National Funeral Directors' Association, licensing boards and state funeral directors' associations, NY State Bureau of Funeral Direction, and CA Division of Funeral Directors and Embalmers *Cases:* 48 brain cases *Controls:* 265 randomly selected with deaths attributed to other causes excluding cancer of the buccal cavity and pharynx, respiratory system, and eye, brain or other parts of the nervous system	or peak exposure.	

*$P < 0.05$.
8-h TWA = 8-hour time-weighted average; CNS = central nervous system; NR = not reported; PMR = proportionate mortality ratio; RR = relative risk ratio; SPIR = standardized proportionate incidence cancer ratio.
[a]Results not reported for Bertazzi *et al.* 1989, Dell and Teta 1995, Edling *et al.* 1987b, Stellman *et al.* 1998, and Stern *et al.* 2003.
[b]Calculated by IARC.
[c]Dual licensure were both embalmers and funeral directors.

3.6.7 Cancer at other sites

The association between formaldehyde exposure and cancers of sites other than the head and neck, the respiratory and lymphohematopoietic system, and brain and central nervous system has been examined in both historical cohort and case-control studies. These cancer sites include (but are not limited to): urinary bladder, breast, colo-rectum, esophagus, kidney, liver, pancreas, prostate gland, stomach, and skin or dermis as well as intraocular melanoma. In general, reported estimates were null or slightly elevated but statistically nonsignificant, and studies have not consistently reported an elevated risk in cancer associated with formaldehyde exposure at any of these sites. The following review primarily focuses on findings of elevated risk for specific solid cancer sites reported in at least two case-control or cohort studies, in addition to statistically significant findings. Not all cohort studies report findings for all cancer sites, or do not report confidence intervals or *P*-values. [Most of the cohort and case-control studies are of male workers, so that associations between formaldehyde and cancers among women and of the female reproductive system are underrepresented.]

3.6.7.1 Cancers of the gastrointestinal system and associated organs

Several studies have reported small but consistent increases in stomach cancer. Bertazzi *et al.* (1989) reported an increase in risk of gastrointestinal cancers in a cohort of resin production workers exposed to formaldehyde (SMR = 1.34, 11 deaths), with a stomach cancer risk of 1.64 (5 deaths). Coggon *et al.* (2003) reported a statistically significant increase in the risk of stomach cancer in a large cohort study of plastics and chemical manufacturing workers exposed to formaldehyde (SMR = 1.31, 95% CI = 1.11 to 1.54, 150 deaths), and Stellman *et al.* (1998) found an elevated risk of stomach cancer among a group estimated to have potential exposure to formaldehyde in an internal analysis of a population-based cohort (RR = 1.69, 95% CI = 0.94 to 2.86, 11 deaths). In addition, Andjelkovich *et al.* (1995) reported a small increase in stomach cancer in association with formaldehyde exposure in a cohort study of iron foundry workers (SMR = 1.64, 95% CI = 0.82 to 2.94, 11 deaths), together with borderline elevations in cancers of the esophagus, large intestine, and rectum. Walrath and Fraumeni (1984) reported an excess of colon cancer among embalmers in California (PMR = 1.87, 30 observed vs. 16 expected deaths, $P < 0.05$), and in a previous study of embalmers in New York (PMR = 1.43, 29 observed vs. 20.3 expected deaths, $P < 0.05$) (Walrath and Fraumeni, 1983). Hayes *et al.* (1990) also reported increases in gastrointestinal cancers combined, including rectum (PMR = 2.31, 95% CI = 0.64 to 6.00, 4 deaths) and colon (PMR = 2.31, 95% CI = 1.32 to 3.76, 16 deaths), among non-white embalmers; in white embalmers, nonsignificant increases were observed. Coggon *et al.* (2003) reported a nonsignificant increase in cancers of the large intestine (SMR = 1.30, 95% CI = 0.93 to 1.77, 40 deaths) and rectum (SMR = 1.26, 95% CI = 0.82 to 1.84, 26 deaths) among the subgroup of chemical workers with high exposure to formaldehyde, and Hansen and Olsen (1995) also reported a statistically significant increase in the risk of colon cancer in association with occupational formaldehyde exposure (SPIR = 1.2, 95% CI = 1.1 to 1.4, 166 cases) in a population-wide study of the Danish Cancer Registry. A subsequent analysis of a subgroup of "blue-collar" workers with estimated formaldehyde exposure but no wood dust exposure, showed a slightly reduced risk (SPIR = 1.1, 95% CI = 0.9 to 1.4, 73 cases)

(Hansen and Olsen 1996). In a population-based case-control study of rectal cancer in men, Dumas *et al.* (2000) reported a statistically significant increase in this endpoint in association with "substantial" exposure to formaldehyde (OR = 2.4, 95% CI = 1.2 to 1.6, 36 deaths). Marginal but statistically nonsignificant increases in this cancer have been noted only in the cohort studies of Walrath and Fraumeni (1984) and Andjelkovich *et al.* (1990).

An increase in the risk of liver cancer was noted in the population studied by Hansen and Olsen (1996) (SPIR = 1.2, 95% CI = 0.9 to 1.8, 29 cases), and Bertazzi *et al.* (1989) reported an increase in the risk of liver cancer (SMR = 2.44, CI not reported, 2 deaths) among formaldehyde resin producers.

3.6.7.2 Meta-analyses: pancreas

Two meta-analyses have been published summarizing data from multiple studies of pancreatic cancer (Ojajärvi *et al.* 2000, Collins *et al.* 2001a). Ojajärvi *et al.* consolidated epidemiologic data on formaldehyde exposure and pancreatic cancer estimates from two analytic studies and three proportionate mortality studies; the resulting mRR was 0.8 (95% CI = 0.5 to 1.0). Collins *et al.* reported a similar mRR of 1.1 (95% CI = 1.0 to 1.3) using data from 14 studies of workers exposed to formaldehyde where pancreatic cancer rates were reported. The small increase in risk was attributable to embalmers (mRR = 1.3, 95% CI = 1.0 to 1.6) and pathologists and anatomists (mRR = 1.3, 95% CI = 1.0 to 1.7). For industrial workers with the highest exposure levels on average, no increased risk in pancreatic cancer was observed (mRR = 0.9, 95% CI = 0.8 to 1.1). In Section 3.5.7, a case-control study of pancreatic cancer is summarized (Kernan *et al.* 1999) in which some evidence of an increased risk was observed with higher levels of formaldehyde exposure probability and intensity.

3.6.7.3 Cancers of the genitourinary system

Small but generally statistically nonsignificant excesses of kidney cancers have been reported in a number of cohort studies. No case-control studies of this endpoint have been identified. Hansen and Olsen (1995) reported a borderline statistically significant increase in kidney cancer (SPIR = 1.3, 95% CI = 1.0 to 1.6, 60 cases) among a population with potential occupational formaldehyde exposure in a population-wide Danish Cancer Registry study, and Walrath and Fraumeni (1983, 1984) found an increase in kidney cancers among white male embalmers in New York (PMR = 2.47, 6 observed vs. 2.4 expected deaths, $P < 0.05$) but not among embalmers in California (PMR = 1.00, 4 observed vs. 4 expected deaths).

With respect to urinary bladder cancer, cohort studies have generally reported no excesses of cancer for this site, with the exception of a nonsignificant increase (SMR = 1.20, 7 deaths) among finishing department workers by Stern (2003). Two case-control studies of bladder cancer have been conducted. In a population-based study by Siemiatycki *et al.* (1994) the authors found a marginal increase in bladder cancer in association with "nonsubstantial" exposure to formaldehyde (OR = 1.2, 95% CI = 0.9 to 1.6, 67 exposed cases, adjusted for demographic and lifestyle variables and other occupational exposures) but not with "substantial" exposure (adjusted OR = 0.9, 95% CI

= 0.5 to 1.7, 17 exposed cases). In a population-based case-control mortality study of bladder cancers among all male deaths under the age of 50 in the United Kingdom from 1975 to 1979 (Coggon *et al.* 1984), no association with occupations with any potential for exposure to formaldehyde was observed (OR = 1.0, 95% CI = 0.7 to 1.3, 132 exposed deaths), and a borderline association was found with occupations with a high probability of formaldehyde exposure (OR = 1.5, 95% CI = 0.9 to 2.8, 30 deaths).

3.6.7.4 Other cancers

Few other cancers have been reported in excess in the cohort studies. [In a number of studies, the all-cause mortality was decreased, suggesting the possibility of a healthy worker effect, which would tend to bias rates based on external population comparisons toward the null.] Walrath and Fraumeni (1983) found a statistically significant increase in skin cancer among white male embalmers in New York state (PMR = 3.26, 5 observed vs. 1.5 expected deaths, $P < 0.05$); among those who practiced both as embalmers and funeral directors, the risk was reduced (PMR = 1.44, 3 observed vs. 2.1 expected deaths). This finding was not replicated in a subsequent study of white male Californian embalmers (2 observed vs. 3.4 expected deaths) (Walrath and Fraumeni 1984), and increases in this cancer risk have not been reported in other studies of embalmers, pathologists, or anatomists. Small excesses of prostate cancers were reported in a study of pathologists (SMR = 3.30, 95% CI = 0.39 to 11.8, 2 deaths) (Hall *et al.* 1991), and in a study of embalmers by Hayes *et al.* (1990) (PMR = 1.06, 95% CI = 0.84 to 1.32, 79 deaths, white males, and PMR = 1.35, 95% CI = 0.82 to 2.12, 19 deaths, non-white males) but not in other studies of embalmers and anatomists. Pinkerton *et al.* (2004) also reported nonsignificant increases in prostate cancer (SMR = 1.58, 11 deaths) and other male genital cancers (SMR = 3.89, 2 deaths) in their cohort of garment workers.

Cantor *et al.* (1995) conducted a population-based case-control study of breast cancer among women in the United States using death certificates from 24 states from 1984 to 1989, and coded occupations by probability and intensity of exposure to formaldehyde and other agents. Statistically significant excesses of breast cancer were noted among black women with a high probability of exposure (OR = 1.45, 95% CI = 1.2 to 1.7, 311 deaths) or all levels of intensity of exposure (ORs from 1.11 to 1.31, all CIs 1.0 or above); among white women, breast cancer was statistically significantly associated with a high intensity of exposure (OR = 1.19, 95% CI = 1.1 to 1.3, 1,815 deaths) only. Ray *et al.* (2007) reported only two cases of breast cancer in a case-control study of women textile workers in China that were potentially exposed to formaldehyde, however.

Finally, a single case-control study of uveal (eye) cancer among white men by Holly *et al.* (1996) reported a statistically significant association with any possible formaldehyde exposure (estimated only by personal interview with subjects) (OR = 2.9, 95% CI = 1.2 to 7.0, 3 exposed cases) and a nested case-control study of thyroid gland cancer among female textile workers (Wong *et al.* 2006) found a statistically significant association for 10 or more years of estimated formaldehyde exposure (hazard ratio = 8.33, 95% CI = 1.16 to 6.60, 2 exposed cases). Excesses of thyroid gland cancer have not been reported in cohort studies, with the exception of a statistically nonsignificant increase in the cohort study of garment workers by Pinkerton *et al.* (2004) (SMR = 1.16, 95% CI = 0.14 to 4.18, based on only 2 deaths).

3.6.8 Summary of studies used in meta-analyses

The meta-analyses discussed above analyzed the possible association between number of specific tissue sites and cancer for exposure to formaldehyde. Collins *et al.* (1997) analyzed upper respiratory cancers; Collins *et al.* (2001a) and Ojajarvi *et al.* (2000), pancreatic cancer; Collins and Lineker (2004) and Zhang *et al.* (2009a), lymphohematopoietic cancers; Bosetti *et al*. (2008), all cancers, oral cavity and pharyngeal, nasopharyngeal, sinonasal, lung, brain, and lymphohematopoietic (note that not all studies listed were used in analyses of specific sites); Bachand *et al.* (2010), nasopharyngeal cancers and leukemia.

Table 3-10. Meta-analyses of cohort and case-control studies of formaldehyde exposure

Study	Year	Collins 1997	Collins 2001a	Collins-Lineker 2004	Ojajarvi 2000	Bosetti 2008	Zhang 2009a	Bachand 2010
Andjelkovich	1995	X	X	X		X	X	X
Armstrong	2000							X
Beane Freeman	2009							X
Bertazzi	1986	X						
Bertazzi	1989	X				X	X	
Blair	1986	X	X			X		
Blair	1993						X	
Blair	2001							X
Boffetta	1989						X	
Bond	1986	X						
Brinton	1984	X						
Brinton	1985	X						
Chiazze	1993	X						
Coggon	1984	X						
Coggon	2003			X		X	X	X
Dell	1993			X				
Dell and Teta	1995			X			X	X
Edling	1987b			X		X		
Fayerweather	1983	X						
Gardner	1993	X	X		X			
Gérin	1989	X						
Gustavsson	1998							X
Hall	1991	X	X	X		X	X	X
Hansen and Olsen	1995			X	X	X		
Harrington and	1984			X				

Study	Year	Collins 1997	Collins 2001a	Collins-Lineker 2004	Ojajarvi 2000	Bosetti 2008	Zhang 2009a	Bachand 2010
Oakes								
Harrington and Shannon	1975	X		X		X	X	X
Hauptmann	2003			X		X	X	
Hauptmann	2004					X		X
Hayes	1990	X		X		X	X	
Hayes	1986		X					
Heineman	1992						X	
Hernberg	1983a,b	X						
Hildesheim	2001							X
Jensen and Andersen	1982	X						
Kernan	1999		X					
Levine	1984	X	X		X	X	X	X
Liebling	1984							
Linos	1980			X				
Logue	1986					X		
Luce	1993	X						
Marsh	1982						X	
Marsh	1994a	X						
Marsh	1996						X	
Marsh and Youk	2004							X
Marsh and Youk	2005							X
Marsh	2007a							X
Matanoski	1991	X	X	X		X		X
Olsen	1984	X						
Olsen	1986	X						
Ott	1989			X				
Partanen	1985	X						
Partanen	1990	X						
Partanen	1993							X
Pinkerton	2004			X		X	X	X
Pottern	1992						X	
Robinson	1987							X
Roush	1987				X			X
Siemiatycki	1994							
Stayner	1985						X	

Study	Year	Collins 1997	Collins 2001a	Collins-Lineker 2004	Ojajarvi 2000	Bosetti 2008	Zhang 2009a	Bachand 2010
Stayner	1988	X	X		X			
Stellman	1998						X	X
Stern	1987						X	X
Stone	2004						X	
Stroup	1986	X	X	X		X		X
Vaughan	2000							X
Vaughan	1986b	X						X
Walrath and Fraumeni	1983	X	X	X		X	X	
Walrath and Fraumeni	1984	X	X	X		X	X	
West	1993	X						
Wong	1983						X	

3.7 Summary

A large number of epidemiological studies have evaluated the relationship between formaldehyde exposure and carcinogenicity in humans. The studies fall into the following main groups: (1) historical cohort studies and nested case-control studies of workers in a variety of industries that manufacture or use formaldehyde, including the chemical, plastics, fiberglass, resins, and woodworking industries, as well as construction, garment, iron foundry, and tannery workers; (2) historical cohort studies and nested case-control studies of health professionals, including physicians, pathologists, anatomists, embalmers, and funeral directors; (3) population-based cohort or cancer registry studies; and (4) population-based or occupationally based case-control incidence or mortality studies of specific cancer endpoints. In addition, several studies have re-analyzed data from specific cohort or case-control studies or have conducted pooled analyses or meta-analyses for specific cancer endpoints.

The largest study available to date is the cohort mortality study of combined mixed industries conducted by the National Cancer Institute (NCI). This cohort includes 25,691 male and female workers, enrolled from 10 different formaldehyde-producing or -using plants, employed before 1966 and followed most recently to 1994 and 2004, most of whom were exposed to formaldehyde (Hauptmann *et al.* 2003, 2004 and Beane Freeman *et al.* 2009). Quantitative exposure data were used to construct job-exposure matrices for individual workers, some of whom experienced peak exposures to formaldehyde ≥ 4 ppm. This cohort is the only study in which exposure-response relationships between peak, average, cumulative, and duration of exposure and mortality for multiple cancer sites were investigated. Two other large cohort studies are available: (1) a large multi-plant cohort study (N = 14,014) of workers in six chemical manufacturing plants in the United Kingdom (Coggon *et al.* 2003), which calculated SMRs among ever-exposed and highly exposed workers for formaldehyde, and (2) a NIOSH cohort of garment workers

(N = 11,039) (Pinkerton *et al.* 2004) which evaluated mortality for duration of exposure, time since first exposure, and year of first exposure to formaldehyde for selected cancer sites. The other cohort studies (for both industrial and health professional workers) were smaller, and in general only reported mortality or incidence for ever-exposed workers in external (SMR or PMR) analyses, although some of the studies of health professional workers attempted indirect measures of exposure (such as length in a professional membership) as a proxy for exposure duration. Several of the nested case-control studies attempted to evaluate exposure-response relationships, but were limited by small numbers of exposed cases, and many of the population-based case-control studies lacked quantitative data or sufficient numbers of cases to evaluate exposure-response relationships. However, the nested case-control study of lymphohematopoietic, nasopharyngeal, and brain cancers among U.S. embalmers and funeral directors by Hauptmann *et al.* (2009) had large numbers of exposed cases of lymphohematopoietic cancer and used both questionnaire- and experimental model-based exposure metrics of exposure, including average, cumulative, peak, and duration of exposure, and number of embalmings. [Since most of the cohorts have relatively low statistical power to evaluate rare cancers such as sinonasal and nasopharyngeal cancers, case-control studies are generally more informative for these outcomes.] Findings across studies for cancer sites that have been the principal focus of investigation are summarized below.

3.7.1 Sinonasal cancers

In cohort studies, increased risks of sinonasal cancers were observed among male (SPIR = 2.3, 95% CI = 1.3 to 4.0, 13 exposed cases) and female (SPIR = 2.4, 95% CI = 0.6 to 6.0, 4 exposed cases) Danish workers exposed to formaldehyde (Hansen and Olsen 1995, 1996) and among formaldehyde-exposed workers in the NCI cohort (SMR = 1.19, 95% CI = 0.38 to 3.68, 3 deaths) (Hauptmann *et al.* 2004). One death from squamous-cell sinonasal cancer was reported in the study of tannery workers among formaldehyde-exposed workers by Stern *et al.* (1987). No increase in risk was found among formaldehyde-exposed workers in the other large cohort studies (Coggon *et al.* 2003, Pinkerton *et al.* 2004). The smaller cohort studies did not report findings or did not observe any deaths for this specific endpoint. [Sinonasal cancers are rare, and even the larger cohort studies have insufficient numbers of exposed workers and expected deaths (e.g., approximately three in the NCI cohort) to be very informative.]

Of the six case-control studies reviewed, four (Olsen *et al.* 1984 and Olsen and Asnaes 1986; Hayes *et al.* 1986; Roush *et al.* 1987; and Luce *et al.* 1993) reported an association between sinonasal cancers and formaldehyde exposure; statistically significant risks were found in three studies among individuals ever exposed to formaldehyde or with higher probabilities or levels of exposure (Olsen *et al.* 1994 and Olsen and Asnaes 1986; Hayes *et al.* 1986; and Luce *et al.* 1993). All of these studies found elevated risks among individuals with low or no exposure to wood dust or after adjusting for exposure to wood dust. Stronger associations were found for adenocarcinoma, with higher risks for this endpoint observed among individuals with higher average and cumulative exposure, duration of exposure, and earlier dates of first exposure (Luce *et al.* 1993). A pooled analysis of 12 case-control studies of sinonasal cancer from seven countries (Luce *et al.* 2002) found statistically significant increases in adenocarcinoma among subjects in the highest exposure groups (OR = 3.0, 95% CI = 1.5 to 5.7, 91 exposed cases for men,

adjusted for wood dust exposure; and OR = 6.2, 95% CI = 2.0 to 19.7, 5 exposed cases for women, unadjusted for wood dust exposure). For squamous-cell carcinoma, the corresponding ORs were 1.2 (95% CI = 0.8 to 1.8, 30 exposed cases) for men and 1.5 (95% CI = 0.6 to 3.8, 6 exposed cases) for women; neither OR was adjusted for wood dust exposure. A statistically significant increase in risk for sinonasal cancers (mRR = 1.8, 95% CI = 1.4 to 2.3, 933 deaths) was found in a meta-analysis of 11 case-control studies by Collins *et al.* (1997); however, no increase in risks was found in meta-analyses of three cohort studies by Collins *et al.* (1987) or in eight industrial cohort studies by Bosetti *et al.* (2008).

3.7.2 Nasopharyngeal cancers

Similar to sinonasal cancers, nasopharyngeal cancers are rare [and most of the risk estimates reported in the cohort studies are based on small numbers of expected cases or deaths]. Among cohort studies, a statistically significant increase in mortality from nasopharyngeal cancer was observed in the large NCI cohort (SMR = 2.10, 95% CI = 1.05 to 4.21, 8 deaths) (Hauptmann *et al.* 2004), and statistically nonsignificant elevated risks were observed among white embalmers from the United States (PMR = 1.89, 95% CI = 0.39 to 5.48, 3 deaths) (Hayes *et al.* 1990) and among male Danish workers exposed to formaldehyde (SPIR = 1.3, 95% CI = 0.3 to 3.2, 4 cases) (Hansen and Olsen 1995, 1996). One incident case of nasopharyngeal cancer was reported among Swedish workers in the abrasive materials industry (expected deaths not reported, but only 506 workers were potentially exposed) (Edling *et al.* 1987b). No associations between formaldehyde exposure and nasopharyngeal cancer were found in the other two large cohorts: one death was observed (vs. 2 expected) in the British chemical workers cohort (Coggon *et al.* 2003) and no deaths were observed (vs. 0.96 expected) in the NIOSH cohort (Pinkerton *et al*. 2004). The other, smaller, cohort studies did not report findings or did not observe any deaths for nasopharyngeal cancer.

Exposure-response relationships between formaldehyde exposure and nasopharyngeal cancer were evaluated in the large NCI cohort study. Among seven exposed and two unexposed deaths, relative risks of nasopharyngeal cancers increased with cumulative exposure (P_{trend} = 0.025 among exposed groups) and with peak and average exposure (P_{trend} = 0.044 and 0.126, respectively, across exposed and unexposed groups, using unexposed as the referent as no deaths were observed in the lowest exposed group). Adjustment for duration of exposure to a number of potentially confounding substances and plant type did not substantively alter the findings. Most of the deaths occurred at one factory (Plant 1), which appears to have had the largest numbers of highly exposed workers. In a nested case-control analysis of nasopharyngeal deaths in this plant, Marsh *et al.* (2007b) reported that several of the nasopharyngeal cancers occurred among workers with previous employment in metal-working occupations.

Six of the nine available case-control studies reported increases in nasopharyngeal cancers in association with probable exposure to formaldehyde or at higher levels or duration of estimated exposure (Olsen *et al.* 1984 [women only], Vaughan *et al.* 1986a, Roush *et al.* 1987, West *et al.* 1993, Vaughan *et al.* 2000, and Hildesheim *et al.* 2001). Risks of nasopharyngeal cancers increased with exposure duration and cumulative exposure in two population-based case-control studies (Vaughan *et al.* 2000, Hildesheim

et al. 2001). In some studies, higher risks were found among individuals in the high-exposure groups (Vaughan *et al.* 1986a, Roush *et al* 1987), or with more years since first exposure (West *et al.* 1993), and some studies reported that risks were still elevated after taking into account smoking (Vaughan *et al.* 2000, Vaughan *et al.* 1986a, West *et al.* 1993) or exposure to wood dust (Hildesheim *et al.* 2001, Vaughan *et al.* 2000, West *et al.* 1993). No associations between nasopharyngeal cancer and formaldehyde exposure were found in population-based case-control studies in Denmark (Olsen *et al.* 1984 [men only]), and Malaysia (Armstrong *et al.* 2000), a case-cohort study among Chinese textile workers (Li *et al*. 2006), or in a nested case-control study among embalmers (Hauptmann *et al.* 2009).

Several meta-analyses were available. A statistically significant increase in risk (mRR = 1.3, 95% CI = 1.2 to 1.5, 455 deaths) was reported in a large meta-analysis of 12 case-control and cohort studies (Collins *et al.* 1997), and a nonsignificant increase in risk in a small meta-analysis of three other cohort mortality studies (SMR = 1.33, 95% CI = 0.69 to 2.56, 9 deaths) (Bosetti *et al.* 2008). Bachand *et al*. (2010) reported a borderline statistically significant risk in a meta-analysis of seven case-control studies (mRR = 1.22, 95% CI = 1.00 to 1.50) but did not find an increase in risk (mRR = 0.72, 95% CI = 0.4 to 1.29) in an analysis of data from six cohort studies, which excluded Plant 1 of the NCI cohort and used the re-analysis data from Marsh *et al.* (2005) for the other plants. [The Bachand meta-analysis used data for all pharyngeal cancer or buccal cavity cancer from some cohort studies and one case-control study, however.]

3.7.3 Other head and neck cancers, and respiratory cancer

Most of the cohort studies reported risk estimates for cancers of the buccal cavity, pharynx, larynx, and lung, or combinations of these cancers. Most of these studies, including two of the large cohorts (Pinkerton *et al.* 2004 and Coggon *et al.* 2003), three of the professional health worker studies (Hayes *et al.* 1990, Walrath and Fraumeni 1983 and 1984), and two of the smaller industrial cohorts (Andjelkovich *et al.* 1995 and Hansen and Olsen 1995, 1996) found elevated (between approximately 10% and 30%) but statistically nonsignificant risks for cancers of the buccal cavity or buccal cavity and pharynx combined; risk estimates were usually based on small numbers of deaths or cases. In the NCI cohort, increased risks for all upper respiratory cancers or buccal cavity cancer combined were generally found among workers in the highest categories of exposure (compared with the lowest category), but trends were not statistically significant (Hauptmann *et al*. 2004).

Most of the population-based or nested case-control studies that reported on head and neck cancers found small increases (usually statistically nonsignificant) in risks for formaldehyde exposure and cancers of the buccal cavity and pharynx (or parts of the pharynx) (Vaughan *et al.* 1986a, Merletti *et al.* 1991, Gustavsson *et al.* 1998, Laforest *et al.* 2000, Marsh *et al.* 2002, Wilson *et al.* 2004, Berrino *et al.* 2003) or of the upper respiratory tract (Partanen *et al.* 1990). Exposure-response relationships were not clear in most of the available studies; however, positive exposure-response relationships between probability and duration of exposure and cancers of the hypopharynx and larynx combined were reported by Laforest *et al.* (2000) and between combined probability and intensity of exposure and salivary cancer by Wilson *et al.* (2004). No associations

between formaldehyde exposure and pharyngeal cancers (subtypes or combinations) were observed in case-control studies by Shangina *et al.* (2006) and Tarvainen *et al.* (2008). Most of the cohort studies and two of the four available case-control studies found no association between formaldehyde exposure and laryngeal cancer. Two case-control studies (Wortley *et al.* 1992, Shangina *et al.* 2006) reported increased risk among subjects with the highest exposure to formaldehyde.

Small excesses of mortality or incidence of cancers of the lung or respiratory system among formaldehyde-exposed workers were observed in four cohort studies (Andjelkovich *et al.* 1995, Dell and Teta 1995, Hansen and Olsen 1996 [women only], and Coggon *et al.* 2003). A statistically significant increase in risk of lung cancer was observed in the large study of British chemical workers (SMR = 1.22, 95% CI = 1.12 to 1.32, 594 deaths, among all workers) (Coggon *et al.* 2003). In this study, risks increased with increasing exposure level ($P_{trend} < 0.001$) but not with duration of exposure. No association between formaldehyde exposure and lung cancer was observed in the other two large cohorts (Pinkerton *et al.* 2004, Hauptmann *et al.* 2004), in several of the smaller cohorts (Bertazzi *et al.* 1989, Hansen and Olsen 1995 [in men], Edling *et al.* 1987b, Stellman *et al.* 1998, Stern 2003), or in the six studies of health professional workers. Findings from the population-based or nested case-control studies were also mixed. Increases in risk were reported in several studies (De Stefani *et al.* 2005, Gérin *et al.* 1989, Andjelkovich *et al.* 1994, Chiazze *et al.* 1997), and were statistically significant in two studies (Marsh *et al.* 2001, Coggon *et al.* 1984). Risks did not increase with increasing exposure in most of the studies. An exception is the study by De Stefani *et al.* (2005), in which a statistically significant trend with duration of employment was observed. No association between lung cancer and formaldehyde exposure was reported in three other occupational case-control studies (Bond *et al.* 1986, Jensen and Andersen 1982, Partanen *et al.* 1990) and one population-based study (Brownson *et al.* 1993).

3.7.4 Lymphohematopoietic cancers

Among workers in the NCI cohort study, peak exposure to formaldehyde was associated with increased mortality for several types of lymphohematopoietic cancers (Beane Freeman *et al.* 2009). For all lymphohematopoietic cancers combined, for leukemias combined, and for myeloid leukemia, relative risks increased with increasing peak exposure: statistically significant increased risks were found among workers with the highest peak exposure (≥ 4 ppm) vs. the lowest exposed category for all lymphohematopoietic cancers (RR = 1.37, 95% CI = 1.03 to 1.81, 108 deaths, P_{trend} = 0.02), and statistically nonsignificant increases for all leukemias combined and peak exposure ≥ 4 ppm (RR = 1.42, 95% CI = 0.92 to 2.18, 48 deaths, P_{trend} = 0.12) and for myeloid leukemia and peak exposure ≥ 4 ppm (RR = 1.78, 95% CI = 0.87 to 3.64, 19 deaths, P_{trend} = 0.13; trends among exposed person-years). No associations were found with cumulative or average exposure.

An excess of leukemia, especially myeloid leukemia, was also found among garment workers in the large NIOSH cohort (Pinkerton *et al.* 2004), but not in the British chemical workers cohort (Coggon *et al.* 2003). In the NIOSH cohort, risks for leukemia, myeloid leukemia, and acute myeloid leukemia were higher among workers with longer duration of exposure (10+ yrs), longer time since first exposure (20+ years), and among

those exposed prior to 1963 (when formaldehyde exposure was thought to be higher) (Pinkerton *et al*. 2004). In the smaller industrial cohort studies, some studies reported excesses for all lymphohematopoietic cancers combined among formaldehyde-exposed workers (Bertazzi *et al.* 1989, Stellman *et al.* 1998) or leukemia (Hansen and Olsen 1995, 1996), but others observed no association for all lymphohematopoietic cancers combined (Andjelkovich *et al.* 1995, Stern 2003, Pinkerton *et al.* 2004) or leukemia (Andjelkovich *et al.* 1995, Stellman *et al.* 1998, Stern 2003).

Each of the six cohort studies of health professionals, and the nested case-control study of embalmers from three of these studies, found elevated mortality for lymphohematopoietic cancers. Hall *et al.* (1991), Hayes *et al.* (1990), Stroup *et al.* (1986), Levine *et al.* (1984) and Walrath and Fraumeni (1983, 1984) reported increases in risk for all lymphohematopoietic cancers combined and for leukemia. Most estimates were statistically nonsignificant with the exception of the studies of Hayes *et al.* (1990) and Stroup *et al.* (1986), where statistically significant excess mortality was found for all leukemia combined or for myeloid leukemia in association with formaldehyde exposure. In the nested case-control study by Hauptmann *et al.* (2009), sufficient numbers of cases of lymphohematopoietic cancer deaths among embalmers and funeral directors were identified to enable evaluation of exposure-response relationships, using models of potential formaldehyde exposure. A significant increase in nonlymphoid lymphohematopoietic cancers was observed among ever-embalmers (OR = 3.0, 95% CI = 1.0 to 9.5, 44 exposed cases), and significant increases in risk were observed at the highest levels of cumulative, average, and peak exposure. Most of the increase was attributable to myeloid leukemia, which was significantly elevated among ever-embalmers (OR = 11.2, 95% CI = 1.3 to 95.6, 33 exposed cases) and showed significant trends with duration of exposure and peak exposure, and a more attenuated trend with 8-hour time-weighted average intensity of exposure. In further analyses of non-lymphoid lymphohematopoietic cancers using workers with < 500 lifetime embalmings as the reference group, statistically significant increases in relative risks were found among workers with the longest duration of working in jobs with embalming, the highest number of lifetime embalmings, and the highest cumulative exposure to formaldehyde.

With respect to other case-control studies, a population-based study found no clear association between leukemia and exposure to formaldehyde (Blair *et al.* 2001), and two nested case-control studies reported statistically nonsignificant increases in leukemia risk based on small numbers of exposed cases (Partanen *et al.* 1993, Ott *et al.* 1989).

Few cohort or case-control studies reported findings for subtypes of lymphohematopoietic cancers other than leukemia. Most of the cohort studies had relatively low power to detect effects, and either did not report findings or did not evaluate exposure-response relationships. For Hodgkin's lymphoma, the NCI study was the only cohort or case-control study that reported an increase in risk. In an external analysis, an SMR of 1.42 (95% CI = 0.96 to 2.10, 25 deaths) was observed among formaldehyde-exposed workers and, in internal analyses, statistically significant exposure-response relationships were observed with peak (P_{trend} = 0.01 among the exposed group) and average exposure (P_{trend} = 0.05 among the exposed group), but not with cumulative exposure (Beane Freeman *et al.* 2009). For non-Hodgkin's lymphoma,

statistically non-significant increases in risks were observed in one cohort study (Hayes *et al.* 1990), and in most of the population-based or nested case-control studies (Partanen *et al.* 1993, Ott *et al.* 1989, Richardson *et al.* 2008, Wang *et al.* 2009a, Tatham *et al.* 1997, Blair *et al.* 1993). The risk of non-Hodgkin's lymphoma (large B cell type) increased with increasing probability of exposure ($P_{trend} < 0.01$) in a large case-control incidence study of U.S. women (Wang *et al.* 2009a). No increase in non-Hodgkin's lymphoma was reported in the population-based case-control study by Gérin *et al.* (1989), or in the nested case-control study of embalmers by Hauptmann *et al.* (2009). For multiple myeloma, peak exposure of ≥ 4 ppm was associated with a statistically significant increase in risk in the NCI cohort (RR = 2.04, 95% CI = 1.01 to 4.12, 21 deaths, P_{trend} = 0.08 among the exposed group) (Beane Freeman *et al.* 2009), although an increase in risk was also seen among unexposed workers for this endpoint. Increased risks also were seen among British chemical workers (Coggon *et al.* 2003), abrasive materials workers (Edling *et al.* 1987b), and U.S. embalmers (Hayes *et al.* 1990). Other cohort studies did not find associations, based on small numbers of observed deaths or cases, or did not report findings. Among case-control studies, statistically nonsignificant increases in risks were observed by Boffetta *et al.* (1989), Pottern *et al.* (1992) (women only), and Hauptmann *et al.* (2009), but not by Heineman e*t al.* (1992) (men only).

Several meta-analyses were available. (Hauptmann et al. [2009] was not available for any of the analyses.) Statistically significant risks were reported for all lymphohematopoietic cancers and leukemia among cohort studies of health professionals by Bosetti *et al.* (2008) (RR = 1.31, 95% CI = 1.16 to 1.47, 263 deaths for all lymphohematopoietic cancers; and RR = 1.39, 95% CI = 1.15 to 1.68, 106 deaths for leukemia) and among studies of occupations with known high formaldehyde exposure by Zhang *et al.* (2009a), (mRR = 1.25, 95% CI = 1.09 to 1.43, 19 studies for all lymphohematopoietic cancers combined; mRR = 1.54, 95% CI = 1.18 to 2.00, $P < 0.001$, 15 studies for leukemia; and mRR = 1.90, 95% CI = 1.31 to 2.76, $P = 0.001$, 6 studies for myeloid leukemia. A statistically nonsignificant increase in leukemia risk was also estimated among the combined studies of health professional workers by Bachand *et al.* (2010). No increased risks for leukemia were found in the available meta-analyses of industrial cohorts (Bosetti *et al.* 2008, Bachand *et al.* 2010), or combined cohort and case-control studies (Collins and Lineker 2004).

3.7.5 Other cancer sites

With the exception of brain and central nervous system cancers, few of the cohort studies reported consistently elevated risks for cancers at other sites. Few case-control studies of other cancer endpoints have been conducted. Excess mortality from brain and central nervous system cancers has been reported in each of the six cohort studies of health professionals, with statistically significant SMRs/PMRs (1.94 to 2.7) reported in three studies (Stroup *et al.* 1986, Walrath and Fraumeni 1983, 1984). However, in the nested case-control analysis of brain cancers among embalmers and funeral directors by Hauptmann *et al.* (2009), which used subjects from cohort studies of Hayes *et al.* (1990) and Walrath and Fraumeni (1983, 1984), a statistically nonsignificant increase in brain cancers was observed in association with ever-embalming (OR = 1.9, 95% CI = 0.7 to 5.3, 42 exposed cases). There were no clear exposure-response patterns with duration of employment in embalming jobs, or estimated cumulative, peak, or average exposure to

formaldehyde, however. No increases in brain and central nervous system cancers have been observed in the industrial cohort studies that have reported findings. A meta-analysis by Bosetti *et al.* (2008) reported a statistically significant increase in the risk of brain cancer among health professional workers (RR = 1.56, 95% CI = 1.24 to 1.96, 74 deaths), but not among industrial workers.

Several industrial studies have reported increases in one or more of stomach, colon, rectal, and kidney cancers, and a case-control study of pancreatic cancer (Kernan *et al.* 1999) suggested an increase in this endpoint at higher levels of formaldehyde exposure. Two meta-analyses of pancreatic cancer (Ojajärvi *et al.* 2000, Collins *et al.* 2001) showed no consistent increase in risk across studies, however, with the exception of a borderline statistically significant increase among pathologists, anatomists and embalmers.

4 Studies of Cancer in Experimental Animals

The carcinogenic effects of formaldehyde have been investigated in mice (inhalation and dermal administration), rats (inhalation and oral administration), and hamsters (inhalation administration). Although no chronic studies of formaldehyde exposure in primates were found, the effects of formaldehyde on monkeys exposed by inhalation for 1 to 26 weeks have been reported. Several studies also have investigated the interactions or promoting effects of formaldehyde in rodents when administered with other substances. IARC (1995, 2006) reviewed the available data on formaldehyde and concluded that there was sufficient evidence of carcinogenicity in experimental animals. This section is organized by route of administration and species and then discusses the effects of co-exposure with other substances.

4.1 Inhalation

Chronic and subchronic inhalation studies have been conducted in mice, rats, and hamsters. In addition, subacute and subchronic inhalation studies have been conducted in monkeys. All studies were conducted in inhalation chambers (i.e., whole-body rather than nose-only exposure), and formaldehyde vapor usually was generated by heating of paraformaldehyde (see Section 1). Exposure concentrations were reported as parts per million (ppm) or milligrams per cubic meter (mg/m^3) of air by the study authors. All tables in this section report concentrations in ppm. For formaldehyde in air, 1 ppm is equivalent to about 1.23 mg/m^3.

Because of the complexity of nasal anatomy, inhalation studies typically examine multiple transverse sections from four or more anatomical levels of the nasal turbinates in order to determine the location and distribution of lesions. The anatomical levels, nasal turbinates, and a few other features of the rat nose are illustrated in Figure 4-1. The mouse nose has a similar anatomic structure.

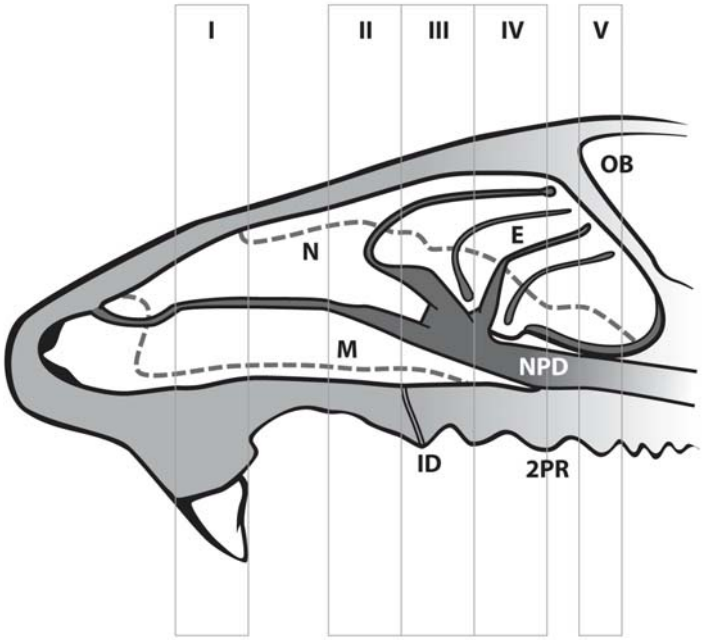

Figure 4-1. Midsagittal section of the rat nose showing the anatomical levels typically examined in inhalation studies.

The Roman numerals identify the positions of the various anatomical levels. The curved dashed lines indicate the junction of the squamous/transitional and respiratory epithelia (anterior line) and the respiratory and olfactory epithelia (posterior line). N = nasoturbinates, M = maxilloturbinates, E = ethmoturbinates, ID = incisive duct, NPD = nasopharyngeal duct, OB = olfactory bulb, 2PR = second palatal ridge.

Source: adapted from Kerns *et al*. 1983a and Mery *et al.* 1994. (Illustration prepared by Donna Jeanne Corcoran, Image Associates, Durham, N.C.)

4.1.1 Mice

Horton *et al.* (1963) conducted a series of experiments in C3H mice to determine whether repeated inhalation of formaldehyde would cause bronchiogenic carcinoma and whether exposure to formaldehyde would make the mice more susceptible to pulmonary carcinoma from subsequent exposure to coal-tar aerosols. Results from the formaldehyde experiment are reported here, and results from the formaldehyde plus coal tar experiment are discussed in Section 4.3. Groups of 42 to 60 mice (sex and age not reported) were exposed to formaldehyde vapor (produced by heating a 2:1 mixture of paraformaldehyde and white mineral oil) at a concentration of 0, 0.05, 0.10, or 0.20 mg/L [about 41, 82, or 163 ppm] for 1 hour/day, 3 days/week, for up to 35 weeks. The low- and medium-exposure groups tolerated formaldehyde reasonably well; normal weight gain throughout the 35-week exposure period was reported for these groups. However, high mortality was observed in the high-exposure group after the second week. Exposure was discontinued in this group after the eleventh exposure, with only 45 of the 60 original mice surviving. Some mice died of pneumonia, but the authors did not report specific mortality data for each exposure group. No pathological examination of the nasal epithelium was performed. Histological changes in the lungs of all mice that died or were killed during

the first 35 weeks are shown in Table 4-1. No statistical analyses were reported. The remaining mice were used in the second experiment (see Section 4.3). No tumors were observed; however, incidences of basal-cell hyperplasia, epithelial stratification, squamous metaplasia, and atypical metaplasia in the trachea and major bronchi were higher in the exposed mice than in the controls. IARC (2006) noted that this study had several limitations, including high doses, short exposure interval, short study duration, and no pathological examination of the nose.

Table 4-1. Histologic changes in the lungs of C3H mice exposed to formaldehyde by inhalation for up to 35 weeks

Conc. (ppm)	N		Incidence [%]				
	Initial	Examined	Basal-cell hyperplasia	Epithelial stratification	Squamous metaplasia	Atypical metaplasia	Lung tumors
0	59	26	0	4 [15]	3 [12]	0	0
[40.8]	60	23	6 [26]	9 [39]	0	0	0
[81.5]	60	34	10 [29]	14 [41]	6 [18]	0	0
[163]	42	35	4 [11]	8 [23]	16 [46]	5 [14]	0

Source: Horton *et al.* 1963.

Kerns *et al.* (1983a) conducted a 2-year inhalation study using groups of 119 to 121 male and female $B6C3F_1$ mice and F344 rats (results for the rats are discussed in Section 4.1.2.2). Beginning at 6 weeks of age, mice were exposed to formaldehyde at a concentration of 0, 2.0, 5.6, or 14.3 ppm for 6 hours/day, 5 days/week, for up to 24 months. After 24 months of exposure, the mice were observed for an additional 6 months without further exposure. Mice were killed at 6, 12, 18, 24, and 27 months. The numbers of mice sacrificed at each scheduled point varied: 10 mice/sex per group were sacrificed at 6 and 12 months; ~ 20 females, and 0 to 1 males at 18 months; 26 to 41 females, and 17 to 22 males at 24 months; and 9 to 16 females and 0 males at 27 months (Kerns *et al.* 1983b). Gross pathology was performed on all animals that died or were sacrificed at scheduled intervals, and the authors reported that hematology, serum chemistry, and urinalysis were performed on 10 animals of each sex and group randomly selected from the sacrificed animals (Kerns *et al.* 1983a). All major tissues from animals in the control and the high-exposure groups were given thorough histological examinations, and multiple sections of nasal turbinates were evaluated in all groups. Cumulative tumor rates and survival curves were calculated from life-table data by the method of Kaplan and Meier. Both unadjusted and adjusted data were analyzed. Data were adjusted to account for differences in time to tumor and survival among the groups. For unadjusted data, exposure groups were compared with Fisher's exact test. Overall and pairwise comparisons of adjusted data were made by the methods of Cox and Tarone.

Female mice in the high-exposure group showed a trend toward lower body weight than the controls after 72 weeks, but body weights returned to normal after exposure stopped. No clear exposure-related effect on body weight was seen in male mice. Survival in the exposed groups was not significantly different from that of the controls; however, survival was slightly lower for exposed male mice from 6 to 24 months. Survival was

lower in all groups of males than females, as a result of fighting and infections of the genitourinary tract. The numbers of mice surviving for at least 18 months were 41, 33, 32, and 25 males and 89, 83, 92, and 88 females in the control, 2.0-, 5.6-, and 14.3-ppm exposure groups, respectively. Nasal lesions, including inflammation, squamous-cell hyperplasia, metaplasia, and dysplasia, were described as "common" in the nasal mucosa of mice exposed to formaldehyde; however, no incidence data were reported. These nasal lesions were first detected at 12 months in the high-exposure group; by 24 months, more than 90% of mice in this group were affected. The onset, distribution, and severity of these lesions were concentration-dependent. Nasal lesions in the low-exposure group were limited to minimal squamous-cell hyperplasia in a few mice at 24 months. Squamous-cell carcinoma of the nasal cavity occurred in 2 of 17 male mice killed at 24 months in the high-exposure group but not in low- or mid-dose groups. (According to Kerns *et al.* [1983b], no male mice were sacrificed after 24 months). [It seems unlikely that any male mice in the high-dose group were alive after 24 months, because the authors stated that by 24 months 82 unscheduled deaths and 37 scheduled deaths (10 each at 6 and 12 months and 17 at 19 months) had occurred.] The authors believed that the squamous-cell carcinoma was caused by formaldehyde exposure because the spontaneous incidence of these tumors is very low in mice (no squamous-cell carcinomas of the nasal cavity have been reported among more than 2,800 historical controls from NTP studies), and because the lesions were similar to those observed in rats[1].

4.1.2 Rats

The carcinogenicity of formaldehyde has been studied more extensively in rats than in mice; including four subchronic (4 to 26 weeks) and seven chronic (≥ 1 year) studies. Two of these studies also evaluated the effects in rats of concomitant or sequential exposure to formaldehyde and other substances (discussed in Section 4.3).

4.1.2.1 Subchronic studies

Rusch *et al.* (1983) conducted 26-week inhalation studies in monkeys, rats, and hamsters. Results from experiments with hamsters and monkeys are presented in Sections 4.1.3 and 4.1.4, respectively. Groups of 20 male and 20 female F344 rats, 7 weeks of age, were exposed to formaldehyde at an average concentration of 0, 0.19, 0.98, or 2.95 ppm for 22 hours/day, 7 days/week, for 26 weeks. The target concentrations of 0.20, 1.00, and 3.00 ppm were selected to represent environmental exposures to the general public. However, after the first six weeks, the initial high-exposure group was terminated because of uncertainty associated with measurements of exposure concentrations. The high-exposure group was replaced with a new group exposed to a target concentration of 3.00 ppm and a corresponding control group. The nasal turbinates, lungs, trachea, and all gross lesions were examined microscopically. No exposure-related effects were seen in the low- and medium-exposure groups. Rats in the high-exposure group showed lower

[1] The Environmental Protection Agency (EPA) reported in a meeting presentation (reviewed by Pyatt *et al.* 2008), that unpublished data from the Batelle study (which is the same study as Kerns *et al.* 1983a,b) showed a significant increase in lymphomas in female mice and a significant dose-response relationship. However, Pyatt *et al.* (2008) disputed EPA's analysis of the unpublished data (see Section 5.7.6). [Since these data are not peer reviewed, they cannot be evaluated in this background document.]

body-weight gain and liver weight than the controls. Incidences of squamous metaplasia and hyperplasia and basal-cell hyperplasia were higher in the high-exposure group than in the controls. No tumors were observed.

Groups of 10 male and 10 female albino Wistar rats (age not reported) were exposed to formaldehyde at a concentration of 0, 1, 10, or 20 ppm for 6 hours/day, 5 days/week, for 13 weeks (Woutersen *et al.* 1987). Growth retardation was evident in the high-exposure groups of both sexes. Formaldehyde exposure caused an exposure-related increase in the incidences and severity of proliferative lesions in the nasal respiratory and olfactory epithelium, including squamous metaplasia and keratinization.

Feron *et al.* (1988) exposed groups of 45 male Wistar rats (age not reported) to formaldehyde at a concentration of 0, 10, or 20 ppm for 6 hours/day, 5 days/week, for 4, 8, or 13 weeks. The primary purpose of this study was to examine the long-term effects following relatively short-term exposure to cytotoxic concentrations of formaldehyde. Five rats per group were killed at the end of the 4- and 8-week-exposure periods, and 10 rats per group were killed at the end of the 13-week exposure period. The remaining rats were necropsied when found moribund or dead, or were killed at the end of the observation period during week 131. All rats were examined for gross pathological changes, and six standard cross sections of the nose were examined by light microscopy. Body weight was significantly lower in the high-exposure group than in the controls during the exposure period but returned to normal after about 8, 40, and 100 weeks in groups exposed for 4, 8, and 13 weeks, respectively. Mortality was not significantly different in the formaldehyde-exposed groups than in the controls. Non-neoplastic changes observed in the high-exposure groups included slight to severe hyperplasia and squamous metaplasia of the respiratory epithelium, moderate to severe rhinitis, and varying degrees of squamous metaplasia in the olfactory epithelium. Similar but more focal and less pronounced lesions were observed in the low-exposure group. A total of 14 nasal tumors were reported, most occurring in the high-exposure groups (Table 4-2). Although the authors did not report *P*-values for pairwise comparisons, they did consider 2 polypoid adenomas, 3 squamous-cell carcinomas, and 1 carcinoma *in situ* observed in groups exposed to 20 ppm for 4 to 13 weeks to be related to formaldehyde exposure. Thus, the incidence of tumors attributed to formaldehyde exposure was 4.5% (6 of 132). IARC (2006) reported that this was significantly higher than the incidence in the controls ($P = 0.01$, Fisher's exact test) and noted that the positive results occurred even though the exposure duration was short.

Table 4-2. Neoplastic responses in the nasal cavity of male Wistar rats exposed to formaldehyde by inhalation for 4 to 13 weeks[a]

Exposure			Incidence [%]		
Duration (wk)	Conc. (ppm)	N	Squamous-cell carcinoma	Polypoid adenoma	Other tumors
4	0	44	0	0	0
	10	44	0	0	0
	20	45	1 [2.2]	1 [2.2][b]	0
8	0	45	2 [4.4]	0	0
	10	44	1 [2.3]	0	0
	20	43	1 [2.3]	1 [2.3][b]	0
13	0	45	0	0	0
	10	44	1 [2.3]	0	0
	20	44	3 [6.8][b]	0	3 [6.8][c]

Source: Feron *et al.* 1988.
[a]Tumor incidence data are for rats killed immediately after the exposure period, rats that died during the observation period, and rats killed during week 131 at the end of the experiment.
[b]Tumors considered to be associated with formaldehyde exposure.
[c]Tumors included 1 cystic squamous-cell carcinoma, 1 carcinoma *in situ,* and 1 ameloblastoma. The authors considered the carcinoma *in situ* to be related to formaldehyde exposure.

Wilmer *et al.* (1989) compared the effects of intermittent versus continuous formaldehyde exposures in male Wistar rats (age not reported). Groups of 25 rats were exposed to formaldehyde at a concentration of 0, 1, or 2 ppm for 8 hours or to a concentration of 2 or 4 ppm during eight 30-minute intervals separated by 30-minute non-exposure periods. At the end of the study, the animals were necropsied and examined for gross pathology. Six standard cross sections of the nasal cavity were processed and examined by light microscopy. Body weight did not differ between any exposure group and the controls. Exposure-related effects in the nasal cavity were seen only in the rats exposed to formaldehyde intermittently at 4 ppm. Increased degrees and incidences of disarrangement, hyperplasia, and squamous metaplasia with or without keratinization of the respiratory epithelium were reported.

4.1.2.2 Chronic studies

Groups of 120 male and 120 female F344 rats, 7 weeks of age, were exposed to formaldehyde at a concentration of 0, 2.0, 5.6, or 14.3 ppm for 6 hours/day, 5 days/week, for up to 24 months (Swenberg *et al.* 1980a,b, Kerns *et al.* 1983a). Interim sacrifices and histopathological examinations were conducted as described in Section 4.1.1 for $B6C3F_1$ mice. The numbers of rats sacrificed at each scheduled time point (6, 12, 18, 24, 27, and 30 months) varied: 10 animals/sex per group were sacrificed at 6 and 12 months, 20 at 18 months, 41 to 54 at 24 months (except for the high-dose group, in which only 14 females and 13 males were sacrificed), and between 0 and 10 at 27 and 30 months) (Kerns *et al.* 1983b). After 24 months of exposure, the rats were observed for an additional 6 months without further exposure. Swenberg *et al.* (1980a,b) reported interim results after 18 months of the study, and Kerns *et al.* (1983a) reported the complete results. Statistical analyses were conducted as described above for mice. Compared with the controls, body-

weight gain was significantly lower from week 3 to week 103 in both sexes in the medium- and high-exposure groups. Mortality of male and female rats was significantly higher in the high-exposure group than in the controls ($P < 0.001$). Rhinitis, epithelial dysplasia, and squamous metaplasia occurred in all exposed groups, and the distribution and severity of these lesions were concentration dependent. Lesions were confined to the nasal cavity and proximal trachea[2]. However, in a later review article, Nelson *et al.* (1986) reported bone marrow hyperplasia in the rats exposed to formaldehyde. This was not considered a primary effect of the formaldehyde exposure by the authors. (No specific details were provided.) Neoplastic lesions of the nasal cavity were first observed on day 358 in females and day 432 in males. Incidences of neoplastic lesions in the nasal cavity are shown in Table 4-3. The incidence of squamous-cell carcinoma was significantly higher in the high-exposure groups than in the controls. There also was a significant exposure-dependent trend for increased incidence of polypoid adenoma in male rats after adjustment for survival differences among groups ($P < 0.05$). [Although the incidences of squamous-cell carcinomas in the mid-dose groups were not statistically significant, it is likely biologically significant because squamous-cell carcinoma of the nasal cavity is extremely rare. For example, these tumors were not observed in 1,396 male and 1,392 female F344 rats used in control groups in NTP inhalation studies. Similarly, nasal carcinomas that occurred in one male and one female in the high-dose groups have not been observed in historical controls in NTP studies.]

[2] The EPA reported at a meeting presentation (reviewed by Pyatt *et al.* 2008), that unpublished data from the Batelle study (which is the same study as Kerns *et al.* 1983a,b) showed a significant increase in leukemias in female rats and a significant dose-response relationship. However, Pyatt *et al.* (2008) disputed EPA's analysis of the unpublished data (see Section 5.7.6). [Since these data are not publically available, or peer reviewed, they cannot be evaluated in this background document.]

Table 4-3. Nasal tumors in F344 rats exposed to formaldehyde by inhalation for up to 24 months

Sex	Exposure (ppm)	N[a]	Incidence [%]			
			Squamous-cell carcinoma	Nasal carcinoma	Polypoid adenoma	Other tumors[b]
Male	0	118	0	0	1 [1][c]	1 [1]
	2.0	118	0	0	4 [3]	0
	5.6	119	1 [1]	0	6 [5]	0
	14.3	117	51 [44]***[d]	1 [1]	4 [3]	3 [3]
Female	0	114	0	0	0 [0]	0
	2.0	118	0	0	4 [3]	0
	5.6	116	1 [1]	0	0 [0]	0
	14.3	115	52 [45]***[e]	1 [1]	1 [1]	0

Source: Kerns *et al.* 1983a, IARC 2006.
***$P < 0.001$ (compared with controls, Fisher's exact test).
[a]Starting number of animals, which includes all animals at interim sacrifices.
[b]Osteochondroma (controls); 2 undifferentiated carcinomas or sarcomas and 1 carcinosarcoma (high-exposure group).
[c]Significant dose-related trend ($P < 0.05$) after adjustment for survival.
[d]After adjustment for survival, incidence at 24 months was 67%.
[e]After adjustment for survival, incidence at 24 months was 87%.

Morgan *et al.* (1986b) reexamined histologic sections from the nasal passages of the rats from the Kerns *et al.* (1983a) study to determine the point of origin of the neoplasms. This study showed that the squamous-cell carcinomas developed from the surface epithelium rather than the underlying glandular epithelium. The apparent sites of origin are shown in Table 4-4. The results were assigned accuracy ratings (low or high) based on the degree of confidence assigned by the pathologists. It was more difficult to determine the point of origin of the large tumors that had extensively invaded the nasal cavity than of smaller tumors. The majority of the tumors occurred at the end of the nose where formaldehyde levels are expected to be highest. More than half (57%) of the tumors were found on the anterior portion of the lateral aspect of the nasoturbinate and adjacent lateral wall (Levels I and II, see Figure 4-1), and 26% were found on the midventral nasal septum (Levels II and III). Polypoid adenomas occurred only in a small region of the anterior nasal cavity and were restricted to the nasoturbinate, maxilloturbinate, and lateral wall. One of the nasal carcinomas was considered a malignant counterpart of the polypoid adenoma and originated on the dorsal margin of the maxilloturbinate at Level II. Some neoplasms were too large or too poorly preserved to determine their site of origin. All of the apparent sites of origin are normally lined by respiratory epithelium.

Table 4-4. Apparent sites of origin of squamous-cell carcinomas in the nasal passages of F344 rats exposed to formaldehyde by inhalation for up to 24 months

Sex	Accuracy rating	Total tumors	% of total carcinomas by area of origin			
			Area I	Area II	Area III	Area IV
Male	high	36	56	28	14	3
	low[a]	25	56	20	8	0
Female	high	45	62	27	7	4
	low[b]	15	47	33	13	0
Total		121	57	26	10	3

Source: Morgan *et al.* 1986b.
Area I = lateral aspect of the nasoturbinate and adjacent lateral wall (Levels I and II, see Figure 4-1).
Area II = midventral septum (Levels II and III, see Figure 4-1).
Area III = dorsal septum and roof of dorsal meatus (Levels I, II, and III, see Figure 4-1).
Area IV = dorsal and lateral aspect of the maxilloturbinate (Levels II and III, see Figure 4-1).
[a]Unable to determine the site of origin for 4 tumors (16%).
[b]Unable to determine the site of origin for 1 tumor (7%).

Appelman *et al.* (1988) conducted a 1-year study to determine the role of cytotoxic damage in formaldehyde-induced carcinogenesis in rats. This was followed by a 28-month study of the same design (Woutersen *et al.* 1989). These authors also tested the hypothesis that damage to the nasal mucosa (induced by bilateral electrocoagulation) with subsequent regenerative hyperplasia might enhance the carcinogenic response following exposure to subcytotoxic concentrations of formaldehyde. These studies are discussed below.

Appelman *et al.* (1988) conducted a 1-year inhalation study in male albino Wistar rats (age not reported) to study whether damage to the nasal mucosa affected the carcinogenic response to subcytotoxic concentrations of formaldehyde. The anterior third of the nasal mucosa of half of the rats was damaged by electrocoagulation, and after 20 to 26 hours, these rats received their first exposure to formaldehyde. Groups of 10 rats with either damaged or undamaged nasal mucosa were exposed to formaldehyde at a concentration of 0, 0.1, 1, or 10 ppm for 6 hours/day, 5 days/week, for 52 weeks. The exposure concentrations were selected based on 13-week studies showing that formaldehyde was noncytotoxic at a concentration of 2 ppm or lower, slightly cytotoxic at a concentration of 3 to 4 ppm, and highly cytotoxic at a concentration of 10 ppm or higher. Rats, with or without damaged noses, in the high-dose groups had significantly lower body weights than controls after 2 weeks exposure until the end of the study. Some common irreversible lesions associated with electrocoagulation included loss of turbinates and perforation of the nasal septum. Rhinitis and basal-cell hyperplasia and squamous metaplasia of the respiratory epithelium were visible after 13 weeks, but after 52 weeks, effects from electrocoagulation were limited to slight basal-cell hyperplasia and rhinitis. The primary effects of formaldehyde in rats with damaged nasal mucosa included basal-cell hyperplasia, squamous metaplasia, and damage to the olfactory epithelium at 10 ppm and focal squamous metaplasia of nasal respiratory epithelium at 0.1 and 1 ppm. No adverse effects were seen in groups of rats with undamaged nasal mucosa exposed to formaldehyde at the two lower concentrations. Rats with undamaged noses in the high-

dose formaldehyde group had increased incidences of rhinitis, basal-cell hyperplasia, and squamous metaplasia. The authors concluded that rats with damaged noses were more susceptible to the cytotoxic action of formaldehyde.

Woutersen *et al.* (1989) conducted a follow-up of the Appelman *et al.* (1988) study. A total of 720 male rats (age not reported) were used in the experiment. Half of the animals were exposed to formaldehyde at a concentration of 0, 0.1, 1, or 10 ppm for 3 months and allowed to recover for 25 months, and the other half were exposed for 28 months. Each exposure group included 30 rats with undamaged noses and 60 rats with damaged noses. (The authors did not report why they used unequal numbers of animals in these groups.) All surviving rats were killed at 29 months and examined for gross lesions. Histological examination was limited to six cross sections of the nose. Rats with undamaged noses exposed to formaldehyde at 10 ppm for 28 months had increased incidences of degenerative, inflammatory, and hyperplastic changes of the nasal respiratory and olfactory mucosa, and a low incidence of squamous-cell carcinoma. Rats with damaged noses had higher incidences of formaldehyde-induced lesions than did rats with undamaged noses, and the group exposed to formaldehyde at 10 ppm for 28 months had a significantly higher incidence of nasal tumors than the control group ($P < 0.001$). [The authors did not report *P*-values; this *P*-value is based on Fisher's exact test conducted by NTP.] Very few tumors occurred in the other groups (Table 4-5). The authors concluded that severe damage to the nasal mucosa can contribute to formaldehyde carcinogenicity.

Table 4-5. Neoplastic responses in the nasal cavity of male albino Wistar rats, with and without damaged nasal mucosa, exposed to formaldehyde by inhalation for 3 or 28 months

Exposure				Incidence [%]		
Duration (mo)	Group	Conc. (ppm)	N	Squamous-cell carcinoma	Polypoid adenoma	Other tumors
3	undamaged	0	26	0	0	0
		0.1	30	0	0	0
		1	29	0	0	0
		10	26	1 [3.8]	1 [3.8]	0
	damaged	0	57	0	0	0
		0.1	57	2 [3.5]	0	0
		1	53	2 [3.8]	0	0
		10	54	1 [1.9]	0	1 [1.9][a]
28	undamaged	0	26	0	0	0
		0.1	26	1 [3.8]	0	0
		1	28	1 [3.6]	0	0
		10	26	1 [3.8]	0	0
	damaged	0	54	1 [1.9]	0	0
		0.1	58	1 [1.7]	0	0
		1	56	0	0	0
		10	58	15 [25.9***]	0	2 [3.4][b]

Source: Woutersen *et al.* 1989.
***[$P < 0.001$ (compared with controls, Fisher's exact test conducted by NTP)].
[a]Carcinoma *in situ*.
[b]1 adenosquamous carcinoma and 1 adenocarcinoma.

Sellakumar *et al.* (1985) exposed groups of 99 or 100 9-week-old male Sprague-Dawley rats to formaldehyde at a concentration of 15 ppm for 6 hours/day, 5 days/week, for life. This study also investigated the effects of a mixture of formaldehyde and hydrogen chloride (gas) (see Section 4.3.2). A complete necropsy was performed on each animal, with particular attention to the respiratory tract. Multiple cross sections spaced 1.5 to 2 mm apart were taken beginning just behind the nostrils and extending back to the orbits. Histologic sections also were prepared from the lungs, trachea, larynx, liver, kidneys, testes, and other organs where gross pathology was observed. After 16 weeks, rats exposed to formaldehyde had markedly lower body weight than controls; however, mortality was not significantly affected by formaldehyde exposure. Nasal tumors, arising from the anterior portion of the nasal cavity, included polyps or papillomas (10 of 100 animals examined) and squamous-cell carcinomas (38 of 100 animals examined) in formaldehyde-exposed rats. One fibrosarcoma and one mixed carcinoma also occurred in the exposed group. No nasal tumors were observed in controls. The authors did not statistically compare tumor incidences between these groups; however, IARC (2006) reported that incidences of squamous-cell papilloma and carcinoma were significantly higher than in controls when compared with Fisher's exact test ($P = 0.001$). No tumors were observed in the trachea or lungs, and tumor incidences in organs outside the respiratory tract did not differ significantly between the exposed and control groups.

In a chronic inhalation study conducted by Holmström *et al.* (1989a), groups of 16 female Sprague-Dawley rats, 11 weeks of age, were exposed to formaldehyde at a concentration of 0 or 12.4 ppm for 6 hours/day, 5 days/week, for 104 weeks. This study also investigated the effects of combined exposure to formaldehyde and wood dust (see Section 4.3.2). All rats in the formaldehyde-exposed group survived until the end of the study. Body weight did not differ significantly between the two groups. Histological examinations of the nose (five cross sections from the vestibulum of the nose to the posterior ethmoturbinates) and lungs were conducted. Pathological findings in the nasal cavity included pronounced metaplasia or dysplasia in 10 of 16 rats [62.5%] exposed to formaldehyde and none in the control group. One rat in the formaldehyde-exposed group developed squamous-cell carcinoma. Because this type of tumor is not known to occur spontaneously in rats, the authors concluded that it was related to formaldehyde exposure. Pulmonary epithelial histology did not differ significantly between the exposed and control groups. Non-respiratory-tract tumors, primarily mammary-gland tumors, were common in all groups (46% to 53%). Neither the incidence nor the latency period of the non-respiratory-tract tumors was affected by formaldehyde exposure. IARC (2006) noted the small number of animals used in this study.

Monticello *et al.* (1996) examined the correlation of cell-proliferation indices with sites of formaldehyde-induced nasal tumors in male F344 rats. Groups of 90 to 147 rats, 6 to 7 weeks of age, were exposed to formaldehyde at a concentration of 0, 0.7, 2, 6, 10, or 15 ppm for 6 hours/day, 5 days/week, for up to 24 months. Six rats per group were anesthetized five days before interim sacrifice at 3, 6, 12, and 18 months, and an osmotic pump was surgically implanted subcutaneously over the dorsal thoraco–lumbar area. Each pump contained 2 mCi of [*methyl*-^{3}H]thymidine, which was administered continuously until sacrifice. Cell proliferation was expressed as the number of ^{3}H-labeled cell profiles per millimeter of basement membrane and was determined for seven locations in the nasal passages (anterior lateral meatus, posterior lateral meatus, anterior mid-septum, posterior mid-septum, anterior dorsal septum, anterior medial maxilloturbinate, and maxillary sinus). Cross-sectional blocks of the nasal cavity were prepared at six levels and processed for histopathology. The distribution of nasal tumors was recorded. Compared with the controls, survival was significantly reduced in the high-exposure group (P <0.001), but was similar or slightly higher in the three lower-exposure groups. Non-neoplastic lesions (including epithelial hypertrophy and hyperplasia, squamous metaplasia, mixed inflammatory cell infiltrate, nasal turbinate adhesions, and olfactory degeneration) were generally confined to the transitional and respiratory epithelia of the anterior nasal passages and were most severe at the two highest concentrations. The authors stated the tumor response to formaldehyde exposure was highly nonlinear, showing a sharp increase at the two highest exposure levels. A clear exposure-response relationship was observed for squamous-cell carcinoma and polypoid adenoma (Table 4-6) (statistics not reported by authors). Squamous-cell carcinoma was the primary tumor type and occurred most frequently in the lateral meatus and mid-septum. However, many of the tumors were too large for their site of origin to be determined. Other tumors thought to be related to formaldehyde exposure included two nasal rhabdomyosarcomas and two adenocarcinomas which occurred in the two highest dose groups (specific locations not reported). The population-weighted unit length

labeling index (i.e., S-phase nuclei per millimeter of basement membrane × total number of epithelial cells in the site) showed a good correlation ($r^2 = 0.88$) with regional tumor incidence. The authors concluded that target-cell population size, cell proliferation, and local dosimetry are the primary determinants of formaldehyde carcinogenicity.

Table 4-6. Neoplastic responses in the nasal cavity of male F344 rats exposed to formaldehyde by inhalation for up to 24 months

Conc. (ppm)	N	Incidence [%]			Tumor location[b]				
		Squamous-cell carcinoma	Polypoid adenoma	Other tumors[a]	lm	ms	amm	ads	unk
0	90	0	0	0	0	0	0	0	0
0.7	90	0	0	0	0	0	0	0	0
2	96	0	0	0	0	0	0	0	0
6	90	1 [1]	0	0	1	0	0	0	0
10	90	20 [22.2***]	5 [5.6*]	2 [2.2]	14	0	0	0	6
15	147	69 [46.9***]	14 [9.5***]	2 [1.4]	26	9	4	3	27

Source: Monticello *et al.* 1996.
lm = anterior and posterior lateral meatus; ms = anterior and posterior mid-septum; amm = anterior medial maxilloturbinate; ads = anterior dorsal septum; unk = unknown.
*[$P < 0.05$ (compared with controls, Fisher's exact test conducted by NTP)].
***[$P < 0.001$ (compared with controls, Fisher's exact test conducted by NTP)].
[a]Rhabdomyosarcoma and adenocarcinoma.
[b]For squamous-cell carcinoma only.

Kamata *et al.* (1997) exposed groups of 32 male F344 rats, 5 weeks of age, to formaldehyde at a concentration of 0, 0.3, 2, or 15 ppm for 6 hours/day, 5 days/week, for up to 28 months. A control group was exposed to methanol at a concentration of 4.2 ppm, because the formalin solution used to generate the formaldehyde vapor contained 10% methanol as an antipolymerization agent. An additional room control group was included. Five animals per group were killed at the end of months 12, 18, and 24 for hematological, biochemical, and pathological examination. All animals found dead or moribund were necropsied, and all surviving animals were killed at 28 months. Histopathological examinations were performed on five cross sections of the nasal turbinates and most major organs and tissues. Mortality rates at 28 months were 45.5% and 59.6% in the two control groups, compared with 31.8% in the low-exposure, 55.9% in the medium-exposure, and 88.3% in the high-exposure group. Mortality in the high-exposure group was significantly higher than in the control groups. In addition, the high-exposure group had significantly lower body weight, liver weight, and food consumption than the controls. No lesions related to formaldehyde exposure were observed outside the nasal cavity. Incidences of proliferative lesions in the nasal cavity are shown in Table 4-7. Epithelial-cell hyperplasia with squamous-cell metaplasia occurred in all groups exposed to formaldehyde, and its incidence was significantly higher in the medium- and high-exposure groups than in the controls. These lesions did not appear until month 21 in the low-exposure group, but appeared as early as month 6 in the high-exposure group. Incidences of epithelial-cell hyperkeratosis and squamous-cell carcinoma also were

significantly elevated in the high-exposure group. Neoplastic lesions were observed only in the high-exposure group.

Table 4-7. Proliferative lesions and neoplastic responses in the nasal cavity of male F344 rats exposed to formaldehyde by inhalation for up to 28 months

		Incidence [%]				
Group (ppm)	N	Epithelial-cell hyperplasia with squamous-cell metaplasia	Epithelial-cell hyper-keratosis	Papillary hyper-plasia	Squamous-cell papilloma	Squamous-cell carcinoma
Controls:						
Methanol	32	0	0	0	0	0
Room	32	0	0	0	0	0
0.3	32	4 [12.5]	0	0	0	0
2	32	7 [21.9]**	1 [3.1]	0	0	0
15	32	29 [90.6]**	26 [81.3]**	2 [6.3]	3 [9.4]	13 [40.6]**

Source: Kamata *et al.* 1997.
**$P < 0.01$ (compared with methanol control group, Fisher's exact test).

4.1.3 Hamsters

Two inhalation studies in hamsters, one subchronic and one chronic, were identified. In the subchronic study, groups of 10 male and 10 female Syrian golden hamsters, 6 weeks of age, were exposed to formaldehyde at an average concentration of 0, 0.19, 0.98, and 2.95 ppm for 22 hours/day, 7 days/week, for 26 weeks (Rusch *et al.* 1983). All animals were killed at 26 weeks. The lungs, nasal turbinates, and trachea were fixed and sectioned. No exposure-related mortality or significant toxic effects were seen in any exposure group. The formaldehyde-exposed groups showed slightly higher incidences of rales, nasal discharge, and lacrimation. None of the hamsters developed tumors.

Dalbey (1982) exposed a group of 88 male Syrian golden hamsters (age not reported) to formaldehyde at a concentration of 10 ppm for 5 hours/day, 5 days/week, for life. The non-exposed control group included 132 hamsters. A second experiment was conducted to examine the effect of formaldehyde on diethylnitrosamine (DEN) carcinogenesis (see Section 4.3.3). The second experiment also included a group of 50 male hamsters exposed to formaldehyde at 30 ppm once per week, 5 hours/day, for life. Two transverse sections of the nasal turbinates, longitudinal sections of the larynx and trachea, and all lung lobes were examined. Survival time was significantly lower in the 10-ppm group than in the controls ($P < 0.05$); however, there was very little evidence of toxicity. (Effects on body-weight gain were not reported.) Rhinitis was observed in 31% of the controls, compared with 24% of the 10-ppm exposure group. Hyperplastic and metaplastic lesions of the nasal epithelium occurred in 5% of the 10-ppm group but were not observed in the controls. Weekly exposures to formaldehyde at 30 ppm did not affect mortality. No tumors occurred in either the 10-ppm or 30-ppm exposure group.

4.1.4 Monkeys

Rusch *et al.* (1983) exposed six male cynomolgus monkeys (*Macaca fascicularis*) (age not reported) to formaldehyde for 26 weeks using the same exposure protocol and dose levels as reported above for rats and hamsters. Body weight was not affected by formaldehyde exposure. Squamous metaplasia and hyperplasia was evident in the nasal turbinates of all animals in the high-exposure group. Hoarseness and congestion also occurred in this group. No tumors occurred in the lungs, trachea, or nasal turbinates in any exposure group.

Monticello *et al.* (1989) investigated the effects of acute or subacute exposure to formaldehyde on the respiratory tract of rhesus monkeys. Nine young adult male rhesus monkeys (*Macaca mulatta*), aged 4 to 5 years, were randomly divided into three groups. Group 1 (control) was sham exposed to biologically filtered air for 6 hours/day, 5 days/week, for 6 weeks. Groups 2 and 3 were exposed to formaldehyde at a concentration of 6 ppm for 1 and 6 weeks, respectively. All animals were tranquilized 18 hours after the last scheduled exposure, injected with [^{3}H]thymidine (1 μCi/g b.w.), and killed 2 hours later. A series of transverse sections of the nose, cross sections of the larynx and mid-trachea, a frontal section of the carina of the trachea, and sections from all lung lobes were examined. In addition, tissues were collected from bone marrow, eyes, adrenal glands, duodenum, esophagus, gall bladder, heart, kidneys, liver, lymph nodes, pancreas, stomach, spleen, and tongue and examined by light microscopy. Five transverse sections from the nasal passages and sections of the larynx, trachea, carina tracheae, lung, and duodenum were processed for histoautoradiography to determine the cell-proliferation rate. Formaldehyde exposure did not significantly affect body weight. Eye irritation and lacrimation were observed in the formaldehyde-exposed groups. Exposure-related effects were observed in the respiratory tract only. Lesions within the respiratory tract were characterized by mild degeneration and squamous metaplasia confined to the transitional and respiratory epithelia of the nasal passages and the respiratory epithelia of the trachea and major bronchi. Although there was little progression of histologic changes from 1 to 6 weeks of exposure, the percent of nasal surface area affected was significantly greater at 6 weeks. Cell-proliferation rates in the formaldehyde-exposed groups were up to 18 times the rates in the control group, with the greatest increase in the anterior nasal cavity. Based on a comparison of the extent of lesions and the cell-proliferation rates observed in this study with those seen in previous studies in rats, the authors concluded that monkeys appeared to be more sensitive than rats to the acute and subacute effects of formaldehyde at 6 ppm.

4.1.5 Summary of inhalation studies

This section reviewed two inhalation studies in mice, eleven in rats, two in hamsters, and two in monkeys. Nasal tumors (primarily squamous-cell carcinoma) occurred in three strains of rats and one strain of mice. [Nasal squamous-cell carcinomas and other nasal tumors are extremely rare in mice and rats.] Several of the studies were limited because exposure duration and study duration were short and/or a small number of animals per group were used. Results and study design limitations from these studies are summarized in Table 4-8[3].

[3] According to Pyatt *et al.* (2008), there is an apparent controversy over unpublished data from the Batelle study reported by Kerns *et al.* (1983a,b) (see Section 5.7.6). Some have claimed that these data show an increased incidence of lymphoma in female mice and an increased incidence of leukemia in female rats exposed to formaldehyde, but others have refuted these claims. [Since these data have not been published in a peer-reviewed journal, the NTP could not evaluate these claims.]

Table 4-8. Summary of nasal tumors reported in inhalation studies of formaldehyde in experimental animals

Strain	Exposure		Conc. (ppm)	Squamous-cell carcinoma		Non-squamous tumors				Results and Comments	Reference
						Malignant		Total[a]			
	h/d (d/wk)	# wks		M	F	M	F	M	F		
Mice (subchronic and chronic)											
C3H	1 (3)	35	[0] [41] [82] [163]	0/26 0/23 0/34 0/35		0/26 0/23 0/34 0/35		0/26 0/23 0/34 0/35		Sex and age not reported, lung tissue but not nasal tissue were examined, [short duration, short exposure time, high mortality in high-exposure group]	Horton *et al.* 1963
$B6C3F_1$	6 (5)	104	0 2.0 5.6 14.3	0 0 0 2	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0	All groups initially contained 119 to 121 animals (number of mice in each group not specifically reported)[b]. Interim sacrifices at 6, 12, 18, 24, and 27 mo. Two tumors occurred in 17 males in the high-dose group sacrificed at 24 mo. (Only 1 male mouse sacrified at 18 mo and none at 27 mo.)	Kerns *et al.* 1983a
Rats (subacute and subchronic)											
F344	22 (7)	26	0 0.19 0.98 2.95	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	[Short duration, small number of animals/group], increase in squamous metaplasia/hyperplasia and basal-cell hyperplasia in high-exposure groups	Rusch *et al.* 1983
Wistar	6 (5)	13	0 1 10 20	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	[Short duration, small number of animals/group], exposure-related increase in proliferative lesions of the nasal respiratory and olfactory epithelia, including severe squamous metaplasia and moderate keratinization in both sexes in 10- and 20-ppm dose groups	Woutersen *et al.* 1987

Strain	Exposure		Conc. (ppm)	Squamous-cell carcinoma		Non-squamous tumors				Results and Comments	Reference
						Malignant		Total[a]			
	h/d (d/wk)	# wks		M	F	M	F	M	F		
Wistar	6 (5)	13	0 10 20	0/45 1/44 3/44	NT	0/45 0/44 1/44	NT	0/45 0/44 3/44	NT	[Short duration], 1 carcinoma *in situ* & 2 polypoid adenomas also detected in high-exposure group and thought to be exposure related	Feron *et al.* 1988
Wistar	6 (5)	8	0 10 20	2/45 1/44 1/43	NT	0/45 0/44 0/43	NT	0/45 0/44 1/43	NT	[Short duration], 1 polypoid adenoma detected in high-dose group and thought to be exposure related	Feron *et al.* 1988
Wistar	6 (5)	4	0 10 20	0/44 0/44 1/45	NT	0/44 0/44 0/45	NT	0/44 0/44 1/45	NT	[Short duration], 1 polypoid adenoma detected in high-dose group and thought to be exposure related	Feron *et al.* 1988
Wistar	8 (5) 8 (5) 8 (5) 4[c] (5) 4[c] (5)	13 13 13 13 13	0 1 2 2 4	0/25 0/25 0/25 0/25 0/25	NT	0/25 0/25 0/25 0/25 0/25	NT	0/25 0/25 0/25 0/25 0/25	NT	[Short duration, small number of animals/group], exposure-related effects observed only in high-exposure group and included hyperplasia and squamous metaplasia of the respiratory epithelium	Wilmer *et al.* 1989
Rats (chronic)											
F344	6 (5)	104	0 2.0 5.6 14.3	0/118 0/118 1/119 51/117	0/114 0/118 1/116 52/115	0/118 0/118 0/119 4/117	0/114 0/118 0/116 1/115	1/118 4/118 6/119 8/117	0/114 4/118 0/116 2/115	Nasal carcinoma observed in 1 rat of each sex in the high-exposure groups; polypoid adenoma observed in all groups except female control and medium-exposure groups; undifferentiated carcinoma or sarcoma and carcinosarcoma observed in high-exposure males	Kerns *et al.* 1983a

Strain	Exposure		Conc. (ppm)	Squamous-cell carcinoma		Non-squamous tumors				Results and Comments	Reference
						Malignant		Total[a]			
	h/d (d/wk)	# wks		M	F	M	F	M	F		
Wistar	6 (5)	52	0 0.1 1.0 10	0/10 0/10 0/10 0/10	NT	0/10 0/10 0/10 0/10	NT	0/10 0/10 0/10 0/10	NT	[Low number of animals/group] Reported that rats with damaged nasal mucosa were more susceptible to the cytotoxic action of formaldehyde; squamous metaplasia/basal-cell hyperplasia in high-dose groups for damaged and undamaged noses; neither group had neoplasias	Appelman *et al.* 1988
Wistar	6 (5)	120	0 0.1 1.0 10	1/54 1/58 0/56 15/58	NT	0/54 0/58 0/56 2/58	NT	0/54 0/58 0/56 2/58	NT	Reported results are for groups with damaged noses; 1 or 2 nasal tumors also occurred in groups with undamaged noses or in groups exposed for only 3 months; for undamaged nose group, 1 SCC detected in every exposed group	Woutersen *et al.* 1989
Sprague-Dawley	6 (5)	life	0 15	0/99 38/100	NT	0/99 2/100	NT	0/99 2/100	NT	Squamous papillomas observed in 10 rats- total squamous-cell tumors 48/100; mixed carcinoma and fibrosarcoma observed in 1 rat each	Sellakumar *et al.* 1985
Sprague-Dawley	6 (5)	104	0 12.4	NT	0/15 1/16	NT	0/15 0/16	NT	0/15 0/16	[Small number of animals] Pronounced squamous-cell metaplasia or dysplasia reported in 10 of the exposed rats and none of the controls	Holmström *et al.* 1989a
F344	6 (5)	104	0 0.7 2 6 10 15	0/90 0/90 0/96 1/90 20/90 69/147	NT	0/90 0/90 0/96 0/90 2/90 2/147	NT	0/90 0/90 0/96 0/90 7/90 16/147	NT	Polypoid adenoma; one rhabdomyosarcoma, and one adenocarcinoma also observed in the two highest exposure groups. The population-weighted unit length labeling index was correlated with regional tumor incidence.	Monticello *et al.* 1996

Strain	Exposure		Conc. (ppm)	Squamous-cell carcinoma		Non-squamous tumors				Results and Comments	Reference
						Malignant		Total[a]			
	h/d (d/wk)	# wks		M	F	M	F	M	F		
F344	6 (5)	120	0 0.3 2 15	0/32 0/32 0/32 13/32	NT	0/32 0/32 0/32 0/32	NT	0/32 0/32 0/32 0/32	NT	[Small number of animals/group] Squamous-cell papilloma also observed in 3 rats in the high-exposure group; total squamous-cell tumors 16/32 in high-dose group.	Kamata *et al.* 1997
Hamsters (subchronic and chronic)											
Syrian golden	22 (7)	26	0 0.19 0.98 2.95	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	0/10 0/10 0/10 0/10	[Short exposure duration and small number of animals], no significant responses reported	Rusch *et al.* 1983
Syrian golden	5 (5) 5 (1)	life life	0 10 30	0/132 0/88 0/50	NT	0/132 0/88 0/50	NT	0/132 0/88 0/50	NT	Minimal increase in hyperplastic and metaplastic areas in the nasal epithelium of 5% of the exposed animals	Dalbey 1982
Monkeys (subacute and subchronic)											
Cynomolgus	22 (7)	26	0 0.19 0.98 2.95	0/6 0/6 0/6 0/6	NT	0/6 0/6 0/6 0/6	NT	0/6 0/6 0/6 0/6	NT	[Short exposure duration, small number of animals], squamous metaplasia/hyperplasia in the nasal turbinates in the high-dose group	Rusch *et al.* 1983

Strain	Exposure		Conc. (ppm)	Squamous-cell carcinoma		Non-squamous tumors				Results and Comments	Reference
						Malignant		Total[a]			
	h/d (d/wk)	# wks		M	F	M	F	M	F		
Rhesus	6 (5)	6	0 6	0/3 0/3	NT	0/3 0/3	NT	0/3 0/3	NT	[Short exposure duration and small number of animals], increased cell-proliferation rates and squamous metaplasia of the transitional and respiratory epithelia of the nasal passages and respiratory epithelia of the trachea and major bronchi	Monticello *et al.* 1989

NT = not tested.
[a]Total non-squamous tumors are other carcinomas plus polypoid adenomas.
[b]Survival at 18 months (estimated from survival graphs) for males were 82% (14.3 ppm), 94% (5.6 ppm), 98% (2 ppm), and 100% (controls); for females they were 82% (14.3 ppm), 96% (5.6 ppm), 100% (2 ppm), and 98% (controls).
[c]Exposed for 30-min intervals, 8 times/day, separated by 30-min non-exposure periods.

4.2 Oral and dermal administration

Formaldehyde was administered to rats via their drinking water in five studies (Takahashi *et al.* 1986, Til *et al.* 1989, Tobe *et al.* 1989, Soffritti *et al.* 1989, 2002a) and by skin application in one study (Iversen 1986).

4.2.1 Drinking-water studies

Takahashi *et al.* (1986) investigated the tumor-promoting activity of orally administered formaldehyde on stomach carcinogenesis in 7-week-old male Wistar rats (see Section 4.3.2 for a complete description). One group of 10 rats was exposed to formaldehyde in drinking water (0.5% formalin [5,000 mg/L, 5,000 ppm]) from weeks 8 to 40, and a control group of 10 rats was given tap-water only. Of 10 formaldehyde-exposed rats, 8 developed squamous-cell papilloma of the forestomach. No tumors occurred in the control group.

Til *et al.* (1989) administered formaldehyde (obtained as paraformaldehyde) in drinking water to groups of 70 male and 70 female Wistar rats, aged 5 weeks, for up to 24 months. Target doses were 5, 25, and 125 mg/kg of body weight (b.w.) for both sexes. Average formaldehyde concentrations in the drinking water were 20, 260, and 1,900 mg/L (ppm). Based on water consumption, the average daily doses were 0, 1.2, 15, or 82 mg/kg b.w. for males and 0, 1.8, 21, or 109 mg/kg b.w. for females. Subgroups of 10 male and 10 female rats were killed after 12 and 18 months. Formaldehyde exposure did not affect mortality. The high-exposure group of each sex had lower body weight and food intake than the controls, and liquid consumption was about 40% less than in the controls. The high-exposure groups also had severe damage to the gastric mucosa and significantly increased incidences of epithelial hyperplasia and hyperkeratosis of the forestomach and hyperplasia of the glandular stomach (Table 4-9). No tumors were reported at any exposure level.

Table 4-9. Non-neoplastic responses in Wistar rats given formaldehyde in drinking water for 24 months

			Forestomach		Glandular stomach
Sex	Dose (mg/kg)	N	Epithelial hyperplasia	Focal hyperkeratosis	Hyperplasia
Male	0	47	1	2	0
	1.2	45	2	6	1
	15	44	1	4	0
	82	47	45***	24***	20***
Female	0	48	1	3	0
	1.8	49	0	5	0
	21	47	2	3	0
	109	48	45***	33***	13***

Source: Til *et al.* 1989.
***$P < 0.001$ (compared with controls, Fisher's exact test).

Tobe *et al.* (1989) exposed groups of 20 male and 20 female Wistar rats (age not reported) to formaldehyde (obtained as paraformaldehyde) in drinking water for 24 months at a concentration of 0, 200, 1,000, or 5,000 mg/L (ppm). Based on water consumption, the estimated average daily formaldehyde intakes were 0, 10, 50, and 300 mg/kg b.w. Food intake, water intake, and body weight were significantly lower in the high-exposure groups of both sexes than in the controls. Mortality was 100% in the high-exposure groups by 24 months, occurring as early as 9 days after the beginning of exposure. For males and females, respectively, mortality at 24 months in the other groups was 12.5% and 28.6% in the controls, 46.9% and 33.7% in the low-exposure group, and 0% and 14.3% in the medium-exposure group. Non-neoplastic lesions associated with formaldehyde exposure (primarily in the high-exposure group) included erosions, ulcers, hyperkeratosis, basal-cell hyperplasia, and hyperplasia of the squamous epithelium in the forestomach. Similar lesions were observed in the glandular stomach and included erosions and/or ulcers accompanied by submucosal inflammatory-cell infiltrates and glandular hyperplasia. Only a few lesions of the gastrointestinal tract were seen in the medium-exposure groups, and no toxicological effects were observed in the low-exposure groups. Incidences of non-neoplastic lesions were reported only for 6 animals per group at 12 months. All tumors observed (i.e., of the pituitary gland, thyroid gland, testes, adrenal glands, mammary glands, and skin) were the typical spontaneously occurring tumors for this strain. The incidences of these tumors did not differ significantly between the formaldehyde-exposed groups and the controls.

Soffritti *et al.* (1989, 2002a) examined the carcinogenicity of formaldehyde in male and female Sprague-Dawley rats when administered in the drinking water for two years. Oral administration was selected (1) because humans are exposed to formaldehyde in foods and (2) to determine whether formaldehyde might prove to be a multipotential carcinogen (i.e., causing more than one tumor type by various routes of administration). One study examined the effects of age at the start of the experiment (Soffritti *et al.* 1989). This study included two groups of 18 to 20 male and female breeder rats (25 weeks old) exposed to formaldehyde at a concentration of 0 or 2,500 mg/L for up to 104 weeks, and their offspring, initially exposed to formaldehyde *in utero* beginning on gestation day 13. Postnatally, the offspring were exposed to formaldehyde via drinking water at 0 or 2,500 mg/L for up to 104 weeks. Survival rates were similar in the exposed and control groups. All animals were necropsied and given a thorough histopathological examination. No exposure-related, non-neoplastic effects were reported for either experiment. This is in contrast to Til *et al.* (1989) and Tobe *et al.* (1989) where non-neoplastic lesions were found in the stomach of Wistar rats.

Soffritti *et al.* (1989) reported that formaldehyde exposure was associated with a slight increase in hemolymphoreticular neoplasms in male and female breeder rats (Table 4-10). Gastrointestinal-tract tumors occurred in two breeder rats but were more prevalent in their offspring. These included both benign tumors (adenoma, papilloma, and acanthoma) and malignant tumors (adenocarcinoma and leiomyosarcoma). Leiomyosarcoma was the most frequent malignant tumor. The authors noted that these gastrointestinal tumors were very rare in the historical controls from the colony used in these experiments and that none of these tumors were observed in the concurrent controls. [No statistical analyses were reported for these results; however, the rarity of these tumors in historical controls

suggests biological significance.] IARC's review (IARC 2006) of this study reported that the incidence of leiomyosarcoma in the intestine was significantly increased in the exposed female offspring alone and in exposed female and male offspring combined ($P \leq 0.01$, χ^2 test) and that the incidence of malignant intestinal tumors in the female offspring was significantly higher than in controls (pairwise comparisons with Fisher's exact test).

Table 4-10. Tumor incidences in Sprague-Dawley rats exposed to formaldehyde in drinking water at two different ages for up to 104 weeks

Group	Sex	Conc. (mg/L [ppm])	N	Incidence (%)				
				Hemolympho-reticular	Stomach		Intestine	
					Benign	Malignant	Benign	Malignant
Breeders	M	0	20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	M	2,500	18	2 (11.1)	0 (0)	1 (5.6)	0 (0)	0 (0)
	F	0	20	1 (5)	0 (0)	0 (0)	0 (0)	0 (0)
	F	2,500	18	2 (11.1)	1 (5.6)	0 (0)	0 (0)	0 (0)
Offspring[a]	M	0	59	3 (5.1)	0 (0)	0 (0)	0 (0)	0 (0)
	M	2,500	36	4 (11.1)	1 (2.8)	2 (5.6)[b]	1 (2.8)	1 (2.8)
	F	0	49	3 (6.1)	0 (0)	0 (0)	0 (0)	0 (0)
	F	2,500	37	0 (0)	0 (0)	2 (5.4)[b]	0 (0)	6 (16.2)[b]**

Source: Soffritti *et al.* 1989.
**$P < 0.01$ (compared with controls, χ^2 test conducted by IARC 2006); no statistical analyses were reported by the study authors.
[a]Transplacental exposure beginning on gestational day 13, then postnatal exposure continued via drinking water.
[b]Included at least one leiomyosarcoma, which is a very rare tumor in historical controls.

In the second experiment conducted by Soffritti and co-workers, groups of 50 male and 50 female rats, 7 weeks of age, were exposed to formaldehyde at a concentration of 10, 50, 100, 500, 1,000, or 1,500 mg/L for 104 weeks and then observed for life (Soffritti *et al.* 1989, 2002a). The formalin solution used to prepare the test solutions contained 30% formaldehyde and 0.3% methanol. All animals died by week 163. Additional groups of 50 male and 50 female rats were exposed to methanol at a concentration of 15 mg/L, because methanol was used in the formaldehyde solution as a stabilizer. (Based on a concentration of 0.3% methanol in the stock solution, the concentrations of methanol in the formaldehyde test solutions ranged from about 0.1 to 15 mg/L.) The control group included 100 male and 100 female rats given tap water only. Information on animal health monitoring, such as sentinel animal testing, was not provided by the authors. [However, survival was approximately 50% at weeks 104 to 112 across all groups of males and approximately 50% at weeks 112 to 120 across all groups of females, suggesting adequate survival.]

No exposure-related non-neoplastic effects were reported, which IARC (2006) noted was a limitation of this study. Tumor incidences were analyzed with the χ^2 test, and dose-response relationships with the Cochrane-Armitage test for trend. The authors did not

report statistical comparisons between the formaldehyde-exposed groups and the methanol group; however, IARC (2006) conducted statistical analyses for trend and incidence between these groups (results presented below). The incidence of total malignant tumors was significantly higher in male rats exposed to formaldehyde at 1,500 mg/L than in the unexposed controls. The total number of malignant tumors per 100 animals was significantly increased in males at 500 or 1,500 mg/L and in females at 100, 1,000, or 1,500 mg/L (Table 4-11). IARC reported that the total number of animals that had malignant tumors was also significantly increased compared with the methanol controls ($P < 0.01$) [The NTP questioned the appropriateness of applying a χ^2 test (which is designed for dichotomous response data) to tumor counts such as total number of tumors per 100 animals. There is also concern that the authors' χ^2 test considered the individual tumor rather than the animal as the experimental unit and did not take into account the variability in tumor response among animals.]

Table 4-11. Total malignant tumors in Sprague-Dawley rats exposed to formaldehyde in drinking water for up to 104 weeks

Sex	Concentration (mg/L [ppm])	N	Tumor-bearing animals (%)	Total no. tumors (per 100 animals)[a]
Male	0	100	38 (38)	50 (50)
	methanol only	50	21 (42)	29 (58)
	10	50	14 (28)	19 (38)
	50	50	12 (24)	15 (30)
	100	50	22 (44)	23 (46)
	500	50	24 (48)	36 (72)*
	1,000	50	23 (46)	30 (60)
	1,500	50	36 (72)**	56 (112)**
Female	0	100	43 (43)	49 (49)
	methanol only	50	23 (46)	32 (64)
	10	50	20 (40)	22 (44)
	50	50	20 (40)	26 (52)
	100	50	25 (50)	41 (82)**
	500	50	19 (38)	25 (50)
	1,000	50	29 (58)	39 (78)**
	1,500	50	27 (54)	48 (96)**

Source: Soffritti *et al.* 2002a.
*$P < 0.05$, **$P < 0.01$ (compared with controls, χ^2 test).
[a] [The NTP questioned the validity of the χ^2 test for these data (see text).]

The incidence of hemolymphoreticular neoplasms (including lymphoblastic leukemia and lymphosarcoma, immunoblastic lymphosarcoma, other leukemias, and hemolymphoreticular sarcoma) was significantly increased in males at concentrations of 100 mg/L or higher and in females at the two highest concentrations (Table 4-12a) (Soffritti *et al.* 2002a, IARC 2006); a significant exposure-response relationship also was found for the increased incidences of hemolymphoreticular tumors in males ($P < 0.01$, as reported by IARC). The incidence of hemolymphoreticular tumors in high-dose males

was significantly increased compared with the methanol-exposed group ($P < 0.01$, as calculated by IARC). (The incidence of hemolymphoreticular neoplasms was higher in males exposed to methanol only than in the control group, but the difference was not reported as statistically significant.) IARC (2006) noted several limitations of these findings, including (1) the total number of rats with hemolymphoreticular tumors listed in Sofritti *et al.* (2002a) had increased by 71 from the preliminary report on the same study (Sofritti *et al.* 1989) with no explanation provided by the author, (2) lymphomas and leukemias were pooled and designated as hemolymphoreticular tumors, and (3) the absence of information on incidences of hemolymphoreticular tumors in historical controls in this study.

Soffritti *et al.* (2002a) reported a significant increase in the number of total malignant mammary-gland tumors (most were adenocarcinomas) in females (100, 1,000, and 1,500 mg/L) and number of testicular interstitial-cell adenomas in males (500, 1,000, and 1,500 mg/L) (Table 4-12a). A statistical analysis of the tumor incidence data by IARC (IARC 2006) showed that when compared with the methanol-only group, the formaldehyde-exposed rats had a significantly increased incidence of testicular interstitial-cell adenoma in the mid-exposure group ($P < 0.01$), but the incidence of mammary-gland tumors was not increased. Several stomach and intestinal tumors, including a few of the very rare leiomyomas or leiomyosarcomas, were observed in some of the formaldehyde-exposed groups but not in the methanol or control groups (Table 4-12b).

Table 4-12a. Incidences of mammary, testicular, and hemolymphoreticular tumors in Sprague-Dawley rats exposed to formaldehyde in drinking water for up to 104 weeks[a]

Sex	Conc. (mg/L [ppm])	N	Incidence (%)					
			Mammary gland					
			Adeno-carcinoma	Fibro-sarcoma	Lipo-sarcoma	Total[b]	Testes	Hemolymphoreticular[c]
Male	control	100	1 (1)	0	0	1 (1)	10 (10)	8 (8)
	methanol	50	0	1 (2)	0	1 (2)	3 (6)	10 (20)
	10	50	0	0	0	0	3 (6)	4 (8)
	50	50	0	0	0	0	6 (12)	10 (20)
	100	50	0	0	1 (2)	1 (2)	6 (12)	13 (26)**
	500	50	0	0	0	1 (2)[d]	10 (20)	12 (24)*
	1,000	50	0	0	0	0	12 (24)*[e]	11 (22)*
	1,500	50	1 (2)	0	0	1 (2)	9 (18)	23 (46)**[f,g]
Female	control	100	11 (11)	0	0	11 (11)	–	7 (7)
	methanol	50	7 (14)	0	1 (2)	8 (16)	–	5 (10)
	10	50	2 (4)	1 (2)	0	3 (6)	–	5 (10)
	50	50	4 (8)	0	1 (2)	5 (10)	–	7 (14)
	100	50	8 (16)	2 (4)	0	10 (20)	–	8 (16)
	500	50	3 (6)	1 (2)	2 (4)	6 (12)	–	7 (14)
	1,000	50	9 (18)	1 (2)	0	10 (20)	–	11 (22)*
	1,500	50	11 (22)	0	1 (2)	12 (24)*	–	10 (20)*

Source: Soffritti *et al.* 2002a, IARC 2006.

*$P < 0.05$, **$P < 0.01$ (compared with untreated controls, χ^2 test, test conducted by IARC).

[a]Statistical analyses for incidence data (tests performed by IARC 2006) are reported in the table; statistical analyses for total tumor numbers (Soffritti *et al.* 2002a) are reported in the text.

[b]Total tumors reported by IARC, which also noted that this category is an aggregate of tumors of different cellular origins.

[c]IARC also noted that this category is an aggregate of tumors of different cellular origins.

[d]Angiosarcoma also reported in 1 rat.

[e]Significantly different from the methanol control group ($P < 0.01$, 2-tailed Fisher's exact test conducted by IARC).

[f]Significantly different from the methanol control group ($P < 0.01$, χ^2 test conducted by IARC).

[g]Test for trend, $P < 0.01$, Cochran-Armitage, calculated by IARC

Table 4-12b. Incidences of stomach and intestinal tumors in Sprague-Dawley rats exposed to formaldehyde in drinking water for up to 104 weeks

Sex	Conc. (mg/L [ppm])	N	Incidence (%)			
			Stomach- leiomyosarcoma[a]		Intestine	
			Forestomach	Glandular stomach	Leiomyoma[a]	Leiomyosarcoma[a]
Male	control	100	0	0	0	0
	methanol	50	0	0	0	0
	10	50	1 (2)	0	0	0
	50	50	0	0	0	0
	100	50	0	0	0	0
	500	50	0	0	0	0
	1,000	50	0	1 (2)	0	0
	1,500	50	0	0	0	2 (4)
Female	control	100	0	0	0	0
	methanol	50	0	0	0	0
	10	50	0	0	2 (4)[b]	0
	50	50	0	0	1 (2)	1 (2)
	100	50	0	0	0	0
	500	50	0	0	0	0
	1,000	50	0	0	0	0
	1,500	50	0	0	3 (6)	0

Source: Soffritti *et al.* 2002a, IARC 2006.

[a]Statistical analyses were not provided for these tumors, which were reported as being very rare in Sprague-Dawley rats [not significantly different from controls, Fisher's exact test conducted by NTP].

[b]IARC 2006 reported only 1 tumor (2%) for this group, without an explanation.

4.2.2 Skin application

Formaldehyde is widely used in laboratories as a fixative for tissue; therefore, researchers and technicians may be chronically exposed by skin contact. Iversen (1986) conducted skin-painting experiments with hairless Oslo mice to test the potential carcinogenic potency of formaldehyde at concentrations typically used in pathology laboratories. Two groups of 16 male and 16 female mice (age not reported) received two weekly topical applications of 200 μL of aqueous solutions of 1% or 10% formaldehyde for up to 60 weeks. Formaldehyde was also tested as a skin-tumor promoter (see Section 4.3.1). Mortality was not increased in groups exposed to 1% or 10% formaldehyde. No lesions were observed in the mice exposed to 1% formaldehyde, while mice in the 10% formaldehyde group had slight hyperplasia of the epidermis. The author concluded that 1% or 10% formaldehyde applied to the skin of hairless mice did not have an observable carcinogenic effect. IARC (2006) noted that there was no water-only control group. [This study is also limited by the small number of animals and less-than-lifetime exposure duration.]

4.2.3 Summary of oral and dermal exposure studies

Five drinking-water studies and one skin-painting study of the carcinogenicity of formaldehyde were reviewed. Some of the studies were limited because exposure duration was relatively short and/or a small number of animals per group was used. Ingestion of formaldehyde at high concentrations was primarily associated with gastrointestinal-tract tumors in two studies in rats and included the very rare leiomyosarcomas and leiomyomas. One study reported increased incidences of total malignant tumors, testicular tumors, malignant mammary-gland tumors, and hemolymphoreticular tumors. No tumors were observed in the skin-painting study in mice. Results and study limitations are summarized in Table 4-13.

Table 4-13. Summary of oral and dermal carcinogenicity studies of formaldehyde in experimental animals

Animals	Exposure			Gastrointestinal tumor incidence		Results and comments	Reference
	Route	Duration (wk)	Conc. (mg/L [ppm])	Male	Female		
Wistar rats	oral	32	0 5,000	0/10 8/10	NT	[Small number of animals/group, short exposure duration], all tumors were forestomach papilloma.	Takahashi *et al.* 1986
Wistar rats	oral	104	0 20 260 1,900	0/70 0/70 0/70 0/70	0/70 0/70 0/70 0/70	Rats in the high-concentration groups had extensive damage to the gastric mucosa and an increase in proliferative lesions of the forestomach and glandular stomach.	Til *et al.* 1989
Wistar rats	oral	104	0 200 1,000 5,000	0/20 0/20 0/20 0/20	0/20 0/20 0/20 0/20	[Small number of animals/group], no exposure-related tumors. Increased proliferative lesions and ulcers of the forestomach and glandular stomach in high-concentration group. High mortality in high-concentration groups.	Tobe *et al.* 1989
Sprague-Dawley rats	oral	104	0 2,500	0/20 1/18	0/20 1/18	[Small number of animals/group], two hemolympho-reticular tumors in exposed groups; one in female controls.	Soffritti *et al.* 1989
Sprague-Dawley rats (offspring)	*in utero* and oral[a]	104	0 2,500	0/59 5/36[b]	0/49 8/37[b]	Three hemolymphoreticular tumors in each control group; four in the male exposed group.	
Sprague-Dawley rats	oral	104	0 10 50 100 500 1,000 1,500	0/100 2/50[b] 0/50 0/50 0/50 1/50 6/50[b]	0/100 2/50 3/50[b] 0/50 0/50 0/50 5/50[b]	Males: increased numbers of tumor-bearing animals (highest concentration); increased incidence of testicular tumors (1,000 mg/L concentration) and hemolymphoreticular tumors (4 highest concentrations). Females: increased numbers of mammary-gland tumors (highest concentration only) and hemolymphoreticular tumors (2 highest concentrations).	Soffritti *et al.* 2002a, IARC 2006
Oslo hairless mice	dermal	60	1%[c] 10%[c]	0/16 0/16	0/16 0/16	[No water-only control group, small number of animals per group, less-than-lifetime exposure.]	Iversen 1986

NT = not tested.
[a]Offspring exposed *in utero* from gestation day 13; postnatal exposure via drinking water.
[b]Total number of stomach and intestinal tumors (benign and malignant). See Tables 4-10 and 4-12b.
[c]Given two weekly applications of 200 µL of test solution.

4.3 Co-exposure with other substances

This section reviews studies of various designs that investigated the carcinogenic effects in mice, rats, and hamsters following concurrent or sequential exposure to formaldehyde and other substances. In some cases, the primary purpose was to determine whether formaldehyde exposure enhanced or promoted the carcinogenicity of another substance. In other cases, the primary purpose was to determine whether co-exposure to other substances enhanced the carcinogenicity of formaldehyde.

4.3.1 Mice

One of the objectives of the Horton *et al.* (1963) study (discussed in Section 4.1.1) was to determine whether exposure to formaldehyde increased susceptibility to the carcinogenic effects of coal tar. A group of 60 C3H mice (sex and age not reported) was exposed to formaldehyde vapor at a concentration of 100 mg/m^3 [81 ppm] for 1 hour/day, 3 days/week, for 35 weeks and then exposed to a coal-tar aerosol at a concentration of 300 mg/m^3 [243 ppm] for 2 hours/day, 3 days/week, for up to 36 weeks. Another group of 59 mice was exposed only to coal tar starting after week 35 and continuing for up to 36 weeks. A third group of 60 mice was exposed to formaldehyde at 50 mg/m^3 [41 ppm] for 1 hour/day, 3 days/week, for 35 weeks and then exposed to formaldehyde at 150 mg/m^3 [122 ppm] for 1 hour/day, 3 days/week, for an additional 29 weeks. The control group consisted of 30 unexposed mice that were killed at 82 weeks. Incidences of lung tumors in these mice are shown in Table 4-14. There was no evidence that exposure to formaldehyde increased susceptibility to lung tumors in mice exposed to coal-tar aerosol. No squamous-cell lung tumors were observed in mice exposed to formaldehyde for up to 64 weeks.

Table 4-14. Incidences of squamous-cell lung tumors in C3H mice exposed to formaldehyde and coal tar by inhalation

	Exposure (mg/m^3) [ppm formaldehyde]				
N	Formaldehyde wk 1–35	Coal tar wk 36–71	Formaldehyde wk 36–64	No. examined	Tumor incidence [%]
30	0 [0]	0	0 [0]	30	0
59	0 [0]	300	0 [0]	33	5 [15]
60	100 [81]	300	0 [0]	26	1 [4]
60	50 41]	0	150 [122]	36	0

Source: Horton *et al.* 1963.

Iversen (1986) tested the potential promoting effect of formaldehyde on skin carcinogenesis in hairless Oslo mice initiated with dimethylbenz(*a*)anthracene (DMBA). Solutions were applied to the skin of the back. Two groups of 16 male and 16 female mice (age not reported) were given two weekly applications of 200 µL of an aqueous solution of 1% or 10% formaldehyde for up to 60 weeks (results reported in Section 4.2.2). A third group of 16 male and 16 female mice received an initial topical application of 51.2 µg of DMBA in 100 µL of reagent-grade acetone and, beginning

9 days later, two weekly applications of 200 µL of 10% formaldehyde, for up to 60 weeks. The positive control group of 16 male and 16 female mice received DMBA followed by two weekly applications of 17 nmol 12-*O*-tetradecanoylphorbol 13-acetate (TPA [vehicle not reported]). An additional group of 176 mice (sex not reported) received a single application of 51.2 µg of DMBA and was observed for 80 weeks. One accidental death of a mouse exposed to DMBA + formaldehyde occurred at week 26. Lesions observed in this group included epidermal hyperplasia in 1 mouse, lung adenomas in 3 mice, and skin tumors in 11 mice (3 squamous-cell carcinomas and 22 papillomas). The authors did not consider the lung adenoma to be exposure related; they reported an incidence of about 1 in 30 in unexposed mice from unpublished data. The first skin tumors occurred at week 10 in mice given DMBA + formaldehyde. In the positive-control group (DMBA + TPA), survival at 20 weeks was 80%, and the experiment was terminated at week 46 with only 11 of 32 mice still alive. Tumors first appeared in the DMBA + TPA group after 5 weeks, and all mice that survived until week 20 had skin papillomas; however, no carcinoma or sarcoma was observed. Most of the mice in the DMBA-only group survived until the end of the experiment, and 225 skin tumors (primarily papilloma) occurred in 85 mice; the first tumors in this group appeared after 20 weeks.

The authors reported that there was no difference in tumor yields between groups given DMBA + formaldehyde and mice given DMBA only. The final tumor yield (the total number of tumors as a function of time) was evaluated according to the method of Gail *et al.* (1980). The final tumor rate (the percentage of tumor-bearing mice in relation to the number of mice alive at the appearance of the first tumor) was not significantly higher in mice given DMBA + formaldehyde than in mice given DMBA only; however, the time to appearance of the first tumor and the mean latency period were significantly reduced (P = 0.01, Peto's test). Tumor incidence and the total number of reported tumors are shown in Table 4-15. The authors concluded that 10% formaldehyde applied twice a week to the skin of Oslo hairless mice following one application of DMBA did not increase the total number of tumors but significantly reduced the mean latency period for tumor formation. This effect was much weaker than that observed with TPA.

Table 4-15. Skin tumor promotion study of formaldehyde in Oslo hairless mice

Group	Study length (wk)	N	Time to first tumor (wk)	Tumor incidence [%][a]	Total number of tumors		
					Papilloma	Carcinoma	Total
DMBA	80	176	[22][b]	85 [48]	219	6	225
DMBA + HCHO	60	32	10	11 [34]	22	3	25
DMBA + TPA	46	32	[8][b]	26 [100][c]	NR	0	NR

Source: Iversen 1986.
DMBA = dimethylbenz(*a*)anthracene; HCHO = formaldehyde; NR = not reported; TPA = 12-*O*-tetradecanoylphorbol 13-acetate.
[a]Tumor incidences cannot be compared directly because of the differing study lengths and because they are not adjusted for survival differences.
[b]Estimated from a figure.
[c]Six mice died before week 20 and were not included in the analysis.

4.3.2 Rats

Albert *et al.* (1982) and Sellakumar *et al.* (1985) investigated the carcinogenicity of a mixture of formaldehyde and hydrogen chloride (HCl) in rats. Previous studies had shown that low levels of bis(chloromethyl)ether (BCME), which is highly carcinogenic in the respiratory tract of rats and is a known human carcinogen, could form from the gas-phase reaction of formaldehyde and hydrogen chloride. In the first study (Albert *et al.* 1982), 8-week-old male Sprague-Dawley rats were divided into three groups of 50 unexposed colony controls, 50 controls sham-exposed to air, and 99 rats exposed to a mixture of approximately 14-ppm formaldehyde and 10-ppm HCl (the gases were premixed at high concentrations before introduction into the inhalation chamber, to maximize formation of BCME). Exposures were for 6 hours/day, 5 days/week, for life. A complete necropsy was performed on each animal. Formation of BCME was monitored by gas chromatography. BCME levels in the mixing vessel ranged from 8 to 179 ppb (mean = 75 ppb); however, BCME concentrations in the exposure chamber were less than the detection limit (not identified by study authors) and were estimated to be no greater than 1 ppb, based on a 75-fold dilution factor. The exposed group had substantially lower body-weight gain and higher mortality than the controls. Early deaths in the exposed group and controls were attributed to bronchopneumonia. The exposed group showed high incidences of squamous metaplasia of the nasal cavity and epithelial hyperplasia with and without atypia. Nasal tumors (3 squamous-cell papillomas and 25 squamous-cell carcinomas) were observed in the exposed group but not in the controls (Table 4-16). Incidences of non-respiratory-tract tumors were higher in the control groups (23 of 100) than in the exposed rats (7 of 99). These tumors included lymphoma, pituitary gland and adrenal cortical adenoma, subcutaneous fibrosarcoma, and 1 splenic hemangioma. No statistical analyses were reported by the study authors. However, the IARC (2006) evaluation of this study reported that the incidence of squamous-cell carcinoma was significantly higher in the exposed group than in the controls ($P < 0.001$, Fisher's exact test).

Sellakumar *et al.* (1985) conducted a follow-up of the Albert *et al.* (1982) study to examine the carcinogenic effects of formaldehyde and HCl when administered alone or in combination. Groups of 99 or 100 male Sprague-Dawley rats, 9 weeks of age, were randomly assigned to six treatment groups: (1) colony controls, (2) controls sham-exposed to air, (3) exposed to formaldehyde at a target concentration of 15 ppm and HCl at a target concentration of 10 ppm, premixed before being introduced into the inhalation chamber, (4) exposed to formaldehyde (15 ppm) and HCl (10 ppm) introduced separately into the exposure chamber, (5) exposed to formaldehyde alone (15 ppm), and (6) exposed to HCl alone (10 ppm). Rats were exposed for 6 hours/day, 5 days/week, for life. Formation of BCME from the premixed formaldehyde and HCl was again monitored by gas chromatography. BCME concentrations in the mixing vessel ranged from 3.6 to 33.7 ppb, and the calculated concentrations in the inhalation chamber ranged from 0.1 to 0.4 ppb. Complete necropsies were performed, with particular attention to the respiratory tract. Histologic sections were prepared from the lungs, trachea, larynx, liver, kidneys, testes, and any other organs with gross pathology. After 16 weeks, groups exposed to formaldehyde alone or formaldehyde plus HCl had lower body weights than the controls. Mortality rates among all the groups were similar up to 32 weeks. After 32 weeks, the

group exposed to premixed formaldehyde plus HCl showed a higher mortality rate than the other groups. Nasal tumors occurred only in groups exposed to formaldehyde alone or in combination with HCl (Table 4-16). No tumors developed in the trachea or lungs. The total number of non-respiratory-tract tumors did not differ between the exposed and control groups. The authors reported that the incidence of nasal tumors was significantly higher in the group exposed to premixed formaldehyde plus HCl than in the formaldehyde-only group ($P < 0.025$, χ^2 test). IARC's review (IARC 2006) of this study also reported that the incidence of squamous-cell carcinoma and papilloma combined was significantly higher in the formaldehyde-only group than in the controls ($P < 0.001$, Fisher's exact test). [In statistical analysis conducted by NTP, the incidences of squamous-cell carcinoma in the groups exposed to formaldehyde only, premixed formaldehyde plus HCl, and non-premixed formaldehyde plus HCl were significantly higher than in the controls ($P < 0.001$, Fisher's exact test).] The authors noted that the higher incidences in the group exposed to premixed formaldehyde plus HCl could have been due to traces of alkylating agents other than BCME formed by the interaction of formaldehyde and HCl. Nevertheless, the authors concluded that HCl had little to no effect on the carcinogenicity of formaldehyde and that formaldehyde accounted for most, if not all, of the carcinogenic activity of the mixture.

Table 4-16. Proliferative and neoplastic lesions in the nasal cavity of male Sprague-Dawley rats exposed to formaldehyde and hydrogen chloride

	Nasal-cavity lesion [%]					
Group	N	Epithelial hyper-plasia	Squamous meta-plasia	Squamous-cell papilloma or polyps	Squamous-cell carcinoma	Other[a]
Study 1						
Colony controls	50	8 [16]	0	0	0	NR
Sham air	50	NR	NR	NR	NR	NR
HCl + HCHO	99	71 [72]	64 [65]	3 [3]	25 [25***]	NR
Study 2						
Colony controls	99	45 [45]	6 [6]	0	0	0
Sham air	99	51 [52]	5 [5]	0	0	0
HCl	99	62 [63]	9 [9]	0	0	0
HCHO[b]	100	57 [57]	60 [60]	10 [10]	38 [38***]	2 [2]
Premixed HCl + HCHO[c]	100	54 [54]	64 [64]	13 [13]	45 [45***]	3 [3]
Non-premixed HCl + HCHO	100	53 [53]	68 [68]	11 [11]	27 [27***]	2 [2]

Source: Albert *et al.* 1982, Sellakumar *et al.* 1985, IARC 2006.
HCl = hydrogen chloride; HCHO = formaldehyde; NR = not reported.
***$P < 0.001$ (compared with controls, Fisher's exact test conducted by IARC 2006 or [NTP]).
[a]Includes adenocarcinoma, mixed carcinoma, fibrosarcoma, or esthesioneuroepithelioma of the nasal mucosa.
[b]IARC reported that the incidence of squamous-cell carcinoma and papilloma combined was significantly higher in this group than in the controls ($P < 0.001$, Fisher's exact test).
[c]The study authors reported a significantly higher incidence of nasal cancer in this group than in the formaldehyde-only group ($P < 0.025$, χ^2 test).

Homma *et al.* (1986) investigated whether repeated intravesical instillation of formalin would promote urinary-bladder carcinogenesis in male F344 rats. Heterotopically transplanted bladders were used, because transient generalized hyperplasia can be readily and repeatedly induced by intravesical instillation of formalin without the risk of infection or calculus formation, which are unavoidable when homotopic bladders are used. The rats were randomly divided into four groups of 35 animals each. Four weeks after bladder transplant, three groups received 0.25 mg of *N*-methyl-*N*-nitrosourea (MNU) in 0.9% saline to initiate bladder carcinogenesis. At week 5, group 1 was given an intravesical instillation of 0.5 mL of 0.3% formalin, followed by instillation of 0.5 mL of normal rat urine 24 hours later and 0.5 mL of 2.1% sodium chloride (NaCl) solution 1 week after the urine instillation. Group 2 was treated similarly to group 1 except that the order of the urine and salt solution instillation was reversed. Group 3 received 0.9% NaCl solution at week 5 instead of formalin, then 2.1% NaCl 24 hours later and rat urine 1 week later. Group 4 was treated the same as group 1 but without MNU initiation. The alternating instillation schedule was repeated every 2 weeks for 15 cycles in each group, and the experiment was terminated at week 34. The heterotopically transplanted bladders were inflated with Bouin's solution, fixed overnight, and examined for gross tumors. In addition, longitudinal strips were examined microscopically. Repeated formalin exposure did not enhance bladder carcinogenesis.

Takahashi *et al.* (1986) tested formaldehyde and other compounds for tumor-promoting activity in a two-stage stomach carcinogenicity study. Stomach tumors were initiated by giving two groups of 7-week-old male Wistar rats *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine (MNNG) in drinking water at a concentration of 100 mg/L and a diet supplemented with 10% sodium chloride for 8 weeks. Thereafter, one group of 30 rats received no further treatment (i.e., no exposure to a promoter), and one group of 20 rats received 0.5% formalin in drinking water from week 8 to 40. Two additional groups of 10 rats received no MNNG; one of these groups was exposed only to formaldehyde from week 8 to 40, and a control group received no treatment. All animals that survived beyond week 30 were included in the analysis; 3 rats in the MNNG plus formaldehyde group died early and were not included in the analysis. For the first 8 weeks, the two groups that received MNNG showed lower body-weight gain than the groups that did not receive MNNG; however, their weight gain increased after week 8. Throughout the study, growth retardation was most marked in the group that received MNNG plus formaldehyde. Formaldehyde showed possible tumor-promoting effects in the pylorus of the glandular stomach, and the incidence of squamous-cell papilloma of the forestomach was significantly increased in groups exposed to formaldehyde with or without initiation. In addition, the incidence of adenomatous hyperplasia of the fundus was significantly higher in the MNNG plus formaldehyde group than in the MNNG-only group (88.2% vs. 0). Results are summarized in Table 4-17.

Table 4-17. Effects of formaldehyde on gastric carcinogenesis in male Wistar rats initiated with MNNG

Group	N	Forestomach papilloma (%)	Glandular stomach adenocarcinoma (%)		
			Fundus	Pylorus	Duodenum
Control	10	0	0	0	0
MNNG only	30	0	0	1 (3.3)	3 (10)
MNNG + HCHO	17	15 (88.2)**	0	4 (23.5)*,[a]	1 (5.9)
HCHO only	10	8 (80)**	0	0	0

Source: Takahashi *et al.* 1986.
HCHO = formaldehyde; MNNG = *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine.
*$P < 0.05$; **$P < 0.01$ (compared with MNNG group, Fisher's exact test).
[a][$P = 0.051$, Fisher's exact test conducted by NTP].

Holmström *et al.* (1989a) investigated the cocarcinogenic effects of formaldehyde (average concentration of 12.4 to 12.7 ppm) and wood dust. Concurrent exposure to formaldehyde and wood dust is common, particularly in the furniture industry. Groups of 16 female Sprague-Dawley rats, 11 weeks of age, were exposed to formaldehyde alone (results reported in Section 4.1.2), wood dust alone (25 mg/m^3), or formaldehyde plus wood dust for 104 weeks. No nasal or lung tumors occurred in the wood-dust or formaldehyde plus wood-dust exposure groups. One squamous-cell carcinoma of the nasal mucosa occurred in the group exposed to formaldehyde only. Squamous-cell metaplasia with dysplasia was most common in the group exposed to both formaldehyde and wood dust. Pulmonary emphysema was most common in the group exposed only to wood dust. The authors considered that the most important finding of this study was the additive deleterious effect of combined exposure to formaldehyde and wood dust. The IARC (2006) evaluation of this paper noted that a small number of animals was used in this study.

IARC (2006) also reviewed a study published in Russian (Yanysheva *et al.* 1998) that investigated the promoting effects of formaldehyde administered by inhalation at low concentrations. Groups of 50 white non-inbred female rats (age and strain not reported), including a control group, were exposed to formaldehyde at a concentration of 0.003, 0.03, or 0.3 mg/m^3 [0.002, 0.02, or 0.24 ppm] either alone or in combination with benzo[*a*]pyrene. Benzo[*a*]pyrene was administered by intratracheal injection once every 2 weeks for 20 weeks (for a total dose of 0.02, 1, or 5 mg). Formaldehyde was administered by inhalation for 7 hours/day, 5 days/week, for 1 year. Animals were held until natural death. Tumors were observed in all groups. Two rats in the control group developed reticulosarcoma of the lung, and two others developed fibroadenoma of the mammary gland. Similar incidences of these tumors were observed in the three formaldehyde-only exposure groups. In rats given only benzo[*a*]pyrene, the total incidence of tumors ranged from 13% to 28%, and incidence of lung tumors ranged from 9% to 19%. A dose-dependent tumor response was observed in groups exposed to both benzo[*a*]pyrene and formaldehyde. The most significant effect was an increase in lung tumors (43%) and total tumors (69%) in the group exposed to the highest levels of benzo[*a*]pyrene and formaldehyde. Tumors also developed earlier in this group and had

greater multiplicity than in the other groups. The authors concluded that combined exposure to benzo[*a*]pyrene and formaldehyde enhanced the tumor response in rats.

4.3.3 Hamsters

Although inhalation exposure to formaldehyde alone did not induce respiratory-tract tumors in male Syrian golden hamsters (see Section 4.1.3), there was evidence that it could be a cofactor in the induction of respiratory-tract tumors by DEN (Dalbey 1982). A group of 50 male hamsters (age not reported) was exposed to formaldehyde at a concentration of 30 ppm for 5 hours/day, 1 day/week, for life (also reported in Section 4.1.3). Two additional groups of hamsters were exposed to formaldehyde at 30 ppm: a group of 27 hamsters also received weekly subcutaneous injections of 0.5 mg of DEN 48 hours after the weekly formaldehyde exposure for the first 10 weeks, and then formaldehyde weekly for life; the other group consisted of 23 that hamsters received 10 weekly DEN injections before beginning formaldehyde exposure, which then continued weekly for life. An unexposed control group consisted of 50 hamsters, and a DEN-only control group consisted of 100 hamsters injected once per week for 10 weeks.

The lungs, trachea, larynx, nasal turbinates, and lower jaw were examined for tumors. Tumor incidence data were analyzed with a χ^2 test (the statistical method used to analyze tumor multiplicity was not identified). Mortality was not affected by exposure to formaldehyde but was significantly increased in the DEN-only group and both DEN plus formaldehyde groups. Because of mortality due to an exposure accident at 48 weeks, the sizes of the DEN plus formaldehyde groups were reduced to 27 and 23 hamsters. No tumors occurred in the unexposed controls or in the formaldehyde-only group. The tumor incidence (primarily tracheal tumors) was 77% in the DEN-exposed group and was not significantly higher than this in the DEN plus formaldehyde groups (the incidences were not reported). However, tumor multiplicity (tumors per tumor-bearing animal) was significantly higher in the group that received DEN plus formaldehyde simultaneously than in the DEN-only group (Table 4-18). All tumors were adenomas. Nasal tumor incidence was only 2% in the DEN-only group and the group exposed to DEN plus formaldehyde sequentially, but no nasal tumors occurred in the other three groups.

Table 4-18. Effects of formaldehyde on induction of respiratory-tract tumors by DEN in male Syrian hamsters

Group	N	Tumor incidence (%)	[Tumors/tumor-bearing animal][a]		
			Larynx	Trachea	Lung
Unexposed control	50	0	0	0	0
HCHO only	50	0	0	0	0
DEN only	100	77	1	1.6	1.4
HCHO + DEN, then HCHO	27	NR	1	2.8*	1.0
DEN, then HCHO	23	NR	1	1.7	2.0

Source: Dalbey 1982.
DEN = diethylnitrosamine; HCHO = formaldehyde; NR = not reported; however, the authors stated that the incidence was not significantly different from that of the DEN-exposed group.
*$P < 0.05$ (compared with the DEN-only group, statistical test not identified).
[a]Values were estimated from Figure 3 in Dalbey 1982.

4.3.4 Summary of promotion and cocarcinogenicity studies

Several studies investigated the promoting or cocarcinogenic effects of formaldehyde. Formaldehyde did not enhance lung carcinogenesis in mice exposed to coal tar but did reduce the latency period for skin tumors in mice initiated with DMBA. Studies in rats indicated that formaldehyde exhibited possible tumor-promoting effects in stomach and lung but not in the urinary bladder. In another study, hydrogen chloride had little or no effect on the carcinogenicity of formaldehyde. One study in hamsters indicated possible tumor-promoting effects in the respiratory tract. Results from all co-exposure studies of formaldehyde and other substances are summarized in Table 4-19.

Table 4-19. Co-exposure carcinogenicity studies of formaldehyde and other substances in experimental animals

Species and strain (sex)[a]	Exposure			Results	Reference
	Route	Exposure (concentration)	Duration (wk)		
C3H mice	inhalation	HCHO (100 mg/m^3 [81 ppm[) + coal tar (300 mg/m^3)	35 + 33	Did not enhance induction of lung tumors	Horton *et al.* 1963
Oslo mice	skin	DMBA (51.2 µg) + HCHO (10%)	1[b] + 60	Tumor latency was decreased; no effect on tumor incidence	Iversen 1986
Sprague-Dawley rats (male)	inhalation	HCHO (14 ppm) + HCl (10 ppm)	life[c]	Increased nasal tumor incidence, compared with colony controls	Albert *et al.* 1982
Sprague-Dawley rats (male)	inhalation	HCHO (15 ppm) + HCl (10 ppm)	life[c]	HCl had little effect on induction of nasal tumors by formaldehyde	Sellakumar *et al.* 1985
F344 rats (male)	intravesical	MNU (0.25 mg) + HCHO (3,000 ppm)	1[b] + 34	Did not promote urinary bladder carcinogenesis	Homma *et al.* 1986
Wistar rats (male)	drinking water	MNNG (100 ppm) + HCHO (5,000 ppm)	8 + 32	Possible weak promotion effect for adenocarcinoma in the glandular stomach	Takahashi *et al.* 1986
Sprague-Dawley rats (female)	inhalation	HCHO (12.7 ppm) + wood dust (25 mg/m^3)	104	One squamous-cell carcinoma in formaldehyde-only group; squamous-cell metaplasia with dysplasia increased in combined exposure group	Holmström *et al.* 1989a
White non-inbred rats (female)	inhalation	HCHO (0.3mg/m^3 [0.24 ppm]) + B[*a*]P (5 mg)	52[d]	Combined exposure enhanced induction of lung and total tumors	Yanysheva *et al.* 1998 (cited in IARC 2006)
Syrian golden hamsters (female)	inhalation	DEN (0.5 mg) + HCHO (30 ppm)	10 + life[e]	Tumor multiplicity was increased	Dalbey 1982

B[*a*]P = benzo[a]pyrene; DEN = diethylnitrosamine; DMBA = dimethylbenz[*a*]anthracene; HCHO = formaldehyde; HCl = hydrogen chloride; MNNG = *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine; MNU = *N*-methyl-*N*-nitrosourea.
[a]When only one sex was used.
[b]Single application of the initiator.
[c]Exposed to a mixture of formaldehyde and hydrogen chloride.
[d]Exposed for one year and observed until death.
[e]DEN given in 10 weekly injections either before or concurrently with formaldehyde exposure.

4.4 Summary

Formaldehyde has been tested for carcinogenicity in mice, rats, and hamsters. Studies reviewed include chronic and subchronic inhalation studies in mice, rats, and hamsters; chronic and subchronic drinking-water studies in rats; and one chronic skin-application study in mice (see Table 4-20 for neoplasms associated with exposure). No chronic studies in primates were found, but one subchronic inhalation study and one acute/subacute inhalation study in monkeys was reviewed. [Several of these studies were limited by a small number of animals per group, short exposure duration, short study duration, incomplete pathology or data reporting, and/or incomplete statistical analysis.]

Formaldehyde exposure resulted in nasal tumors (primarily the extremely rare squamous-cell carcinoma) in several strains of rats when administered chronically by inhalation (Kerns *et al.* 1983a, Sellakumar *et al.* 1985, Appelman *et al.* 1988, Woutersen *et al.* 1989, Monticello *et al.* 1996, Kamala *et al.* 1997). Only two inhalation studies in mice or hamsters were found. No tumors were reported in C3H mice exposed to formaldehyde at 200 mg/m^3 [163 ppm] for 1 hour/day, 3 days/week, for 35 weeks (Horton *et al.* 1963), but squamous-cell carcinoma of the nasal cavity occurred in 2 of 17 B6C3F$_1$ male mice exposed at 14.3 ppm for 6 hours/day, 5 days/week, and sacrificed at 24 months (Kerns *et al.* 1983a). Although the increase was not statistically significant, the authors concluded that the tumors were exposure-related. [Biological significance is implied because these tumors are extremely rare in non-exposed mice and rats; no nasal squamous-cell carcinomas have been observed in more than 2,800 B6C3F$_1$ mice and 2,800 F344 rats used as controls in NTP inhalation studies.] No tumors were reported in Syrian golden hamsters exposed at 10 ppm 5 hours/day, 5 days/week for life (Dalbey 1982) or at 2.95 ppm 22 hours/day, 7 days/week for 26 weeks (Rusch *et al.* 1983). No tumors occurred in male cynomolgus monkeys exposed at 2.95 ppm for 22 hours/day, 7 days/week for 26 weeks (Rusch *et al.* 1983) or in male rhesus monkeys exposed at 6 ppm for 6 hours/day, 5 days/week for 6 weeks (Monticello *et al.* 1989); however, squamous metaplasia and hyperplasia in the nasal passages and respiratory epithelia of the trachea and major bronchi occurred.

Male Wistar rats administered formaldehyde in drinking water at 5,000 ppm for 32 weeks developed forestomach tumors (squamous-cell papillomas) in one study (Takahashi *et al.* 1986); however, in two other drinking-water studies, no tumors were reported in either male or female Wistar rats administered formaldehyde at concentrations ranging from 20 to 5,000 ppm for two years (Til *et al.* 1989, Tobe *et al.* 1989). In another study, male and female Sprague-Dawley breeder rats administered formaldehyde at 2,500 ppm in drinking water. Offspring of these breeder rats exposed transplacentally beginning on gestation day 13 and postnatally via drinking water for life showed increased incidences of benign and malignant tumors of the gastrointestinal tract, particularly intestinal leiomyosarcoma (a very rare tumor). Male Sprague-Dawley rats administered formaldehyde at concentrations up to 1,500 ppm showed increased incidences (compared with control groups given tap water) of the number of animals bearing malignant tumors, hemolymphoreticular neoplasms (leukemia and lymphoma combined), and testicular tumors (interstitial-cell adenoma) (Soffritti *et al.* 2002a). Compared with the vehicle control group (tap water containing 15 mg/L methanol), the incidence of testicular tumors

was significantly higher in the 1,000-ppm exposure group, and the incidence of hemolymphoreticular tumors was higher in the 1,500-ppm exposure group. Female rats in the 1,500-ppm exposure group showed higher incidences of malignant mammary-gland tumors and hemolymphoreticular neoplasms than the tap-water control group; however, the incidences were not significantly higher than in the vehicle control group. In addition, some rare stomach and intestinal tumors occurred in a few male and female rats in the exposed groups but not in the control groups.

Other studies examined the promoting effects of formaldehyde when administered after initiation with DBMA, DEN, MNU, or MNNG or cocarcinogenic effects when administered with coal tar, benzo[*a*]pyrene, wood dust, and hydrogen chloride. Some of these studies did not show an enhanced tumor response. However, a few studies, including a skin-painting study in mice (Iverson *et al.* 1986), a drinking-water study in rats (Takahashi *et al.* 1986), and inhalation studies in rats (Albert *et al.* 1982, Holmström *et al.* 1989a) and hamsters (Dalbey *et al.* 1986), indicated that formaldehyde could act as a tumor promoter or act as a co-carcinogen when administered with other substances.

Table 4-20. Summary of neoplasms associated with formaldehyde exposure in experimental animals

Organ or system	Tumor type	B6C3F$_1$ Mouse	F344 Rat		Wistar Rat		Sprague-Dawley Rat	
		Male	Male	Female	Male	Female	Male	Female
Inhalation studies								
Nasal epithelium	squamous-cell carcinoma	×	+	+	×		+	×
	papilloma or polyps						+	
	polypoid adenoma		+[t]	×	×			
	carcinoma *in situ*				×			
	Rhabdomyo-sarcoma		×					
	adenocarcinoma		×					
	combined tumor types				+[a]			
Ingestion studies								
Gastrointestinal	forestomach papilloma				+			
	adenoma, papilloma, acanthoma						×	×
	adenocarcinoma						×	×
	leiomyosarcoma						×[b,c]	+[c]
	leiomyoma							×
Hemolympho-reticular	leukemia and lymphoma						+	+[d]
Mammary-gland	total malignant (primarily adenocarcinoma)							+[d]
Testicular	interstitial-cell						+	

Organ or system	Tumor type	$B6C3F_1$ Mouse	F344 Rat		Wistar Rat		Sprague-Dawley Rat	
		Male	Male	Female	Male	Female	Male	Female
	adenoma							

+ = Statistically significant increase in tumor incidence reported.
$+^{t=}$ Statistically significant dose-related trend.
× = Statistical results were not reported or were not significant, but study authors reported the effect to be exposure related.
[a]Incidence of formaldehyde-related tumors (squamous-cell carcinoma, carcinoma *in situ*, and polypoid adenoma) (incidence = 4.5%; 6 tumors/132 rats) reported as significant ($P = 0.01$, Fisher's exact test) by IARC 2006.
[b]Significant when combined with female rats.
[c]Transplacental exposure beginning on gestation day 13 and postnatal exposure via drinking water for life.
[d]Not significant when compared with the control group given methanol at 15 mg/L in tap water.

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5 Other Relevant Data

Other data that are relevant for evaluating the carcinogenicity of formaldehyde are reviewed in this section. This includes absorption, distribution, metabolism and excretion, general toxic effects, carcinogenicity data for metabolites and analogues, genetic and related effects, and potential mechanisms of action.

5.1 Absorption, distribution, and excretion

As discussed in Section 2, formaldehyde exposure occurs from both endogenous and exogenous sources. Formaldehyde is an essential metabolic intermediate used in the biosynthesis of purines, thymidine, and some amino acids. Formaldehyde can also be produced from metabolism of serine, glycine, methionine, and choline, as well as from a variety of xenobiotics, such as drugs, food additives, and other environmental chemicals (IARC 2006). The endogenous concentration of formaldehyde measured in the blood of six human subjects was 2.66 ± 0.14 (mean ± SE) μg/g (equivalent to about 0.1 mM) and was similar to concentrations measured in the blood of monkeys and rats (Heck *et al.* 1985, Casanova *et al.* 1988, Heck and Casanova 2004).

Although formaldehyde is a gas at room temperature, in aqueous solution, it hydrates rapidly and is in equilibrium with its hydrated form, methylene glycol (methanediol) (Fox *et al.* 1985). The equilibrium lies far in favor of methanediol. The relative concentrations of formaldehyde and methanediol are dependent on temperature, with the chemical equilibrium constant for hydration calculated as $K_h = e^{3769/T-5.494}$, where T is temperature in degrees Kelvin (Winkleman *et al.* 2002). At both room temperature (298°K) and body temperature (310°K), the dominant form is methanediol because the equilibrium is far to the right (i.e., toward methanediol where K_h = 1,279 at room temperature and 784 at body temperature). While the hydrated form predominates at these temperatures, Matubayasi *et al.* (2007) reported that the unhydrated form is predominant when the temperature of water exceeds ~200°C. This propensity of reactive formaldehyde to hydrate (forming methanediol) and thereafter to slowly be regenerated (from methanediol) to free formaldehyde explains how such a reactive molecule can be distributed and undergo metabolism throughout the body. In tissues, formaldehyde in solution reacts readily with macromolecules (e.g., proteins, glycoproteins, nucleic acids, and polysaccharides) resulting in more formaldehyde forming from dissociation of methylene glycol. The equilibrium between formaldehyde and methylene glycol helps explain why formaldehyde penetrates rapidly (as methylene glycol) and fixes slowly (as carbonyl formaldehyde).

The metabolic pathways for formaldehyde are the same in all tissues of the body. Formaldehyde is rapidly metabolized to formic acid (formate + H^+) (see Section 5.3) at the site of contact and by erythrocytes in the blood, or is incorporated into serum proteins and other macromolecules via the one-carbon metabolic pool. The reported half-life of formaldehyde in the plasma of rats and monkeys is about 1 to 1.5 minutes (McMartin *et al.* 1979, IARC 2006). Burkhart (1990) reported an apparent plasma half-life for formate

of 3.1 hours and for formaldehyde of 3.3 hours in a 58-year-old man that committed suicide by ingesting 4 ounces of formaldehyde.

5.1.1 In vitro *studies*

Loden *et al.* (1986b) investigated the skin permeability of formaldehyde and other chemicals using excised human skin in a flow-through diffusion cell. ^{14}C-Formaldehyde was diluted in either concentrated formalin (37% formaldehyde in water containing 10% to 15% methanol) or a 10% v/v solution of formalin in 0.1 M phosphate buffer and applied to full thickness skin mounted in Teflon flow-through diffusion cells. Phosphate-buffered saline (pH 7.4) was used as the receptor medium. The rate of resorption (i.e., the uptake by the receptor fluid beneath the skin) of formaldehyde in concentrated formalin was 319 μg/cm^2 per hour and that of 10% formalin was 16.7 μg/cm^2 per hour. The total amount absorbed (i.e., the amount in the skin and the receptor medium) at steady state was 6.02 mg/cm^2 (concentrated formalin) and 0.48 mg/cm^2 (10% formalin). The effect of methanol on the uptake of formaldehyde was not determined. Up to approximately half the radioactivity absorbed was retained in the skin.

5.1.2 In vivo *studies*

Formaldehyde is rapidly and almost completely absorbed from the respiratory and gastrointestinal tracts but is poorly absorbed from the skin (IARC 1995, 2006, ATSDR 1999). In addition, Myers *et al.* (1997) reported rapid absorption of formalin following rectal instillation in dogs. In rats, almost all inhaled formaldehyde is absorbed in the nasal passages, while in primates, although almost all is absorbed in the nasal passages, some absorption occurs in the trachea and proximal regions of the major bronchi (Chang *et al.* 1983, Heck *et al.* 1983, Monticello *et al.* 1989, Casanova *et al.* 1991). Nasal anatomy, which is highly variable among species, and breathing patterns are the primary factors associated with the efficiency and specific location of formaldehyde absorption.

5.1.2.1 Inhalation exposure

Formaldehyde concentrations and air flow patterns in the nasal passages of rodents, monkeys, and humans have been correlated with the location of nasal lesions and levels of DNA-protein crosslinks (IARC 2006). One important physiological difference is that rats are obligate nose breathers while monkeys and humans are oronasal breathers. Thus, during oronasal breathing, a significant amount of the inhaled formaldehyde would bypass the nose and be absorbed directly into the lower respiratory tract of humans. Overton *et al.* (2001) conducted dosimetry modeling of inhaled formaldehyde in the respiratory tract of humans at four activity levels. The respiratory tract was divided into segments or generations beginning at nose and mouth and ending at the alveolar sacs. These authors predicted that for each activity state, the respiratory tract would retain over 95% of inhaled formaldehyde and that the rate of mass flow across a unit area of the respiratory tract (i.e., flux) in the first few tracheobronchial model generations would be more than 1,000 times higher than in the first pulmonary region, with no flux to the alveolar region. Egle (1972) reported similar findings in dogs exposed to formaldehyde at concentrations of 0.15 to 0.35 μg/mL [122 to 285 ppm]. Uptake of formaldehyde by the upper respiratory tract was near 100% regardless of the concentration.

Heck *et al.* (1982) exposed male F344 rats to 6-ppm formaldehyde for 6 hours/day for 10 days. The rats were killed within 10 minutes of exposure termination. Formaldehyde concentrations in the nasal mucosa of exposed rats (0.39 ± 0.12 μmol/g) were not significantly different from controls (0.42 ± 0.09 μmol/g).

Heck *et al.* (1983) conducted several experiments in groups of four male F344 rats to investigate the distribution, elimination, and pharmacokinetics of ^{14}C-formaldehyde following inhalation exposure (head only). No unexposed control groups were included in this study. Total radioactivity in the nasal mucosa, trachea, and plasma were measured immediately after a 6-hour exposure to 5, 10, 15, or 24 ppm ^{14}C-formaldehyde. Concentrations were highest in the nasal mucosa and ranged from about 0.5 to 2.3 μmole equivalents/g tissue and were related to dose. Concentrations in the trachea (about 0.3 μmole equivalents/g) and plasma (about 0.1 μmole equivalents/g) were not affected by dose, which indicates that absorption occurs primarily in the upper respiratory tract. The ratio of levels of ^{14}C (total radioactivity) in internal organs to that in plasma ranged from 0.31 in the testes to 4.94 in the esophagus and was not affected by dose. The higher concentrations in the esophagus were thought to reflect mucociliary clearance from the upper respiratory tract. Values for other organs declined in the order of kidney, liver, intestine, lung, spleen, heart, and brain. Another experiment examined the effects of pre-exposure to formaldehyde on tissue concentrations. One group was pre-exposed to 15 ppm formaldehyde 6 hours/day for 9 days while the other group was not pre-exposed to formaldehyde (naïve animals). On the tenth day, both groups were exposed (head-only) to ^{14}C-formaldehyde at 14.9 ppm for 6 hours. There were no differences in tissue concentrations between these groups, thus, pre-exposure to formaldehyde did not influence either the absorption or distribution to plasma.

Other groups of male F344 rats were exposed to 0.63- or 13.1-ppm ^{14}C-formaldehyde for 6 hours (Heck *et al.* 1983). Following exposure, the rats were placed in metabolism cages for 70 hours and then sacrificed. Radioactivity was measured in urine, feces, expired air, and the carcass. The dose did not affect the proportion recovered from the various elimination pathways (Table 5-1). Exhalation accounted for about 40% of the total dose. The authors noted that exhalation of $^{14}CO_2$ was biphasic, with a rapid decline over the first 12 hours followed by a more gradual decline. About 17.5% was eliminated in the urine and 4% to 5% was eliminated in the feces. The amount of radioactivity remaining in the carcass was 38.9% (low dose) and 35.2% (high dose). The authors noted that since formaldehyde is a precursor for many biological compounds, the high levels of radioactivity remaining in the carcass were probably due to metabolic incorporation.

Table 5-1. Disposition of inhaled ^{14}C-formaldehyde in male F344 rats (% radioactivity ± SD)

Source of Radioactivity	Exposure concentration (ppm)	
	0.63	13.1
Expired air	39.4 ± 1.5	41.9 ± 0.8
Urine	17.6 ± 1.2	17.3 ± 0.6
Feces	4.2 ± 1.5	5.3 ± 1.3
Tissues and carcass	38.9 ± 1.2	35.2 ± 0.5

Source: Heck *et al.* 1983.

Heck *et al.* (1983) also investigated the uptake and disappearance of radioactivity from the blood of male F344 rats following exposure to formaldehyde by inhalation (6 hours, head only) or a single intravenous injection of formaldehyde or formate. Blood samples were collected during and after exposure through a cannula implanted in the jugular vein. The concentrations of radioactivity in plasma increased during the exposure period, peaked at approximately the time of removal from the exposure chamber, and then gradually declined over a period of several days. The terminal half-life of radioactivity in plasma was approximately 55 hours; however, the authors stated that the radioactivity most likely indicated incorporation into serum proteins because the half-life of these proteins is about 2.9 days in the rat, and the half-life for free formaldehyde in rat plasma is approximately 1 minute (Rietbrock 1965, as cited in IARC 2006). [The half-life includes the half-life of both formaldehyde and its hydrated form (methanediol) because they are in equilibrium.] Radioactivity in the packed cell fraction of the blood showed a multiphasic profile that increased during exposure but declined rapidly within the first post-exposure hour. This was followed by an increase that peaked at about 35 hours post-exposure. The terminal phase showed a slow decline that was consistent with incorporation into the erythrocytes. The kinetic profiles following intravenous injection of formaldehyde or formate were similar and exhibited the same characteristics as described above following inhalation exposure. There was a rapid decline in radioactivity in both the plasma and the packed-cell fraction following intravenous administration of formaldehyde or formate. Plasma concentrations then gradually declined. Concentrations in the packed-cell fraction increased after the initial decline, peaked after about 35 hours, and then slowly declined just as was observed following inhalation exposure.

Chang *et al.* (1983) investigated nasal cavity deposition and toxicity of formaldehyde in male F344 rats and B6C3F$_1$ mice. Groups of naïve and pretreated rats and mice (whole-body exposure to 6- or 15-ppm formaldehyde, 6 hours/day for 4 or 5 days were exposed (head only) to ^{14}C-formaldehyde at 15 ppm for 6 hours. The amounts of radioactivity deposited in the nasal cavity of pretreated and naïve male F344 rats were similar, while naïve male B6C3F$_1$ mice had more radioactivity in the nasal cavity than pretreated mice. In both rats and mice, pretreated animals had less visceral radioactivity than naïve animals. This was attributed to decreased grooming and impaired mucociliary clearance in pretreated animals.

The concentrations of formaldehyde in the blood of rats, monkeys, and humans did not increase after inhalation exposure to formaldehyde. Heck *et al.* (1985) investigated the

effect of formaldehyde exposure on the concentrations in blood of rats and humans. Eight male F344 rats were exposed by inhalation to 14-ppm formaldehyde for 2 hours, and blood samples were collected immediately after exposure. The concentration (mean ± S.E.) of formaldehyde in the exposed group was 2.25 ± 0.07 µg/g of blood compared to 2.24 ± 0.07 µg/g in eight unexposed rats. Formaldehyde concentrations in human blood were measured in six volunteers before and after exposure to 1.9 ppm for 40 minutes. Mean formaldehyde concentrations before exposure were 2.61 ± 0.14 µg/g compared with 2.77 ± 0.28 µg/g after exposure and were not significantly different. However, there was considerable interindividual variation with both increases and decreases observed after exposure (Table 5-2).

Table 5-2. Concentrations of formaldehyde in human blood before and after exposure to 1.9 ppm for 40 minutes

Subject (gender)	Concentration (µg/g of blood)	
	Before exposure	After exposure
1 (female)	3.09 ± 0.41	2.18 ± 0.09
2 (female)	2.56 ± 0.10	3.31 ± 0.34
3 (male)	2.66 ± 0.17	3.74 ± 0.13
4 (male)	2.61 ± 0.34	1.93 ± 0.05
5 (male)	2.05 ± 0.16	2.76 ± 0.21
6 (male)	2.73 ± 0.14	2.72 ± 0.31
Mean	**2.61 ± 0.14**	**2.77 ± 0.28**

Source: Heck *et al.* 1985.

Formaldehyde concentrations in the blood of three rhesus monkeys were measured immediately after exposure to 6 ppm for 6 hours/day, 5 days/week, for 4 weeks and compared with unexposed controls (Casanova *et al.* 1988). The concentration of formaldehyde (mean ± S.E.) in the exposed group was 1.84 ± 0.15 µg/g of blood and did not change significantly over the next 45 hours without further exposure (2.04 ± 0.40 µg/g). The average concentration in the blood of unexposed controls was 2.42 ± 0.09 µg/g, which indicates that subchronic exposure to formaldehyde did not have a significant effect on formaldehyde concentrations in the blood of monkeys. McMartin *et al.* (1979) slowly infused a dose of 1 mmol/kg b.w. ^{14}C-formaldehyde into the femoral vein of two cynomolgus monkeys over a 3- to 4-minute period and collected blood samples from the femoral artery on the same side. The specific activity of the solution was 1,500 dpm/µmol for one monkey and 115,000 dpm/µmol for the other. Formaldehyde was detected for about 5 minutes after infusion with the lower specific activity solution, but was detected for up to 60 minutes when the higher specific activity solution was used. In both cases, the elimination half-life from the blood was about 1.5 minutes.

The mucociliary apparatus in the upper respiratory tract can provide protection of the underlying epithelium from gases and vapors. Schlosser (1999) investigated the relative roles of convection and chemical reaction for the disposition of formaldehyde in the nasal mucus in the rat. According to his calculations, the chemical reaction of formaldehyde with amino groups was negligible compared with the convective mucous transport. As

much as 22% to 42% of inhaled formaldehyde might be removed by mucous flow, whereas the amount removed by chemical reaction was calculated to be less than 0.54% of that removed by mucous flow.

5.1.2.2 Oral exposure

Feeding studies in rats, mice, rabbits, and livestock (described below) show that formaldehyde is absorbed readily from the gastrointestinal tract (Galli *et al.* 1983, Buckley *et al.* 1988, Nishi *et al.* 1988, Barry and Tomé 1991); however, no studies specifically reporting absorption and distribution of radiolabeled formaldehyde were identified. In addition, several cases of formaldehyde poisoning by ingestion in humans have been described (ATSDR 1999). These studies show that formic acid accumulates rapidly in the blood following formaldehyde ingestion.

Galli *et al.* (1983) fed grana cheese that contained ^{14}C-formaldehyde to groups of male Sprague-Dawley rats and male Swiss albino mice. Commercial grana cheese is normally made with milk that has formaldehyde added as a bacteriostatic agent. In this experiment, unlabeled and ^{14}C-labeled formaldehyde were added to the milk to obtain a final concentration of 35 to 40 ppm, and grana cheese was made following the usual process. Animals were placed individually in metabolism cages and fed 2.2 g (rats) or 0.5 g (mice) of radiolabeled cheese. Controls were fed unlabeled cheese. Rats were killed at 4, 8, 16, 32, and 64 hours, and mice were killed after 2, 4, 8, 16, 32, 64, and 96 hours, and 8 and 12 days after the end of treatment. The decay of radioactivity was measured in the plasma, liver, gastrointestinal tract, kidneys, spleen, testes, brain, muscle, adipose tissues, urine, and feces. The toxicokinetic profile was similar in rats and mice. The half-lives of the elimination phase were 27.8 hours in mice and 26.4 hours in rats. Excretion of radioactivity was essentially complete after 32 hours in both species with about 64% to 67% eliminated in the urine and feces and 24% to 28% eliminated as expired CO_2. In rats, maximum radioactivity in the tissues occurred at 16 hours while maximum activity in the blood reached about 0.08% of the dose after 8 hours. In mice, peak concentrations in the tissues occurred at 4 hours. The highest concentration measured in the blood was about 0.03% of the dose and occurred after 2 hours. However, the authors noted that ^{14}C-activity did not accumulate in the tissues of rats or mice, and that the low levels of radioactivity still present 32 hours after administration were likely due to residues of labeled fractions in milk proteins that had not been completely metabolized.

Buckley *et al.* (1988) measured the levels of formaldehyde in milk and blood of Holstein dairy cows fed diets that included formalin-preserved whey. The experiment was divided into three trials lasting 35 days each with a 2-week interval between trials. Six cows were fed untreated whey, and six cows were fed whey treated with 0.05% (0.0185% formaldehyde) (trial 1), 0.1% (0.037% formaldehyde) (trial 2), or 0.15% (0.0555% formaldehyde) (trial 3) formalin. Morning milk samples were collected 3 days prior to beginning each trial, on days 2 through 6, 13, 27, and 34 of each trial, and 46 hours after the end of trial 3. Blood samples were collected 3 days prior to the beginning of trial 3, and on days 9, and 33 of that trial. Levels of formaldehyde in milk samples from the control group were below the detection limit of 0.026 mg/kg. Formaldehyde was detected in milk samples collected in the treatment groups at average concentrations of 0.034, 0.095, and 0.208 mg/kg in the three trials; however, levels were below the detection limit

prior to beginning each trial and at 46 hours after the end of trial 3. During the first trial, formaldehyde was detected in milk samples from only 3 of the 6 cows. Formaldehyde concentrations did not increase over time and there was no significant effect due to day of milk collection during any of the trials. Concentrations in blood were significantly higher ($P < 0.01$) in the treatment group at day 33 of trial 3 compared with the control group. In another experiment, bull calves were fed diets containing 0, 0.05%, or 0.1% formalin and sacrificed at days 81, 88, and 95. Formaldehyde concentrations were measured in blood, muscle, kidney, liver, and heart tissue. Formaldehyde concentrations were higher in the muscle tissue of the high-dose group but did not differ among treatment groups in the other tissues. About 0.0038% to 0.0067% of ingested formaldehyde was eliminated in the milk. Barry and Tomé (1991) also reported a dose-related increase in formaldehyde concentrations in milk from goats fed 0, 0.63, or 1.26 g of formaldehyde daily in soybean oil-meal. Approximately 0.02% of the ingested formaldehyde was excreted in the milk.

Nishi *et al.* (1988) published a case report of a 52-year-old man that had committed suicide apparently by ingesting formalin. There was an obvious odor of formaldehyde in the stomach and air passages. Formaldehyde and formic acid were detected in the serum, brain, heart, lungs, liver, spleen, pancreas, kidneys, and gastric contents (Table 5-3). Formic acid is the primary metabolite of formaldehyde (see Section 5.3). The urine contained methanol, but neither formic acid nor formaldehyde were detected. These authors also conducted a study in two male rabbits that were administered an oral dose of 15 mL/kg b.w. of formalin. These animals died after 12 minutes. Formaldehyde, methyl alcohol, and formic acid were detected in serum, brain, heart, lungs, liver, spleen, and kidneys (Table 5-3).

Table 5-3. Formaldehyde and formic acid concentrations detected in body fluids and tissues following formaldehyde ingestion

	Concentration (µmol/g)			
	Human[a]		Rabbits[b]	
Tissue/body fluid	Formaldehyde	Formic acid	Formaldehyde	Formic acid
Brain	1.5	5.39	4.33–6.63	3.60–5.12
Heart	1.63	11.60	1.70–1.87	9.42–10.59
Lungs	0.77	13.99	0.40–0.53	14.19–14.68
Liver	5.63	16.44	10.76–23.48	21.39–24.71
Spleen	6.89	11.48	1.80–2.00	5.80–5.93
Pancreas	11.09	14.42	NR	NR
Kidneys	1.4	11.54	5.71–5.86	14.82–15.53
Gastric contents	233.10	ND	NR	NR
Serum	1.10	11.79	6.39–7.03	9.75–11.48
Urine	ND	ND	NR	NR

Source: Nishi *et al.* 1988.
ND = not detected; NR = not reported.
[a]52-year-old male suicide case.
[b] Range for two rabbits.

5.1.2.3 Dermal exposure

Very few studies have investigated absorption and distribution of formaldehyde following dermal exposure, but the available data indicate that formaldehyde is poorly absorbed from the skin. However, Maibach (1983) noted that if some amount of formaldehyde or its metabolites did not penetrate, allergic contact dermatitis could not occur (see Section 5.4.2.2). Jeffcoat *et al.* (1983) administered 10 µL of an aqueous solution containing 0.1 mg of ^{14}C-formaldehyde or 40 µL containing 11.2 mg of ^{14}C-formaldehyde to the skin of F344 rats or Dunkin-Hartley guinea-pigs (5 to 6 males and females per group), and 2 mg in 200 µL to three cynomolgus monkeys. Urine, feces, expired air, and evaporation products were collected. Blood samples were collected from a catheter implanted in the carotid artery at 1, 2, 3, 4, 7, and 24 hours after dosing. Animals were sacrificed 72 hours after dosing, and tissue samples from the heart, liver, lung, spleen, kidney, leg, brain, gonads, skin at the application site, distant skin, and the remaining carcass were analyzed for ^{14}C content. The mean values of recovered ^{14}C are shown in Table 5-4. There was no accumulation of ^{14}C in any tissue in any species. Blood concentrations were stable throughout the experiment, averaging about 0.015% of the administered dose in monkeys and about 0.1% of the dose in rats and guinea-pigs. In rats and guinea pigs, about 4.5% to 8.3% of the applied radioactivity was detected in the urine, 0.7% to 1.5% in the feces, and 21.4% to 28.3% in the air traps; 22.2% to 28.4% remained in the carcass. Almost the entire air-trapped radioactivity was due to evaporation from the skin because less than 3% was $^{14}CO_2$. The amount of radioactivity remaining in the skin ranged from 3.8% to 15.6% in guinea-pigs and 3.4% to 16.2% in rats. Although the percentage of the dose remaining in the skin was lower for the high dose, the actual amount of radioactivity was still higher compared with the low dose. In monkeys, about 0.24% of the applied dose was excreted in the urine, 0.2% was excreted in the feces, 0.37% was exhaled, and about 9.5% remained in the skin at the site of application. Data were not reported for the amount remaining in the carcass of monkeys. The authors concluded that the skin of the monkey was much less permeable to formaldehyde than that of rodents, and that the large majority of applied radiolabel was lost to evaporation.

Table 5-4. Distribution of ^{14}C-labeled formaldehyde in rodents and monkeys during the first 72 h after topical administration[a]

Species	Dose (mg)	Air traps	Urine	Feces	Skin (application site)	Carcass	Total ^{14}C recovered	Mean blood content
Rat	0.1	28.3 ± 2.4	5.0 ± 0.6	1.5 ± 0.5	16.2 ± 1.4	22.2 ± 1.2	73.4 ± 3.1	0.12 ± 0.01
Guinea-pig	0.1	21.4 ± 1.6	4.5 ± 1.0	1.4 ± 0.2	15.6 ± 2.5	27.1 ± 1.7	70.0 ± 3.7	0.10 ± 0.02
Rat	11.2	22.1 ± 2.6	8.3 ± 1.0	0.7 ± 0.1	3.4 ± 0.4	25.9 ± 1.9	60.4 ± 2.6	0.13 ± 0.01
Guinea-pig	11.2	23.8 ± 3.1	6.8 ± 1.1	1.2 ± 0.4	3.8 ± 0.5	28.4 ± 1.6	63.6 ± 2.6	0.09 ± 0.01
Monkey	2.0	0.37 ± 0.17	0.24 ± 0.1	0.2 ± 0.12	9.49 ± 3.9	NA	[~10]	0.015 ± 0.0006

Source: Jeffcoat *et al.* 1983.
NA = not analyzed.
[a]Data are reported as % of administered dose ± SE.

Bartnik *et al.* (1985) applied ^{14}C-formaldehyde and non-labeled formaldehyde mixed into a cream at a concentration of 0.1% to the clipped backs of male and female rats. Radioactivity was measured in feces, urine, expired air, carcass, and treated skin. Between 60% and 70% of the radioactivity remained in the skin. Levels in the urine ranged from about 1.2% to 3.5% of the applied radioactivity. Feces contained 0.2% to 0.8%, and the expired air contained 0.8% to 1.3% of the applied radioactivity.

Iverson *et al.* (1986) treated Oslo hairless mice with topical applications of 200 µg of 1% or 10% formaldehyde on the back skin twice a week, and mice were observed for 60 weeks. (No blood or tissue samples were examined for the presence of formaldehyde or its metabolites.) Slight hyperplasia of the epidermis was reported for animals treated with 10% formaldehyde. A few animals had small skin ulcers or scratches, and two animals had small nonspecific granulomas in the lungs. No lesions were reported in the brain or other tissues. (See Section 4.2.2.)

5.1.2.4 Parenteral and transplacental exposure

Keefer *et al.* (1987) injected ^{14}C-labeled formaldehyde and sodium formate intraperitoneally into male Sprague-Dawley rats and measured the cumulative excretion of carbon dioxide. Approximately 70% of the administered dose was excreted as carbon dioxide within the first 12 hours. The data showed that excretion was biexponential with half-lives of approximately 0.4 hours and 3 hours for the two phases.

Katakura *et al.* (1993) administered ^{14}C-formaldehyde intravenously to pregnant mice and measured the distribution in maternal and fetal tissues and blood. Radioactivity was found immediately after injection and showed strong accumulation and retention 3 hours after injection. Maternal liver, intestinal mucosa, bone marrow, kidneys, and salivary glands showed the highest activity. Radioactivity was found in the fetus 6 hours after injection at concentrations similar to those in maternal tissues. Elimination of radioactivity from the placenta and fetus was slower than from maternal tissues.

Thrasher and Kilburn (2001) also investigated the distribution of ^{14}C-labeled formaldehyde in maternal and fetal tissues. Pregnant ICR mice were injected with 0.05 mL of a 1% formalin solution that contained 3.5 mg of labeled compound via the tail vein on the 16th day of gestation. The animals were killed at intervals from 5 minutes up to 48 hours. There was a rapid uptake of radioactivity into maternal liver, lung, heart, salivary glands, gall bladder, spleen, kidney, bone marrow, nasal mucosa, uterus, placenta, and fetal tissues. The placenta, uterus, and fetal tissues had the highest concentrations, and the fetal brain had twice the concentration of radioactivity that was observed in the maternal brain. Radioactivity appeared in urine and feces up to 6 hours after treatment. The DNA fraction from maternal and fetal liver contained 20% and 50% of the total radioactivity, respectively after 6 hours. These values showed little change at 24 hours. Elimination was slower from fetal tissues than maternal tissues.

5.2 Airway deposition models

Morgan and Monticello (1990) reviewed the literature on the site specificity of nasal lesions induced by exposure to inhaled gases with special reference to nasal airflow and

effects of formaldehyde. These authors reported that the distribution of nasal lesions is influenced by the regional deposition of inhaled material, local tissue susceptibility, or a combination of these factors. Nasal airflow patterns are particularly important in determining lesion distribution for highly water-soluble or reactive gases such as formaldehyde. Their review suggested that differences in nasal airflow patterns in rats and monkeys were likely responsible for the characteristic differences in the distribution of nasal lesions induced by formaldehyde in these species. This hypothesis has since been investigated by several researchers using three-dimensional, anatomically accurate, computational fluid dynamics (CFD) models.

It is very difficult to determine formaldehyde uptake patterns in nasal passages of experimental animals because of its rapid metabolism and reactivity, and because of the low resolution of dissection techniques used to obtain tissues samples from different locations in the rat nasal epithelium (Kimbell *et al.* 2001a). Therefore, CFD models of the nasal passages of the rat, monkey, and human have been developed (1) to determine the primary factors affecting nasal uptake, (2) to make interspecies dosimetric comparisons, (3) to provide detailed anatomical information for the nasal passages of these species, and (4) to provide estimates of regional air-phase mass transport coefficients (a measure of the resistance to gas transport from inhaled air to airway walls) in the nasal passages (Kimbell and Subramaniam 2001). These models allow investigators to examine the relationship between the delivered dose at various sites in the respiratory tract to biomarkers of dose or effect (e.g., DNA-protein crosslinks or regional cell proliferation) (Kimbell *et al.* 2001a). This section provides a brief review of these models. Section 5.7 discusses how these models have been used to predict crosslink and tumor formation in rats, monkeys, and humans.

CFD models have been developed for the F344 rat (Kimbell *et al.* 1993, 1997), rhesus monkey (Kepler *et al.* 1998), and human (Subramaniam *et al.* 1998) with the primary objective of improving human health risk assessment. These models were developed in three stages: (1) computer reconstructions of the nasal passages using sequential cross-sectional data, (2) simulation of steady-state inspiratory airflow for several volumetric flow rates (predicted flow streams and velocities from the simulations were compared with observations and measurements made in hollow molds), and (3) simulation of regional formaldehyde flux resulting from inspiratory airflow patterns and absorption characteristics of the gas (Kimbell and Subramaniam 2001). None of the papers cited above mention calibration of the models; however, according to Kimbell and Subramaniam (2001), two sets of data were used to calibrate and confirm formaldehyde uptake simulations. The first set of data consisted of overall formaldehyde uptake measured in rat nasal passages as reported in an abstract (Patterson *et al.* 1986). A proportionality constant between the wall absorption rate and air-phase concentration adjacent to the nasal wall was estimated so that the overall formaldehyde uptake predicted in the rat CFD model was consistent with uptake data. The proportionality constant was assumed to be associated with solubility and was used in all uptake simulations for the rat, monkey, and human. The second set of data consisted of DNA-protein crosslinks measured in the entire respiratory epithelium, or in two separate regions of the nasal passages of exposed rats as reported by Casanova *et al.* (1989, 1994).

A physiologically based pharmacokinetic model was calibrated using the entire respiratory epithelium data.

CFD models use mathematical descriptions to simulate movement of inspired air in respiratory air spaces and movement of inhaled chemical within air spaces via airflow and diffusion (Kimbell *et al.* 1993). The concentrations of a chemical of interest that are distributed throughout the respiratory tract are simulated by solving these equations. The method involves dividing the nasal cavity into geometrically simple three-dimensional elements to obtain a wire-frame grid of the nasal passage. The mass transport equations are solved in each element, and the elements are reassembled to produce simulated flow and transport throughout the entire grid. Air-phase delivery is calculated as the mass flux of inhaled chemical at specific sites within the airway and incorporates airflow patterns and air-phase diffusion.

The CFD models have been used to test the hypothesis that the distribution of formaldehyde-induced lesions can be attributed to species-specific patterns in formaldehyde flux to various regions of the upper respiratory tract (Kimbell and Subramaniam 2001). These studies show a strong correspondence between simulated airflow-dependent transport patterns and local nasal lesion sites (see Section 5.7).

5.3 Metabolism

As discussed above, inhaled formaldehyde is absorbed rapidly by the epithelial cells of the nasal mucosa of mammalian species. Once inside the epithelial layer, formaldehyde binds rapidly and reversibly to glutathione and forms *S*-hydroxymethylglutathione (IARC 2006). This reactive conjugate is detoxified in a reaction catalyzed by formaldehyde dehydrogenase (FDH) (also known as alcohol dehydrogenase 3 [ADH3] which results in the formation of *S*-formylglutathione. This latter metabolite is converted to formic acid and glutathione by *S*-formylglutathione hydrolase [Figure 5-1].)

ADH3 is the same enzyme as glutathione-dependent formaldehyde dehydrogenase, which is officially designated "ADH5 alcohol dehydrogenase 5 (class III), chi polypeptide" (EC 1.1.1.1). Other names include ADHX, *S*-nitrosoglutathione reductase (GSNO), and FDH. The ADH5 gene is ubiquitously expressed in human tissues, albeit with tissue-specific variation in levels of expression; it has been measured in all human tissues from embryos through adults (Thompson *et al.* 2008). Therefore, formaldehyde metabolism can occur throughout the body (ATSDR 1999). Øvrebø *et al.* (2002) demonstrated that cultured human bronchial epithelial cells have formaldehyde biotransforming activity similar to that of hepatocytes and are capable of oxidizing formaldehyde at a relatively fast rate at concentrations up to 3 mM. Casanova-Schmitz *et al.* (1984b) tentatively identified both FDH and aldehyde dehydrogenase in nasal mucosal tissues from the rat nose and showed that homogenates from both respiratory and olfactory epithelia efficiently oxidized formaldehyde. ADH5 is polymorphic, and several studies have identified polymorphisms that may be functional including (but not limited to) (1) a SNP in the promoter region, which was associated with decreased transcriptional activity (Hedberg *et al.* 2001), and (2) a common haplotype (frequency 41.8%) and two SNPs that were associated with increased risk of childhood asthma in a study of Mexican children (Wu *et al.* 2007). The health impacts of these polymorphisms have not been evaluated.

Other enzymes that may catalyze the oxidation of formaldehyde to formate include catalase, aldehyde dehydrogenase, xanthinoxidase, peroxidase, aldehyde oxidase, and glycerinaldehyde-3-phosphate dehydrogenase (WHO 1989). The contribution of aldehyde dehydrogenases (ALDHs) increases with increasing concentrations of formaldehyde (IARC 2006).

Formate, the primary metabolite of formaldehyde, enters the one-carbon pool, and can either be excreted in the urine as the sodium salt, or be further oxidized to carbon dioxide and exhaled (ATSDR 1999). Elimination of formate shows intra- and interspecies variability, but elimination is generally slower than its formation. The plasma half-life of formate in mammals ranges from about 1 to 90 minutes, with humans near the middle of the range (WHO 1989). Øvrebø *et al.* (2002) investigated the capacity of human bronchial epithelial cells and rat hepatocytes to metabolize formaldehyde to formate. Normal human bronchial explants, primary bronchial epithelial cells, and rat hepatocytes were grown in medium containing 0.5 to 5 mM formaldehyde for up to 48 hours. Human bronchial explants and epithelial cells were shown to metabolize formaldehyde to formate at a relatively fast rate, which was comparable with that measured for rat hepatocytes.

Unmetabolized formaldehyde also may react non-enzymatically with sulfhydryl groups, urea, or amino groups (Bolt 1987). Hydroxymethyl adducts (methylol groups) are formed with urea, and thiazolidine-4-carboxylic acid is formed with cysteine (Figure 5-2). These adducts can be detected in the urine of formaldehyde-treated animals. Reaction of formaldehyde with amino groups in amino acids was reported by Metz *et al.* (2004), who treated model peptides with excess formaldehyde and analyzed the reaction products by liquid chromatography/mass spectrometry. They demonstrated that formaldehyde reacted with the amino group of the *N*-terminal amino acid residue and side-chains of arginine, cysteine, histidine, and lysine residues. Three types of chemical modifications (methylol groups, Schiff-bases, and methylene bridges) were identified and were dependent on the peptide sequence. Formaldehyde first reacts with an amino or thiol group of amino acids and forms hydroxymethyl adducts (methylol groups). In some cases these protein adducts with formaldehyde can undergo further reactions to form crosslinks with other amino acids or with deoxynucleotides in DNA (see Figure 5-2). Methylol adducts of primary amino groups can undergo condensation to form an imine (also called a Schiff-base). Further, the Schiff-bases can form methylene bridges and crosslink with other amino acid residues (e.g., glutamine, aparagine, tryptophan, histidine, arginine, cysteine, and tyrosine). In addition to these protein-protein crosslinks, methylene bridges also may result in protein-DNA crosslinks or nucleic acid-nucleic acid crosslinks (Figure 5-2).

The genetic effects of formaldehyde (see Section 5-6) are probably linked to the reactivity of formaldehyde with amino groups of nucleic acids. Exocyclic amino groups of purines are especially susceptible. Zhong and Que Hee (2004a,b, 2005) showed that formaldehyde caused N^6-dA, N^2-dG, and N^4-dC adducts in human epithelial cells and placental DNA. DNA adducts with formaldehyde also can react further in some instances with other nucleotides to form DNA-DNA crosslinks (see Figure 5-2). Huang *et al.* (1992) and Huang and Hopkins (1993) reported that formaldehyde preferentially forms

dA-to-dA crosslinks at the dinucleotide sequence 5′-d(AT) in certain AT-rich sequences of duplex DNA.

Formaldehyde, as well as formate (see above), can combine with tetrahydrofolate enzymatically and enter the single-carbon intermediary metabolic pool (IARC 2006) (see Figure 5-2). Because binding to tetrahydrofolate is reversible, there is a physiological presence of formaldehyde in all cells.

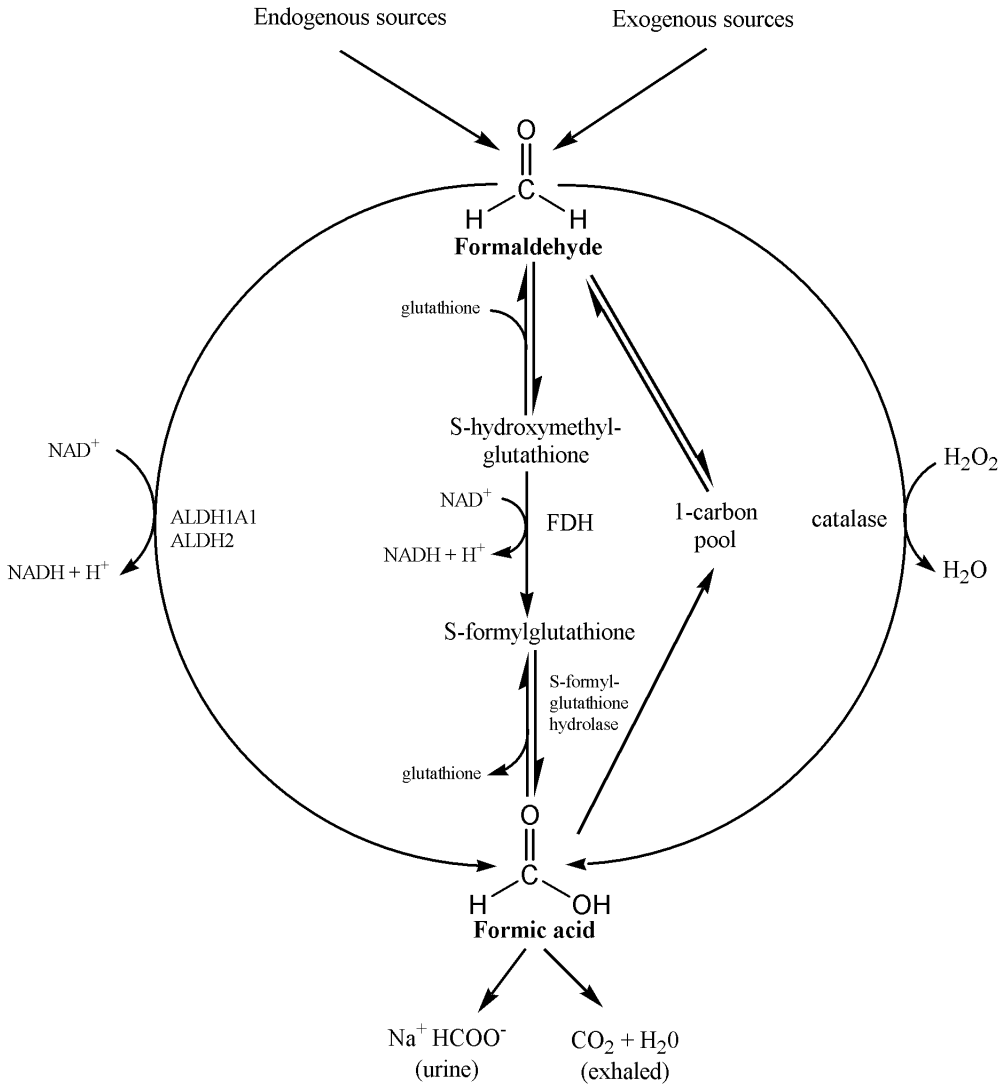

Figure 5-1. Metabolism and fate of formaldehyde
Adapted from IARC 2006.

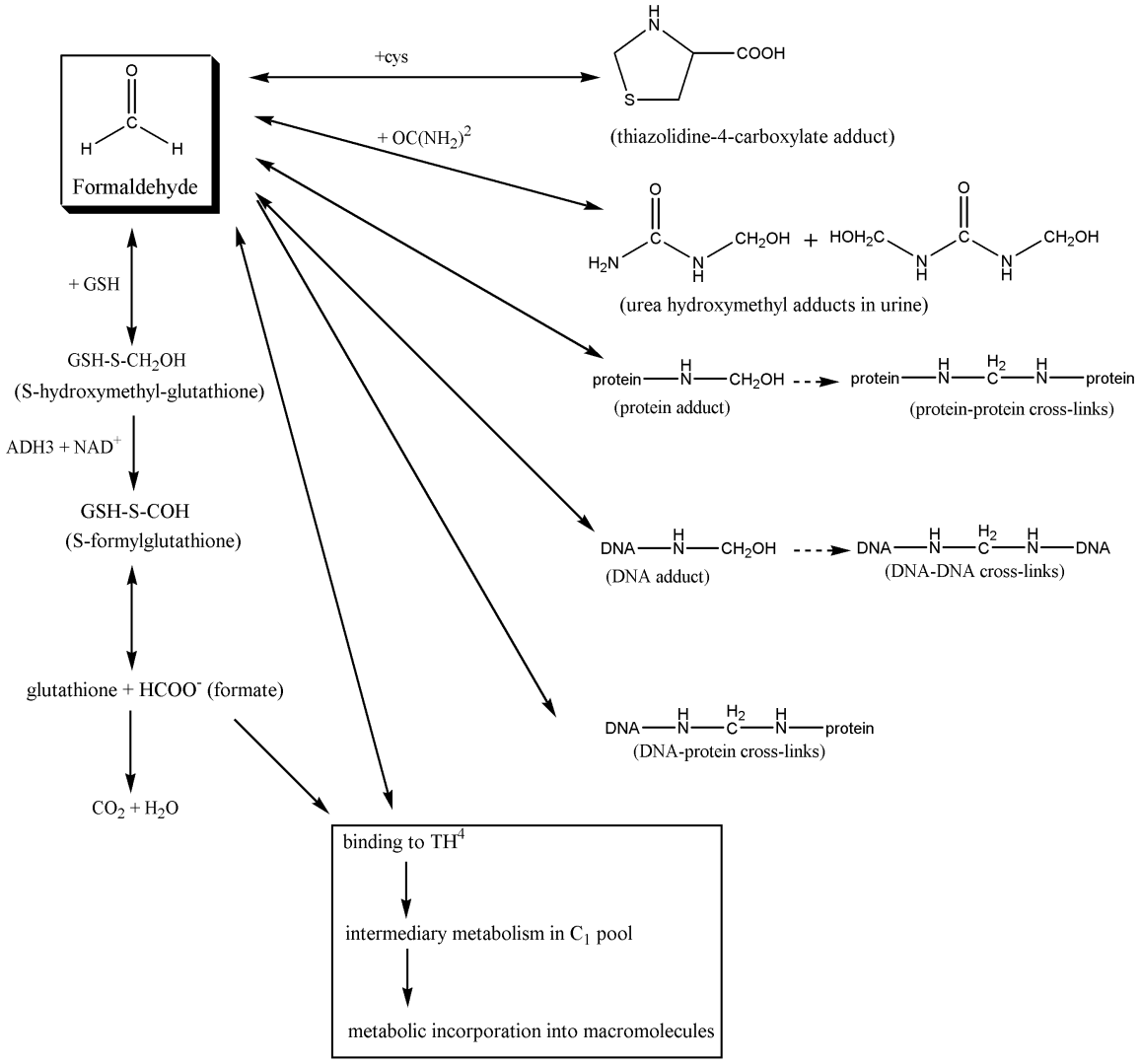

Figure 5-2. Biological reactions of formaldehyde

Adapted from Bolt 1987: cys = cysteine, C_1 = single carbon pool, TH^4 = tetrahydrofolate.

5.4 Toxic effects

The toxicity of formaldehyde has been extensively reviewed (ATSDR 1999, WHO 2002, IARC 2006); however, the exact mechanisms are not completely understood. Although formaldehyde is a normal intermediary cellular metabolite, it is cytotoxic at high concentrations (≥ 6 ppm in the rat and rhesus monkey) (Chang *et al.* 1983, Monticello *et al.* 1991, Casanova *et al.* 1994, Monticello *et al.* 1996). The carbonyl atom of formaldehyde is electrophilic; thus, it readily reacts with nucleophilic sites on cell membranes and in body tissues such as amino groups in protein and DNA (ATSDR 1999). This section provides an overview of the toxic effects reported from *in vitro* studies, humans, and experimental animals. The following discussion summarizes the findings from the IARC (2006) and other reviews, as well as relevant studies published after the IARC review.

5.5 *In vitro* toxicity studies

In vitro studies conducted with human and animal cells demonstrate that formaldehyde is cytotoxic, and affects cell proliferation, gene expression, apoptosis, and the mucociliary apparatus (IARC 2006).

Schäfer *et al.* (1999) showed a reduced frequency of ciliary beat in cultured human nasal epithelial cells exposed to 5,000 μg/m^3 [4 ppm] for 2 hours but no effect when exposed to 5,000 μg/m^3 [4 ppm] for 1 hour or 500 μg/m^3 [0.4 ppm] for 2 hours.

Lovschall *et al.* (2002) investigated the cytotoxic effects of formaldehyde in human dental pulp fibroblasts, human buccal epithelial cells, and HeLa cervical cancer cells. The purpose of this study was to compare the relative sensitivity of human target tissue cells with that of an established human cancer cell line. Dose-response relationships and TC_{50} values were determined using three different assays: bromodeoxyuridine (BrdU) incorporation, neutral red uptake, and methylthiazole tetrazolium (MTT) conversion. Cell cultures were exposed for 24 hours to graded formaldehyde dilutions based on TC_{50} estimates obtained in pilot studies for each cell type. Dental pulp fibroblasts and buccal epithelial cells had significantly lower TC_{50} values in both the BrdU and neutral red assays compared with HeLa cells. There were no statistically significant differences among the cell types with the MTT assay. Overall dental pulp fibroblasts and buccal epithelial cells appeared to be more sensitive to formaldehyde toxicity than HeLa cells.

Other *in vitro* studies reported effects on glutathione levels and oxidative stress. These studies are discussed in Section 5.7.4.

5.5.1 Toxic effects in humans

A wide range of health effects have been associated with exposure to formaldehyde in both residential and occupational settings. These effects are summarized below and are route dependent. The most common effects include irritation at the point of contact following inhalation (upper respiratory tract and eyes), oral (mouth and gastrointestinal tract), or dermal exposure (skin and eyes). Other effects include allergic contact

dermatitis, histopathological abnormalities (e.g., hyperplasia, squamous metaplasia and mild dysplasia) of the nasal mucosa, occupational asthma, reduced lung function, neurophysiological disorders (e.g., insomnia, memory loss, mood alterations, and loss of appetite), and altered blood cell counts and immunological parameters. Formaldehyde concentrations associated with reported effects in humans show wide interindividual variation as illustrated in Table 5-5. Although some symptoms have been reported at concentrations as low as 0.05 ppm (primarily sensory irritation), they occur only rarely at concentrations below 0.5 ppm (IARC 2006). Paustenbach *et al.* (1997) reviewed approximately 150 articles in order to recommend an occupational exposure limit for formaldehyde based on irritation. They reported that eye irritation did not occur in most people at concentrations < 1 ppm, and that moderate to severe irritation did not occur until airborne concentrations exceeded 2 to 3 ppm. Persons exposed to 0.3 ppm for 4 to 6 hours in chamber studies reported eye irritation at a rate similar to that reported by persons exposed to clean air. Arts *et al.* (2006) also reviewed data on respiratory irritation of formaldehyde and reported that mild/slight eye irritation was observed at levels ≥ 1 ppm, and mild/slight respiratory tract irritation at levels ≥ 2 ppm. As listed in Table 5-5, Newell (1983) reported that neurophysiological effects, odor threshold, and eye irritation could occur at formaldehyde concentrations as low as 0.05 ppm, and upper airway irritation at 0.1 ppm and greater.

Table 5-5. Formaldehyde concentrations associated with various health effects

Reported effects	Formaldehyde concentration (ppm)
Neurophysiological effects	0.05–1.05
Odor threshold	0.05–1.0
Eye irritation	0.05–2.0
Upper airway irritation	0.1–25
Lower airway and pulmonary effects	5.0–30
Pulmonary edema, inflammation, pneumonia	50–100
Death	≥ 100

Source: Newell 1983.

5.5.1.1 Inhalation exposure

Inhalation is an important exposure pathway for formaldehyde in occupational, domestic, and environmental settings. In addition to the epidemiologic studies and case reports, a number of controlled studies of human exposure to formaldehyde have been conducted. The most common and consistently reported effects include sensory and airway irritation. Some studies indicate an association with occupational asthma. Effects associated with acute and chronic exposures are discussed. Studies that indicate an association with occupational asthma are reviewed briefly in a separate section.

Acute exposure

IARC reviewed 10 controlled experimental studies of acute inhalation exposure to formaldehyde (Table 5-6). These studies included healthy individuals, asthmatics, and individuals with allergic symptoms due to exposure to formaldehyde. These individuals were exposed to 0.4 to 3 ppm formaldehyde for 30 minutes to 3 hours. Reported effects included eye, nose, and throat irritation; nasal itching; congestion; and sneezing. Nasal itching and congestion occurred at exposures as low as 0.5 mg/m^3 [0.41 ppm] for 2 hours (Pazdrak *et al.* 1993, Krakowiak *et al*. 1998, both as cited in IARC 2006). Eye irritation was reported to increase linearly at doses from 0.5 to 3.0 ppm, but no effects were observed at 0.5 ppm (Kulle *et al.* 1987, Kulle 1993, both as cited in IARC 2006). Exposure to 3 ppm for 1 hour while exercising resulted in moderate to severe eye irritation in 27% of healthy subjects and 19% of asthmatics. Moderate to severe nose and throat irritation occurred in 32% of the healthy subjects and 31% of asthmatics (Green *et al.* 1987, as cited in IARC 2006). IARC (2006) also cited a review by Bender *et al*. (2002) who reviewed 9 controlled chamber studies of asthmatic subjects. Exposure to 2 to 3 ppm for up to 3 hours did not provoke asthma in unsensitized asthmatics, and exposure to 0.1 to 3 ppm did not provoke asthma in men or women who reported chest tightness, cough, and wheeze when exposed to formaldehyde at home or work. All of the studies reviewed by IARC (2006) were published later than the studies summarized by Newell (1983) in which even lower thresholds for irritation to the eyes (0.05 to 2.0 ppm) and upper airways (0.1 to 25 ppm) were reported.

Table 5-6. Irritant effects of formaldehyde following acute inhalation exposures

Subjects (no.)	Exposure, in ppm	Results	References (as cited in IARC 2006)
Healthy (22) Asthmatics (16)	3 (1 h)	Moderate to severe symptoms in both groups Eye (27%), nose/throat (32%) (healthy) Eye (19%), nose/throat (31%) (asthmatics)	Green *et al.* 1987
Healthy (10) Asthmatics[a] (10)	0.5 (2 h)	Nasal itching and congestion in all subjects Avg. score 4.3 (0 – 7 point scale, healthy) Avg. score 4.6 (asthmatics)	Krakowiak *et al.* 1998
Healthy (19)	3 (3 h)	Eye irritation increased linearly with dose; mild nose and throat irritation threshold at 1 ppm [1.2 mg/m^3]	Kulle 1993, Kulle *et al.* 1987
Healthy (11) Contact dermatitis (9)	0.5 (2 h)	Mean nasal score (sneezes, itching and congestion) of 4 at 10 minutes in both groups	Pazdrak *et al.* 1993
Healthy (9)	3 (3 h)	Increase in mean symptom scores for eyes, nose and throat irritation after exposure	Sauder *et al.* 1986
Asthmatics (9)	3 (3 h)	Eye and nose irritation after 2 min	Sauder *et al.* 1987
Healthy (15)	2 (40 min)	Odor (80%), sore throat and nasal irritation (0%), eye irritation (47%)	Schachter *et al.* 1987
Asthmatics (15)	2 (40 min)	Odor (100%), sore throat (33%), nasal irritation (47%), eye irritation (73%)	Witek *et al.* 1987
Healthy (9) Asthmatics[b] (9)	3 (2 h) 1 (90 min) 2 (30 min)[c]	Eye (83%), nose (39%) and throat (28%) irritation; no significant differences between groups	Day *et al.* 1984

Adapted from IARC 2006.
[a]Subjects had allergic symptoms due to formaldehyde exposure.
[b] Subjects with urea-formaldehyde foam insulation symptoms.
[c]Exposure to urea-formaldehyde foam insulation.

Nasal lavage studies of workers who had skin hypersensitivity (positive patch test) to formaldehyde and healthy men with a negative patch test showed similar responses following a 2-hour exposure to 0.5 mg/m^3 [0.41 ppm] formaldehyde (Pazdrak *et al.* 1993). In both groups, eosinophils peaked shortly after exposure and were still elevated after 18 hours, while the percentage of epithelial cells was reduced. Albumin levels also were increased. The authors concluded that a non-specific, non-allergic pro-inflammatory effect occurred from exposure to low concentrations (0.5 mg/m^3 [0.41 ppm]) of formaldehyde.

Lang *et al.* (2008) conducted a controlled study in Germany of sensory irritation in 21 healthy volunteers (11 males and 10 females) exposed to formaldehyde. Each subject was exposed for 4 hours to each of 10 selected exposure conditions on 10 consecutive working days. The 2-week exposure sequences were randomized. Formaldehyde concentrations ranged from 0 to 0.5 ppm. During three of the exposures, the concentration of formaldehyde was doubled to generate intermittent exposure to peak concentrations four times during the exposure period. Once the peak concentration was

reached, forced ventilation of the exposure chamber was used to reduce the concentration back to the desired base level. During 4 of the 10 exposures, ethyl acetate at 12 to 16 ppm was used as a masking agent for formaldehyde. Measurements included conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function, and reaction times. There were no significant treatment effects on nasal flow and resistance, pulmonary function, and reaction times. Blinking frequency and conjunctival redness were significantly increased by short-term peak exposures of 1 ppm. Subjective ratings indicated eye and olfactory symptoms at concentrations as low as 0.3 ppm. Eye irritation was the most sensitive parameter. All increased symptom scores returned to normal levels 16 hours after the end of the exposures.

Tang *et al.* (2009) reported that 17 employees at a pharmaceutical company in China who were continuously exposed to formaldehyde vapors experienced what the authors describes as acute poisoning. The workers showed symptoms of eye irritation, tearing, sneezing, coughing, chest congestion, fever, heartburn, lethargy, and loss of appetite. Some of the workers also experienced vomiting, abdominal pain, and tachycardia.

Chronic exposure

IARC (2006) reviewed six occupational studies (Berke 1987, Edling *et al.* 1987a, 1988, Holmström *et al.* 1989b, Boysen *et al.* 1990, Ballarin *et al.* 1992) and one residential study with a one-year follow-up (Broder *et al.* 1988, 1991) that investigated the effects of chronic inhalation exposure to formaldehyde on the nasal mucosa (Table 5-7). The average length of employment ranged from 10 to 20 years in the occupational studies. Time-weighted average exposure levels ranged from 0.007 to 2.0 ppm with a peak concentration as high as 15 ppm. The most common effects on the nasal mucosa in the exposed groups were loss of cilia, goblet-cell hyperplasia, and squamous metaplasia. Irritation of the upper respiratory tract and eyes was also common among the exposed groups. Histological scores, based on severity of effect, were significantly higher in the exposed group compared with matched controls in most of the occupational studies (Edling *et al.* 1987a, 1988, Holmström *et al.* 1989b, Ballarin *et al.* 1992); however, there was not always a clear association with exposure to formaldehyde [i.e., no concentration-response relationship or no correlation between histological score and duration of exposure] (Edling *et al*. 1988, Holmström *et al.* 1989b). Two of the six occupational studies did not show significant differences between the exposed and control groups (Berke 1987, Boysen *et al*. 1990). Atypical squamous metaplasia was associated with age but not with formaldehyde in at least one study (Berke 1987). The residential study reported that the prevalence of squamous metaplasia was significantly increased in occupants of urea-formaldehyde foam-insulated homes compared with subjects who lived in homes without this type of insulation (Broder *et al.* 1988, 1991).

IARC (2006) also reviewed three studies (Kriebel *et al.* 1993, Akbar-Khanzadeh *et al.* 1994, Akbar-Khanzadeh and Mlynek 1997) that investigated the effects of formaldehyde exposure on lung function in groups of physical therapy or medical students and their instructors. Pulmonary function (peak expiratory flow or forced expiratory volume in 1 second) was measured before and after completing laboratory sessions, or was compared

with a group of unexposed controls. Formaldehyde concentrations ranged from about 0.07 to 2.94 ppm. These studies included 24 to 50 subjects that were exposed to formaldehyde during anatomy classes. Eye nose and throat irritation were common in the exposed groups. Formaldehyde exposure was associated with lung function decrements in all three studies.

In a review of occupational formaldehyde exposure in China, Tang *et al.* (2009) identified six reports of pulmonary disorders in factory workers chronically exposed to formaldehyde. One study reported that workers exposed to 3.07 ± 5.83 mg/m^3 [2.5 ± 4.7 ppm] had decreased pulmonary ventilation compared with a control group. Another study reported that chronic exposure to a lower concentration (1.3 mg/m^3) [1 ppm] significantly decreased mid-expiratory airflow and forced vital capacity values (data not reported). Other studies showed exposure-related increases in pulmonary damage over time, more abnormalities in the small airways, and higher resistance to pulmonary ventilation.

Lyapina *et al.* (2004) reported a statistically significant ($P = 0.02$) predominance of subjective symptoms and clinical findings of chronic upper respiratory tract inflammation among 29 workers (13 men and 16 women) occupationally exposed to formaldehyde for an average of 12.7 years. Results were compared with 21 non-exposed, age- and gender-matched controls. Further details of this study are provided in Section 5.4.2.

Table 5-7. Effects on the nasal mucosa from chronic exposure to formaldehyde

Exposure setting	Concentration[a] (ppm)	No.	Histological score[b]	Comments	Reference
Laminate plant	0 [0.4–0.9]	25 38	1.8 2.8*	Smoking had a slight modifying effect; no correlation of histological score and exposure duration; four cases of mild dysplasia in the exposed group	Edling *et al.* 1987a
Particle board or laminate plant	0 [0.08–0.9] (peaks to 4)	25 75	1.8 2.9*	Some exposure to wood dust, but no dose-response relationship; no differences between workers exposed only to formaldehyde compared with those exposed to formaldehyde and wood dust; six exposed men had mild dysplasia	Edling *et al.* 1988
Phenol-formaldehyde resins used in paper processing	0 [0.02–2.0] (peaks to [8.9–15])	38 42	NR	Higher prevalence of mucosal irritation was reported in non-smoking exposed workers compared with controls ($P = 0.04$); however, cytologic exams did not show a statistical relationship to formaldehyde exposure	Berke 1987
Formaldehyde and formaldehyde resins production plant	0 0.5–> 2.0	37 37	1.4 1.9	Incidence of subjective nasal complaints was significantly higher ($P < 0.01$) in the exposed group, mild dysplasia in 3 exposed workers	Boysen *et al.* 1990
Formaldehyde resin or particle board production	0 [0.04–0.4] [0.19–0.59]	32 62 89[b]	1.56 2.16* 2.07[c]	No correlation between duration of exposure and histological changes, 2 cases of dysplasia among particle board workers who ground wood for > 4 h/d	Holmström *et al.* 1989b
Plywood factory and warehouse	0 [0.08–0.32]	15 15	1.6 2.3**	Co-exposure to wood dust, significantly higher ($P < 0.01$) incidence of micronuclei in exposed workers, one case of mild dysplasia in the exposed group	Ballarin *et al.* 1992
Residential (homes with and without urea-formaldehyde foam insulation)	[0.006–0.11] [0.007–0.23]	720 1,726	NR	Positive relationships between level of exposure and the presence of symptoms, a number of exposure-response relationships were enhanced by urea-formaldehyde, small but significant increase in incidence of squamous-metaplasia in occupants of urea-formaldehyde insulated homes	Broder *et al.* 1991, 1988

Adapted from IARC 2006.
*$P < 0.05$; **$P < 0.01$.
NR = not reported.
[a]Time-weighted average concentrations for occupational settings.
[b]Several different scales were used by the authors. Edling *et al.* 1987, 1988 and Holmström *et al.* 1989b used an 8-point scale (0 = normal to 8 = carcinoma); Boysen *et al.* 1990 used a 5-point scale (0 = pseudostratified columnar epithelium to 5 = dysplasia), and Ballarin *et al.* 1992 used a 6-point scale (1 = normal cellularity to 6 = malignant cells).
[c]Co-exposed to wood dust.

Occupational asthma

Inhalation exposure to formaldehyde has also been identified as a potential cause of occupational asthma. IARC (2006) reviewed eight studies (some were case reports) of occupational asthma in workers (Table 5-8). Hypersensitivity is thought to be the likely mechanism because the reactions were often delayed and unsensitized asthmatics did not react to the same concentrations. Asthmatic reactions may also be caused by an irritant mechanism at high concentrations. Tang *et al.* (2009) reported that the likelihood of developing allergic asthma increases proportionately with indoor formaldehyde concentrations, especially at concentrations > 0.12 mg/m^3 [0.1 ppm]. One residential study of asthmatics and non-asthmatics exposed to 0.017 to 0.029 mg/m^3 [0.014 to 0.024 ppm] of formaldehyde reported a significant relationship between formaldehyde concentrations in the homes of subjects and asthma-like symptoms (Norbäck *et al.* 1995).

Table 5-8. Studies of occupational asthma and formaldehyde exposure

Study population (no.)	Sex	Concentration ppm	Duration	Results	References
Workers (NR)	NR	NR	NR	Immediate and late reaction in 2 workers	Popa *et al.* 1969 (cited in IARC 2006)
Neurology resident (1)	Male	NR	2 h	Acute pneumonitis; breath smelled of formaldehyde, resolved in 5 wk	Porter 1975 (cited in IARC 2006)
Nurse (1) Pathologist (1) NR (1)	Female	5 5 3	15 min 1 h 5 min	Late asthmatic reaction No reaction Late asthmatic reaction	Hendrick and Lane 1975, 1977, Hendrick *et al.* 1982 (cited in IARC 2006)
Workers (15)	Both	[1.9] [3.9] [3.9] [25.2]	30 min 30 min 30 min 7 min	One late asthmatic reaction Two immediate and late asthmatic reactions No reaction in unsensitized asthmatics One irritant asthmatic reaction	Burge *et al.* 1985 (cited in IARC 2006)
Workers (230)	Both	[1] [2]	30 min 30 min	One early reaction Five early and six late reactions	Nordman *et al.* 1985 (cited in IARC 2006)
Worker (1)	Male	0.06 0.01 0.5	6 mo 20 min 20 min	Asthma None Late asthmatic reaction, IgE negative	Kim *et al.* 2001 (cited in IARC 2006)
Residential Controls (41) Asthmatics (47)	Both	 [0.014] [0.024]	NR	There was a significant relationship between formaldehyde concentrations and asthma-like symptoms	Norbäck *et al.* 1995

Adapted from IARC 2006.
NR = not reported.

5.5.1.2 Dermal exposure

Although formaldehyde is recognized as a skin irritant, very few quantitative data are available. Maibach (1983) reported that it is likely that formulations containing formalin at 300 ppm or greater would induce clinical irritation. Unlike contact dermatitis (discussed below) skin irritation is non-immunologic (ConsensusWorkshop 1984). Sensory irritation may be caused by nucleophilic addition, disulfide bond cleavage, and physical interaction. Nucleophilic addition at -SH or -NH_2 groups on proteins is probably the most important mechanism for formaldehyde. Approximately 5% of subjects exposed to a single application of 1% formalin in water with occlusion will develop skin irritation.

Formaldehyde is a primary skin sensitizing agent and has been associated with both immediate, anaphylactic reactions (Type I allergy), and contact dermatitis (Type IV allergy) (ConsensusWorkshop 1984). More quantitative data were available for contact dermatitis than for skin irritation. The Consensus Workshop reported that the threshold level for induction of contact dermatitis in humans is less than 5% formalin in water. Approximate thresholds for elicitation of allergic contact dermatitis in sensitized subjects range from about 30 ppm for patch testing to 60 ppm for actual use concentrations of formalin. Flyvholm *et al.* (1997) conducted patch tests with formaldehyde solutions ranging from 25 to 10,000 ppm in 20 formaldehyde-sensitive individuals and 20 healthy controls and reported a threshold concentration of 250 ppm. No positive reactions were observed in the control group. Maibach (1983) reported rates of allergic contact dermatitis (patch test responders) ranging from about 3.5% to more than 6%. More recent results indicated positive reaction rates of 7.9% in 1,324 patients at the Mayo Clinic and 9.2% from 5,830 patients tested by the North American Contact Dermatitis Group (Wetter *et al.* 2005). Warshaw *et al.* (2007) reported that formaldehyde was the second most common allergen associated with contact dermatitis of the hands in a cross-sectional analysis of more than 22,000 patients patch tested between 1994 and 2004 in North America. Zug *et al.* (2008) conducted a retrospective cross-sectional analysis of North American contact dermatitis data from 2001 to 2004. Formaldehyde was the fourth most frequently positive allergen (positive patch test in 170 of 1,496) among patients with a scattered generalized distribution of dermatitis. De Groot *et al.* (2009) reported that the frequency of contact allergy to formaldehyde was consistently higher in the United States (8% to 9%) than in Europe (2% to 3%). Although the concentration of formaldehyde that is safe for sensitive patients is unknown, the authors reported that levels of 200 to 300 ppm in cosmetic products have been shown to induce dermatitis following short-term use on normal skin.

There are several case reports that document contact dermatitis from exposure to formaldehyde in clothing. Formaldehyde resins were added to clothing to make permanent creases, to make the garments wrinkle resistant, to preserve their new appearance, for mothproofing, and to reduce shrinking. O'Quinn and Kennedy (1965) and Shellow and Altman (1966) reported cases of intermittent or persistent dermatitis that had lasted for years and typically involved the neck, shoulders, upper arms, lower legs, feet, hands, and peripheral areas of the axillae. The patients also had positive patch tests when exposed to 2% or 5% formaldehyde solutions, or when exposed to some samples of clothing that contained formaldehyde. Fowler (2003) also reported a case of urticaria that

was associated with formaldehyde use in leather dresses in Finland, and a case of shoe dermatitis in a woman who wore formaldehyde-treated leather shoes. Carlson *et al.* (2004) conducted patch tests on 852 patients in the University Hospitals of Cleveland Environmental and Occupational Dermatitis Clinic from August 1999 to April 2004. Reactions to formaldehyde and to several formaldehyde textile resins were recorded. Positive reactions to a 1% aqueous solution of formaldehyde were reported for 61 patients (7.2%), while 17 patients had a positive reaction to an ethylene urea/melamine formaldehyde resin. Donovan and Skotnicki-Grant (2007) reported a case of severe contact dermatitis in a 49-year-old pediatrician that was caused by contact with formaldehyde textile resins in her hospital "greens" (or "scrubs") and mask. Patch testing revealed a very strong reaction to melamine formaldehyde and milder reactions to urea formaldehyde and ethylene urea/melamine formaldehyde.

De Groot *et al.* (1988) investigated the relationship between allergic contact dermatitis to formaldehyde and patch test reactions to dimethyloldimethyl hydantoin (a formaldehyde donor used as a preservative in cosmetic products). Patients that had positive patch tests to 0.1% or 0.3% formaldehyde tended to have a higher incidence of positive patch tests to the preservative than those who reacted only to 1% formaldehyde. Takahashi *et al.* (2007) reported that 2 of 60 medical students had a positive patch test to 1% formaldehyde at the end of a human anatomy class. None of the students had a positive patch test prior to taking the anatomy class. Ravis *et al.* (2003) reported a 2% incidence of formaldehyde-induced allergic contact dermatitis among 101 dental hygienists or dental assistants. The incidence in 51 control subjects also was 2%.

Kiec-Swierczynska (1996) reported incidences of occupational allergic contact dermatitis among 1,619 patients in Poland that were examined over a 5-year period (1990 to 1994). A total of 332 patients were diagnosed with contact dermatitis. Medical histories and occupational exposure data were obtained, and all patients were patch-tested with the standard Polish series of allergens. Sixty individuals had a positive patch test to formaldehyde. Geier *et al.* (2008) also reported positive patch tests to several formaldehyde releasers in a 39-year-old metalworker with work-related dermatitis of the hands and lower arms. Formaldehyde releasers were used as a biocide in the water-based metalworking fluid used by this worker.

Tang *et al.* (2009) reported cases of contact dermatitis in 4 of 10 operators of chemical melting devices in a phenol-formaldehyde factory and two thirds of the workers on a mushroom farm that were exposed to formaldehyde developed dermatitis on their arms and forearms. Symptoms included red spots, swelling, irritation, pain, and a burning sensation.

5.5.1.3 Oral exposure

Formaldehyde ingestion is rare because it is a strong irritant and has an unpleasant odor. Only 13 cases of formalin ingestion (usually suicidal or homicidal attempts) have been reported in the English literature since 1950. At least 15 cases have been published in the Japanese literature (Yanagawa *et al.* 2007), and other cases have been reported in China (Tang *et al.* 2009). These cases suggest that the fatal oral dose of formaldehyde is 60 to 90 mL (Bartone *et al.* 1968, Yanagawa *et al.* 2007). In addition to severe corrosive

damage to the gastrointestinal tract, other effects may include central nervous system (CNS) depression, myocardial depression, circulatory collapse, multiple organ failure, kidney and liver damage, and metabolic acidosis. The primary late complication for survivors is cicatrical stricture of the stomach which may require a gastrectomy (Yanagawa *et al.* 2007).

Köppel *et al* (1990) presented case reports of two patients (a 55-year-old female and a 34-year-old male) that died after ingesting an unknown quantity of formaldehyde. Both patients survived the initial gastrointestinal necrosis and renal failure, but died several weeks later from respiratory distress and cardiac failure. Autopsy findings in one of the patients included burns of the entire digestive tract, including the colon, with extensive hemorrhagic jejunitis, ileitis, and colitis. Plasma levels of formic acid were elevated in both patients, but no free formaldehyde was detected in blood or plasma. These authors speculated that formaldehyde may exert systemic toxicity in the form of its labile Schiff's base with proteins, but not as free formaldehyde. One patient died 28 hours after ingesting 120 mL of a formaldehyde/methanol solution (Eells *et al.* 1981). Plasma methanol, formaldehyde, and formate levels were measured in a 50-year-old male who was found unconscious and unresponsive at a meat packing plant after drinking about 4 ounces of a formaldehyde solution (Burkhart *et al.* 1990). The clinical course included an initial CNS depression followed by abdominal pain, retching, seizures, hypotension, and cardiac arrest. The patient died 13 hours after exposure. Methanol levels increased throughout the 13-hour course, while formate and formaldehyde levels increased until bicarbonate and ethanol therapy were instituted after 6 hours. Hilbert *et al.* (1997) reported a case of fatal poisoning in a 46-year-old woman who deliberately ingested 50 to 100 mL of formalin. She was admitted to the intensive care unit 2 hours later and presented with metabolic acidosis, gastric ulceration, and circulatory shock. The patient died 44 hours after ingesting the formalin from multiple organ failure, including severe ventricular failure.

Two cases of nonfatal poisoning were reviewed (Bartone *et al.* 1968, Yanagawa *et al.* 2007). Bartone *et al.* (1968) reported that a 46-year-old woman drank an estimated 120 mL of a 10% formaldehyde solution and experienced shock and severe abdominal pain, and developed diffuse ulceration, fibrosis, and contracture of most of the stomach. She was admitted to the hospital 3 months after the incident after experiencing frequent episodes of weakness, loss of appetite, weight loss, and nausea and vomiting. The lesion culminated in an almost complete, high gastric obstruction and required a total gastrectomy. A 28-year-old man also survived after reportedly ingesting 150 mL of a 40% formalin solution in an attempted suicide (Yanagawa *et al.* 2007). This patient was admitted to the hospital 2 hours after ingesting the formalin. Endoscopy on hospital day 4 showed esophageal erosion and diffuse corrosive gastric ulcers. By day 6, ascites with multiple spotty hemorrhages on the gastric serosa and omentum had developed. Further complications included bacterial pneumonia, sepsis, enteritis, toxic epidermal necrolysis, and gastric outlet obstruction. The patient was discharged on day 73. Gastroscopy was repeated on day 132 and showed that the stomach surface was covered by a regenerated mucosa with scattered linear scars. The gastric outlet obstruction had improved by day 148.

In two separate incidences in China, 60 and 38 middle-school students reported symptoms of nausea, vomiting, and dizziness 30 minutes to 2 hours after eating fish illegally preserved in formaldehyde (no further information provided) (Tang *et al.* 2009).

5.5.1.4 Hematological and immunological effects

Intravascular coagulopathy was described in a 58-year-old man who swallowed 4 ounces of formalin (Burkhart *et al.* 1990). This patient died shortly thereafter from cardiac arrest.

Kuo *et al.* (1997) investigated the possible effects of formaldehyde exposure in 50 hemodialysis nurses in four teaching hospitals in Taiwan. The control group included 71 ward nurses who did not work in the hemodialysis unit. A questionnaire was used to gather information on health history, demographic data, exposure to formaldehyde, and symptoms. Symptoms included itching, dizziness, nausea and vomiting, fatigue, impaired concentration, tearing, nasal discharge, cough, and difficulty breathing and were scored as never (0), seldom (1), occasionally (2), and frequently (3). The values for the symptoms were totaled to derive a total symptom score. The control group was younger, less likely to be married, and more likely to have allergic rhinitis than the exposure group. There was a significant positive correlation between airborne formaldehyde concentrations and total symptom score. Multiple regression analysis indicated that the exposure group's white blood cell count was significantly lower than the control group. No differences in other hematologic indices were noted in this study.

Tang *et al*. (2009) summarized eight reports of formaldehyde-induced hematotoxicity from Chinese studies (Table 5-9). In general, these studies showed a significant decrease in total white blood cell counts (leucopenia) in exposed workers when compared with controls, and some studies reported that exposed workers had decreased numbers of platelets. In the largest study (239 exposed subjects and 200 controls Yang *et al*. 2007) reviewed by Tang *et al.*, a statistically significant higher percentage of exposed subjects had blood abnormalities (white blood cells, platelets, and hemoglobin) than controls. Tang *et al.* also reported a case report of pancytopenia (a type of anemia) in a previously apparently healthy woman after she lived 3 months in a newly remodeled apartment. This woman had lower than normal white blood cell, red blood cell, platelet, and hemoglobin counts (data not reported in Table 5-9). Formaldehyde air concentrations were 4-fold higher than the indoor exposure standard, whereas benzene and toluene were within indoor concentration limits.

Table 5-9. Summary of blood cell counts in Chinese workers exposed to formaldehyde

Subject[a]		Concentration ppm	WBC (× 10^9/L)	Plt (× 10^9/L)	Hb (g/L)[b]	Notes	Reference (as cited in Tang *et al.* 2009)
Group	N						
Exposed Control	65 70	N/A	5.42 ± 2.04*** 6.61 ± 1.66	172.48 ± 87.57*** 243.10 ± 84.08	125.66 ± 21.83 128.59 ± 13.11	WBC and Plt counts decreased with increasing work years	Tong *et al.* 2007
Exposed Control	239 200	[0.018–0.036]	33/239 (14%)**[b] 8/200 (4%)	26/239 (11%)**[b] 2/200 (1%)	77/239 (32%)**[b] 43/200 (21.5%)	All counts decreased with increasing work years	Yang 2007a
Exposed Control	72 150	[0.20–0.76]	10/72 (14%)*[b] 8/150 (5%)	N/A	N/A		Cheng *et al.* 2004
Exposed Control	110 120	N/A	4.91 ± 1.17 5.92 ± 1.51	N/A	N/A	WBC count decreased with increasing work years	Tang and Zhang 2003
Exposed Control	50 71	[0.15]	NR	NR	NR	Significant correlation of decreased WBC count with increased [FA]	Kuo *et al.* 1997
Exposed Control	55 41	[~2.4] (estimated)	5.39*** 6.22	N/A	N/A	Reported increase in IgM, IgA, and eosinophil counts	Qian *et al.* 1988
Exposed Control	10 10	[0.36–5.56]	5.74 ± 1.35 6.48 ± 2.15	122.46 ± 32.87 118.84 ± 22.52	119.77 ± 11 120 ± 10	WBC counts decreased, but NS	Xu *et al.* 2007b
Exposed Control	104 68	[0.6–15.6]	NS	N/A	NS	Original data not provided	Feng *et al.* 1996

Source : Tang *et al.* 2009.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
[FA] = formaldehyde concentration; Hb = hemoglobin; N/A = not available; NR = not reported; NS = not significant; Plt = platelet; WBC = white blood cells.
[a]Most exposed subjects are industrial workers, with the exception of pathologists in the Cheng *et al.* 2004 study, and nurses in the Kuo *et al*. 1997 study.
[b]Numbers of subjects with decreased blood cell counts are given. Percentage (%) is calculated from subjects with abnormal counts among total subjects.

Zhang *et al.* (2010) investigated the ability of formaldehyde to disrupt hematopoiesis in 43 Chinese factory workers who had been exposed to high levels of formaldehyde (0.6 to 2.5 ppm) for at least three months. Fifty-one control subjects (matched by age and gender) were selected from factories in the same geographic regions as the formaldehyde-exposed workers. The controls had similar smoking and drinking habits but had a lower percentage of recent respiratory infections (29% vs. 40%) compared with the exposed workers. Subjects with a history of cancer, chemotherapy, and radiotherapy, as well as previous occupations with notable exposure to butadiene, styrene, or ionizing radiation were excluded. Urinary benzene levels were low and similar in both the exposed and unexposed workers. All laboratory analyses were performed blinded to exposure status. Complete blood counts (CBC) with differential, and lymphocytes subsets, and peripheral stem/progenitor-cell colony formation (using the colony forming unit-granulocyte macrophage [CFU-GM] colony-forming assay) were performed for each individual. In addition, an *in vitro* assay used mononuclear cells (from a person of Chinese origin) cultured in the presence or absence of formaldehyde, and progenitor cells were measured. Various concentrations of formaldehyde were added to the cultures on day one, and burst forming unit-erythroid (BFU-E), CFU-GM, and colony forming unit- granulocyte, erythrocyte, monocyte (CFU-GEMM) colonies were measured after 14 days. Myeloid progenitor cells from a subset of 10 highly exposed workers and 12 matched controls also were cultured to quantify chromosome changes, including the loss (monosomy) of chromosome 7 and gain (trisomy) of chromosome 8.

Exposed workers had significantly lower counts of total white blood cells ($P = 0.0016$), granulocytes ($P < 0.05$), platelets ($P < 0.05$), red blood cells ($P < 0.001$), and lymphocytes ($P = 0.002$) compared with controls. The mean corpuscular volume of red blood cells was elevated. Exposed workers also had a 20% decrease in colony formation from circulating progenitor cells, but this was not statistically significant ($P = 0.10$). *In vitro* studies indicated that the colony-forming number of all progenitor cell types BFU-E, CFU-GM, and CFU-GEMM was significantly decreased by exposure to formaldehyde in a dose-related manner (Table 5-10). A subset of 10 highly exposed subjects were examined for aneuploidy of chromosomes 7 and 8 and compared with controls. There were significantly higher frequencies of monosomy of chromosome 7 ($P = 0.0039$) and trisomy of chromosome 8 ($P = 0.04$) in exposed workers compared with controls (see Section 5.6.4).

Table 5-10. Colony formation from human myeloid progenitor cells following formaldehyde exposure in cell culture

Formaldehyde, in μM	BFU-E[a]	CFU-GM[a]	CFU-GEMM[a]
0	12	7.5	0.5
100	10	6.0	0.25
150	8	4.5	0.14
200	2	0.5	0.0
P_{trend}[b]	0.023	< 0.01	< 0.001

BFU-E = burst forming unit–erythroid; CFU-GM = colony forming unit, granulocyte; CFU-GEMM = colony forming unit-granulocyte, erythrocyte, monocyte.
[a]Mean number of colonies (from 6 Petri plates) per 100,000 plated mononuclear cells, values estimated from graph.
[b]P_{trend} calculated using negative binominal regression and robust standard errors adjusting for possible residual correlation due to the same dish using a sandwich-type estimate.

Most of the studies on the immunologic effects of formaldehyde have focused on the allergic reactions (i.e., contact dermatitis and occupational asthma); however, several studies have reported that formaldehyde exposure may affect immunological parameters. These studies cover acute, subchronic, and chronic exposures and include workers, medical students, residents, and children.

Madison *et al.* (1991) studied a group of residents who experienced acute symptoms following exposure to formaldehyde and exothermic byproducts of an urea-formaldehyde spill. Three years after the accident, the exposed group was compared with an unexposed group selected from a nearby community. Immunological parameters included white blood cell count, total lymphocyte count, percent and total lymphocyte subsets (CD4, CD5, CD8, CD19, CD25, and CD26 cells), prevalence of autoantibodies, and antibodies to formaldehyde-human serum albumin conjugate. Data were adjusted for age, gender, smoking, mobile home residency, and use of wood stoves. White blood cell, lymphocyte, and T-cell counts were not affected; however, significant differences were reported for elevated percent and absolute numbers of CD26 cells, autoantibodies, and greater titers of isotypes IgG and IgM to formaldehyde-human serum albumin conjugate. The authors concluded that the exposed subjects had an activated immune system in addition to increased autoantibodies.

Vargovà *et al.* (1992) investigated the immunological and cytogenetic effects (see Section 5.6.4) of formaldehyde in a group of 20 workers (10 male and 10 female) who had been occupationally exposed for 5 to more than 16 years. They were compared with a matching control group (similar habits and social status) of 19 individuals from the same plant who had no known exposure to formaldehyde. There were no significant differences between the exposed group and controls in values of natural cellular or specific humoral immunity; however, there were differences in the values of mitogen-induced proliferation of lymphocytes. The authors concluded that formaldehyde exposure interfered with the immune system, but not enough to show changes in the classical clinical-immunological responses.

Ying *et al.* (1999) examined both genetic and immunological parameters to investigate the effects of formaldehyde exposure on peripheral lymphocytes in 23 non-smoking medical students (11 males and 12 females). The study was conducted during an 8-week anatomy laboratory. Students were exposed three times per week for 3 hours per class. Formaldehyde concentrations were measured in the laboratories and in the students' dormitories. Blood samples were collected from each student at the beginning of the anatomy laboratory and after completing the laboratory. Lymphocyte subsets were stained by mouse antihuman monoclonal antibodies against CD3 (total T cells), CD4 (T helper-inducer cells), CD8 (T cytotoxic-suppressor), and CD19 (B lymphocytes) surface markers within 24 hours after collecting the blood samples. Genetic effects are discussed in Section 5.6.4. Formaldehyde concentrations ranged from 0.071 to 1.28 mg/m^3 [0.06 to 1.04 ppm] in the laboratories and 0.011 to 0.016 mg/m^3 [0.009 to 0.013 ppm] in the dormitories. The time-weighted average concentration in the laboratories was 0.508 ± 0.299 mg/m^3 [0.413 ± 0.243 ppm]. The results observed in the study were determined to be similar for both males and females; therefore, the data were pooled. The percentage of lymphocyte subsets did show significant changes at the end of the study (Table 5-11). There was a significant increase in B cells, and a significant decrease in total T cells, T-helper-inducer cells, and T-cytotoxic-suppressor cells. There also was a higher ratio of T-helper-inducer cells to T-cytotoxic-suppressor cells.

Table 5-11. Effects of formaldehyde exposure on peripheral lymphocyte subsets in anatomy students

Subset	Before exposure (%)	After exposure (%)
B cells	16.87 ± 1.52	23.98 ± 4.52***
Total T cells	72.63 ± 2.90	65.46 ± 4.65***
T-helper-inducer cells (T_4)	48.87 ± 4.20	44.68 ± 4.36**
T-cytotoxic-suppressor cells (T_8)	29.18 ± 3.94	20.14 ± 3.04***
T_4/T_8	1.71 ± 0.34	2.25 ± 0.44***

Source: Ying *et al.* 1999.
**$P < 0.01$; ***$P < 0.001$ (t-test).

Lyapina *et al.* (2004) reported that their previous studies demonstrated that the immunotoxic action of formaldehyde resulted in delayed type skin sensitization and reduced resistance to infections (recurrent rhinitis, upper respiratory tract infections and pneumonitis) in exposed workers and suggested that formaldehyde exposure may result in functional changes in neutrophils. Therefore, they examined the effects of formaldehyde exposure on neutrophil respiratory burst activity in 29 workers exposed to formaldehyde. The exposed group was further divided into 12 individuals (group 1a) with a history of frequent viral or bacterial inflammatory relapses of the upper respiratory tract and clinical observations of hypertrophy or atrophy of the upper respiratory mucous membranes, chronic pharyngitis, rhinitis, rhinosinusitis and rhinopharyngitis. Group 1b included the other 17 exposed workers, 12 of whom had no history or clinical findings of upper respiratory tract infections, and 5 who had a history of rare, short, predominantly acute, inflammatory relapses of viral etiology in the upper respiratory tract. The control group included 21 non-exposed, age- and gender-matched healthy individuals. Formaldehyde concentrations measured in the workplace of the exposed group ranged

from 0.64 mg/m^3 [0.52 ppm] to 1.92 mg/m^3 [1.56 ppm] with a mean of 0.87 ± 0.39 mg/m^3 [0.71 ± 0.32 ppm]. Although routine hematological tests did not show any differences between the exposed and control groups, there was a statistically significant negative correlation between the duration of exposure and erythrocyte count and hematocrit level. Exposed workers had a statistically significant decreased resistance to infection. Neutrophils generate reactive oxygen species (the respiratory burst) in response to tissue damage or local invasion of microorganisms. Although there were no significant differences in the spontaneous or stimulated neutrophil respiratory burst activity between the exposed group and the control group, there was a decrease of spontaneous neutrophil respiratory burst activity in workers with a history and clinical findings of frequent and long-lasting relapses of chronic inflammation of the upper respiratory tract (group 1a). Therefore, functional changes in polymorphonuclear neutrophil granulocytes could serve as an early indicator of an impact of formaldehyde on neutrophil respiratory burst activity.

Erdei *et al.* (2003) examined the relationship between immune biomarkers and indoor air quality in 176 school children aged 9 to 11 years. These children had immunologically related respiratory diseases and lived in Hungarian cities. Nitrogen dioxide, formaldehyde, benzene, xylene, and toluene were measured in indoor air of the homes of these children. Higher indoor formaldehyde concentrations were associated with significantly increased monocyte concentrations and bacterial-specific IgGs. [There were several limitations of this study including selection bias (i.e., only the most polluted houses were chosen, and the investigators did not control for other socioeconomic variables), the effects were correlated with nitrogen dioxide levels (thus the effects of formaldehyde could not be differentiated from the effects of nitrogen dioxide), and the subjects were exposed to dust mites (which could complicate any assessment of immunologic effects).]

Ye *et al.* (2005) examined two populations of formaldehyde-exposed workers in China. One group of 18 workers was exposed in a formaldehyde manufacturing facility while a second study group included 16 waiters who were exposed to low levels of formaldehyde while working in a newly fitted ballroom for 12 weeks. The control group included 23 college students. [Students are poor controls for a worker population.] All study participants were nonsmokers. There was a significantly increased percentage of B cells accompanied by significantly decreased percentages of total T cells (CD3) and T-cytotoxic-suppressor cells (CD8) in the manufacturing workers compared with the student controls. T-suppressor (CD4) cells were unchanged. These authors also investigated clastogenic effects in these workers (see Section 5.6.4).

Veraldi *et al.* (2006) evaluated the immunotoxic effects of 20 chemicals (including formaldehyde) that are widely used in the work environment. The primary purpose of this study was to document the evidence and to construct a matrix that can be used to estimate the relative risk of the chemicals. This evaluation consisted of three primary steps: (1) conduct a systematic literature search and review the data on immunotoxicity testing and testing schemes, (2) document the evidence (type of immunotoxicity, strength of evidence, and power) in summary tables for each chemical, and (3) assign an index (strong, intermediate, weak, or nil) based on the evidence of toxicity and the type of

effect (immunosuppression, autoimmunity, hypersensitivity). The evaluation included both human and experimental animal studies. Based on the overall evidence, these authors placed formaldehyde in the "weak" category. The main immunotoxic effect of formaldehyde was hypersensitivity.

Sasaki *et al.* (2009) obtained peripheral blood mononuclear cells from nonatopic healthy donors. T cells were isolated and stimulated with anti-CD3/anti-CD28 monoclonal antibodies. Pretreatment with formaldehyde selectively suppressed interferon-γ and interleukin-10 mRNA expression and protein production in stimulated T cells. Formaldehyde also suppressed nuclear factor kappa B (NF-κB) signaling and activated mitogen-activated protein kinases (MAPKs). The authors reported that formaldehyde had both transcriptional and nontranscriptional effects on T cell signaling that promoted a T helper type 2-skewed immune response.

5.5.1.5 Neurophysiological effects

Neurobehavioral effects have been reported to be related to exposure to formaldehyde in histology technicians (Kilburn *et al.* 1985a, Kilburn *et al.* 1987, Kilburn and Warsaw 1992) and fiberglass manufacturing workers (Kilburn 2001, Kilburn *et al.* 1985a); these effects include lack of concentration and loss of memory, disturbed sleep, impaired balance, variations in mood, alterations of appetite, indigestion, nausea, headache, and fatigue. Many of these studies were reviewed by WHO (2002), and the conclusion of that review was that there was little convincing evidence that formaldehyde is neurotoxic in occupationally exposed populations. Other studies that reported neurobehavioral effects in relation to exposure to formaldehyde include individuals living in homes insulated with urea-formaldehyde foam (Harris *et al.* 1981, Thun *et al.* 1982) and in manufactured homes or conventional homes (Main and Hogan 1983, Ritchie and Lehnen 1987, Kilburn 2000). Ritchie and Lehnen (1987) reported a higher frequency of headaches among individuals (over age 7) exposed to concentrations of formaldehyde greater than 0.1 ppm in the home in a study of 2,000 residents of nearly 397 mobile and 494 conventional homes in Minnesota. Thun *et al.* (1982) did not find any significant differences for headache, insomnia, or dizziness among individuals in 395 households whose homes had been insulated with urea-formaldehyde foam compared with 1,395 controls in New Jersey; no measurements of formaldehyde were reported in this study.

Kuo *et al.* (1997) (also discussed above under hematological and immunological effects) reported that incidences of dizziness, nausea, difficulty concentrating, tearing, nasal discharge, cough, and difficulty breathing were higher in a group of 50 hemodialysis nurses from four teaching hospitals in Taiwan compared with a control group of 71 ward nurses who did not work in the hemodialysis unit.

5.5.1.6 Reproductive effects

Epidemiological studies have investigated the reproductive effects of occupational exposures to formaldehyde; however, most of the available studies were not designed specifically for formaldehyde and are confounded by co-exposures to other chemicals (IARC 2006). The reproductive effects examined in these studies included spontaneous abortion, congenital malformations, birth weight, infertility, and sperm abnormalities.

IARC reviewed five case-control studies and one meta-risk analysis that included 11 studies. Another study (Saurel-Cubizolles *et al.* 1994) that was not included in the IARC review investigated pregnancy outcome among operating room nurses. This study surveyed 17 hospitals in Paris as part of mandatory annual occupational practitioner visits; analyses were adjusted for age, number and outcome of previous pregnancies, and tobacco use. Controls were selected from hospital employees that did not work in the operating room and were matched by hospital, age, and duration of employment. These studies showed inconsistent reports of higher rates of spontaneous abortion, birth defects, and low birth weights in women occupationally exposed to formaldehyde. Results are summarized in Table 5-12.

Table 5-12. Reproductive effects of formaldehyde in humans

Subjects	Endpoint	Results	References
Hospital staff	Spontaneous abortion	No correlation when adjusted for age, parity, decade of pregnancy, tobacco, and alcohol use	Hemminki *et al.* 1982 (as cited in IARC 2006)
Nurses	Spontaneous abortion Congenital defects	No correlation with spontaneous abortion, OR of 1.74 (95% CI = 0.39–7.7) for malformations based on 8 exposed subjects	Hemminki *et al.* 1985 (as cited in IARC 2006)
Laboratory workers	Spontaneous abortion Congenital defects Birth weight	OR of 3.5 (95% CI = 1.1–11.2) for spontaneous abortion in women exposed to formalin at least 3 d/wk. No association with congenital malformations	Taskinen *et al.* 1994 (as cited in IARC 2006)
Woodworkers	Time to pregnancy Spontaneous abortion	Significant association with delayed conception density and spontaneous abortion	Taskinen *et al.* 1999 (as cited in IARC 2006)
Meta-risk analysis	Spontaneous abortion Birth weight	Four studies had higher rates of spontaneous abortion while 5 studies did not. No association with birth weights	Collins *et al.* 2001b (as cited in IARC 2006)
Autopsy service workers	Sperm abnormality	No significant differences between the exposed and control groups	Ward *et al.* 1984 (as cited in IARC 2006)
Nurses	Spontaneous abortion Birth defects	Significant increase ($P < 0.05$) in spontaneous abortion and all birth defects combined in operating room nurses. No significant difference for major birth defects	Saurel-Cubizolles *et al.* 1994

CI = confidence interval; OR = odds ratio.

Tang *et al.* (2009) noted two Chinese studies on formaldehyde exposure and menstrual disorders. In a food additive factory, 70% of women exposed to formaldehyde through inhalation (0.82 to 5.96 mg/m^3 [0.67 to 4.85 ppm]) reported abnormal menstrual cycles, whereas 17% reported menstrual abnormalities in the control group. In a separate study, anatomy teachers exposed to over 0.5 mg/m^3 [0.4 ppm] formaldehyde reported menstrual disorders and, in some cases, dysmenorrhea (data not reported).

5.5.2 Toxic effects in experimental animals

The acute and chronic toxicity of formaldehyde has been extensively studied in experimental animals and recently reviewed by IARC (2006). Acute effects include irritation, pulmonary hyperreactivity, and cytotoxicity and cell proliferation in the nose and upper respiratory tract. Mice are more sensitive than rats to respiratory depression. The primary chronic effects also include cytotoxicity and cell proliferation in the upper respiratory tract, gastrointestinal irritation and ulceration, and skin sensitization. Developmental toxicity studies have been conducted on pregnant dams and generally have not shown a developmental effect at exposure levels that were not maternally toxic. Other effects reported include oxidative stress, neurotoxicity, immunotoxicity, and decreased thyroid gland, liver, and testis weights. Testicular toxicity has been reported in rats, mice, and birds. However, effects on male reproductive performance were not tested.

5.5.2.1 Irritation and respiratory effects

The irritant effects of formaldehyde in experimental animals range from mild irritation to severe ulceration (IARC 2006). Skin contact sensitization has been reported in mice and guinea-pigs. Formaldehyde is a potent respiratory tract irritant in rodents, causing slow and shallow breathing, and histopathological lesions in the nose and upper respiratory tract. $B6C3F_1$ mice exposed to 4.9 ppm and F344 rats exposed to 31.7 ppm had a 50% reduction in respiratory rate. Pulmonary hyper-reactivity and bronchoconstriction were reported in guinea-pigs exposed to 0.3 ppm for 8 hours or > 9 ppm for 2 hours. Ingestion of 82 to 109 mg/kg body weight formaldehyde for 2 years caused severe damage to the gastric mucosa in male and female Wistar rats (Til *et al.* 1989).

Both acute and chronic inhalation exposures to formaldehyde can cause cytotoxicity and cell proliferation in the nasal mucosa and upper respiratory tract of rodents (IARC 2006). These studies generally show that formaldehyde increases cell proliferation and cell turnover, inhibits mucociliary function, and causes histopathological changes in the nasal mucosa in a concentration- and site-specific manner. Histopathological changes include squamous metaplasia, epithelial erosion, epithelial hyperplasia, degeneration of the respiratory and olfactory epithelium, and necrosis. Rats are more susceptible than mice, presumably because mice reduce their minute ventilation more than rats when exposed to high concentrations (Chang *et al.* 1983, Swenberg *et al.* 1983a). Furthermore, Swenberg *et al.* (1983a) and Wilmar *et al.* (1987) reported that the severity of cytotoxic effects was more dependent upon formaldehyde concentration than the cumulative dose in their studies. Liteplo and Meek (2003) reviewed short-term, subchronic, and chronic studies of the effects of formaldehyde on cell proliferation within the respiratory epithelium of rats and reported that histopathological lesions and a sustained increase in proliferation of nasal epithelial cells were not observed at concentrations of 2 ppm or less. More information on respiratory tract cytotoxicity and cell proliferation is presented in Section 5.7.5 as it relates to mechanistic considerations for cancer.

Lino dos Santos Franco (2006) investigated the mechanisms underlying rat lung injury and airway reactivity changes caused by formaldehyde exposure. Male Wistar rats were exposed to a 1% formaldehyde solution (air concentrations generated from the solution

were not reported) for 30, 60, or 90 minutes/day for four days. Methanol (0.32%) was added to the solution to prevent polymerization. Both a non-exposed and a methanol-exposed control groups were included. Animals were killed one day after the final exposure. The reactivity of isolated trachea and intrapulmonary bronchi were assessed by generating dose-response curves to methacholine. Local and systemic inflammatory responses were evaluated by counting leukocytes in bronchoalveolar lavage fluid, blood, bone marrow lavage, and spleen. Tracheal reactivity was not affected by formaldehyde exposure, but there was a significant bronchial hyporesponsiveness in exposed rats. Formaldehyde exposure was associated with a significant increase in the total cell numbers in bronchoalveolar lavage fluid, peripheral blood, and spleen, but not in bone marrow. The effect was time dependent in bronchoalveolar fluid with the maximum response observed after 90 minutes exposure. Leukocytes in the bronchoalveolar fluid were composed mainly of mononuclear cells in rats exposed for 30 or 60 minutes, but both mononuclear cells and neutrophils were observed in rats exposed for 90 minutes. The authors proposed that formaldehyde exposure may affect lung resident cells, including macrophages and mast cells that could mediate the lung inflammatory response and the systemic release of inflammatory mediators. The inflammatory mediators may trigger systemic immune responses and be implicated in the increased number of cells in the spleen.

5.5.2.2 Sensitization and other immunologic effects

IARC (2006) reviewed several studies that investigated immunologic effects of formaldehyde in mice and rats. $B6C3F_1$ mice exposed to 15-ppm formaldehyde 6 hours/day, 5 days/week for 3 weeks did not have any significant changes in immune function (including routine hematology, bone-marrow cellularity, and CFU progenitor-cell number) except for an increase in host resistance to *Listeria monocytogenes* infection (Dean *et al.* 1984). In other studies in mice, formaldehyde exposure did not alter the number or impair the function of resident peritoneal macrophages. BALB/c mice exposed to 2 mg/m^3 [1.6 ppm] formaldehyde for 6 hours/day for 10 days had enhanced anti-ovalbumin IgE titer; however, in another study, the IgG1 response of ICR mice to a mite allergen in the respiratory tract was not enhanced after exposure to a 0.5% formaldehyde aerosol. There was no evidence that long-term exposure to high concentrations (12.6 ppm) of formaldehyde impaired B-cell function.

Hilton *et al.* (1996) conducted a series of tests to study the sensitizing properties of formaldehyde. These included the guinea-pig maximization test, the occluded patch test, the murine local lymph node assay, and the mouse IgE test. The mouse IgE test was used to determine the potential for sensitization of the respiratory tract. Chemicals known to cause respiratory allergy in humans stimulate a significant increase in serum IgE concentrations, while contact allergens do not. Female BALB/c mice and albino Dunkin-Hartley guinea-pigs were used. Formaldehyde elicited strong positive responses in the guinea-pig maximization test, the occluded patch test, and the murine local lymph node assay. The mouse IgE test was negative. The authors concluded that these data indicate that formaldehyde is a potent contact allergen but did not cause sensitization of the respiratory tract.

Long-term exposure to formaldehyde vapor induced differential immunogenic and neurogenic inflammatory responses in female C3H/He mice (Fujimaki *et al.* 2004). Mice were exposed to 0, 0.080, 0.40, or 2.0 ppm formaldehyde for 16 hours/day, 5 days/week for 12 weeks. Some mice were given intraperitoneal injections of ovalbumin (OVA) before exposure to formaldehyde. These mice also were exposed to aerosolized OVA during weeks 3, 6, 9, and 11 for 6 minutes as a booster. Mice were killed the day after the final formaldehyde exposure. No significant increases were observed in various types of inflammatory cells in bronchoalveolar lavage fluid in non-immunized mice, but in the high-dose OVA-immunized group, the number of bronchoalveolar cells, macrophages, and eosinophils increased significantly. There was no histological evidence that formaldehyde caused impairment of the epithelial cells in the lung of any of the exposed groups. Formaldehyde-exposed immunized mice had significantly lower production of IL-1β and nerve growth factor compared with controls, but TNF-α, IL-6, and granulocyte/macrophage colony stimulating factor remained at control levels. Spleen cells, stimulated with lipopolysaccharide to induce cell proliferation, produced significantly higher levels of interferon-γ (IFN-γ) in the high-dose nonimmunized group. Immunized mice exposed to 0.4- or 2.0-ppm formaldehyde had a significant increase in the production of monocyte chemoattractant protein from spleen cells cultured for 24 hours with OVA. Antigen-specific antibody titers in plasma did not show any significant differences in anti-OVA IgE, total IgE, or anti-OVA IgG2a production. Anti-OVA IgG1 and anti-OVA IgG3 production were significantly decreased in the 0.4-ppm exposure group. There was a dose-dependent increase in substance P levels in the plasma of nonimmunized mice but not in OVA-immunized mice. The authors noted that if the decreased nerve growth factor in the OVA-immunized mice is related to modulation of sensory neurons and immune abnormalities, these associations might provide an explanation for the multi-organ symptoms in patients with chemical sensitivities.

Lino dos Santos Franco *et al.* (2009) investigated the lung allergic response to ovalbumin in male Wistar rats exposed to formaldehyde vapors produced from a 1% aqueous solution for 90 minutes daily on three consecutive days. The rats were subsequently sensitized with ovalbumin and aluminum hydroxide by intraperitoneal injection. Two weeks later, the rats were challenged with aerosolized ovalbumin. Rats treated with formaldehyde had a lower intensity of lung inflammation response (i.e., reduced number of inflammatory cells in bronchoalveolar lavage) compared with rats that were not treated with formaldehyde. Furthermore, the formaldehyde-treated rats had a reduced number of bone marrow cells and blood leukocytes suggesting that the effects were not localized just to the airways. The authors concluded that formaldehyde might impair the lung cell recruitment after an allergic stimulus, thereby leading to a nonresponsive condition against inflammatory stimuli.

Kuper *et al.* (in press) investigated the effects of formaldehyde on nasopharynx-associated lymphoid tissues (NALT) and upper respiratory-tract draining lymph nodes. Nine-week-old male F344 rats (8 rats/treatment group) and female B6C3F$_1$ mice (6 mice/treatment group) were exposed to whole body formaldehyde vapor for 6 hours/day, 5 days/week for 4 weeks at a concentration range of 0.5 to 15 ppm. At sacrifice, superficial and posterior cervical lymph nodes and the heads were immersed in fixative (after fixation of the nasal tissues by injection of fixative via the nasopharyngeal opening

in the palate) and NALT were collected from the nasopharynx. Paraffin-embedded tissues were sectioned, stained, and scored for size of NALT and numbers of germinal centers. None of the lymphoid tissues of mice were affected by formaldehyde exposure. In rats exposed to 15 ppm, there was a statistically significant increase in proliferation rate ($P < 0.01$) of NALT lymphoepithelium, and moderate hyperplasia was evident by light microscopy, but no other treatment-related effects were observed (size, cellularity, or germinal center development) in NALT. However, there were statistically significant decreases in germinal centers development from superficial but not posterior cervical lymph nodes in rats treated at 2 and 15 ppm, but no other effects were observed.

Vargová *et al.* (1993) evaluated immune function in male Wistar rats administered formaldehyde by gastric lavage 5 days per week for 4 weeks at doses of 0, 20, 40, or 80 mg/kg body weight. Other routine parameters, including hematology, clinical chemistry, and body and organ weights also were examined. Immune system parameters evaluated included cell-mediated immunity, humoral-mediated immunity, and immunopathology. Lymph node weights were significantly increased in the dosed groups, but the cellularity of lymphoid organs was not affected. The percentage of monocytes was significantly increased, but the percentage of lymphocytes was significantly reduced. There was a dose-dependent decrease in antibody response (IgG + IgM), but there was no significant reduction in the number of antibody-producing (IgM) cells in the spleen. There was a nonsignificant reduction in microbicidal activity of blood phagocytes (measured by interaction with the yeast *Candida albicans*). Phagocytic activity (measured by adhesion of hydrophilic synthetic microspheric particles to leukocytes) was significantly reduced only at the 40 mg/kg dose for polymorphonuclear leukocytes and monocytes combined.

5.5.2.3 Cytotoxicity

Wilmer *et al.* (1989) compared the effects of intermittent versus continuous formaldehyde exposures in male Wistar rats (age not reported). Groups of 25 rats were exposed to formaldehyde at a concentration of 0, 1, or 2 ppm for 8 hours or to a concentration of 2 or 4 ppm during eight 30-minute intervals separated by 30-minute non-exposure periods. These concentrations were selected to represent marginally cytotoxic levels as determined from previous studies. Exposures were carried out 5 days/week for 13 weeks. For examination of cell proliferation, 5 rats from each group were given a single dose (74 kBq/g) of [^{3}H]thymidine 18 hours after the third day of exposure and were killed 2 hours later. The cell-proliferation procedure was repeated in 5 additional rats from each group after 13 weeks. At the end of the study, the animals were necropsied and examined for gross pathology. Six standard cross sections of the nasal cavity were processed and examined by light microscopy. Body weight did not differ between any exposure group and the controls. Exposure-related effects in the nasal cavity were seen only in the rats exposed to formaldehyde intermittently at 4 ppm. Increased degrees and incidences of disarrangement, hyperplasia, and squamous metaplasia with or without keratinization of the respiratory epithelium were reported. The cell-proliferation study indicated that after 13 weeks, the cell-turnover rate of the nasal respiratory epithelium was three times as high in the 4-ppm group as in the controls. The cell-proliferation rates in the other groups were comparable to control values. The authors

concluded that the severity of the cytotoxic effects was determined by the exposure concentration rather than total dose (concentration × exposure time).

5.5.2.4 Neurotoxicity

IARC (2006) reviewed two animal studies by Pitten *et al.* (2000) and Malek *et al.* (2003c) that reported possible neurobehavioral effects of formaldehyde. Pitten *et al.* (2000) reported that exposure to formaldehyde by inhalation at either 2.6 or 4.6 ppm significantly increased the time required to find food and the number of mistakes made during the trials, and these effects increased with the length of the exposure period. However, the IARC Working Group concluded that there was no evidence that the changes seen in this study were due to formaldehyde-induced neurotoxicity and suggested that loss of olfactory capacity and visual difficulties with irritant effects to the cornea, changes that would have improved after treatment was stopped, could explain the results. The study by Malek *et al.* reported the effects of exposure to formaldehyde on the performance of male and female Lewis rats in a water maze. The formaldehyde-exposed rats (0.5 and 5.4 ppm) required significantly longer swimming periods to reach the finish and made significantly more errors that the control animals. Although the authors concluded that formaldehyde affected the learning behavior and memory of rats, IARC noted that complications of blurry vision and loss of olfactory cues were not controlled for, and the Working Group suggested that the treatment-related response was not due to a CNS effect.

A number of other studies of neurobehavioral effects in rats or mice exposed to formaldehyde have been published. Malek *et al.* (2003a) reported that a single exposure to formaldehyde significantly affected the locomotor and explorative behavior of rats, but the effects did not show any linear trends with respect to the formaldehyde concentrations (1, 2.5, or 5 ppm). Malek *et al.* (2003b) reported that locomotor behavior in male and female rats was significantly affected by exposure to 0.1, 0.5, or 5 ppm for 2 hours. Malek *et al.* (2004) also exposed male AB mice to 1.1-, 2.3-, or 5.2-ppm formaldehyde vapor for 2 hours, and locomotion and explorative activity in the open field were significantly affected at both 2 and 24 hours after exposure. Usanmaz *et al.* (2002) reported that low concentrations (1.8 ppm) of formaldehyde increased the excitability of the CNS in male and female BALB/c mice but, as the concentration increased (up to 14.8 ppm), a general depressant effect on the CNS became more pronounced.

Cellular and biochemical changes in the brains of rats and mice have also been proposed to be related to exposure to formaldehyde. These studies involved measurements of cell number or protein expression in the hippocampus, a region of the brain related to memory and learning. Songur *et al.* (2003) reported increases in heat shock protein 70 kDa (Hsp70)-positive neurons in the hippocampus of formaldehyde-exposed Wistar rats (0-, 6-, or 12-ppm formaldehyde). The number of pyknotic neurons also increased in the exposed groups. Gurel *et al.* (2005) reported that male Wistar rats that received intraperitoneal injections of formaldehyde for 10 days had degenerated neurons with pyknotic nuclei and fewer neurons in the frontal cortex and hippocampus compared with controls. Aslan *et al.* (2006) and Sarsilmaz *et al.* (2007) reported that male Wistar rats exposed neonatally to 0-, 6-, or 12-ppm formaldehyde for 30 days had significantly

increased numbers of granule cells in the hippocampal formation in both low- and high-dose groups (Aslan *et al.*) and significantly fewer pyramidal cells in the hippocampus in the high-dose group (Sarsilmaz *et al.*).

Other reports of changes in the hippocampus were published in a series of studies of formaldehyde exposure to ovalbumin-immunized mice by Fujimaki *et al.* (2004), Tsukuhara *et al.* (2006), and Ahmed *et al.* (2007). Exposure to 400-ppb [0.4-ppm] formaldehyde significantly increased brain nerve growth factor (NGF) levels and NGF mRNA in immunized mice (Fujimaki *et al.*). Exposure to 0.400-ppm formaldehyde in immunized mice also significantly increased the ratio of Bcl-2 to Bax protein, which the authors concluded would exert a protective effect against cell death by apoptosis (Tsukuhara *et al.*). In the third paper, Ahmed *et al.* reported that formaldehyde exposure upregulated expression of hippocampal genes (NR2A, D1 and D2 receptors, and CREB-1) known to play an essential role in the hippocampal synaptic plasticity underlying learning and memory in immunologically sensitized mice.

Lu *et al.* (2008b) reported that inhaled formaldehyde negatively affected learning and memory in Kun Ming mice (an outbred stock of Swiss albino mice). Mice exposed 6 hours/day to 3 mg/m^3 [2.4 ppm] formaldehyde by inhalation for 1 week had decreased water maze performance and lower dismutase superoxide activity and glutathione levels compared with a control group. Malondialdehyde content and NR1 and NR2B expression increased. Mice exposed to 1 mg/m^3 [0.8 ppm] formaldehyde were not affected. Oxidative stress-induced neuron damage to the brain was identified as a possible mechanism.

5.5.2.5 Other effects: liver, thyroid, and spleen

Beall and Ulsamer (1984) reviewed the hepatotoxic effects of formaldehyde. They reported that formaldehyde appeared to be associated with hepatotoxicity in mice, rats, hamsters, guinea-pigs, rabbits, dogs, and humans following injection, ingestion, or inhalation. Effects included alterations in weight, centrilobular vacuolization, focal cellular necrosis, and increased alkaline phosphatase concentrations. The hepatic changes were generally not extensive, and were reversible following acute exposure, but the authors believed that the effects could become progressively more serious with repeated exposures. Quantification of dose-response relationships was not possible because the chemical purity, exposure concentrations, and measurement methods were not always reported. Possible mechanisms, depending on the route of exposure, suggested by the authors included direct effects on hepatocytes, indirect effects through the circulatory and immune systems, and possible additive effects with hepatotoxic chemicals due to glutathione depletion. Some of the effects were probably caused by secondary mechanisms such as passive hepatic congestion, serum pH fluctuations, or tissue damage at other sites.

Woutersen *et al.* (1987) conducted a 13-week inhalation toxicity study in rats exposed to formaldehyde at 0, 1, 10, or 20 ppm for 6 hours/day, 5 days/weeks. At the high dose, uncoordinated locomotion and excitation was observed during the first 30 minutes of each exposure. Other effects included yellowing of the fur, growth retardation, decreased plasma protein levels, and squamous metaplasia of the nasal epithelium, and slightly

increased activities of plasma aspartate amino transferase, alanine amino transferase, and alkaline phosphatase (males only). At 100 ppm, the only effects were yellowing of the fur and squamous metaplasia of the nasal epithelium. There was no histopathological evidence of hepatotoxicity in any treatment group.

Patel *et al.* (2003) exposed groups of 10 male albino rats to 5, 10, or 15 mg/kg body weight formaldehyde per day for 30 days by intraperitoneal injection. A control group was injected with saline for 30 days. Animals were killed on the 31st day. Rats exposed to 10 or 15 mg/kg had a significantly lower thyroid gland weight, follicular regression, decreased triiodothyronine (T_3) and thyroxine (T_4), and enhanced thyroid stimulating hormone (TSH). Rats in the low-dose group had significantly decreased T_3 and enhanced TSH. Histological examination showed follicular degeneration in the mid-dose group and follicular atrophy in the high-dose group.

Golalipour *et al.* (2008) reported that exposure to formaldehyde vapor caused morphometric changes in the spleen of albino Wistar rats. A total of 28 rats were divided into 4 groups, including a control group that was not exposed to formaldehyde. The treatment groups were exposed to 1.5-ppm formaldehyde for 2 hours/day on 2 days/week, 2 hours/day on 4 days/week, or 4 hours/day on 4 days/week for 18 weeks. The germinal center diameter, germinal center area, and marginal zone diameter were increased by formaldehyde exposure, while the mantle layer diameter was decreased.

5.5.2.6 Reproductive and developmental effects

The reproductive and developmental toxicity of formaldehyde by various routes of exposure has been investigated in rats, mice, hamsters, rabbits, and dogs (IARC 2006). Reported effects included prolongation of pregnancy, changes in fetal organ weights, and various clinical and biochemical changes in the spleen, liver, kidney, thymus, and lymphocytes. There was no evidence of embryolethal or developmental effects when pregnant Sprague-Dawley rats were exposed to 0, 5, 10, 20, or 40 ppm for 6 hours/day from gestational day 6 to 20. IARC (2006) noted that 20 ppm would be considered a toxic dose. Another study in Sprague-Dawley rats reported reduced ossification in offspring at 5 and 10 ppm, but none of the reproductive parameters were affected. At 10 ppm, there was a significant decrease in food consumption and weight gain. Formaldehyde was applied dermally to the shaved backs of anesthetized pregnant Syrian hamsters for a 2-hour period on days 8 to 11 of gestation. The incidence of resorptions increased, but no malformations were reported. The authors noted that the increased resorptions might have been caused by the stress of anesthesia. Female Wistar rats exposed to 0.5 or 1.5 mg/m^3 [0.4 or 1.2 ppm] formaldehyde, 4 hours/day for up to 4 months, were mated with untreated males. There was a significant increase in the number of degenerating embryos (attributed to structural impairment in blastomeres) in the high-dose group.

Thrasher and Kilburn (2001) reviewed the embryo toxicity and developmental toxicity of formaldehyde. Depending upon the exposure period of the dam, the available studies resulted in increased embryo mortality, increased fetal anomalies, decreased concentrations of ascorbic acid, and abnormalities in lysosomal, mitochondrial and endoplasmic reticular enzymes. Rats exposed before mating had increased embryo

mortality while those exposed during mating had increased fetal anomalies. They also reported that ^{14}C-labelled formaldehyde (tail-vein injection) crosses the placenta and that concentrations in fetal brain were higher than in maternal brain. Using a similar protocol, Katakura *et al*. (1993) also studied the distribution of radioactivity from ^{14}C-labelled formaldehyde in pregnant ICR mice. They reported formaldehyde or its metabolites are rapidly transported to the fetus and that elimination of radioactivity is slower in fetal tissues than in maternal tissues, especially in the fetal brain and liver.

5.5.2.7 Testicular toxicity

Ten studies (seven in rats, one in mice, and two in birds) were located that investigated the effect of formaldehyde exposure on the testis and are briefly discussed below. After formaldehyde exposure, decreased testis weights, decreased seminiferous tubule diameters, and abnormal spermatogenesis and sperm morphologies were reported.

Exposure to formaldehyde vapor caused morphometric changes in the seminiferous epithelium of Wistar rats (Golalipour *et al.* 2007). A total of 28 rats were divided into 4 groups. The treatment groups were exposed to 1.5-ppm formaldehyde for 2 hours/day on 2 days/week (E3); 2 hours/day on 4 days/week (E2), or 4 hours/day on 4 days/week (E1) for 18 weeks. The mean seminiferous tubular diameter and seminiferous epithelial height showed a significant decrease with increasing duration of exposure (Table 5-13). The authors also reported a decrease in germ cells in E1 and E2 exposure groups, disruption of the association between Sertoli cells and germinal cells in the E3 exposure group, and arrested spermatogenesis in the E1 exposure group (no quantitative data provided).

Table 5-13. Seminiferous tubular diameter and height in Wistar rats

Effect	Control, mean ± SD	Treatment group		
		E1[a] mean ± SD	E2[b] mean ± SD	E3[c] mean ± SD
Seminiferous tubular diameter (μm)	252.12 ± 4.82	204.55 ± 3.29*	232.45 ± 2.42*	238.94 ± 4.37*
Seminiferous epithelial height (μm)	82.77 ± 2.00	65.26 ± 1.43*	69.46 ± 1.78*	72.80 ± 2.03*

Source: Golalipour *et al.* 2007.
*$P < 0.05$ (compared with controls).
[a]Exposed 4 h/d, 4 d/wk.
[b]Exposed 2 h/d, 4 d/wk.
[c]Exposed 2 h/d, 2 d/wk.

Özen *et al.* (2005) also reported decreases in seminiferous tubule diameter and serum testosterone levels and a concomitant increase in immunochemical staining for Hsp 70 in Wistar rats with increasing inhalation exposure to formaldehyde over a 13-week period (Table 5-14).

Table 5-14. Mean seminiferous tubular diameters and testosterone serum levels after 13-week exposure to formaldehyde by inhalation in rats

Treatment (ppm)	Tubule diameter mean ± SEM (µm) N = 100	Serum testosterone mean ± SEM (ng/dL) N = 6
Control	259.22 ± 16.18	406.54 ± 16.82
5	236.17 ± 13.09***	244.01 ± 23.86***
10	233.24 ± 10.13***	141.30 ± 8.56***

Source: Özen *et al*. 2005.
***$P < 0.001$.

In a separate study, Özen *et al.* (2002) measured trace element concentrations in the testis after subacute (4 weeks) and subchronic (13 weeks) formaldehyde exposures for 8 hours/day and 5 days/week. Both copper and zinc tissue concentrations decreased ($P < 0.001$) with subacute and subchronic exposure; however, iron levels increased with both exposure durations. The authors noted that decrease in zinc and copper concentrations might affect the functions of some antioxidant metalloenzymes that require these cofactors, such as superoxide dismutase.

Özen *et al.* (2008) investigated the effect of formaldehyde exposure on antioxidant enzymes in the testis. Adult Wistar rats (7 per group) were injected with formaldehyde (10 mg/kg b.w., intraperitoneally every other day for one month). Glutathione peroxidase, superoxide dismutase, and malondialdehyde testicular enzyme levels were determined; the levels of superoxide dismutase and glutathione peroxidase decreased significantly ($P < 0.001$) with formaldehyde exposure, whereas, the level of malondialdehyde increased significantly ($P < 0.001$) compared with control values. Co-treatment with melatonin (25 mg/kg of b.w., intraperitoneally) inhibited these effects.

A significant dose-related increase in rat sperm-head abnormalities 3 weeks after intraperitoneal injection of formaldehyde for five days (0.125, 0.250, and 0.50 mg/kg b.w. per day) was reported by Odeigah (1997). There was a lower frequency of fertile matings within the first two weeks after treatment, but not after 3 weeks. IARC (2006) questioned the biological significance of these findings because of the reactivity of formaldehyde and the parenteral route of exposure.

Majumder and Kumar (1995) treated adult male Wistar rats with intraperitoneal injections of formaldehyde (10 mg/kg b.w. per day) for 30 days. Animals were sacrificed on the 31st day, and testis, prostate, seminal vesicles, and epididymis were removed. Significant decreases were noted in sperm counts, viability, and motility in the treated group (Table 5-15). Protein and DNA content were measured in these tissues. Significant decreases in DNA content of the testis (9.8 ± 1.01 vs. 4.6 ± 0.37 µg/mg tissue, $P < 0.001$) and prostate (6.1 ± 1.39 vs. 1.2 ± 0.49 µg/mg tissue, $P < 0.001$) were reported for the treated group.

Table 5-15. *In vivo* effect of formaldehyde on spermatozoa

Parameters	Control mean ± SEM (N = 10)	Treated mean ± SEM (N = 8)
Sperm count (10^6/mL)	46.30 ± 5.01	20.40 ± 2.01***
Sperm viability (%)	87.10 ± 0.83	72.60 ± 2.32***
Sperm motility (%)	75.00 ±10.90	22.00 ± 6.40***

Majumder and Kumar 1995.
***$P < 0.001$ (compared with controls).

Chowdhury *et al.* (1992) treated Charles Foster rats with formaldehyde at intraperitoneal doses of 5, 10, and 15 mg/kg b.w. over 30 days. A significant decrease in testicular 3-ß,-Δ^5-hydroxy steroid dehydrogenase (determined by histochemical reaction intensity) and serum testosterone (420, 200, 195, 150 ng/dL for control and increasing dose groups, respectively, $P < 0.01$) was reported for formaldehyde-exposed groups. Leydig-cell nuclear diameter and cell number/cm^2 decreased.

Ward *et al.* (1984) investigated the effect of oral administration of 100 mg/kg b.w. formalin solution (37% formaldehyde, 10% methanol in water) by giving 5 daily doses to B6C3F$_1$ mice. Animals were sacrificed 5 weeks after treatment and sperm morphology analyzed. A nonsignificant increase in the percentage of abnormal sperm was reported for the formalin-exposed group as compared with the water-exposed control group (1.49 ± 0.90 vs. 1.12 ± 0.39%).

Two studies in birds examined testicular pathology after oral administration of formaldehyde. Japanese quail (Anwar *et al.* 2001) were fed formalin-containing feed (20, 10, 5, 2.5, and 0 mL/kg feed) for 8 weeks; relative testis weights and seminiferous tubule diameters were decreased significantly at the three highest doses ($P \leq 0.05$). In a separate study (Khan *et al.* 2003), formalin was either mixed in feed (2.5, 5, or 10 mL of 37% w/w formalin/kg feed) or a 3% solution was administered into the crops of White Leghorn cockerels (5, 10, 15, 20 mL/day). All of the groups given formalin had significantly smaller diameter seminiferous tubules than the control birds ($P \leq 0.05$). Further, testes absolute and relative mass and volumes were significantly decreased in the groups administered 3% formalin in the crop at 15 and 20 mL/day ($P \leq 0.05$).

5.6 Carcinogenicity studies of metabolites and analogues

Formic acid has not been evaluated for carcinogenicity. Acetaldehyde and glutaraldehyde are analogues of formaldehyde that have been tested for carcinogenicity by the NTP, as has the aromatic aldehyde benzaldehyde (see Section 1 for structures of the formaldehyde analogues). Other simple aldehydes, propionaldehyde, butyraldehyde, and n-pentanal, have not been tested in 2-year bioassays by the NTP, and no information on other chronic assays were identified.

Acetaldehyde is currently listed in NTP's Report on Carcinogens as *reasonably anticipated to be a human carcinogen*. Rats exposed by inhalation to acetaldehyde developed respiratory tract tumors (primarily adenocarcinoma and squamous-cell carcinoma of the nasal mucosa), while hamsters developed laryngeal carcinoma (IARC

1999). Epidemiological studies have reported increased risks of cancers of the upper digestive tract (especially esophageal) and stomach in people who have genetic polymorphisms leading to higher internal levels of acetaldehyde following heavy alcohol intake (reviewed by Salaspuro 2009, Lee *et al.* 2008b). In addition, there have been case reports of bronchial and oral cavity tumors among chemical workers exposed to various aldehydes.

Glutaraldehyde was tested for carcinogenicity in F344 rats and $B6C3F_1$ mice (NTP 1999). Rats were exposed to 0, 0.25, 0.5, or 0.75 ppm, and mice were exposed to 0-, 0.0625-, 0.125-, or 0.250-ppm glutaraldehyde vapor 6 hours/day, 5 days/week for 104 weeks. The NTP concluded that there was no evidence of carcinogenic activity of glutaraldehyde in either rats or mice. Hester *et al.* (2005) concluded that glutaraldeyde's lack of carcinogenicity might be due to a combination of its greater toxicity from lack of DNA repair, greater mitochondrial damage, and increased apoptosis compared with formaldehyde (see Section 5.6.5). Benzaldehyde in corn oil was administered by gavage 5 days/week to F344 male and female rats at 0, 200, or 400 mg/kg b.w. for 103 weeks, to male $B6C3F_1$ mice at 0, 200, or 400 mg/kg b.w. for 104 weeks, and to female $B6C3F_1$ mice at 0, 300, or 600 mg/kg b.w. for 103 weeks (NTP 1990). The NTP concluded that there was no evidence of carcinogenic activity of benzaldehyde for male and female rats and some evidence of carcinogenic activity for male and female mice as indicated by increased incidences of squamous-cell papilloma and hyperplasia of the forestomach.

5.7 Genetic and related effects

The genetic toxicology of formaldehyde has been investigated in a variety of *in vitro* and *in vivo* assays and has been reviewed (WHO 1989, IARC 1995, 2006, Conaway *et al.* 1996, ATSDR 1999, Liteplo and Meek 2003). This section summarizes the genetic effects in prokaryotes, non-mammalian eukaryotes, *in vitro* studies with mammalian and human cells, and *in vivo* studies in experimental animals. The genetic effects of formaldehyde in exposed humans are described in more detail in Section 5.6.4.

5.7.1 Prokaryotes

The studies summarized in this section include those reviewed by Conaway *et al.* (1996) and IARC (2006) (Table 5-16). Only one additional study published after IARC (2006) was identified (see discussion below).

All of the studies with *Salmonella typhimurium* strains TA102, TA104 and TA 7005 (one study) were positive for base-pair mutations in the presence or absence of metabolic activation. Most (67%) of the studies with TA100 were positive and all studies with TA1535 were negative. Results were mixed for frameshift mutations with *S. typhimurium* strains TA97, TA98, TA1537, and TA1538. One study with TA97 was positive without metabolic activation. Only two of seven studies with TA98 were positive without metabolic activation, but three studies with this strain were weakly positive with metabolic activation. All studies with TA1537 or TA1538 were negative, with or without metabolic activation. Ma and Harris (1988) reported that about 75% of the reverse mutation studies in *S. typhimurium* strains were positive. These authors noted that, in general, the mutation efficiency was higher in studies that used the preincubation

protocol (a test tube containing a suspension of the tester strain plus S9 mix or plain buffer without S9 is incubated for 20 minutes with the test chemical before adding agar and pouring into Petri dishes containing bacterial culture medium) compared with studies that used the plate incorporation protocol (no preincubation step prior to plating in Petri dishes).

Studies with *Escherichia coli* were positive for forward or reverse mutations without metabolic activation (Table 5-15) (Conaway *et al.* 1996, IARC 2006). The mutational spectrum in *E. coli* varied with concentration (Liteplo and Meek 2003). At 4 mmol/L, formaldehyde induced 41% large insertions, 18% large deletions, and 41% point mutations. Most of the point mutations were transversions at GC base pairs. However, at 40 mmol/L, point mutations (primarily transitions at a single AT base pair) accounted for 92% of the genetic alterations. In addition, formaldehyde caused differential toxicity, DNA strand breaks, DNA-protein crosslinks, and related DNA damage in *E. coli* (Table 5-16).

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Nakano *et al.* (2007) analyzed the roles of nucleotide excision repair and homologous recombination systems in the repair of DNA-protein crosslinks using *E. coli*. Wild-type and repair-deficient mutants were exposed to formaldehyde. Mutants included *E. coli* cells deficient in nucleotide excision repair (*uvrA*), homologous recombination (*recA*), translesion synthesis (*umuDC*), and both nucleotide excision repair and homologous recombination (*uvrA recA*). Both the *uvrA* and *recA* mutants were hypersensitive to formaldehyde (*recA* > *uvrA*), and a combination of these two mutants were more sensitive than single mutants. These data suggest that both nucleotide excision repair and homologous recombination systems are involved in repair of crosslinks, but differentially. Further tests indicated that nucleotide excision repair is involved with proteins of sizes less than 12 to 14 kDa, while larger crosslinks are repaired exclusively by RecBCD-dependent homologous recombination systems.

Salem *et al.* (2009) also reported differential toxicity in repair-deficient *E. coli* mutants exposed to formaldehyde. This study examined the sensitivities of *E. coli* mutants defective in nucleotide excision repair, homologous recombination, replication restart, translesion synthesis, base excision repair, transcription, and topological changes of chromosomes to formaldehyde. Nucleotide excision repair mutants exhibited varying degrees of sensitivity to formaldehyde, with the *dksA* mutant showing slight, but significant sensitivity. Among enzymes for homologous recombination, RecQ but RecJ was slightly sensitive to formaldehyde. Replication restart depends on PriA, PriB, and

PriC proteins, but only the *priA* mutant was hypersensitive to formaldehyde. The authors concluded that mutations in genes responsible for nucleotide excision repair, homologous recombination, and replication restart conferred slight but significant sensitivity to formaldehyde. They also noted that not much is known about the role of DNA topoisomerases in DNA repair in *E. coli*, but they reported that *topA* mutants were slightly sensitive to formaldehyde.

Wang *et al*. (2007) reported that formaldehyde treatment of *E. coli* resulted in a dose-dependent microsatellite instability. Their results showed that with 2.5 mM formaldehyde treatment, the complementary dinucleotide repeat microsatellites $(GpT)_n$ and $(ApC)_n$ were induced at different frequencies (13- to 24-fold vs. 2- to 3-fold higher than controls, respectively). The authors postulated that this could be due to the unprotected syn position of the guanosine nucleotides in the DNA; this may specifically involve the formation of a Z-DNA structure, which is a conformation that is more difficult for DNA repair enzymes to repair. They further hypothesized that the mutagenic mechanism of formaldehyde and the formation of Z-DNA might account for the observed microsatellite instability.

Table 5-16. Genetic effects of formaldehyde in bacteria

Test system	Effect	Results[a]	
		Without S9	With S9
S. typhimurium (strains not reported)	Forward mutation	+ (1/1)	+ (1/1)
	Reverse mutation	– (0/1)	– (0/1)
S. typhimurium			
TA100	Reverse mutation (base-pair)	(+) (8/12)	(+) (6/9)
TA102		+ (5/5)	+ (1/1)
TA104		+ (3/3)	+ (1/1)
TA1535		– (0/5)	– (0/5)
TA7005		+ (1/1)	NT
S. typhimurium			
TA97	Reverse mutation (frameshift)	+ (1/1)	NT
TA98		– (2/7)	± (3/6)
TA1537		– (0/5)	– (0/5)
TA1538		– (0/4)	– (0/3)
E. coli	Forward mutation	+ (3/3)	NT
	Reverse mutation	+ (13/13)	NT
	Strand breaks, crosslinks, related damage	+ (2/2)	NT
	Differential toxicity	+ (2/2)	NT
E. coli	Instability of induced microsatellites	+ (1/1)	NT

Source: Conaway *et al.* 1996, IARC 2006, Wang *et al*. 2007.
+ = positive studies; – = negative studies; (+) = mostly positive; (–) = mostly negative; ± = equal numbers of positive and negative studies; NT = not tested.
[a]Number of positive studies/total number of studies reviewed shown in parentheses.

5.7.2 Non-mammalian eukaryotes

Formaldehyde induced mutations, DNA damage, strand breaks, crosslinks, and other genetic effects (Table 5-17) in all studies in yeast, fungi, plants, insects, and nematodes (IARC 2006). A micronucleus study in newt larvae was negative. All of these studies were conducted in the absence of metabolic activation. Several of these studies compared effects in wild type and DNA repair-deficient organisms. For example, Magaña-Schwencke *et al.* (1978) reported that *Saccharomyces cerevisiae* strains that were deficient in excision repair were more susceptible to the lethal effects of formaldehyde and had a reduced capacity to undergo single-strand breaks compared with the wild type. The authors concluded that this indicates that single-strand breaks may be a step in the repair process for formaldehyde-induced lesions. The mutagenic effects of formaldehyde were also different in DNA repair-proficient and repair-deficient strains of *Neurospora crassa* (de Serres and Brockman 1999). The mutant frequencies in the repair-deficient strain were higher than in the repair-proficient strain.

Table 5-17. Genetic effects of formaldehyde in non-mammalian eukaryotes

Test system	Effect	Results[a] (without S9)
Saccharomyces cerevisiae	Gene conversion	+ (1/1)
	Strand breaks, crosslinks, related damage	+ (2/2)
	Homozygosis	+ (1/1)
Neurospora crassa	Forward mutation	+ (4/4)
	Reverse mutation	(-) (1/3)
Tradescantia pallida	Micronucleus	+ (1/1)
Various plants	Mutation	+ (1/1)
	DNA damage	+ (1/1)
Drosophila melanogaster	Genetic cross-over or recombination	+ (3/3)
	Sex-linked recessive lethal mutations	+ (8/8)
	Dominant lethal mutations	+ (2/2)
	Heritable translocation	+ (2/2)
	Gene mutation	+ (1/1)
Caenorhabditis elegans	Recessive lethal mutation	+ (1/1)
Pleurodeles waltl (newt larvae)	Micronucleus	– (0/1)

Sources: IARC 2006, Conaway *et al.* 1996.
+ = all studies were positive; ± = both positive and negative studies; – = negative study; (-) = mostly negative.
[a] Number of positive studies/total number of studies reviewed shown in parentheses.

5.7.3 Mammalian systems

Data are reported here for genetic tests in mammalian cells, including human cells, and in experimental animals. The reported effects of formaldehyde in mammalian systems include DNA adducts, DNA-protein crosslinks, strand breaks, clastogenic effects, mutations, unscheduled DNA synthesis, inhibition of DNA repair, and cell transformation. Section 5.6.5 discusses effects on gene expression in humans.

5.7.3.1 DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, and DNA damage

Findings from studies that evaluated exposure to formaldehyde and DNA adducts, DNA-protein crosslinks, and DNA strand breaks are summarized in Tables 5-18 (*in vitro* studies) and 5-19 (*in vivo* studies).

In vitro *studies*

Formaldehyde has been shown to react with mammalian cell DNA to form hydroxymethyl derivatives. Formaldehyde induced DNA adducts when reacted with deoxyribonucleosides (Cheng *et al.* 2008), calf thymus DNA (Von Hippel and Wong 1971, Beland *et al.* 1984), Chinese hamster ovary cells (Beland *et al.* 1984), human placental DNA (Zhong and Que Hee 2004a, 2005) and human nasal epithelial cells (Zhong and Que Hee 2004b, Speit *et al.* 2008b) (Table 5-18). Cheng *et al.* (2008) demonstrated that nitrosamines that generate formaldehyde during metabolism also form formaldehyde adducts when reacted with calf thymus DNA and deoxyribonucleosides. Using HPLC and NMR analysis, hydroxymethyl derivatives at the exocyclic amines of deoxyadenosine, deoxycytidine, and deoxyguanosine were identified after formaldehyde exposure of calf thymus DNA, and hydroxymethyl deoxythymidine derivatives were detected after exposure of Chinese hamster ovary cells (Beland *et al.* 1984). Formaldehyde (in solution, but not in air) was demonstrated to form the adducts N^6-hydroxymethyldeoxyadenosine (N^6-dA), N^2-hydroxymethyldeoxyguanosine (N^2-dG), and N^4-hydroxymethyldeoxycytidine (N^4-dC) in DNA of human nasal epithelial cell exposed to formaldehyde *in vitro* (Zhong and Que Hee 2004b) and in isolated human placental DNA reacted directly with formaldehyde *in vitro* (Zhong and Que Hee 2005). Formaldehyde-treated DNA and RNA have also yielded methylene-bridged crosslinks connecting exocyclic amino groups between nucleosides (Chaw *et al.* 1980). Huang *et al.* (1992) and Huang and Hopkins (1993) examined DNA interstrand crosslinking (DNA-DNA crosslinks) by formaldehyde and determined that dA to dA crosslinks at the sequence 5′-d(AT) were more abundant (no quantitation of duplexes reported) than the other five potential duplex dinucleotides of dA to dA at the sequence 5′-d(TA), dG to dG at either 5′-d(CG) or 5′-d(GC), or dA to dC at either 5′-d(AG) or 5′-d(GA).

Recently Lu *et al.* (2009) demonstrated that formaldehyde crosslinks DNA and glutathione to form *S*-[1-(N^2-deoxyguanosinyl)methyl]glutathione. The intermediate in this reaction, *S*-hydroxymethylglutathione, is involved in formaldehyde detoxification and is highly reactive. However, the authors noted that the adduct formed is reasonably stable and may be useful in biomarker studies of exogenous formaldehyde exposure.

Numerous *in vitro* studies have shown that formaldehyde exposure (concentrations ranging from 0.01 mM to 62.5 mM) causes DNA-protein crosslinks in human cells (EBV-Burkitt's lymphoma cells, fibroblasts, lymphocytes, gastric mucosa cells, lung/bronchial epithelial cells, skin keratinocytes, Jurkat E6-1 cells, HeLa cells, and whole blood) and rodent cells (Chinese hamster ovary cells, Chinese hamster V79 cells, mouse hepatocytes, mouse leukemia L1210 cells, rat Yoshida lymphosarcoma cells, rat tracheal epithelial cells, and rat hepatocytes) (Table 5-18). Formaldehyde readily reacts with hydrogens of amino groups forming stable methylene-bridged crosslinks between the amines of proteins and nucleic acids (Conaway *et al.* 1996). This reaction is specific for single-stranded DNA because hydrogen bonding with the opposite strand in double-

stranded DNA hinders the reactivity. DNA-protein crosslinks can lead to other genotoxic effects through subsequent DNA replication errors (Casanova *et al.* 1989, Liteplo and Meek 2003). In a later report, more than 100 proteins involved in formaldehyde-induced crosslinks were identified by mass spectrometry (Qiu and Wang 2009). HL-60 human acute promyelocytic leukemia cells were treated for 10 minutes with 45 mM formaldehyde. Crosslinks were purified from the nuclei and the crosslinking was reversed. The subsequent proteins were resolved by SDS-PAGE and identified via mass spectrometry of the in-gel tryptic digests. Many of the identified proteins are involved in transcription, gene regulation, DNA replication, and DNA repair. While the formaldehyde concentrations employed in this study were high, similar proteins are likely to be involved in crosslinks at concentrations employed in the studies outlined in Table 5-18 (*in vitro* studies of DNA adducts, DNA–protein crosslinks, and strand breaks in mammalian systems).

The reported removal half-times for these lesions in *in vitro* studies ranged from about 2 to 4 hours (Conaway *et al.* 1996, Cosma and Marchok 1988, Grafström *et al.* 1983, 1984). Craft *et al.* (1987) reported complete removal of DNA-protein crosslinks from human lymphoblasts within 24 hours. Liu *et al.* (2006) reported that DNA-protein crosslinks were significantly repaired in HeLa cells within 18 hours after removal of formaldehyde compared with a group without formaldehyde removal. In addition, single-strand breaks were significantly repaired within 30 minutes and were almost completely repaired within 90 minutes. Schmid and Speit (2007) treated human blood cultures with formaldehyde concentrations of up to 300 μM. DNA-protein crosslinks were significantly increased by concentrations ≥ 25 μM. Crosslinks induced by 100 μM formaldehyde were completely removed within 8 hours; however, at higher concentrations (200 or 300 μM), some crosslinks remained after 24 hours.

Formaldehyde exposure (concentrations ranged from 0.001 to 0.8 mM) also caused single-strand breaks in human cells (fibroblasts, lymphocytes, lung/bronchial epithelial cells, and HeLa cells, but not skin keratinocytes) and rodent cells (mouse leukemia L1210, rat Yoshida lymphosarcoma cells, rat tracheal epithelial cells, and rat hepatocytes, but not Chinese hamster V79 cells) (Table 5-18).

Using the alkaline comet assay, Speit *et al*. (2008b) compared the human cell response to formaldehyde in an established cell line (A549 lung cells) with that of primary cultured cells (human nasal epithelial) under various treatment conditions. They reported no fundamental differences in response between these cells, e.g., observing nonsignificant decreases in tail moment for both cell cultures at 0.1 mM formaldehyde treatment but a significant (1% level for Dunnett test) effect after a 4-hour treatment with 0.2 mM formaldehyde.

Table 5-18. *In vitro* studies of DNA adducts, DNA-DNA crosslinks, DNA-protein crosslinks and strand breaks in deoxyribonucleosides, synthetic oligonucleotides, mammalian DNA, and mammalian cells

Test system	Concentration (LEC or HIC)	Effect	Results	References
Deoxyribonucleosides	0.1 mM	Adducts	+	Cheng *et al.* 2008
Deoxyguanosine	0.5 mM	Adducts	+	Lu *et al.* 2009
Calf thymus DNA	[0.166 mM] 200 mM	Adducts	+ +	Beland *et al.* 1984 Von Hippel and Wong 1971
Chinese hamster ovary cells	1 mM	Adducts	+	Beland *et al.* 1984
Human placental DNA	3.34 mM	Adducts	+	Zhong and Que Hee 2004a, 2005
Human nasal epithelial cells	0.33 mM	Adducts	+	Zhong and Que Hee 2004b
DNA duplexes	25 mM	DDX	+	Huang *et al.* 1992, Huang and Hopkins 1993
Chinese hamster ovary cells	0.20 mM 0.25 mM 0.125 mM	DPX	+ + +	Zhitkovich and Costa 1992 Olin *et al.* 1996 Garcia *et al.* 2009
DNA	200 mM	DDX	+	Chaw *et al.* (1980)
Yeast RNA	200 mM	RRX	+	Chaw *et al.* (1980)
DNA + glutathione	0.5 mM	DNA-GSH	+	Lu *et al.* (2009)
Chinese hamster V79 cells	0.12 mM 0.01 mM 0.125 mM 0.2 mM 62.5 mM	DPX	+ +[a] + –[b] +	Swenberg and al. 1983b Speit *et al.* 2007a Merk and Speit 1998 Speit *et al.* 2007a Merk and Speit 1999
Mouse hepatocytes	0.5 mM 0.5 mM	DPX	+ +	Casanova and Heck 1997 Casanova *et al.* 1997
Mouse leukemia L1210 cells	0.125 mM 0.2 mM	DPX	+ +	Ross *et al.* 1981 Ross and Shipley 1980
Rat Yoshida lymphosarcoma cells	0.25 mM	DPX	+	O'Connor and Fox 1987
Rat tracheal epithelial cells	0.05 mM	DPX	+	Cosma *et al.* 1988a
Rat hepatocytes	0.5 mM	DPX	+	Casanova and Heck 1997
Human EBV-Burkitt's lymphoma cells	0.003%	DPX	+	Costa *et al.* 1997
Human fibroblasts (skin or bronchus)	0.1 mM 0.2 mM 0.25 mM	DPX	+ + +	Snyder and Van Houten 1986 Grafström *et al.* 1984 Olin *et al.* 1996
Human lymphocytes	0.05 mM 0.05 mM 0.1 mM	DPX	+ + +	Craft *et al.* 1987 Liu *et al.* 2006 Shaham *et al.* 1996a

Test system	Concentration (LEC or HIC)	Effect	Results	References
	0.1 mM		+	Andersson *et al.* 2003
Human gastric mucosa cells	1 mM	DPX	+	Blasiak *et al.* 2000
Human nasal epithelial cells	0.20 mM	DPX	+	Speit *et al.* 2008b
Human lung/bronchial epithelial cells	0.1 mM 0.2 mM 0.2 mM 0.2 mM 0.4 mM 0.8 mM	DPX	+ + + + + +	Saladino *et al.* 1985 Grafström *et al.* 1984 Grafström *et al.* 1986 Speit *et al.* 2008b Grafström 1990 Fornace *et al.* 1982
Human skin keratinocytes and fibroblasts	0.025 mM	DPX	+	Emri *et al.* 2004
Human Jurkat E6-1 cells	1 mM	DPX	+	Saito *et al.* 2005
HeLa cells	0.05 mM	DPX	+	Liu *et al.* 2006
Human whole blood	0.025 mM	DPX	+	Schmid and Speit 2007
Mouse leukemia L1210 cells	0.125 mM 0.2 mM	SB	– +	Ross *et al.* 1981 Ross and Shipley 1980
Rat Yoshida lymphosarcoma cells	0.25 mM	SB	+	O'Connor and Fox 1987
Rat tracheal epithelial cells	0.2 mM	SB	+	Cosma *et al.* 1988a
Rat hepatocytes	0.75 mM	SB	+	Demkowicz-Dobrzanski and Castonguay 1992
Chinese hamster V79 cells	0.2 mM	SB	–	Speit *et al.* 2007a
Human fibroblasts (skin or bronchus)	0.1 mM 0.1 mM	SB	+ +	Grafström *et al.* 1984 Snyder and Van Houten 1986
Human lymphocytes	0.005 mM	SB	+	Liu *et al.* 2006
Human lung/bronchial epithelial cells	0.1 mM 0.3 mM 0.4 mM 0.8 mM 1 mM	SB	+ + + + +	Saladino *et al.* 1985 Grafström *et al.* 1984 Grafström 1990 Fornace *et al.* 1982 Vock *et al.* 1999
Human skin keratinocytes and fibroblasts	0.1 mM	SB	–	Emri *et al.* 2004
HeLa cells	0.005 mM	SB	+	Liu *et al.* 2006

+ = positive result for indicated effect; – = negative result for the indicated effect.
DDX = DNA-DNA crosslinks; DNA-GSH = *S*-[1-(N^2-deoxyguanosinyl)methyl]glutathione; DPX = DNA-protein crosslinks; HIC = highest ineffective concentration; LEC = lowest effective concentration; RRX = RNA-RNA crosslinks; SB = DNA strand breaks (most were single-strand breaks).
[a]Extended electrophoresis time.
[b]Standard conditions.

In vivo *studies*

No *in vivo* studies were identified that evaluated DNA adducts in experimental animals exposed directly to formaldehyde, but one study reported induction of DNA adducts of formaldehyde in rats treated with carcinogenic nitrosamines. Several studies reported DNA-protein crosslinks and strand breaks (Table 5-19) in animals exposed directly to formaldehyde. Inhalation exposure to formaldehyde caused DNA-protein crosslinks (0.3 ppm to 6 ppm) in rodents (nasal mucosa but not bone marrow) and rhesus monkeys (nasal turbinates, nasopharynx, trachea, and bronchi, but not sinus or lung), and strand breaks (5 ppm) in rats (lymphocytes and liver). Instillation of formaldehyde into rat tracheal implants also caused DNA-protein crosslinks. Transplacental exposure to formaldehyde caused both DNA-protein crosslinks and single-strand breaks in the rat fetal liver. These findings are discussed in greater detail below.

Wang *et al.* (2007b) demonstrated that formaldehyde-based DNA adducts were formed in the lung and liver of rats treated subcutaneously with two *N*-nitrosomethyl carcinogens, which both metabolize to formaldehyde. The authors provided qualitative and quantitative (statistical significance not given) evidence for *in vivo* formaldehyde-DNA adduct formation for both compounds and suggested that the formaldehyde released by the metabolism of the carcinogens contributes to adduct formation and may, therefore, play a role in the carcinogenic process.

Crosslink formation is an important indicator of tissue and DNA exposure; however, the shape of the concentration-response curve is highly non-linear, showing a sharp increase in the nasal epithelium of rats at concentrations greater than 2 ppm, and without accumulation on repeated exposure (Casanova-Schmitz *et al.* 1984a, Casanova *et al.* 1989, Casanova *et al.* 1994). Casanova-Schmitz *et al.* (1984a) exposed male F344 rats for 6 hours to formaldehyde concentrations of 0.3, 2, 6, 10, or 15 ppm. Covalent binding of formaldehyde to respiratory mucosal DNA occurred at concentrations ≥ 2 ppm; however, the concentration bound to DNA at 6 ppm was 10.5-fold higher than at 2 ppm. Casanova *et al.* (1989) exposed groups of F344 rats to formaldehyde concentrations of 0.3, 0.7, 2, 6, or 10 ppm for 6 hours. DNA-protein crosslinks occurred at all concentrations, but the slope of the concentration-response curve at 10 ppm was 7.3-fold greater than at 0.3 ppm. Casanova *et al.* (1994) compared the yield of crosslinks between groups of pre-exposed and naïve male F344 rats. Groups were pre-exposed to 0.7, 2, 6, or 15 ppm in one experiment and 6 or 10 ppm in another experiment (6 hours/day, 5 days/week) for 11 weeks and 4 days while naïve rats were exposed to room air. On the fifth day of the twelfth week animals were simultaneously exposed (3 hours) to the same concentrations used in pre-exposure. Crosslink yields increased nonlinearly in a concentration-dependent manner in both pre-exposed and naïve groups, but the yields were smaller in pre-exposed rats, suggesting that accumulation of crosslinks did not occur. At low concentrations (≤ 2 ppm) crosslink yields were similar in pre-exposed and naïve rats, but at higher concentrations, crosslink yields were greater in naïve than in pre-exposed rats.

Cosma *et al.* (1988b) used an open-ended, flow-through rat tracheal implant model to investigate DNA-protein crosslinks caused by benzo[*a*]pyrene and formaldehyde. Two tracheas from male F344 rats were implanted subcutaneously in the retroscapsular region

of syngeneic recipients. After 4 weeks, both ends of the tracheal implants were connected to the surface by two terminal tracheostomies. The tracheas were exposed twice weekly for 2, 4, or 8 weeks to gelatin pellets containing 0.005, 0.01, 0.05, or 2% formaldehyde. There was a dose-dependent increase in crosslinks in the tracheal epithelium. The authors also compared the induction and removal of crosslinks following single and multiple exposures. The response was virtually identical for exposure either once or 5 times twice weekly to 0.2% formaldehyde when measured 3 hours after the last exposure. The removal of crosslinks following one or four exposures demonstrated nearly complete repair in either case by 72 hours.

DNA-protein crosslink yields were about six-fold higher in the lateral meatus (an area of high tumor yield) than in the medial or posterior meatuses (areas with low tumor yield) of the rat nose (Casanova *et al.* 1994). In male rhesus monkeys, crosslink concentrations in the nose were highest in the middle turbinates while lower concentrations occurred in the anterior lateral wall, septum, and nasopharynx (Heck *et al.* 1989, Casanova *et al.* 1991). Low, but statistically significant concentrations of crosslinks were found in the larynx, trachea, carina, or the proximal portions of the major bronchi in monkeys exposed to 2 or 6 ppm but not to 0.7 ppm. No crosslinks were found in the maxillary sinuses or lung parenchyma in any of the nine monkeys tested.

Crosslinks and strand breaks in tissues other than the upper respiratory tract also have been reported in rodents. Wang and Liu (2006) (reported in an English abstract) investigated developmental and maternal toxicity in mice. Pregnant mice were injected with 0.2 to 20 mg/kg b.w. per day from gestation day 6 to 19. Single-cell gel electrophoresis was used to test for DNA damage (crosslinks and breaks) in maternal and fetal liver cells. There was no DNA damage in the livers of fetal mice in the low-dose group; however, increased DNA breakage was observed in the group exposed to ≥ 1 mg/kg per day, and increased DNA-protein crosslinks occurred at 2 to 20 mg/kg per day. DNA damage increased with dose in the dams, beginning at 0.2 mg/kg per day, but no increase in DNA-protein crosslinks was observed.

Im *et al.* (2006) evaluated the genotoxic effects of formaldehyde exposure in rat lymphocytes and liver. Male Sprague-Dawley rats (10 per group) were exposed to 0-, 5-, or 10-ppm formaldehyde 6 hours/day, 5 days/week for 2 weeks in an inhalation chamber. The comet assay was used to evaluate DNA single-strand breaks. Exposure to 5- or 10-ppm formaldehyde resulted in a significant, and dose-dependent, increase in single-strand breaks in both lymphocytes and liver. Speit (2006) criticized this study and stated that formaldehyde-induced DNA-protein crosslinks would be expected to reduce DNA migration as measured by the comet assay. One study found no crosslinks in bone marrow of rats exposed to 15-ppm formaldehyde for 6 hours (Casanova-Schmitz *et al.* 1984a).

Lutz (1986) evaluated the levels of DNA-protein crosslinks produced from endogenous formaldehyde generation. This author determined the level of DNA-protein crosslinks in rat liver under conditions of maximum intracellular formaldehyde generation and compared the results with positive control data from *in vitro* incubations of liver homogenate with formaldehyde and methanol and with literature data on crosslinks in the

rat nasal epithelium. Since endogenous formaldehyde is generated by oxidation of methanol (primarily in the liver), male Sprague-Dawley rats were given 1 g methanol per kg body weight by gavage. Another group also received 0.6 g/kg disulfiram, an inhibitor of acetaldehyde oxidation, under the assumption that higher steady-state levels of formaldehyde might be achieved. After 4 hours, the rats were given ethanol by gavage to inhibit further methanol oxidation, and were killed to isolate the chromatin fraction from the liver. The levels of endogenous formaldehyde formed in the liver did not cause an increase in DNA-protein crosslinks.

Table 5-19. *In vivo* studies of DNA-protein crosslinks and strand breaks in mammalian systems

Test system	Concentration (LEC or HIC)[a]	Effect	Results	References
Rat (nasal mucosa)	0.3 ppm	DPX	+	Casanova *et al.* 1989
	0.7 ppm[b]		+	Casanova *et al.* 1994
	2 ppm		+	Casanova-Schmitz *et al.* 1984a
	2 ppm		+	Heck *et al.* 1986
	2 ppm		+	Casanova and Heck 1987
	6 ppm		+	Lam *et al.* 1985
Rat (bone marrow, olfactory mucosa)	15 ppm	DPX	–	Casanova-Schmitz *et al.* 1984a
Rat (tracheal implant)	0.005%[c]	DPX	+	Cosma *et al.* 1988b
Rat (fetal liver)	0.2 mg/kg[d]	DPX	+	Wang and Liu 2006
Rhesus monkey (nasal turbinates)	0.7 ppm	DPX	+	Heck *et al.* 1989
	0.7 ppm		+	Casanova *et al.* 1991
Rhesus monkey (larynx, trachea, carina, bronchi)	2 ppm	DPX	+	Casanova *et al.* 1991
Rhesus monkey (maxillary sinuses, lung)	6 ppm	DPX	–	
Rat (lymphocytes)	5 ppm[e]	SB	+	Im *et al.* 2006
Rat (liver)	5 ppm[e]	SB	+	
Rat (maternal liver)	0.2 mg/kg[d]	SB	+	Wang and Liu 2006
Rat (fetal liver)	1 mg/kg[d]	SB	+	

+ = positive result for indicated effect; – = negative result for indicated effect.
DPX = DNA-protein crosslinks; HIC = highest ineffective concentration; LEC = lowest effective concentration; SB = DNA strand breaks (most were single-strand breaks).
[a]Single inhalation exposure (3-6 h) unless otherwise noted.
[b]Included pre-exposed groups (6 h/day, 5 d/wk, 11 wk + 4 d).
[c]Instillation exposure twice weekly for 2, 4, or 8 wk.
[d]Intraperitoneal injection to pregnant mice on gestation days 6 to 19.
[e]5 d/wk for 2 wk.

5.7.3.2 Cytogenetic effects

Studies evaluating cytogenetic effects (SCE, micronucleus formation, and chromosomal aberrations) due to formaldehyde exposure are described below and summarized in Tables 5-20 and 5-21.

In vitro *studies*

In human and animal cells formaldehyde exposure (0.03 to 2 mM) caused SCE (Chinese hamster ovary cells, Chinese hamster V79 lung fibroblast cells, human lymphocytes, and human whole blood), chromosomal aberrations (Chinese hamster ovary cells, Chinese hamster lung cells, Syrian hamster embryo cells, human lymphocytes and human fibroblasts), and micronuclei (Chinese hamster V79 cells, human MRC5CV cells, and human whole blood) (Table 5-20). All of the reported studies showed a positive correlation between formaldehyde treatment and observed effect, although the lowest effective concentration varied with different test systems, as well as for the same cell assay under similar or modified conditions.

Recent studies have characterized the cytogenetic effects in more detail. Speit *et al.* (2000) reported that the frequency of micronuclei was increased (statistics not reported) in two different DNA-repair-deficient cell lines (xeroderma pigmentosum and Fanconi anemia) compared with human cell lines with normal repair. Repeated treatments with formaldehyde (3 treatments with time intervals of 3 hours) to Chinese hamster V79 cultures increased micronucleus frequency (statistics not reported) compared with cultures receiving a single treatment, but the effect was not seen when the interval between treatments was 24 hours) (Speit *et al.* 2007a). Schmid and Speit (2007) reported that exposure to formaldehyde only increased micronucleus formation in human blood cultures using protocols in which formaldehyde was added 44 hours after the start of culture (i.e., the last cell cycle before preparation). In their study, 81% of micronuclei were centromere negative, compared with 55% centromere-negative micronuclei in controls.

Characterization of the genotoxic action of formaldehyde was investigated in a study utilizing the SCE assay in two mammalian cell lines, Chinese hamster V79 lung fibroblasts and human A549 lung cells (Neuss and Speit 2008). For each of these cell lines, treatment with 0.1 mM formaldehyde for 1 hour, then growth in the presence of BrdU for two cell cycles, resulted in statistically significant ($P < 0.01$) SCE induction. When the V79 cells were treated with formaldehyde for 1 hour then cultured with BrdU 4 hours later, the effective concentration was increased to 0.2 mM, suggesting DNA repair. Further, when the A549 cells were treated with 0.05 mM formaldehyde for 1 hour then co-cultured with V79 cells immediately, there was enough formaldehyde still present to significantly ($P < 0.05$) induce SCE in the V79 cells. When the A549 cells were treated at a maximum dose of 0.3 mM, then washed before co-cultivating with V79 cells, there was no SCE induction in the V79 cells. The authors suggested that this lack of response indicated that the formaldehyde was bound and/or inactivated in the A549 cells.

Although most of these *in vitro* studies did not report any cytotoxicity findings, in five of the studies cytotoxic effects were observed in cells treated with doses at which significant cytogenetic effects were also reported. In 1986, Schmid *et al.* noted that 0.25 and 0.5 mM formaldehyde treatments had a marked effect on cultured human lymphocytes and that there was no cell proliferation at all in cells treated with 1.0 mM formaldehyde. Merk and Speit (1998) evaluated cytotoxicity in V79 cells using relative cloning efficiency as a measure of long-term survival. In this study, treatment of cells with 0.125 mM formaldehyde significantly ($P < 0.05$) reduced the clonal growth of the cells to about

72% of controls. Treatments of clearly genotoxic doses of 0.25 and 0.5 mM formaldehyde reduced the relative cloning efficiency in these cells to 40% and less than 10%, respectively.

According to Schmid and Speit (2007), the cytotoxic effect of formaldehyde appears to be concurrent with, or may even precede, the genotoxic response. Specifically, they noted a reduction in the proliferation index (i.e., increased cytotoxicity) of the blood cultures treated with 0.2 mM formaldehyde, a dose at which SCE were significantly induced. Further, there was a nonsignificant cytotoxic effect noted at 0.1 mM formaldehyde treatment, which also showed an increased, although not statistically significant, induction of SCE. Interestingly, in a different paper that used V79 Chinese hamster cells, the same authors (Speit *et al.* 2007a), reported that SCE was significantly ($P < 0.01$) induced at 0.1 mM formaldehyde treatment; however, in these cells the proliferation index was not reduced, but was equivalent to the control value.

Cytotoxic effects of formaldehyde were evaluated in the human A549 cell line by Speit *et al*. (2008b) by measuring colony-forming ability and cell growth inhibition. With continuous two-week exposure to 0.02 mM formaldehyde, colony-forming ability was significantly reduced to approximately 40% of controls; cell growth was reduced to less than 20% with a continuous 48-hour treatment with 0.2 mM formaldehyde (significance for both determined using Dunnett's test, 1% level [$P < 0.01$] of significance). Also reported was a nonsignificant reduction (about 80% of controls) in cell growth measured after a one-hour treatment with up to 0.5 mM formaldehyde.

Table 5-20. *In vitro* studies of cytogenetic effects of formaldehyde in mammalian cells

Effect	Test system	Lowest effective concentration[a], treatment duration		Result	Cytotoxicity or RTG (% survival)	References
SCE	Chinese hamster ovary cells	[0.03 mM]	24 h	+	ND	Obe and Beek 1979
		[0.2 mM]	2 h	+	ND	Natarajan *et al.* 1983
		[0.04 mM]	26 h	+	NA	Galloway *et al.* 1985
		0.15 mM	1 h	+	ND	Garcia *et al.* 2009
	Chinese hamster V79 cells	0.067 mM	28 h	+	ND	Basler *et al.* 1985
		0.13 mM	2 h	+	ND	Basler *et al.* 1985
		0.1 mM	2 h	+	100[b]	Speit *et al.* 2007a
		0.125 mM	4 h	+	72[c],92[c]	Merk and Speit 1998, 1999
	Co-cultivation study[d]					
	A549 human lung cells	0.1 mM	1 h	+	ND	Neuss and Speit 2008
	V79 cells (4 h recovery)	0.2 mM	1 h	+	ND	
	V79 cells + A549 cells	0.05 mM	1 h	+[c]	ND	
	Human lymphocytes	0.125 mM	1 h	+	67[c,e]	Schmid *et al.* 1986
		[0.167 mM]	24 h	+	ND	Obe and Beck 1979
		[0.167 mM]	72 h	+	20	Kreiger and Garry 1983
	Human whole blood	0.2 mM	72 h	+	75[c]	Schmid and Speit 2007

Effect	Test system	Lowest effective concentration[a], treatment duration	Result	Cytotoxicity or RTG (% survival)	References
CA	Chinese hamster ovary cells	[0.53mM] 8–12 h [0.2 mM] 2 h 0.15 mM 2 h	+ + +	NA ND ND	Galloway *et al.* 1985 Natarajan *et al.* 1983 Garcia *et al.* 2009
	Chinese hamster lung fibroblasts	[0.6 mM] 24 h	+	ND	Ishidate *et al.* 1981
	Syrian hamster embryo cells	0.033 mM 24 h 0.33 mM[f] 24 h	+ +	94 91	Hikiba *et al.* 2005 Hagiwara *et al.* 2006
	Human lymphocytes	0.5 mM 1 h 0.33 mM NA 0.125 mM 1 h	+[c] +[g] +[h]	0[c,e] NA ND	Schmid *et al.* 1986 Miretskaya and Shvartsman 1982 Dresp and Bauchinger 1988
	Human fibroblasts	2 mM 0.25 h	+	ND	Levy *et al.* 1983
MN	Chinese hamster V79 cells	0.075 mM 2 h 0.125 mM 4 h	+ +	ND 72[c]	Speit *et al.* 2007a Merk and Speit 1998
	Human MRC5CV (normal) XP cell line (repair deficient) FA cell line (repair deficient)	0.125 mM 2 h	+[i]	ND	Speit *et al.* 2000
	Human whole blood	0.3 mM 72 h	+[j]	77[c]	Schmid and Speit 2007

+ = positive result for indicated effect; – = negative result for indicated effect.
CA = chromosomal aberration; FA = Fanconi anemia; MN = micronucleus; NA = not available; ND = not done; RTG = relative total growth; SCE = sister chromatid exchange; XP = xeroderma pigmentosum.
[a]Units in brackets [ ] were converted to mM from reported exposure data to facilitate comparison.
[b]Cytotoxicity measured by calculating proliferation index, which was equal to control (estimated from graph) at this dose.
[c]Estimated data from graph.
[d]A549 cells treated with formaldehyde for 1 h then co-cultivated with V79 showed induction of SCE in V79; however, when A549 cell medium was changed after formaldehyde treatment, no SCE induction was observed in V79 cells.
[e]Cytotoxicity was based on third cycle metaphase measured, as compared with control.
[f]Treatment substance was formocresol, potential confounding effect due to formaldehyde component.
[g]As cited by IARC 2006.
[h]Dose was negative with standard method, but positive in modified (premature chromosome condensation) technique.
[i]The effect was enhanced in the repair-deficient cell lines compared with the normal cell line.
[j]Modified protocol: cells were cultured 44 hours before treatment; treatments at 0 and 24 hours were negative at this dose.

In vivo *studies*

Formaldehyde did not cause micronucleus formation (in the bone marrow, peripheral blood or reticulocytes) or chromosomal aberrations (in bone marrow, spleen, or spermatocytes) of mice exposed to formaldehyde by intraperitonealor intravenous injection or by mouth; no inhalation studies were available in mice. *In vivo s*tudies in rats gave mixed results. Kligerman *et al.* (1984) did not find SCE or chromosomal aberrations

in lymphocytes of F344 rats exposed to 15-ppm formaldehyde 6 hours/day for 5 days. Increasing the duration of the 15-ppm formaldehyde treatment to 4 weeks did not yield SCE, chromosomal aberrations, or micronuclei in peripheral blood of F344 male rats (Speit *et al.* 2009). When administered in a single oral dose of 200 mg/kg to Sprague-Dawley rats, formaldehyde induced micronuclei in the gastrointestinal tract (Migliore *et al.* 1989). Dallas *et al.* (1992) investigated chromosomal aberrations in pulmonary lavage cells and bone marrow of male Sprague-Dawley rats exposed to 0-, 0.5-, 3-, or 15-ppm formaldehyde for 6 hour/day, 5 days/week, for 1 to 8 weeks. There was no significant increase in chromosomal aberrations in bone marrow, but there was a statistically significant increase in chromosomal aberrations in pulmonary lavage cells in the high-dose group. Kitaeva *et al.* (1990) investigated cytogenetic effects of inhaled formaldehyde in the bone marrow of female Wistar rats exposed to 0.5 or 1.5 mg/m^3 [0.4-ppm or 1.2-ppm] formaldehyde for 4 hours/day (except weekends and holidays) for 4 months. Bone marrow was collected within 48 to 72 hours after exposure was stopped. There was a statistically significant increase in the number of bone marrow cells with chromosomal aberrations at both dose levels compared with controls.

Table 5-21. Cytogenetic effects of formaldehyde in mammals *in vivo*

Effect	Test system	Concentration LEC/HIC	Result	References
SCE	F344 rat (lymphocytes, inh., 6 h/d, 5 d)	15 ppm	–	Kligerman *et al.* 1984
	F344 male rat (peripheral blood, inh., 6h/d, 5 d/wk, 4 wk)	15 ppm	–	Speit *et al.* 2009
CA	F344 rat (lymphocytes, inh., 6 h/d, 5 d)	15 ppm	–	Kligerman *et al.* 1984
	F344 male rat (peripheral blood, inh, 6h/d, 5 d/wk, 4 wk)	15 ppm	–	Speit *et al.* 2009
	Sprague-Dawley rat (bone marrow, inh., 6 h/d, 1–8 wk)	15 ppm	–	Dallas *et al.* 1992
	Sprague-Dawley rat (pulmonary lavage cells, inh., 6 h/d, 1–8 wk)	15 ppm	+	
	Wistar rat (bone marrow, inh., 4 h/d, 4 mo)	0.4 ppm	+	Kitaeva *et al.* 1990
	Mouse (bone marrow, i.p.)	25 mg/kg	–	Natarajan *et al.* 1983
	Mouse (spleen, i.p.)	25 mg/kg	–	Natarajan *et al.* 1983
	Mouse (spermatocytes, i.p.)	50 mg/kg	–	Fontignie-Houbrechts 1981
MN	Sprague-Dawley rat (p.o.)	200 mg/kg	+	Migliore *et al.* 1989
	F344 male rat (peripheral blood, inh, 6 h/d, 5 d/wk, 4 wk)	15 ppm	–	Speit *et al.* 2009
	Mouse (bone marrow, i.p.)	30 mg/kg	–	Gocke *et al.* 1981
	CD-1 mouse (bone marrow or peripheral blood, p.o.)	200 mg/kg	–	Morita *et al.* 1997
	CD-1 mouse (reticulocytes, i.v.)	30 mg/kg	–	

+ = positive result for indicated effect; – = negative result for indicated effect.
CA = chromosomal aberration; LEC = lowest effective concentration; HIC = highest ineffective concentration; inh. = inhalation; i.p. = intraperitoneal; i.v. = intravenous; MN = micronucleus; p.o. = *per os* (by mouth); SCE = sister chromatid exchange.

5.7.3.3 Mutations

Formaldehyde exposure has caused mutations in mammalian cells *in vitro* and dominant lethal mutations in mice and rats (Table 5-22). All but one of the *in vitro* studies was positive. Two intraperitoneal injection studies reported negative results for dominant lethal mutations in mice, while one study (given a higher dose) reported a weak positive response. Dominant lethal mutations were observed in rats exposed to formaldehyde by inhalation and intraperitoneal injection.

Heritable mutations in mice were reported in a study by Liu *et al*. (2009b) exposing male specific-pathogen-free ICR mice to 2 to 200 mg/m^3 [1.6 to 163-ppm] formaldehyde (formalin vapor) for 2 hours. After a 6-week recovery, the mice were bred and sperm DNA was extracted from the male mice. Somatic DNA for analysis was extracted from tail tissue of both parents as well as from offspring. Utilizing three expanded simple

tandem repeats (ESTR) probes, mutation rates were quantitatively and qualitatively evaluated to be both dose dependent and mainly inherited from the paternal germ line. The authors speculated that ramifications of this altered DNA, and subsequent abnormal protein expression, could result in malformations in the offspring.

Table 5-22. Mutagenic effects of formaldehyde in mammalian systems

Test system	Concentration LEC/HIC	Result	References
In vitro			
Chinese hamster V79 cells (*Hprt* locus)	0.3 mM 0.5 mM	+ –	Grafström *et al.* 1993 Merk and Speit 1998, 1999
Mouse lymphoma L5178Y cells ($Tk^{+/-}$ locus)	0.8 mM > 0.067 mM	+ +	Mackerer *et al.* 1996 Speit and Merk 2002
Human lymphoblast (TK6)	0.13 mM 0.03 mM 0.15 mM 0.15 mM	+ + + +	Goldmacher and Thilly 1983 Craft *et al.* 1987 Crosby *et al.* 1988 Liber *et al.* 1989
Human bronchial fibroblasts and epithelial cells (HPRT locus)	0.1 mM 0.1 mM	+ +	Grafström *et al.* 1985 Grafström 1990
In vivo			
Mouse (dominant lethal, i.p.)	20 mg/kg 20 mg/kg 50 mg/kg	– – (+)	Epstein and Shafner 1968 Epstein *et al.* 1972 Fontignie-Houbrechts 1981
Rat (dominant lethal, inh., 4 h/d, 4 mo)	1.2 ppm	(+)	Kitaeva *et al.* 1990
Rat (dominant lethal, i.p.)	0.125 mg/kg	+	Odeigah 1997
Mouse (heritable mutation, inh.)	200 mg/m^3	+	Liu *et al*. 2009b

+ = positive study; (+) = weak positive study; – = negative study.
inh. = inhalation; i.p. = intraperitoneal; LEC = lowest effective concentration; HIC = highest ineffective concentration.

5.7.3.4 Other effects

Other genetic and related effects reported in mammalian *in vitro* studies include unscheduled DNA synthesis (UDS), inhibition of DNA repair, and cell transformation (Table 5-23). UDS was observed in rat hepatocytes (Williams *et al.* 1989), Syrian hamster embryo cells (Hamaguchi and Tsutsui 2000), and human HeLa cells (Martin *et al.* 1978), but not in human bronchial epithelial cells (Doolittle *et al.* 1985). Other studies indicate that formaldehyde can inhibit DNA repair processes (Grafström *et al.* 1984, Speit *et al.* 2000, Emri *et al.* 2004) and induce cell transformation (Ragan and Boreiko 1981). Emri *et al.* (2004) investigated the interactions of low concentrations of formaldehyde and UV radiation in human skin cells. Keratinocytes and fibroblasts exposed to 10 µM formaldehyde prior to UV irradiation inhibited DNA repair kinetics after UVB and UVC, but not after UVA irradiation. Single-strand breaks that were repaired within 3 to 6 hours following exposure to UVB or UVC radiation, were still present at these time points in the presence of formaldehyde. UVC-induced chromosomal

damage was also increased in the presence of formaldehyde at a concentration (12.5 μM) that did not cause micronuclei. These authors concluded that environmental exposure to formaldehyde might contribute to UV-induced skin carcinogenesis.

Table 5-23. Other genetic effects of formaldehyde in mammalian systems *in vitro*

Test system	Concentration LEC/HIC	Effect	Result	References
Rat hepatocytes	400 mM	UDS	+	Williams *et al.* 1989
Syrian hamster embryo cells	0.1 mM	UDS	+	Hamaguchi and Tsutsui 2000
Human HeLa cells	10^{-5} mM	UDS	+	Martin *et al.* 1978
Human bronchial epithelial cells	0.1 mM	UDS	–	Doolittle *et al.* 1985
Human bronchial epithelial cells and fibroblasts and skin fibroblast	0.2 mM	DNA repair (inhibition)	+	Grafström *et al.* 1984
Human MRC5CV normal cells XP cell line (repair defcient) FA cell line (repair deficient)	0.125 mM	DNA repair (inhibition)	+	Speit *et al.* 2000
Human skin fibroblasts and keratinocytes	10 mM	DNA repair (inhibition)	+	Emri *et al.* 2004
C3H10T1/2 mouse cells	0.017 mM	Cell transformation	+[a]	Ragan and Boreiko 1981

+ = positive study; – = negative study.
HIC = highest ineffective concentration; LEC = lowest effective concentration; UDS = unscheduled DNA synthesis.
[a]Positive only in the presence of 12-*O*-tetradecanoylphorbol 13-acetate.

5.7.4 Human in vivo *studies*

The genetic effects of formaldehyde have been investigated in humans that were exposed in a number of settings (e.g., hospitals, pathology and anatomy laboratories, woodworking facilities, formaldehyde manufacturing facilities, mortuaries, and residences) and are described below. Most of these studies were reviewed by WHO (1989), Conaway *et al.* (1996), IARC (1995, 2006), or Liteplo and Meek (2003).

5.7.4.1 Protein and DNA adducts, DNA-protein crosslinks and strand breaks

Pala *et al.* (2008) investigated the relationship between occupational exposure to formaldehyde with biological markers of exposure (formaldehyde human serum albumin conjugate) and biological markers of effect (chromosomal aberrations, SCE, and micronuclei). This study included 36 laboratory workers at a cancer research institute. The workers were divided into a high-formaldehyde-exposure group (≥ 26 μg/m^3 [≥ 21 ppm]) that included 9 subjects (5 males, 4 females, mean age 41.6, 11.1% light smokers and 88.9% non-smokers) and a low-exposure group (< 26 μg/m^3 [< 21 ppm]) that included 27 subjects (7 males, 20 females, mean age 39.7, 18.5% light smokers, 81.5% non-smokers). No unexposed control group was included. Formaldehyde-albumin adducts were significantly higher in the workers with high exposure to formaldehyde

compared with workers with low exposure to formaldehyde, and the effect remained statistically significant after adjustment for sex, age, and exposure to paints. This study also evaluated biomarkers of effect such as chromosomal aberrations, micronuclei, and SCE measured in peripheral blood lymphocytes (see Section 5.6.4). [Limitations of this study include the lack of an unexposed control group and a small number of subjects in the high-exposure group.]

Wang *et al.* (2009b) was the first study to identify a specific formaldehyde-DNA adduct in humans. DNA was isolated from leukocytes from 32 smokers (at least 10 cigarettes per day) and 30 nonsmokers. Each group was equally divided between males and females. The age range was 26 to 66 years (mean 42 years) for smokers and 21 to 78 years (mean 48 years) for the nonsmokers. Liquid chromatography-electrospray ionization-tandem mass spectrometry was used to quantify N^6-hydroxymethyldeoxyadenosine (N^6-HOMe-dAdo) adducts. [$^{15}N_5$]N^6-Me-dAdo was added to the leukocyte DNA as the internal standard and N^6-HOMe-dAdo was converted to N^6-Me-dAdo during enzyme hydrolysis of the DNA because the latter is more stable. Adducts were detected in 29 of 32 smokers (179 ± 205 fmol/µmol dAdo) compared with 7 of 30 nonsmokers (15.5 ± 33.8 fmol/µmol dAdo). The difference was highly significant ($P < 0.001$). The authors reported that such clear differences in leukocyte DNA adduct levels between smokers and nonsmokers have rarely been reported, and they suggested that these adducts indicate a previously unrecognized and potentially important role for formaldehyde-DNA damage in smoking induced cancer. The formaldehyde source could be tobacco smoke, metabolism of a tobacco-specific compound, or a secondary metabolite formed as a result of lipid peroxidation or inflammation.

Shaham *et al.* (1996a, 1997) conducted a pilot study to investigate the use of DNA-protein crosslinks as a biomarker of formaldehyde exposure in humans. DNA-protein crosslinks were measured in white blood cells from 12 exposed workers (physicians and technicians at the Pathology Institute [location not specified by authors]) and 8 controls. The workers had been exposed to formaldehyde from 2 to 31 years with a mean of 13 years. Formaldehyde concentrations were measured in the room air and by personal samples. Concentrations ranged from about 1.4 to 3.1 ppm. There was a significant difference ($P = 0.03$, *t*-test) between the levels of crosslinks in exposed workers and controls, and a significant difference ($P < 0.05$) between the most-exposed workers (technicians) and less-exposed workers (physicians) (Table 5-24). Furthermore, there was a linear relationship between the years of exposure and levels of crosslinks. Smoking did not influence the results. This was the first study to measure DNA-protein crosslinks in humans exposed to formaldehyde.

Shaham *et al.* (2003) conducted a follow-up study of the relationship of occupational exposure to formaldehyde and DNA-protein crosslinks. This study also investigated effects on p53 protein expression. The workers included physicians, laboratory assistants and technicians, and hospital orderlies from 14 hospital pathology departments that had a mean exposure period of 15.9 years (range 1 to 51 years). Fifty-nine (59) men and 127 women were included in the exposed group and were further divided into subgroups based on low and high exposures. The low-exposure group (0.04 to 0.7 ppm) included laboratory assistants and technicians, while the high-exposure group (0.72 to 5.6 ppm)

included physicians and orderlies. [No explanation was given for physicians being in the less highly exposed group in the 1996-97 study but in the highly exposed group in the 2003 study.] The control group included 213 administrative workers (127 men and 86 women) from the same hospitals. There were significant differences in the age distribution, sex, origin, and education between the exposed and control group. Therefore, the data were adjusted for these variables. DNA-protein crosslinks were measured in the mononuclear cell fraction of peripheral blood. Also, p53 proteins, including pantropic p53 (wild type and mutant) and mutant p53, were measured in serum. The adjusted means of crosslinks between the exposed and unexposed groups were compared by analysis of variance, the comparison between the two levels of exposure was evaluated by the Mann-Whitney U test, and the Chi square test was used to compare prevalence of high p53 levels. The adjusted mean amount of crosslinks was significantly higher ($P < 0.01$) in the total exposed group compared with the control group (Table 5-24). Age, smoking habits, years of education, and origin were not significant confounders. The mean amount of crosslinks did not show significant differences based on level of exposure or median years of exposure (≤ 16 versus > 16). Formaldehyde exposure was associated with an increased risk of having a higher level of pantropic p53 protein above 150 pg/mL. A significantly higher proportion of exposed workers with DNA-protein crosslink levels above the median level of 0.187 had elevated pantropic p53 protein levels compared with exposed workers with crosslink levels less than 0.187. Zhang *et al.* (2009a) noted that the controls had high levels of DNA-protein crosslinks compared with other biomonitoring studies.

Table 5-24. DNA-protein crosslinks and pantropic p53 protein levels in medical workers exposed to formaldehyde

Group	N	DNA-protein crosslinks/total DNA	Pantropic p53 > 150 pg/mL (%)	Reference
Control	8	0.23 ± 0.067[a]	NT	Shaham *et al.* 1996a, 1997
Exposed (total)	12	0.28 ± 0.055*		
Low exposure	6	0.26 ± 0.044		
High exposure	6	0.32 ± 0.043*[b]		
Control	213	0.14 ± 0.006[c]	36.3	Shaham *et al.* 2003
Exposed	186	0.21 ± 0.006**	44.1	
Low DPX	NR	≤ 0.187	33.3	
High DPX	NR	> 0.187	55.7**[b]	

*$P < 0.05$; **$P < 0.01$ (compared with controls, unless otherwise noted, see text for method).
NR = not reported; NT = not tested.
[a]± SD.
[b]Compared with low-exposure group.
[c]± SE.

Costa *et al.* (2008) compared DNA damage as measured by the comet assay in 30 pathology anatomy laboratory workers in four hospitals in Portugal with 30 matched controls (age, sex, lifestyle factors, and smoking habits) selected from administrative staff in the same hospitals. This study also examined SCE and micronuclei (discussed below) and the association between biomarkers and polymorphic genes of xenobiotic metabolizing and DNA-repair enzymes. The exposed group had been employed for 5 months to 27 years (mean 11 years). The mean level of exposure measured at the breathing zone of the subjects was 0.44 ppm (range 0.04 to 1.58 ppm). The subjects began work at 9 a.m. and blood samples were collected between 10 and 11 a.m. The alkaline version of the comet assay was used to evaluate DNA damage in lymphocytes. There was a significant increase ($P < 0.05$) in comet tail length in exposed workers compared with controls, and a positive association was found between formaldehyde exposure level and comet tail length. The polymorphisms, age, and smoking status examined did not have a significant effect on DNA damage. DNA damage was significantly increased in exposed females compared with exposed males, but no effect on gender was observed in controls. Age and smoking status did not affect DNA damage.

Genotoxicity studies published on peripheral lymphocytes of Chinese workers exposed to formaldehyde were reviewed by Tang *et al*. (2009). Increases in DNA damage to lymphocytes (comet assay) were reported in three studies in exposed workers (Yu *et al.* 2005, Jiang *et al.* 2006, Tong *et al.* 2006).

5.7.4.2 DNA repair and mutations

Three studies were reviewed that examined the effects of formaldehyde exposure on DNA repair (Hayes *et al.* 1997, Schlink *et al.* 1999, Orsière *et al.* 2006). The study populations included medical or mortuary science students and anatomy laboratory workers. One study investigated the mutagenicity of urine samples collected from medical workers (Connor *et al.* 1985a).

Hayes *et al.* (1997) examined the effects of formaldehyde exposure on DNA repair capacity in mortuary science students. O^6-alkylguanine DNA alkyltransferase (AGT) activity was measured in peripheral blood lymphocytes of 23 students (16 males and 7 females) before and after a 9-week course in embalming techniques. Personal formaldehyde exposure was measured at the breathing zone during embalming, and short-term (peak) exposure was measured with a continuous reading instrument. Cumulative formaldehyde exposure was measured as ppm-hours formaldehyde for each subject. The average air concentration of formaldehyde during embalming was about 1.5 ppm, but short-term monitoring during some embalmings showed that peak exposures were 3 to 9 times higher than the time-weighted average concentration. Most students performed between five and nine embalmings during the class. However, 15 students reported prior exposure to formaldehyde during embalming procedures conducted within 90 days of the class. Differences in AGT activity were assessed by the Wilcoxon signed rank test and by analysis of variance. Baseline AGT activity was somewhat lower (P = 0.08) in students who reported a prior history of embalming. There were no significant differences in baseline AGT activity based on gender, age, or current tobacco use. At the end of the study, AGT activity decreased in 17 students and increased in 6 students compared with baseline values ($P < 0.05$). Among the eight students with no previous embalming experience, AGT activity decreased in all but one. Although post-exposure AGT activity tended to decrease, no clear link was established between formaldehyde exposure and AGT activity. The authors noted several study limitations. These included a small number of subjects, many of which had prior exposure to formaldehyde, and the study did not allow for a detailed temporal association between formaldehyde exposure and AGT activity.

In a subsequent study by the same group of researchers, Schlink *et al.* (1999) measured AGT (also known as O^6-methylguanine DNA methyltransferase [MGMT]) activity in mononuclear blood cells in 57 medical students before and after taking an anatomy course. The students were exposed to an average formaldehyde concentration of 0.2 mg/m^3 [0.16 ppm] for 6 hours/week for about 16 weeks. Age, sex, cigarette smoking, alcohol consumption, and allergic disease did not significantly affect MGMT activity. The mean MGMT activity after 111 days of exposure was 128.2 $fmol/10^6$ cells, which was not significantly different from the baseline value of 133.2 $fmol/10^6$ cells. There also was no significant difference in MGMT activity in a second group of 16 medical students with mean formaldehyde exposure of 0.8 mg/m^3 [0.64 ppm] compared with a group of 51 students without formaldehyde exposure. Thus, formaldehyde did not affect MGMT activity in mononuclear blood cells in medical students in this study.

Orsière *et al.* (2006) examined the genotoxic effects of formaldehyde in 59 pathology and anatomy laboratory workers from five hospitals. Personal air sampling was conducted for short-term (15 minutes) and long-term (8 hours) intervals. The mean formaldehyde concentrations were 2 ppm (range < 0.1 to 20.4 ppm) in the short-term air samples and 0.1 ppm (range < 0.1 to 0.7 ppm) in the long-term samples. The highest formaldehyde concentrations were recorded during macroscopic examination of formaldehyde-preserved specimens. Blood samples were collected from each worker in the morning before beginning work and at the end of the work day. The chemiluminescence microplate assay was used to measure primary DNA damage (*ex vivo* base or nucleotide

excision-repair activity) in peripheral lymphocytes. Data were expressed in relative light units (RLU) per ng of DNA. Chromosomal damage was determined using the cytokinesis-blocked micronucleus assay (see Section 5.6.4 for a description of these results). There was no difference in DNA damage at the beginning of the work day compared with the end of the work day. The mean pre-shift RLU was 3.9 ± 0.5 compared with the post-shift value of 3.6 ± 0.5. There was no correlation of DNA damage with work practices or with personal air sampling data.

Connor *et al.* (1985) tested the mutagenicity of urine samples from 19 autopsy service and pathology department workers at the University of Texas medical school. The control group included 20 individuals selected from the staff, faculty, and student populations and were matched to the exposure group based on sex, age, and alcohol, tobacco, and marijuana use. Medical history, past use of medications, exposure to industrial chemicals, and other factors that could possibly affect the outcome of the study were considered in the analysis. Urine samples were collected three times at 2-month intervals and were tested for mutagenicity in *S. typhimurium* strains TA98 and TA100 with and without S9 metabolic activation. Formaldehyde concentrations ranged from 0.1 ppm (detection limit) outside the immediate work area to 5.8 ppm in the work area. The estimated time-weighted average formaldehyde concentrations in the work areas ranged from 0.61 to 1.32 ppm. Urine concentrates were tested at 50 and 100 µL per plate. There was no difference in mutagenicity between the autopsy service workers and the control group. The only samples that demonstrated substantial levels of mutagenicity were from two individuals in the control group. One of these had received metronidazole therapy during the study and was not included in the final analysis. The other individual was a heavy smoker (2 packs a day). Urine samples from this individual contained the mutagenic compound 2-naphthylamine. In addition, urine from two individuals in the exposed group (both smokers) showed slight mutagenic responses when assayed in strain TA98 with the addition of S9. Two individuals from the exposed group were dropped from the final analysis because they had received drug therapy prior to the study. There was a significant difference (*P* value was not reported) in the number of urine samples (13) from the exposed group that were toxic compared with the number of samples (4) from the control group (Table 5-25). Toxicity (determined by plates with a partial or complete absence of a background lawn) was reduced in the presence of S9, and when the urine samples were tested at lower concentrations, no mutagenicity was observed. Analyses of the toxic samples showed that most of them contained a compound identified as a glucuronide conjugate that did not appear to be related to formaldehyde exposure.

Table 5-25. Distribution of autopsy service and pathology department workers with mutagenic or toxic urine samples

Experimental group	Non-mutagenic or non-toxic	Mutagenic	Toxic	Totals
Control	16 (42)[a]	1 (3)[b]	2 (4)	19 (49)[d]
Exposed	11 (27)	2 (5)[b,c]	5 (13)	18 (45)[e]
Total	27 (69)	3 (8)	8[f] (17)	37 (94)

Source: Connor *et al.* 1985a.
[a]The number in parentheses is the total number of samples in each category.
[b]All mutagenic samples are from smokers.
[c]Both individuals were smokers; urine from both was slightly mutagenic in strain TA98, but only with S9 metabolic activation; urine was not mutagenic in strain TA100 with or without S9.
[d]One individual was excluded due to metronidazole therapy.
[e]Two individuals were excluded due to drug therapy.
[f][The numbers are as reported by Connor *et al.*; however, the total number of workers with toxic samples appears to be in error because only 2 controls and 5 exposed were listed above. Connor *et al.* reported that one control subject was not included due to drug therapy, which might explain the apparent discrepancy.]

5.7.4.3 Cytogenetic effects

A number of studies have examined the cytogenetic effects of formaldehyde exposure in peripheral blood lymphocytes or nasal mucosa in humans exposed to formaldehyde. The findings are discussed below and summarized in Table 5-26 (chromosomal aberrations) Table 5-27 (SCE) and Table 5-28 (micronuclei).

Genotoxicity studies published on peripheral lymphocytes in Chinese workers exposed to formaldehyde were reviewed by Tang *et al.* (2009). Increases in micronucleus frequencies in lymphocytes were reported for exposures over 1 year (Wang *et al.* 1997, Yu *et al.* 2005) and in nasal epithelial cells after 8-weeks exposure to high levels (0.508 to 0.985 mg/m^3 [0.413 to 0.8 ppm]) of formaldehyde (Cheng *et al.* 1995). Also, multiple chromosomal aberrations were reported in workers exposed to an average of 2.51 mg/m^3 [2.04 ppm] of formaldehyde for 10.5 years (Jin and Zhu 1992). In contrast, two studies reported no increase in SCE in lymphocytes from formaldehyde-exposed workers (Li *et al.* 1988, Jin and Zhu 1992, Ye *et al.* 2005). (These findings are not discussed in detail in the text or the tables since the information comes from a secondary source.)

Chromosomal aberrations

Fleig *et al.* (1982) conducted a cytogenetic analysis of 15 employees at a formaldehyde manufacturing and processing facility in Germany. The workers had been employed for 23 to 35 years. The control group included 15 administrative or office staff employees at the same facility who were matched by age and sex with the exposed group. Personal air samplers were used to determine 8-hour time-weighted average formaldehyde exposures for each individual. Mean formaldehyde concentrations at the work areas did not exceed the maximum workplace concentrations (MAK value). MAK values were 5 ppm before 1971 and 1 ppm after 1971. Chromosomal aberrations were measured in peripheral blood lymphocytes. One hundred (100) cells per individual were scored. There was no difference in the incidences of aberrant cells including gaps (all types of aberrations with both chromatid and isochromatid gaps between the exposed (3.07%) and control group

(3.33%). The mean incidence of aberrant cells excluding gaps (breaks, fragments, deletions, chromatid exchanges, rings, and dicentric chromosomes) was greater in the exposed group than in the controls (1.67% versus 1.07%); however, this difference was not statistically significant. There was no correlation between formaldehyde exposure and the number of aberrant metaphases. The authors reported that chromosomal aberrations were not increased among smokers.

Suskov and Sasanova (1982) examined peripheral lymphocytes from 31 persons, including individuals of both sexes, exposed to formaldehyde in the air at 0.5 mg/m^3 [0.41 ppm], the average concentration in an area in which phenolformaldehyde resin was produced. The control group included 74 healthy individuals that had no occupational contact with synthetic resins. The control group was matched for sex, smoking, alcohol consumption, and medication. The average frequency of metaphases with chromosomal aberrations was 5.0% for the exposed workers and 2.4% for the control group, which was significant at $P < 0.001$ by χ^2 test. No difference in the average frequency of chromosome breaks per chromosome was found.

Thomson *et al.* (1984) examined incidences of chromosomal aberrations and SCE (results for SCE reported below) in the peripheral blood lymphocytes of six pathology workers and five unexposed controls. Smoking history was obtained for each individual. The pathology workers had been employed for 4 to 11 years and were exposed to formaldehyde for 2 to 4 hours/day, 2 to 3 days/week. Time-weighted average formaldehyde concentrations ranged from 1.14 to 6.93 mg/m^3 [0.93 to 5.65 ppm]. One hundred (100) first-division metaphases from each 48-hour culture were scored for chromosomal aberrations for each individual. There were no significant differences in the incidences of chromosomal aberrations between the exposed and control groups. The most common chromosomal aberrations were aneuploid cells (36 in the exposed group and 15 in the controls) and chromatid aberrations (8 in the exposed group and 6 in the controls). Only one dicentric chromosome was observed, and this was from the control group. [Although smoking history data were reported to be collected, there was no discussion of how these data were used.]

Bauchinger and Schmid (1985) investigated the clastogenic effects of formaldehyde in paper factory workers. Chromosomes were analyzed in peripheral blood lymphocytes from 20 male papermakers who had occupational exposure to formaldehyde for 2 to 30 years. The control group included 20 male workers from the same factory that were not exposed to formaldehyde. The exposed and control groups were matched for age, smoking history, and social environment. The mean accumulated exposure time was estimated to be about 45 to 90 minutes per 8-hour shift. Formaldehyde concentrations in workroom air did not exceed 0.2 ppm; however, workers were required to enter the paper machine for short periods to take samples or change the paper type, and formaldehyde concentrations as high as 3 ppm were encountered. Five hundred (500) cells per individual were scored for chromosomal aberrations, and 50 cells per individual were scored for SCEs from 54-hour cultures (results for SCE are reported below). The Mann-Whitney rank *U* test was used to compare incidences of chromosomal changes. Incidences of dicentrics or dicentrics and ring chromosomes were significantly higher than in controls; however, there were no significant differences in structural chromosome

changes, acentric fragments, chromatid-type aberrations, or gaps. Stratified analyses by supervisors and operators showed that only supervisors (mean occupational exposure 2.5 times higher than operators) had significantly higher incidence of dicentrics and dicentric and ring chromosomes.

Chebotarev *et al.* (1986)[4] reported a significantly higher level of chromosomal aberrations in lymphocytes from 40 woodworkers (2.76%) compared with 22 control workers (1.64%). The incidence of chromosomal breakage was also significantly higher in woodworkers compared with controls (2.95% vs. 1.64%).

Vargová *et al.* (1992) compared chromosomal aberrations in peripheral blood lymphocytes from 20 workers (10 men and 10 women) exposed to formaldehyde in a wood-product manufacturing facility with 19 matched non-exposed workers from the same factory. The control and exposed groups had similar habits and a similar social status. The exposed workers had been employed at the facility for 5 to more than 16 years and were exposed to time-weighted average formaldehyde concentrations of 0.55 to 10.36 mg/m^3 (0.46 to 8.6 ppm). There were no significant differences between the exposed workers and controls for chromatid and chromosome gaps, breaks, exchanges, breaks per cell, or percentage of cells with aberrations. The exposed workers had 3.08% aberrant cells and 0.045 breaks per cell compared with 3.6% aberrant cells and 0.08 breaks per cell in the control group. The authors noted that the frequency of aberrations in the control group was higher than reported in the general population (1.2% to 2%) and noted that smoking and alcohol consumption might have been a factor. The authors concluded that both the exposed and control groups had a potential increased genotoxic risk, but they had no explanation for the increased levels of chromosomal aberrations in the control group. Both controls and the exposed groups had increased numbers of inactive lymphocytes and decreased lymphoblast frequency, and exposed groups had a significant decrease in the mitotic index. Significant differences in immunological effects were also found between the exposed group and the matched controls and the matched controls and background controls (see Section 5.4.2).

Kitaeva *et al.* (1996) evaluated chromosomal aberrations in peripheral blood lymphocytes of 15 workers at a nitrogen fertilizer manufacturing plant who were exposed to formaldehyde concentrations (1.2 to 2.4 mgm^3) two to four-fold greater than the maximum permissible occupational limits for an average of 10 years, and 6 controls. Controls were younger (average age 28 years) than workers (average age 38 years), but no other information was provided. Data after 72 hours of culturing was only available from 8 workers, and the frequency of chromosomal aberrations was significantly higher than for the 6 controls. The authors reported that there was no correlation with sex, age, or length of service.

Vasudeva and Anand (1996) compared chromosomal aberrations in peripheral blood lymphocytes from 30 female medical students, who were exposed to formaldehyde for 15 months during an anatomy laboratory, to 30 age-matched, unexposed controls (non-medical students). All participants were healthy, had unremarkable medical histories, and

[4] Russian publication, information based on the English summary.

had received no or insignificant radiation exposure. The average exposure concentration was less than 1 ppm. The incidences of chromosomal aberrations were not significantly different between the exposed and control groups.

He *et al.* (1998) examined the clastogenic effects of formaldehyde exposure in 13 students during a 12-week anatomy class. The control group included 10 students from the same school who were not exposed to formaldehyde. All participants were nonsmokers, and the sex and age of the two groups were similar. Breathing-zone air samples were collected during dissection procedures and showed a mean formaldehyde concentration of 2.37 ppm. Lymphocytes were examined for chromosomal aberrations, SCE, and micronuclei. (Results for SCE and micronuclei are reported below.) Chromosomal aberrations occurred at a significantly higher frequency in the exposed group than in the controls ($P < 0.01$, [statistical method not identified]). The authors also reported a correlation between micronuclei and chromosomal aberrations.

Lazutka *et al*. (1999) evaluated chromosomal aberrations among 97 (34 male and 63 female) plasticware workers who were exposed to formaldehyde (0.5 to 0.9 mg/m^3 [0.4 to 0.7 ppm]), styrene (4.4 to 6.2 mg/m^3 [3.6 to 5.0 ppm])), and phenol (0.5 to 0.75 mg/m^3 [0.4 to 0.6 ppm]) for 2 months to 25 years. Non-exposed donors were used as controls (64 male and 26 females) and were matched by age and similar smoking habits as the exposed workers. The mean frequency of chromosomal aberrations was significantly higher in the exposed workers than controls. Significant increases in chromosomal aberrations were observed among workers with short and long exposures; however, the frequency of chromosomal aberrations induced did not increase with exposure duration. The study was not able to identify which exposure caused the chromosomal aberrations; however, the authors noted that styrene has been reported to cause chromosomal aberrations.

Neri *et al.* (2006) addressed some of the critical issues of environmental research in pediatric populations. Data from several field studies that were focused on various exposures in children were reviewed. One of these studies evaluated the frequency of chromosomal aberrations in pre-school children (boys and girls, aged 5 to 6 years) and elementary school boys (aged 8 to 12 years) from 1984 to 1986. These children were exposed to elevated levels of formaldehyde from an adhesive that was used to secure pressboard panels in prefabricated schools in Czechoslovakia in the 1980s. Formaldehyde concentrations in the elementary school were 0.32 mg/m^3 [0.26 ppm] in 1984, 0.13 mg/m^3 [0.11 ppm] in 1985, and 0.037 mg/m^3 [0.03 ppm] in 1986. Formaldehyde concentrations in the pre-school were reported as 0.21 to 0.36 mg/m^3 [0.17 to 0.29 ppm] in 1984. Chromosomal aberrations were determined in lymphocytes from 20 elementary school children in 1984, 16 in 1985, and 18 in 1986 and in 13 pre-school children in 1984. The control groups included 17 elementary school children in 1984 and 1985 and 24 pre-school children in 1984. There were significantly increased percentages of aberrant cells in 1984 and 1985 in the elementary school children compared with the controls ($P < 0.01$, [statistical method not reported]).

Pala *et al.* (2008) compared chromosomal aberrations in peripheral blood lymphocytes of workers in different laboratories of a cancer research institute. The workers were divided

into a high-formaldehyde-exposure group (≥ 26 μg/m^3 [≥ 21.1 ppm]) that and a low-exposure group (< 26 μg/m^3 [< 21.1 ppm]). No unexposed control group was included. Age and smoking habits were similar in the two groups, but the low-exposure group had a higher percentage of males than the high-exposure group (see Section 5.6.4.1). Chromosomal aberration results were available on 5 of the 9 workers in the high-exposure group and 19 of the 27 workers in the low-exposure group. (Smoking, age, and sex information was not given for the subset of workers with results.) No significant differences were reported in the frequency of chromosomal aberrations between the high- and low-exposure groups based on regression analysis that included sex, age, smoking habits, and exposure to other chemicals. (This study also evaluated SCE and micronuclei.) [Limitations of this study include the lack of an unexposed control group and the small number of subjects in the high-exposure group.]

Zhang *et al.* (2010) cultured myeloid progenitor cells from 10 Chinese workers exposed to relatively high formaldehyde concentrations and compared the frequency of numerical chromosomal aberrations (monosomy and trisomy 8) with 12 non-exposed workers matched by age and gender. Fixed metaphase spreads were prepared from cultured cells and examined by fluorescence *in-situ* hybridization (FISH). A minimum of 150 cells per subject were scored. The frequency of monosomy of chromosome 7 and trisomy of chromosome 8 was significantly elevated in exposed workers compared with controls. [This study was limited by the small number of subjects.]

Table 5-26. Chromosomal aberrations in peripheral blood lymphocytes from humans exposed to formaldehyde

Study population	N	No. cells examined/ person	Exposure		Aberrant cells (%)	Comments	Reference
			ppm	duration			
Matched controls	15	100	0		3.33 (1.07)[a]	Controls matched for age and sex	Fleig *et al.* 1982
Formaldehyde workers	15	100	< 5	23–35 yr	3.07 (1.67)[a]	CA not increased for smokers	
Matched controls	74	93	0		2.4	Controls matched for sex, smoking, alcohol consumption, and medication	Suskov and Sazonova 1982
Phenolformaldehyde resin workers	31	104	0.41	0.33–30 yr	5.0***		
Controls	5	100	0	4–11 yr	[4.6][b]	Controls consisted of 3 females and 2 males, mean age 27.8; exposed consisted of 2 females and 4 males, mean age 33.5. Smoking histories collected but analyses (if any) not reported	Thomson *et al.* 1984
Pathology workers	6	100	0.9–>9		[7.7][b]		
Matched controls	20	500	0	2–30 yr	0.0005[c]	Controls from the same factory were matched for age, smoking history, and social environment. Stratified analyses by supervisors and operators showed that only supervisors (mean occucptional exposure 2.5 times higher than operators) had significantly higher incidence of dicentrics and dicentric and ring chromosomes.	Bauchinger and Schmid 1985
Papermakers	20	500	0.2–3		0.0013*[c]		
Controls	22	100	NR[d]	NR[d]	1.64		Chebotarev *et al.* 1986
Woodworkers	40	100			2.76*		

Study population	N	No. cells examined/ person	Exposure		Aberrant cells (%)	Comments	Reference
			ppm	duration			
Matched controls Wood-splinter product workers	19 20	100 100	0 0.46–8.6	5–>16 yr	3.60[d] 3.08	Controls from same plant with similar habits and social status Authors stated that smoking and alcohol might have influenced findings, but no data were provided CA frequency in controls exceed the general population, and immunological effects were observed in both control and exposed groups	Vargova *et al.* 1992
Controls Nitrogen fertilizer workers	6 8[e]	NR NR	0 1.2–2.4 mL/m^3	10 yr	1.8 5.4*	Controls were younger than exposed workers, but no other information was provided No correlation was observed between age, sex or length of service. 62% of aberrations were chromosomal	Kitaeva *et al.* 1996
Matched controls Medical students	30 30	100 100	0 < 1	15 mo	0.9 1.2	All subjects were females, aged 17 to 19 Controls were non-medical students matched on age	Vasudeva and Anand 1996
Controls Anatomy class students	10 13	100 100	0 2.37	12 wk	3.4 5.9**	All students were non-smokers and had similar sex and age distributions	He *et al.* 1998
Controls (donors) Plasticware workers	90 97	100 100	[0.4–0.7]	2 mo to 25 yr	1.68 4.2*	Controls matched on age, and had similar smoking habits; however, most of the workers were females and most of the controls were males Workers also exposed to styrene and phenol CA frequency did not increase with increasing duration of exposure	Lazutka *et al.* 1999

Study population	N	No. cells examined/ person	Exposure		Aberrant cells (%)	Comments	Reference
			ppm	duration			
Controls (1984) School children (1984) School children (1985) School children (1986) Controls (preschool, 1984) Preschool children (1984)	17 20 16 18 24 13	100 100 100 100 100 100	0 0.26 0.11 0.03 0 0.17–0.3	 1–3 yr 	1.37 4.71** 2.83** 2.06 1.12 2.40	Children were exposed to formaldehyde from adhesive used to secure pressboard panels in prefabricated schools	Neri *et al.* 2006
Laboratory workers Laboratory workers	19 5	100	[< 0.02] [≥ 0.02]	NR	2.95 2.22	Population consisted of 36 laboratory workers divided into high- (≥ 26 µg/m^3 [≥ 21.1 ppm]) and low-exposure groups (< 26 µg/m^3 [< 21.1 ppm]). No unexposed controls were included. No information on smoking, gender, and age distribution of subset of workers with CA results.	Pala *et al.* 2008
Matched controls Factory workers	12 10	150	0 2.14	NR	5 11**	Levels of monosomy 7 (values estimated from a figure) Controls were matched by age and gender.	Zhang *et al.* 2010
Matched controls Factory workers	12 10	150	0 2.14	NR	3 12*	Levels of trisomy 8 (values estimated from a figure) Controls were matched by age and gender.	

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
CA = chromosomal aberrations, NR = not reported, NS = not significant compared with controls.
[a]Data reported for aberrant cells including gaps and excluding gaps (in parenthesis).
[b]Frequencies were calculated from the totals for aneuploid cells, Cs cells (defined as cells with a stable form of structural abnormality), acentrics, dicentrics, rings, and chromatid aberrations.
[c]Data are mean frequencies of dicentrics/cell. The frequency of dicentrics combined with ring chromosomes was also significantly different from controls. No significant differences were observed for structural chromosome changes, acentric fragments, gaps/cells, or chromatid-type aberrations.
[d]Exceeded the frequency of aberrations (1.2% to 2%) reported in the general population.
[e]Population consisted of 15 workers, but data for analysis (72 h) was only available for 8 workers.

Sister chromatid exchange

Occupational exposure to formaldehyde and SCE was evaluated in 12 studies (see Table 5-27). Three of the earliest published studies (discussed above) did not find increased incidences of SCE among workers exposed to formaldehyde (Thomson *et al.* 1984, Bauchinger and Schmid 1985, Chebotarev *et al.* 1986). Thompson *et al.* examined incidences of SCE in the peripheral blood lymphocytes of six pathology workers and five unexposed controls. Bauchinger and Schmid (1985) studied 20 male paper factory workers who were occupationally exposed to formaldehyde for 2 to 30 years, and Chebotarev *et al.* studied 40 woodworkers.

Yager *et al.* (1986) measured SCE in the peripheral lymphocytes of eight non-smokers exposed to formaldehyde embalming solution during a 10-week anatomy class. The embalming fluid contained 5.6% formalin (37% formaldehyde and 15% methanol), 22.4% ethanol, 10% phenol, and 62% water. The class met two afternoons per week, but students had free access to the laboratory throughout the week. None of the participants had any known exposure to formaldehyde during the preceding year. Blood samples were collected before, and at the end of, the class. The mean concentration of formaldehyde in the classroom air was 0.33 ppm, while the mean concentration from breathing zone samples collected during dissection procedures was 1.2 ppm. The mean number of SCE per cell increased from 6.39 ± 0.11 before taking the class to 7.2 ± 0.33 at the end of the class. The increase was statistically significant ($P = 0.02$, paired *t*-test).

Suruda *et al.* (1993) examined SCE in lymphocytes in mortuary science students following low-level formaldehyde exposure during an embalming class. The students performed an average of 6.9 embalmings (range 2 to 15) during the 85-day study period. However, several of the students lived at funeral homes or had part-time jobs in funeral homes, and participated in embalmings outside the class. Mean formaldehyde concentrations measured during embalming ranged from 0.15 to 4.3 ppm with peak concentrations as high as 6.6 ppm. The calculated 8-hour time-weighted average formaldehyde concentration ranged from 0.1 to 0.96 ppm with an overall mean of 0.33 ppm. Furthermore, air sample measurements indicated little to no exposure to chemicals other than formaldehyde. SCE frequency showed a significant decrease (7.5%, $P < 0.05$, Student's *t*-test) compared with baseline values. No association was observed with cumulative exposure to formaldehyde and SCE frequency.

Shaham *et al.* (1997) evaluated the frequency of SCE in peripheral blood lymphocytes in 13 workers (6 physicians and 7 technicians) described as working at the "Pathology Institute" (location not specifically reported) who were occupationally exposed to formaldehyde compared with 20 unexposed, age-matched controls (sex not reported). There were 3 smokers in the exposed group (23%) and 6 smokers in the control group (30%). The workers had been occupationally exposed to formaldehyde for 2 to 25 years (mean of 13 years). No past exposures to other mutagenic agents were identified. Formaldehyde concentrations were measured in ambient air at various periods throughout the day and ranged from 1.4 to 1.6 ppm in the rooms of the Pathology Institute. Personal samples collected while work was in progress resulted in slightly higher concentrations (2.8 to 3.1 ppm). There was a significant difference in the mean number of SCE per chromosome in the exposed workers compared with controls (0.212 ± 0.039 [mean ± SD]

vs. 0.188 ± 0.035; $P = 0.05$, *t*-test). Significant differences remained after adjustment for smoking. There was a linear relationship between years of exposure and the number of SCE.

Ying *et al.* (1999) examined SCE frequency in lymphocytes of 23 students (11 males and 12 females) enrolled in an anatomy class for 8 weeks. Each student served as their own control and none of the students were smokers. Formaldehyde concentrations were measured in the anatomy laboratory as well as the students' dormitories. The 3-hour time-weighted average formaldehyde concentrations were 0.51 ± 0.3 mg/m^3 [0.41 ± 0.24 ppm] in the anatomy laboratory and 0.012 ± 0.0025 mg/m^3 [0.01 ± 0.002 ppm] in the dormitories. There was no significant difference in SCE frequency in lymphocytes before and after completing the 8-week anatomy course. (See Section 5.4.2 for lymphocyte subset analyses.)

He *et al.* (1998) reported that there was a statistically significant increase ($P < 0.05$, [statistical method not identified]) in SCE frequency in 13 students exposed to formaldehyde during a 12-week anatomy class compared with a control group of 10 students from the same school who were not exposed to formaldehyde. All participants were nonsmokers, and the sex and age of the two groups were similar. Breathing-zone air samples were collected during dissection procedures and showed a mean formaldehyde concentration of 2.37 ppm. (This study also evaluated chromosomal aberrations.)

Shaham *et al.* (2002) investigated the mean number of SCE per chromosome and the proportion of high-frequency cells (HFC, i.e., cells with more than eight SCEs) in the peripheral lymphocytes of 90 workers (25 males and 65 females, mean age 44.2 ± 8.5 years) from 14 hospital pathology departments in Israel. The control group included 52 unexposed workers (44 males and 8 females, mean age 41.7 ± 11.4) from the administrative staff of the same hospitals. The percentage of active smokers was somewhat higher ($P > 0.05$) in the control group (46.9%) than the exposed group (34.4%). Differences between the control and exposed groups were (1) sex, higher percentage of females in the exposed ($P < 0.01$), (2) origin, higher number of workers with European/American origin in the exposed ($P < 0.05$), and (3) education, higher level of education in the exposed ($P = 0.06$). The mean exposure period was 15.4 years (range 1 to 39 years). No one in the exposed group was known to have been occupationally exposed to other genotoxic substances, and no one in the control group was known to have ever been occupationally exposed to formaldehyde. The exposed group was further divided into a low-exposure group (formaldehyde concentrations of 0.04 to 0.7 ppm) and a high-exposure group (formaldehyde concentrations of 0.72 to 5.6 ppm) based on personal and field samples of ambient air in the pathology departments at various times during the typical work day. The low-exposure group primarily included laboratory assistants and technicians and the high-exposure group primarily included physicians and hospital orderlies. Adjustments were made for sex, smoking habits, education, and national origin (age was introduced in the model but it did not correlate with SCE measures). Both measures of SCEs (SCE per chromosome and proportion of HFC) were significantly higher in the exposed compared with the control group ($P < 0.01$, Mann-Whitney test), and were significantly higher among workers with 15 years of exposure compared with workers with less than 15 years of exposure ($P < 0.05$). There were no

significant differences between the low- and high-exposure groups; however, among smokers, both variables of SCE were higher in the high-exposure subgroup.

Ye *et al.* (2005) examined nasal mucosa cells and lymphocytes in two populations of formaldehyde-exposed workers in China. One group of 18 workers (11 males and 7 females) was exposed in a formaldehyde manufacturing facility. The mean length of employment was 8.5 years (range 1 to 15 years). The second group included 16 waiters (4 males and 12 females) who worked in a newly fitted ballroom for 12 weeks and were exposed to low levels of formaldehyde from building material, tobacco smoke, and furniture. The control group included 23 college students (12 males and 11 females). The average ages in each of the groups were: manufacturing workers, 29 years (range 19 to 39); waiters, 22 years (range 19 to 27); and students, 19 years (range 18 to 23). The 8-hour time-weighted average formaldehyde concentration in the formaldehyde factory was 0.99 mg/m^3 [0.8 ppm]. The 5-hour time-weighted average concentration measured in the ballroom was 0.11 mg/m^3 [0.09 ppm]. A background indoor air concentration of 0.011 mg/m^3 [0.009 ppm] was measured in the students' dormitories. All study participants were nonsmokers. The workers, but not the waiters, had a significantly increased frequency of SCEs in lymphocytes compared with the controls ($P < 0.05$, one-way ANOVA). (See Section 5.4.2.4 for lymphocyte subset analyses).

Costa *et al.* (2008) investigated DNA damage (see Section 5.6.4.1), SCE, and micronuclei (results reported below) in 30 workers exposed to formaldehyde in four hospital pathology anatomy laboratories in Portugal. Thirty non-exposed hospital employees (matched by age, gender, lifestyle, and smoking) served as the control group. Formaldehyde concentrations measured in the breathing zone of the laboratory workers averaged 0.44 ppm. SCE values were significantly higher in the exposed group ($P < 0.05$) compared with the control group. There was no association between SCE values and genetic polymorphisms in genes involved with xenobiotic metabolism or DNA repair or with duration of exposure. SCE frequency was higher among control smokers than non-smokers but no differences were observed in the exposed groups. Age and sex did not affect the observed SCE frequency.

Pala *et al.* (2008) compared SCE frequency in peripheral blood lymphocytes of workers in different laboratories of a cancer research institute. The workers were divided into a high-formaldehyde-exposure group ($\geq$ 26 µg/m^3 [$\geq$ 21.1 ppm]) and a low-exposure group ($<$ 26 µg/m^3 [$<$ 21.1 ppm]). No unexposed control group was included. Age and smoking habits were similar in the two groups, but the low-exposure group had a higher percentage of males than the high-exposure group (see Section 5.6.4.1). SCE results were available on 2 of the 9 workers in the high-exposure group and 17 of the 27 workers in the low-exposure group. (Smoking, age, or sex information was not given for the subset of workers with results.) There were no significant differences in the SCE frequency between the high- and low-exposure groups based on regression analysis that included evaluating the confounding effects of sex, age, smoking habits, and exposure to other chemicals. [Limitations of this study include the lack of an unexposed control group and the small number of subjects in the high-exposure group.]

Table 5-27. Sister chromatid exchange in peripheral blood lymphocytes from humans exposed to formaldehyde

Study population	N	No. cells examined/ person	Exposure		SCE frequency/cell (± SE)	Comments	Reference
			ppm	duration			
Controls Pathology workers	5 6	50	0 0.9–> 9	4–11 yr	6.44 ± 0.38 6.78 ± 0.31	Controls consisted of 3 females and 2 males, mean age 27.8 yr, and exposed consisted of 2 females and 4 males, mean age 33.5 yr Smoking histories collected but analyses (if any) not reported	Thomson *et al.* 1984
Matched controls Papermakers	20 20	50	0 0.2–3	2–30 yr	9.53 ± 0.35 8.87 ± 0.24	Controls from the same factory and matched for age, smoking history and social environment	Bauchinger and Schmid 1985
Controls Woodworkers	22 40	NR[a]	NR[a]	NR[a]	8.24 ± 0.37 8.01 ± 0.24		Chebotarev *et al.* 1986
Anatomy class students Pre-exposure Post-exposure	8	80	1.2	10 wk	6.39 ± 0.11 7.20 ± 0.33*	All students were non-smokers	Yager *et al.* 1986
Mortuary science students Pre-exposure Post-exposure	29[b]	50	0.1–0.96	85 d	7.72 ± 0.13 7.14 ± 0.89[b]	Several students had part-time jobs involving formaldehyde exposure No association was observed with cumulative exposure to formaldehyde	Suruda *et al.* 1993
Matched controls Physicians and technicians	20 13	32 28	0 1.4–3.1	13 yr	0.186 ± 0.035[c] 0.212 ± 0.039*[c]	Controls matched on age; 3 (23%) smokers in exposed group, and 6 (30%) in control group Significant differences remained after adjustment for smoking Linear relationship between years of exposure and SCE	Shaham *et al.* 1997
Anatomy class students Pre-exposure Post-exposure	23[b]	30	0.01–0.4	8 wk	6.38 ± 0.41 6.61 ± 0.79	All students were non-smokers without exposure to X-rays (6 months)	Ying *et al.* 1999
Controls	10	25	0	12 wk	5.26 ± 0.51	All students were non-smokers and	He *et al.* 1998

Study population	N	No. cells examined/ person	Exposure		SCE frequency/cell (± SE)	Comments	Reference
			ppm	duration			
Anatomy class students	13		2.37		5.91 ± 0.71*	control and exposed groups had similar sex and age distributions	
Controls Hospital pathology staff	52 90	30–31 30–32	0 0.04–5.6	1–39 yr	0.19 ± 0.004 0.27 ± 0.003*	Controls were similar in age, but signficant differences were found for sex, and level of education. Nonsignificant differences were found for active smokers and place of origin. Analyses adjusted for smoking, sex, education, and origin. The proportion of high-frequency cells (HFC) also was significantly higher in exposed workers Higher SCE and HFC were found among those with longer exposure duration but not among workers with higher level of exposure	Shaham *et al.* 2002
Controls Formaldehyde factory workers Waiters	23 18 16	30	0.009 0.8 0.09	1–15 yr 12 wk	6.38 ± 0.41 8.24 ± 0.89* ~6[d]	All subjects were non-smokers and had similar ages (average ages were 19 for controls, 22 for waiters and 29 for formaldehyde workers)	Ye *et al.* 2005
Matched controls Pathology/anatomy lab workers	30 30	50	0 0.44	0.5–27 yr	4.49 ± 0.16 6.13 ± 0.29*	Controls were matched by age, sex, lifestyle factors, and smoking habits. Age and sex did not affect SCE; higher SCE were seen in control unexposed smokers than control unexposed non-smokers. No association was observed with exposure duration	Costa *et al.* 2008
Laboratory workers	17	30	[< 0.02]	NR	6.57	Population consisted of 36 laboratory workers divided into high- (≥ 26 µg/m^3 [≥	Pala *et al.* 2008

Study population	N	No. cells examined/ person	Exposure		SCE frequency/cell (± SE)	Comments	Reference
			ppm	duration			
Laboratory workers	2		[≥ 0.02]		5.06	21.1 ppm]) and low-exposure groups (< 26 µg/m^3 [< 21.1 ppm]). No unexposed controls were included. No information on smoking, gender, and age distribution of subset of workers with SCE results.	

*P < 0.05; **P < 0.01; ***P < 0.001 compared with controls.
[a]Not reported in the English summary of a Russian publication.
[b]Significant decrease in post-exposure samples compared with baseline values.
[c]Data are SCE per chromosome ± SD.
[d]Value was estimated from a figure (exact value was not provided by the study authors).

Micronuclei

Studies that evaluated micronucleia are reported in Table 5-27. Ballarin *et al.* (1992) reported an increase in micronuclei in plywood factory workers compared with an age- and sex-matched control group, who were university or hospital workers. All subjects were non-smokers. The exposed group included 15 workers employed at the plywood factory for 1.5 to 19 years (mean 6.8 years), 7 of which worked in the warehouse, 6 in the shearing-pressing department, and 2 in the sawmill. The time-weighted average formaldehyde concentrations were about 0.1 mg/m^3 [0.08 ppm] in the sawmill and shearing press and 0.39 mg/m^3 [0.32 ppm] in the warehouse. The highest concentration of 0.6 mg/m^3 [0.5 ppm] was recorded in the warehouse. Wood dust levels also were measured and ranged from about 0.23 mg/m^3 to 0.73 mg/m^3 [0.19 to 0.6 ppm]. Respiratory nasal mucosa cells were scraped from the inner turbinates and examined for micronuclei. No fewer than 6,000 cells were counted for each slide. The frequency of micronucleated cells was significantly higher in the exposed group compared with controls (0.90 ± 0.47 vs. 0.25 ± 0.22, $P < 0.01$, Mann-Whitney *U* test). No significant difference in micronuclei frequency was found between workers in the warehouse (0.97 ± 0.39) and the sawmill and shearing-pressing departments (0.74 ± 0.53).

Two studies (Suruda *et al.* 1993, Titenko-Holland *et al.* 1996) examined micronuclei in buccal cells, nasal epithelial cells, and/or lymphocytes in mortuary science students following low-level formaldehyde exposure during an embalming class. Titenko-Holland *et al.* (1996) used previously unstained and unanalyzed slides collected from participants in the Suruda *et al.* (1993) study, and used FISH rather than a staining method to detect micronuclei. The results of the two studies were similar. Suruda *et al.* reported that post-exposure micronucleus frequencies increased significantly in buccal epithelial cells and lymphocytes compared with baseline values ($P < 0.05$, Wilcoxon sign-rank test). A significant dose-response relationship was reported for increases in buccal micronuclei (but not nasal or lymphocyte micronulei) in the 22 male subjects but not in the 7 female subjects. There was a nonsignificant increase in nasal epithelial micronucleus frequency. Titenko-Holland *et al.* (1996) reported that there was a significant increase in micronucleus frequency in buccal cells ($P = 0.007$, Wilcoxon sign-rank test) but not in nasal epithelial cells. Total buccal micronuclei were weakly associated ($r = 0.44$, $P = 0.06$) with cumulative exposure to embalming fluid (90 days). In both tissues, a higher increase in centromere-negative micronuclei (9-fold, $P = 0.005$ for buccal cells; 2-fold, $P = 0.03$ for nasal cells) was found than for centromere-positive micronuclei (> 2-fold, $P = 0.08$ for buccal cells; no change, $P = 0.31$ for nasal cells), suggesting that the primary mechanism of micronucleus formation appeared to be chromosome breakage.

Kitaeva *et al.* (1996) evaluated micronucleus induction in buccal epithelium among anatomy staff at a university (5 men and 8 women) with long-term exposure to formaldehyde (average 17 years) and 7 female controls; no information was provided on the controls. There was an increased frequency ($P < 0.05$) of micronuclei reported in buccal mucosa cells collected from 8 female workers compared with the controls, but not from 5 male anatomy workers. In a separate study the authors also examined micronucleus induction in buccal mucosa cells among 12 students (6 male and 6 female) prior to and after exposure to formaldehyde (i.e., taking a class involving handling wet

mounts containing formaldehyde). There were significant increases in both female ($P < 0.01$) and male ($P < 0.05$) students after exposure for 40 minutes. The number of micronucleated cells detected in the students remained elevated 48 hours after the class.

Ying *et al.* (1997) examined the changes in the frequency of micronuclei in the nasal mucosa, oral mucosa, and lymphocytes of 25 students (13 males and 12 females) enrolled in an anatomy class for 8 weeks. Each student served as their own control; none of the students were smokers, or had a history of drug use in the last 3 weeks or X-rays in the last 6 months. Formaldehyde concentrations were measured in the anatomy laboratory as well as the students' dormitories. The 3-hour time-weighted average formaldehyde concentrations were 0.51 ± 0.3 mg/m^3 [0.41 ± 0.24 ppm] in the anatomy laboratory and 0.012 ± 0.0025 mg/m^3 [0.01 ± 0.002 ppm] in the dormitories. There was a significantly higher frequency of micronuclei in nasal and oral mucosal cells after exposure to formaldehyde ($P < 0.001$, paired *t*-test). There was no significant difference in the frequency of micronuclei in lymphocytes.

He *et al.* (1998) examined the frequency of chromosomal aberrations, SCE (see above), and micronuclei in peripheral blood lymphocytes in 13 students during a 12-week anatomy class. The control group included 10 students from the same school who were not exposed to formaldehyde. All participants were nonsmokers, and the sex and age of the two groups were similar. Micronuclei occurred at a significantly higher frequency in the exposed group than in the controls ($P < 0.01$, [statistical method not identified]). The authors also reported a correlation between micronuclei and chromosomal aberrations.

Burgaz *et al.* (2001, 2002) reported the frequency of micronuclei in nasal and buccal mucosa cells in individuals exposed to formaldehyde in pathology and anatomy laboratories. The first study examined cells from the nasal mucosa and included 23 pathology or anatomy department staff (11 females and 12 males) and a control group of 25 healthy males selected from university and hospital staff. The number of smokers was much higher in the control group (19/25, 75%) compared with the exposed groups. (9/23, 39%), but the workers had similar ages, dietary habits, and use of medicine. The second study examined cells from the buccal mucosa and included 28 subjects (15 males and 13 females) who worked in pathology and anatomy laboratories and 18 male volunteer controls who were university staff. Some of the subjects were apparently used in both studies; however, details of the overlap were not provided. None of the referents had been occupationally exposed to genotoxic materials. Workers and controls in the second study reported similar diets, alcohol consumption, smoking habits, and use of medications. The formaldehyde concentrations in the laboratories ranged between 2 and 4 ppm. Formaldehyde exposure was associated with a statistically significant increase in micronucleus frequency in nasal ($P < 0.01$, non-parametric statistics) and buccal ($P < 0.05$, Student's *t*-test and Mann-Whitney test) mucosa cells. Nasal mucosa micronucleus frequency was significantly higher in exposed smokers compared with control smokers. There was no significant effect of age, sex, smoking status, or exposure duration.

Ye *et al.* (2005) (see discussion under SCE for details) also examined micronucleus formation in nasal mucosa cells from workers at a formaldehyde manufacturing facility and in a group of waiters who worked in a newly fitted ballroom and were exposed to

low levels of formaldehyde from building material, tobacco smoke, and furniture. All study participants were nonsmokers. The workers, but not the waiters, had a significantly increased frequency of micronuclei in nasal mucosa cells compared with the controls ($P < 0.05$, one-way ANOVA).

Orsière *et al.* (2006) also evaluated the effects of formaldehyde on micronucleus formation in lymphocytes in the study of 59 pathology and anatomy laboratory workers and 37 controls described in Section 5.6.4.2. Both the control and exposed workers were matched for age, gender, and smoking habits. Chromosomal damage was assessed with the cytokinesis-blocked micronucleus assay. Samples of whole blood were cultured and prepared, then smeared on microscope slides and air dried. The frequency of micronuclei was expressed per 1,000 cells. Micronuclei were measured using the cytokinesis-blocked micronucleus (CMBN) assay. The binucleated micronucleated cell rate (BMCR) was significantly higher in the lymphocytes of exposed workers compared with controls (see Table 5-28). BMCR was correlated with exposure duration in unadjusted analyses, but was no longer significant after controlling for age. Age and gender, but not smoking and drinking habits, were associated with BMCR.

The presence of centromeres in the micronuclei was determined using FISH and a pan-centromeric DNA probe in combination with the CMBN assay on 18 exposed and 18 controls randomized from the initial population. Micronucleated cells were classified as centromere positive or negative. Centromere-positive cells were further classified based on the presence of a single centromere or multiple centromeres. BMCR was statistically higher in the exposed group compared with the controls, and the frequencies of micronuclei and centromere-positive micronuclei were higher (but not statistically significant) in the exposed subjects, however, no increased frequency was found for centromere-negative micronuclei. Monocentromeric micronucleus frequency was significantly higher in the exposed group (11.0% ± 6.2% versus 3.1% ± 2.4; $P < 0.001$), but the frequency of micronuclei containing more than one centromere was similar in controls and exposed groups.

Iarmarcovai *et al.* (2007) pooled data from three biomonitoring studies of untreated cancer patients, welders, and the subset of 18 pathologists/anatomists who were exposed to formaldehyde and 18 unexposed controls from the study population reported by Orsière *et al.* (2006). In addition to the findings reported above, they reported the results of multivariate regression analysis that adjusted for age, sex, cigarette smoking, and alcohol consumption, and was weighted for the number of scored cells. Pathologists/anatomists had significantly higher frequency ratios (FR) of centromere-positive micronuclei (FR = 1.65, 95% CI = 1.05 to 2.59), and monocentromeric micronuclei (FR = 3.29, 95% CI = 2.04 to 5.30) compared with the controls. In the pooled studies, alcohol drinking and gender affected endpoints measuring aneuploidy (centromere-positive micronucleus frequency and monocentromeric micronucleus frequency), and total micronuclei whereas age only affected total micronucleus frequency.

Micronuclei were not induced in buccal mucosa cells in a study of healthy volunteers exposed to formaldehyde vapors. In this study by Speit *et al*. (2007b), 10 women and 11

men were divided into 5 groups and exposed to formaldehyde in test chambers 4 hours per day for 10 days. For each group, exposure varied from one day to the next from a constant 0.15 ppm throughout the day, to 0.5 ppm with four peaks of 1.0 ppm for 15 minutes each. Exposure also varied daily across groups. The exposure scenarios resulted in cumulative exposures of 13.5 ppm-hours over the 10 working days. Control buccal smears were prepared for each subject one week prior to treatment as well as immediately prior to the exposure to formaldehyde. Treatment buccal smears were taken following the 10-day exposure and 7, 14, and 21 days afterwards. The authors noted that these results demonstrated that formaldehyde vapors in the range of current Occupational Exposure Limits (e.g., 0.5 ppm in Germany and 2.0 ppm in the United Kingdom) did not induce micronuclei in buccal mucosa cells.

Costa *et al.* (2008) reported a significantly higher frequency ($P = 0.003$) of micronuclei in 30 workers exposed to formaldehyde in four hospital pathology anatomy laboratories in Portugal compared with matched controls. Heparinized whole blood was used to establish duplicate lymphocyte cultures for evaluation by the cytokinesis-blocked micronucleus test. Micronuclei were significantly higher in the exposed group compared with the controls (see Table 5-28), and a positive correlation was found between formaldehyde exposure levels and micronucleus frequency ($r = 0.384$, $P = 0.001$). Genetic polymorphisms of xenobiotic metabolizing or DNA-repair genes did not show a significant effect. Age, gender, and smoking habits were not significantly associated with micronucleus frequency. (This study also evaluated DNA damage and SCE.)

Pala *et al.* (2008) compared micronucleus frequency in peripheral blood lymphocytes of workers in different laboratories of a cancer research institute. The workers were divided into a high-formaldehyde-exposure group (≥ 26 µg/m^3 [≥ 21.1 ppm]) and a low-exposure group (< 26 µg/m^3 [< 21.1 ppm]). No unexposed control group was included. Age and smoking habits were similar in the two groups, but the low-exposure group had a higher percentage of males than the high-exposure group (see Section 5.6.4.1). Micronuclei results were available on 7 of the 9 workers in the high-exposure group and 15 of the 27 workers in the low-exposure group. (Smoking, age, or sex information was not given for the subset of workers with results.) There were no significant differences in the micronucleus frequency between the high- and low-exposure groups based on regression analysis that included evaluating the confounding effects of sex, age, smoking habits, and exposure to other chemicals. [Limitations of this study include the lack of an unexposed control group and the small number of subjects in the high-exposure group.]

Table 5-28. Micronuclei in various cell types from humans exposed to formaldehyde

Study population	N	Cell type	No. cells examined/ person	Exposure		Micronucleus frequency/1,000 cells (± SD)	Comments	Reference
				ppm	duration			
Matched controls Plywood factory workers	15 15	Nasal epithelium	6,000	0.08–0.32	1.5–19 yr	0.25 ± 0.22 0.90 ± 0.47**	All subjects were non-smokers. Controls matched for age and sex	Ballarin *et al.* 1992
Mortuary science students (pre-exposure and post-exposure measurements)	29	*Nasal epithelium* Pre-exposure Post-exposure *Buccal epith.* Pre-exposure Post-exposure *Lymphocytes* Pre-exposure Post-exposure	1,500 1,500 2,000	0.1–0.96	85 d	 0.41 ± 0.52 0.50 ± 0.67 0.046 ± 0.17 0.60 ± 1.27* 4.95 ± 1.72 6.36 ± 2.03*	Several students had part-time jobs involving formaldehyde exposure. Cumulative exposure to formaldehyde was associated with buccal MN among male (22) subjects ($r = 0.5$, $P < 0.01$); no association was observed with nasal or lymphocyte MN.	Suruda *et al.* 1993
Mortuary science students (same participants as Suruda *et al.* 1993)	13[a] 19[a]	*Nasal epithelium* Pre-exposure Post-exposure *Buccal epith.* Pre-exposure Post-exposure	187–5,000 503–4,113	0.1–0.96	90 d	 2 ± 1.3 2.5 ± 1.3[b] 0.6 ± 0.5 2.0 ± 2.0**[b]	Cumulative exposure to embalming fluid and buccal MN ($r = 0.44$, $P = 0.06$) Higher increases in both tissues for CN-negative MN than CN-positive MN; increase in CN-positive MN was significant for nasal cells	Titenko-Holland *et al.* 1996
Anatomy lab workers controls (all female) females males *Anatomy class students* Females pre-exposure	 7 8 5 6	Buccal epithelium	> 2000	NR[c]	 17 yr 40 min	 0.64 2.94** 1.18 0.58	No information was provided on controls for the lab workers Controls for students were pre-exposure measures	Kitaeva *et al.* 1996

Study population	N	Cell type	No. cells examined/ person	Exposure		Micronucleus frequency/1,000 cells (± SD)	Comments	Reference
				ppm	duration			
post-exposure	6					2.50**		
Males								
pre-exposure	6					0.77		
post-exposure	6					2.02*		
Anatomy class students	25	*Nasal epithelium*					All students were non-smokers, and did not have a history of drug use (3 weeks) or X-rays (6 months).	Ying *et al.* 1997`
(pre-exposure and post-exposure measurements)		Pre-exposure	2,870	[0.01–0.41]	8 wk	1.20 ± 0.0.68		
		Post-exposure	2,962			3.84 ± 1.5***		
	25	*Oral epithelium*						
		Pre-exposure	3,167			0.57 ± 0.32		
	23	Post-exposure	3,088			0.86 ± 0.56**		
		Lymphocytes						
		Pre-exposure	4,000			0.91 ± 0.39		
		Post-exposure	4,000			1.11 ± 0.54		
Controls	10	Lymphocytes	1,000		1	3.15 ± 0.146	All students were non-smokers and control and exposed groups had similar sex and age distributions.	He *et al.* 1998
anatomy class students	13			2.37	2 wk	6.38 ± 2.5**		
Controls	25	Nasal epithelium	3,000			0.61 ± 0.27	Controls and exposed group reported similar ages, dietary habits, and medicine use; however, there was a greater number of smokers in the control than in the exposed group	Burgaz *et al.* 2001
pathology/anatomy lab workers	23			2–4	1–13 yr	1.01 ± 0.62**		
Controls	18	Buccal epithelium	3,000			0.33 ± 0.30	Control and exposed reported similar diets, alcohol consumption, smoking habits, and use of medications	Burgaz *et al.* 2002
pathology/anatomy lab workers	28			2–4	1–13 yr	0.71 ± 0.56*		
[study populaton may overlap with that of								

Study population	N	Cell type	No. cells examined/ person	Exposure		Micronucleus frequency/1,000 cells (± SD)	Comments	Reference
				ppm	duration			
Burgaz *et al*. 2001]							No effect of age, sex, smoking status, or exposure duration	
Controls formaldehyde factory workers waiters	23 18 16	Nasal epithelium	3,000	0.009 0.8 0.09	 1–15 yr 12 weeks	1.25 ± 0.65 2.70 ± 1.50* ~1.9 ± 1[d]	Smokers and had similar ages (average ages were 19 for controls, 22 for waiters, and 29 for formaldehyde workers)	Ye *et al.* 2005
Matched controls pathology/ anatomy lab workers	37 59	Lymphocytes	1,000	< 0.1–20.4	0.5–34 yr	11.1 ± 6.0 16.9 ± 9.3***[e]	Controls matched for age, sex, and smoking habits BMCR was correlated with exposure in unadjusted but not age-adjusted analysis BMCR was correlated with age and gender but not smoking or drinking habits	Orsière *et al.* 2006
Controls pathologists/ anatomists (randomly chosen from the 37 controls and 59 exposed workers described above)	18 18	Lymphocytes	1,000	0.4–7	NR	11.9 ± 5.6 19.1 ± 10.1*[e,f]	Controls matched for age, sex, and smoking habits FISH analysis: CN-positive MN but not CN-negative MN were higher in exposed group than controls	Orsière *et al.* 2006 Iarmarcovai *et al.* 2007
Volunteer subjects (10 women and 11 men) pre-exposure post-exposure	21 18	Buccal epithelium	2,000	1.0 peak (with daily variation) max 13.5 ppm-h cum. exp.	10 d	0.86 ± 0.84 1.33 ± 1.45	Subjects served as own controls, measured before first exposure.	Speit *et al.* 2007b

Study population	N	Cell type	No. cells examined/ person	Exposure		Micronucleus frequency/1,000 cells (± SD)	Comments	Reference
				ppm	duration			
Controls pathology/ anatomy lab workers	30 30	Lymphocytes	1,000	0 0.44	0.5–27 yr	3.27 ± 0.69 5.47 ± 0.76**	Controls were matched by age, gender, lifestyle factors and smoking habits MN frequency was significantly associated with formaldehyde exposure levels (r = 0.384, P = 0.001) Age, gender, and smoking did not affect MN	Costa *et al.* 2008
Laboratory workers	25 7	Lymphocytes	2,000	[< 0.02] [≥ 0.02]	NR	0.26 ± 0.24 0.31 ± 0.17	Population consisted of 36 laboratory workers divided into high- (≥ 26 µg/m^3 [≥ 21.1 ppm]) and low-exposure groups (< 26 µg/m^3 [< 21.1 ppm]). No unexposed controls were included. No information on smoking, gender, and age distribution of subset of workers with MN results.	Pala *et al.* 2008

* = P < 0.05; ** = P < 0.01; *** = P < 0.001.

BMCR = binucleated micronucleated cell rate; epith. = epithelium; CN = centromere; MN = micronuclei; NR = not reported; NS = not significant compared with controls.

[a]Total subjects in the study = 28; only 19 with complete data for buccal mucosa and 13 with complete data for nasal mucosa were included in the analyses.

[b]There was a significant increase in centromere-negative micronuclei.

[c]Exposure considered long-term for workers but no measurements reported for them or for anatomy students.

[d]Value estimated from a figure.

[e]Binucleated micronuleated cell rate.

[f]Significant increase in centromere-positive micronuclei and monocentromeric micronuclei frequencies.

5.7.5 Gene expression

Kim *et al.* (2002) investigated the possible role of formaldehyde in sick-building syndrome. These authors reported that formaldehyde increased the surface expressions of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) on human mucosal microvascular endothelial cells (HMMECs), and enhanced the adhesiveness between these cells and eosinophils. HMMECs were incubated with formaldehyde at concentrations ranging from 1 ng/mL to 1 μg/mL for 24 hours. There was a statistically significant up-regulation of both ICAM-1 and VCAM-1 at 0.1 and 1.0 μg/mL. The authors concluded that induction of ICAM-1 and VCAM-1 by formaldehyde might play an important role in allergic inflammation associated with sick-building syndrome.

Parfett *et al.* (2003) measured changes in proliferin mRNA over 1 to 3 days in response to various promoters (including formaldehyde) of morphological transformation of C3H/10T1/2 cells. Members of the proliferin protein family are known to influence aspects of cell differentiation or proliferation. Cell cultures were seeded and grown for 2 to 4 days before treatment with test compounds. Formaldehyde was added to the cell cultures at 50, 100, or 200 μM and incubated for 18 to 20 hours. At 50 μM, proliferin mRNA levels were between 5- and 10-fold higher than in controls but increased to 40-fold higher than control levels at 100 μM. Formaldehyde was thought to be toxic to the cell cultures at 200 μM because induction was reduced to four-fold above control levels.

Hester *et al.* (2003) investigated gene expression in the rat nasal respiratory epithelium after exposure to formaldehyde. Groups of male F344 rats received either 40 μL of distilled water or 400 mM formaldehyde instilled into each nostril. The rats were killed 24 hours later, and the nasal epithelium was removed and examined for gene expression. The analysis revealed that 24 of 1,185 genes queried were significantly upregulated and 22 genes were downregulated. The identified genes belonged to the functional categories involved in xenobiotic metabolism, cell-cycle control, apoptosis, and DNA repair. Thus, multiple pathways are dysregulated by formaldehyde exposure, including those involved in DNA synthesis and repair and regulation of cell proliferation.

Hester *et al.* (2005) compared the effects of formaldehyde and glutaraldehyde in male F344 rats. Groups of rats were exposed to formaldehyde (400 mM) or glutaraldehyde (20 mM) by nasal instillation for 1, 5, or 28 days. Animals were killed at the end of the experiments, and the nasal respiratory epithelium was removed for gene expression analysis. Both compounds induce similar acute and subchronic histopathology characterized by inflammation, hyperplasia, and squamous metaplasia; however, glutaraldehyde does not cause nasal tumors in rats. Differences in the gene expression profiles in rats exposed to formaldehyde and glutaraldehyde help explain the different cancer response from these two aldehydes. Acute exposures generated alterations in gene profiles associated with cellular proliferation, stress, and xenobiotic metabolism; however, longer exposures induced a different subset of genes. Apoptosis gene expression was increased by exposure to formaldehyde compared with controls but was less than observed in glutaraldehyde-exposed rats. In addition, formaldehyde exposure induced a greater increased expression of DNA-repair genes than glutaraldehyde. Decreased DNA repair could stimulate apoptosis, while increased DNA repair following

formaldehyde exposure could increase DNA misrepair. Misrepaired cells could persist and pass on genetic damage.

Li *et al.* (2007c) profiled global gene expression in human Hs 680.Tr human tracheal fibroblasts exposed to formaldehyde concentrations of 0, 20, 50, 100, and 200 µM for 4 and 24 hours. Fifty-four (54) genes were responsive to formaldehyde (i.e., more than a 2-fold difference in expression level). Genes associated with nucleoside, nucleotide, and nucleic acid metabolism were the largest group of affected genes. Genes involved in signal transduction, protein metabolism, and developmental processes were the next most affected groups. Human subjects exposed to high or low levels of formaldehyde were monitored for the expression of these genes. Formaldehyde exposure was monitored by measuring urinary concentrations of thiazolidine-4-carboxylate (a stable cysteinyl adduct of formaldehyde). Nine genes were selected for real-time PCR analysis, and six (*BHLHB2, CCNL1, SE20-4, C8FW, PLK2, and SGK1*) showed elevated expression in subjects with high urinary concentrations of thiazolidine-4-carboxylate, and the authors suggested that these genes have the potential to be developed as biomarkers for formaldehyde exposure.

Sul *et al.* (2007) investigated the effects of formaldehyde exposure on mRNA expression in rat lung tissues. Male Sprague-Dawley rats were exposed to 0-, 5-, or 100-ppm formaldehyde 6 hours/day, 5 days/week for 2 weeks. Cytotoxic effects were determined by the malondialdehyde lipid peroxidation and the carbonyl protein oxidation assays and showed that the cytotoxic effects increased with exposure. Gene expression analysis indicated that there were 2 up-regulated and 19 down-regulated genes. Nine of these genes were confirmed by real time PCR and included cytochrome P450, hydroxymethylbilane synthase, glutathione reductase, carbonic anhydrase 2, natriuretic peptide receptor 3, lysosomal-associated protein transmembrane 5, regulator of G-protein signaling 3, olfactomedin-related ER-localized protein, and poly (ADP-ribose) polymerase-1. These genes are involved in apoptosis, immunity, metabolism, signal transduction, transportation, coagulation, and oncogenesis.

Andersen *et al.* (2008) investigated the relationship between histopathological changes in nasal tissues and changes in gene expression in rats exposed to 0-, 0.7-, 2-, and 6-ppm formaldehyde by inhalation, 5 days/week for up to 3 weeks. In addition, other groups of rats were exposed to 15 ppm for 6 hours or to 40 µL or a 400 mM concentration solution of formaldehyde instilled in the nostrils just inside the nares. Unequivocal treatment-related lesions were evident only in the 6-ppm group. In this group, cell proliferation increased at day 5 but was not increased at the end of day 15. Squamous metaplasia occurred at day 5 and epithelial hyperplasia occurred at day 5 and day 15. Lesions were observed primarily in the transitional and respiratory epithelium and displayed an anterior to posterior gradient. The microarray analysis indicated that about 100 genes showed altered expression across all time points and doses. No significant gene expression changes were observed in the 0.7-ppm group at any time point. One gene showed increased expression in the 2-ppm group on day 1, while on day 5, 1 gene was decreased and 14 were increased. No gene expression changes occurred in the 2-ppm group on day 6 or 15. The majority of gene expression changes were seen in the 6-ppm group (day 1, 24 genes increased and 18 decreased; day 5, 24 increased and 4 decreased; day 6, 9

increased and 0 decreased; day 15, 23 increased and 31 decreased). In the acute studies, inhalation of 15 ppm or instillation of 400 mM formaldehyde altered many more genes than were affected at 6 ppm, and instillation altered more than three times as many genes as the 15-ppm exposure. U-shaped dose-response curves were observed in the acute study for many genes that were also altered at 2 ppm on day 5. Many of the genes that showed increased expression were involved in response to wounding, control and induction of apoptosis, inflammation pathways, and receptor tyrosine kinase signaling.

Lee *et al.* (2008a) exposed Hs 680.Tr human trachea cells to formaldehyde to identify differentially regulated genes using PCR-based suppression subtractive hybridization. Cells were cultured overnight and treated with 10 μM or 100 μM formaldehyde for 1, 4, or 24 hours. In addition formaldehyde-inducible genes were identified in the tracheal epithelium of male Sprague-Dawley rats that were exposed by inhalation to formaldehyde concentrations of 0, 3.1, and 38.1 ppm, 6 hours/day, for 2 weeks. In the human trachea cells, 27 formaldehyde-inducible genes were identified including those coding for the major histocompatibility complex, class IA (HLA-A), calcyclin, glutathione *S*-transferase pi, mouse double minute 2 (MDM2), and platelet-derived growth factor receptor alpha (PDGFRA). These genes are associated with cell proliferation, apoptosis, immunity, and detoxification. Induction of these genes was confirmed by reverse transcription PCR and western blot analysis. In the rat, calcyclin, glutathione *S*-transferase pi, PDGFRA and MDM2 also were significantly induced.

5.8 Mechanistic considerations

Although the biological mechanisms associated with formaldehyde-induced cancer are not completely understood, it is important to recognize that chemicals can act through multiple toxicity pathways and mechanisms to induce cancer or other health effects (Guyton *et al.* 2009). These authors identified at least 15 key events representing diverse carcinogenic modes of action, the relative importance of which may vary with life stage, genetic background, and dose. These events include DNA reactivity (covalent binding), gene mutation, chromosomal breakage, aneuploidy, enzyme-mediated effects on DNA damage or repair, epigenetic effects, cell signaling (nuclear-receptor mediated or other than nuclear-receptor mediated), immune response modulation, inflammation, cytotoxicity and compensatory cell proliferation, mitogenicity, chronic metabolic or physiologic overload, nutrient deficiency, and interference with intercellular communication (e.g., gap junctions). Nine of these (DNA reactivity, gene mutation, chromosomal breakage, aneuploidy, enzyme-mediated DNA damage/repair, cell signaling other than nuclear-receptor mediated, immune response modulation, inflammation, and cytotoxicity) were listed as key events for formaldehyde. Although epigenetic effects were not listed as a key event for formaldehyde, a recent study (Lu *et al.* 2008a) indicates that formaldehyde may alter epigenetic regulation. This section discusses the evidence for genotoxic and cytotoxic modes of action in formaldehyde carcinogenesis and the mutational spectra of these tumors. Most of the literature has focused on upper respiratory tract cancer; however, several investigators have discussed possible modes of action for systemic cancers (i.e., leukemia).

5.8.1 Genotoxicity

Formaldehyde is highly reactive and can induce a number of genotoxic effects (see Section 5.6), including DNA adducts, protein adducts, DNA-protein crosslinks, strand breaks, mutations, cell transformation, SCE, and micronuclei resulting from both aneugenic and clastogenic effects.

Formaldehyde-albumin adducts were significantly higher in workers exposed to high levels of formaldhyde compared with workers exposed to low levels (Pala *et al.* 2008). Formaldehyde DNA adducts have been detected in mammalian cells treated with formaldehyde, and in animals exposed to nitrosamines. Wang *et al.* (2009b) reported a significantly higher frequency of N^6-HOMe-dAdo adducts in the lymphocytes of smokers compared with age- and gender-matched nonsmokers

5.8.1.1 DNA-protein crosslinks

DNA-protein crosslinks, in particular, have been identified as a marker of formaldehyde-induced genotoxicity and have frequently been used as a surrogate for formaldehyde exposure in dose-response modeling. Crosslinks have been detected in many *in vitro* studies with a number of human and experimental animal cell types, and *in vivo* in experimental animals and humans. The *in vitro* studies also showed consistent dose-response relationships, with crosslinks forming at doses that have low cytotoxicity (up to 75% cell survival). DNA-protein crosslinks were not repaired as efficiently in human peripheral blood lymphocytes as in established cell lines. Formaldehyde might interfere with DNA repair by inhibiting repair enzymes, inhibiting removal of DNA lesions, or altering gene expression. Merk and Speit (1998) reported that formaldehyde-induced DNA-protein crosslinks are related to chromosomal effects (SCE and micronuclei), but not directly to mutations in the *hprt* gene in V79 cells.

In vivo studies with rats indicated that inhalation of formaldehyde vapors does result in crosslinks in their nasal mucosa. Furthermore, crosslink yields were highest in the area of the nose (lateral meatus) where tumor yields are the highest. Several studies have examined dose-response relationships for the formation of these crosslinks in nasal tissues of experimental animals and compared these results with nasal tumor data (Casanova-Schmitz *et al.* 1984a, Heck *et al.* 1986, 1989, Casanova *et al.* 1989, 1991, 1994). The dose-response curves for DNA-protein crosslink formation and nasal tumor formation in rats showed a similar pattern (Liteplo and Meek 2003). They are nonlinear, with the slope increasing sharply at concentrations above 2 ppm (Table 5-29). This biphasic dose-response curve suggests protective mechanisms, which may become saturated at high concentrations. Two protective mechanisms have been identified: the mucous layer lining the nasal epithelium and glutathione-mediated oxidation of formaldehyde to formate (Conaway *et al.* 1996). Casanova *et al.* (1994) reported that the yield in pre-exposed versus naïve rats was about the same for formaldehyde exposures at or below 2 ppm only. Crosslinks were not detected in bone marrow or the olfactory mucosa in rats (one study reviewed).

Table 5-29. Formaldehyde exposure, DNA-protein crosslinks, and nasal tumor incidence

Exposure (ppm)	DNA-protein crosslinks (pmol/mg DNA)		Tumor incidence (%)
	High tumor region[a]	Low tumor region[b]	
0	0	0	0/90
0.7	5	5	0/90
2	8	8	0/96
6	30	10	1/90 (1.1)
10	ND	ND	20/90 (22.2)
15	150	60	69/147 (46.9)

Adapted from Liteplo and Meek 2003.
ND = no data.
[a] Includes the complete lateral meatus.
[b] Includes medial aspects of naso- and maxilloturbinates, posterior lateral wall, posterior dorsal septum (excluding olfactory region), and nasopharyngeal meatuses.

In monkeys, crosslink yields were highest in the middle turbinates. Casanova *et al.* (1991) reported that the level of DNA-protein crosslinks in rhesus monkeys declined in the order: middle turbinates > anterior lateral wall-septum > nasopharynx, which is consistent with the location and severity of proliferative lesions reported in another study (Monticello *et al.* 1989) in monkeys exposed to 6-ppm formaldehyde for up to 6 weeks. Low levels of crosslinks also were found in the trachea and carina of some monkeys, but no crosslinks were found in the sinuses or lungs. The yield of crosslinks in monkeys was about an order of magnitude lower than observed in rats, which is primarily attributed to differences in minute volume and quantity of DNA in the nasal mucosa (Casanova *et al.* 1991). These authors used the crosslink data from rats and monkeys to extrapolate crosslink concentrations in humans and predicted that adult men would have significantly lower rates than rats and slightly lower rates than monkeys.

DNA-protein crosslinks were detected in peripheral lymphocytes of health professionals (physicians, laboratory assistants and orderlies from pathology departments) exposed to formaldehyde (see Section 5.6.4). There was a linear relationship between years of exposure and DNA-protein crosslinks.

There is evidence that repair and/or tolerance of DNA-protein crosslinks involves both nucleotide excision repair and homologous recombination; however, the relative contribution of these pathways differs depending on the dose and duration of exposure (de Graaf *et al.* 2009). These authors reported that *Saccharomyces cerevisiae* strains containing deletions in genes that mediated homologous recombination showed the greatest sensitivity to formaldehyde following low-dose, chronic exposure, while deletions in genes associated with nucleotide excision repair conferred only low to moderate sensitivities. In contrast, genes associated with nucleotide excision repair pathways conferred maximal survival following high-dose, acute exposures with little contribution from homologous recombination genes. Thus, these data show that exposure conditions can affect the spectra of gene-deletion strains that are sensitive or resistant to formaldehyde.

Ridpath *et al.* (2007) noted that although DNA-protein crosslinks likely play an important role in the genotoxicity and carcinogenicity of formaldehyde, little is known about which DNA-damage-response pathways are involved in repairing formaldehyde damage. In patients with diseases such as Fanconi anemia (FANC; an inherited blood disorder that leads to bone marrow failure), DNA damage cannot be repaired due to the presence of an abnormal gene in the cells that prevents DNA repair. Ridpath *et al.* investigated the DNA response pathways by measuring the reduction of cell survival in several repair-deficient mutants in two different cell types. Chicken DT40 cells with targeted mutations in various DNA-repair genes were used to assess levels of DNA damage response to formaldehyde. DT40 mutants deficient in the BRCA/FANC pathway, homologous recombination, and translesion DNA synthesis were shown to be hypersensitive (i.e., resulted in reduced cell survival) to formaldehyde. Similar results were observed for the human colorectal cancer (RKO) cell line. Specifically, RKO cells deficient in the *FANCC* and *FANCG* genes showed a dose-dependent hypersensitivity to formaldehyde. These results suggest that the BRCA/FANC response pathway in mammalian cells is important in the prevention of DNA damage from formaldehyde.

In a review by Zhang *et al.* (2009b), the possible roles of formaldehyde, both endogenous and exogenous, on the etiology of leukemia in FANC patients is discussed. The authors hypothesized that endogenous exposure might induce DNA-protein crosslinks, which could play a critical role in the initiation of bone marrow failure or in increasing tumor susceptibility in FANC patients. They suggest that subsequent exogenous exposure to formaldehyde might then result in genotoxic levels of induced DNA-protein crosslinks; however, this assumes that formaldehyde actually reaches the bone marrow cells, which has not yet been demonstrated.

5.8.1.2 Other genetic damage

Other genotoxic endpoints have been examined in *in vitro* and *in vivo* studies. DNA damage (single-strand breaks) was detected in *S. cerevisiae* and in mammalian cells *in vitro*, including human cells such as fibroblasts, lymphocytes, and lung/bronchial epithelial cells. Strand breaks were also reported in rat lymphocytes (inhalation exposure), and in maternal and fetal liver following intraperitoneal injection on gestation days 6 to 19. DNA damage, as assessed by the alkaline comet assay, increased in lymphocytes from pathology laboratory workers exposed to formaldehyde compared with unexposed controls (reviewed in Section 5.6.4): comet tail length for lymphocytes was positively associated with formaldehyde exposure levels.

In prokaryotes, formaldehyde induced mainly base-pair mutations, in either the presence or absence of metabolic activation at 100% frequency in certain *S. typhimurium* strains (TA102, TA104, and TA7005), and in mammalian cells. *In vivo* exposure to formaldehyde in rodents caused dominant lethal mutations in multiple studies in rats and one study in mice, and heritable mutations in mice. Formaldehyde exposure inhibited repair of *N*-nitrosourea-induced O^6-methylguanine DNA lesions in human bronchial fibroblasts (Grafström *et al.* 1985). Low concentrations of formaldehyde (10 μM) delayed DNA repair (as measured by nucleotide excision repair of single-strand breaks) following UV irradiation in human skin cells, and also caused an increase in UVC-induced chromosomal damage (Emri *et al.* 2004). Thus, in addition to causing direct

damage to DNA, formaldehyde may cause genotoxicity by inhibiting repair of mutagenic lesions caused by other agents. However, no reports of mutations in humans were identified, and three studies of health professionals were negative for effects of formaldehyde on DNA repair (see Section 5.6.4).

Chromosomal aberrations were positive in both animal and human cells *in vitro* in all studies summarized in Table 5-20. However, studies in mice with intraperitoneal injection were negative for chromosomal aberrations in bone marrow, spleen, and sperm. Exposure of rats by inhalation caused chromosomal aberrations in pulmonary lavage cells at the highest dose (15 ppm) tested, but not in lymphocytes. One study reported chromosomal aberrations in rat bone marrow following inhalation exposure to 0.4-ppm formaldehyde for 4 months, but another study did not find an increase in chromosomal aberrations in rat bone marrow when exposed to 15 ppm for up to 8 weeks (see Section 5.6.3). The frequency of chromosomal aberrations was increased statistically in seven studies (Suskov and Sazonova 1982, Bauchinger and Schmid 1985, Chebotarev *et al.* 1986, Kitaeva *et al.* 1996, He *et al.* 1998, Lazutka *et al.* 1999, and Neri *et al*. 2006, see Table 5-26) of lymphocytes from humans (mainly workers) exposed to formaldehyde. Tang *et al*. (2009) also reported an additional positive study in their review of the Chinese literature. Zhang *et al*. (2010) reported a statistically significant increase in monosomy 7 and trisomy 8 among formaldehyde-exposed workers compared with matched controls. With respect to the other studies (see Table 5-26): (1) Thomson *et al.* (1984) reported a nonstatistically significant increased frequency in chromosomal aberrations based on small numbers of workers (six exposed and five controls), (2) Vargová *et al.* (1992) noted that the frequency of chromosomal aberrations in the controls in their study was higher than that reported in the general population, (3) Pala *et al.* 2008 did not find an increased frequency of chromosomal aberrations among high-exposed workers compared with low-exposed workers, although there were only five workers in the high-exposure group, and (3) the other two studies (Fleig *et al.* 1982, Vasudeva and Anand 1996), did not find a statistically significant increase in chromosomal aberrations among formaldehyde-exposed workers compared with controls. The results for chromosomal aberrations are potentially of greater interest than other endpoints because of the report by Bonassi *et al.* (2008) that high levels of chromosomal aberrations are associated with increased risk of cancer in otherwise healthy individuals.

Sister chromatid exchange was positive in all studies in mammalian cells summarized in Table 5-20, but negative results were reported for two studies in rats in Table 5-21. With respect to studies of lymphocytes from industrial workers, health professional, or students exposed to formaldehyde (see Table 5-27) six studies reported that formaldehyde exposure was associated with a statistically significant increase in SCE frequency (Yager *et al.* 1986, Shaham *et al.* 1997, 2002, He *et al*. 1998, Ye *et al.* 2005, and Costa *et al.* 2008); some of these studies compared exposed subjects with unexposed controls, whereas others compared SCE levels prior to and post exposure among students enrolled in a class. Six of the reviewed studies (Thomson *et al.* 1984, Bauchinger and Schmid 1985, Chebotarev *et al.* 1986, Suruda *et al.* 1993, Ying *et al.* 1999, and Pala *et al.* 2008) did not find higher levels of SCE in lymphocytes among formaldehyde-exposed subjects; the study by Pala *et al.* did not have an unexposed control group and compared SCE in a high-exposure group, which only had two subjects, with a low-exposure group. A review of the Chinese literature by Tang *et al.* (2009) reported two additional negative studies.

Micronuclei were induced in all *in vitro* studies (see Table 5-28). In rodents, formaldehyde exposure did not cause micronuclei in mice (bone marrow, peripheral blood, or reticulocytes), and results were mixed for rats; one oral study was positive for the GI tract and one intraperitoneal study was negative for bone marrow cells. Speit *et al.* reported that micronucleus formation was enhanced in repair-deficient cell lines, particularly in xeroderma pigmentosum cells, which are deficient in nucleotide excision repair. Loss of glutathione (i.e., GSH) did not affect repair rates.

Micronuclei frequency was also increased in the buccal epithelium, nasal epithelium, and lymphocytes among workers, medical staff, or students exposed to formaldehyde. Increased incidences of micronuclei in lymphocytes were found among mortuary science students after exposure to formaldehyde for 90 days (Suruda *et al*. 1993) and in several studies of anatomy/pathology subjects (He *et al.* 1998, Osière *et al.* 2006, Costa *et al.* 2008), but not in a study of anatomy students exposed for 8 weeks (Ying *et al.* 1997) or a high-exposure group of laboratory workers compared with a low-exposure group (Pala *et al.* 2008). Increased incidences of micronuclei in oral epithelium were reported in all studies (Suruda *et al*. 1993, Titenko–Holland *et al.* 1996, Kitaeva *et al.* 1996, Ying *et al.* 1997, Burgaz *et al.* 2002) except for a study of volunteer subjects exposed to formaldehyde for 10 days (Speit *et al.* 2007b). All (Ballarin *et al.* 1992, Ying *et al*. 1997, Burgaz *et al.* 2001, Ye *et al*. 2005) but one (Suruda *et al*. 1993) of the available studies also reported an association with formaldehyde exposure and increased micronucleus frequency in nasal epithelium; however, a subsequent analysis of a subset of the study population from the negative study found a significantly increased frequency of micronuclei in centromere-negative (but not centromere-positive) micronuclei (Titenko-Holland *et a*l. 1996). In addition, a review of the Chinese literature by Tang *et al.* 2009 of studies of humans exposed to formaldehyde reported increased micronucleus frequency in nasal epithelial cells in one study, and in lymphocytes in three studies of long-term (> 1 year) formaldehyde exposure. Micronuclei may form from clastogenic or aneugenic events. Titenko-Holland *et al.* (1996) reported a greater increase of centromere-negative micronuclei in buccal and nasal mucosa cells from mortuary science students and concluded that chromosome breakage was the primary mechanism responsible for these effects. In contrast, Orsière *et al.* (2006) and Iarmarcovai *et al.* (2007) reported greater increases in centromere-positive micronuclei (evidence of aneugenic effects) in peripheral lymphocytes of pathologists/anatomists exposed to formaldehyde.

5.8.2 Mutational spectra

Shaham *et al.* (2003) reported an association between DNA-protein crosslinks in formaldehyde-exposed workers and increased serum p53 protein. Furthermore, a positive correlation was found between increased p53 and mutant p53 protein, indicating a possible causal relationship between crosslinks and *p53* mutations that might represent steps in formaldehyde carcinogenesis.

Recio (1997) reviewed the literature on oncogene and tumor-suppressor gene alterations in rodent nasal tumors. Molecular genetic studies on nasal squamous-cell carcinomas in rats indicated that *p53* mutations occur at a high frequency. This finding combined with the high prevalence of *p53* mutations among human squamous-cell carcinomas suggests that a common molecular alteration is shared between human and rodent squamous-cell

carcinomas. The *HPRT* mutational spectra in formaldehyde-exposed human lymphoblasts show about 50% deletions and 50% point mutations, with the majority of point mutations occurring at A:T base pairs (Liber *et al.* 1989). However, this finding is inconsistent with the G:C base-pair mutations observed in formaldehyde-induced nasal squamous-cell carcinomas in rats (Recio *et al.* 1992). Recio (1997) concluded that the lack of *p53* point mutations at A:T base pairs in formaldehyde-induced squamous-cell carcinomas suggested an indirect mechanism of genotoxicity rather than a direct effect of formaldehyde on the cellular genome. The origin of the point mutations in *p53* observed in formaldehyde-induced nasal squamous-cell carcinomas in rats is unknown, but inflammation and regenerative cell proliferation are thought to be important factors.

Recio *et al.* (1992) examined the complementary DNA of the tumor-suppressor gene *p53* from 11 primary nasal squamous-cell tumors taken from rats exposed to formaldehyde. Point mutations at G:C base pairs were found in *p53* in 5 of 11 tumors analyzed. All of the mutated *p53* codons found in rat tumors have also been identified in a variety of human cancers. In particular, a mutation that occurred at rat codon 271 (analogous to human codon 273), is known to be a hot spot for *p53* mutations in human cancers. In addition, Wolf *et al.* (1995) used an immunohistochemical technique to measure p53 protein, proliferating cell nuclear antigen (PCNA), and tumor growth factor-α (TGF-α) in these tumors. These authors observed p53-positive immunostaining and preneoplastic hyperkeratotic plaques in the tumors but not in normal nasal mucosa. There was a correlation between both the pattern and distribution of immunostaining of PCNA and p53. Four cell lines were established from these squamous-cell carcinomas (Bermudez *et al.* 1994). All the cell lines were aneuploid and overexpressed keratin, transforming TGF-α, epidermal growth factor receptors, and p53. Expression of TGF-α and epidermal growth factor is a common feature of squamous-cell carcinoma and is frequently found in human tumors. When injected into nude mice, the two cell lines that contained a *p53* mutation were tumorigenic, but the two cell lines that had wild-type *p53* were not.

5.8.3 Epigenetic effects

Lu *et al.* (2008a) reported that formaldehyde induced histone modifications *in vitro*. Lysine residues on histones are subject to post-translational modifications (e.g., methylation, phosphorylation, and acetylation) which impact gene expression. DNA-protein crosslinks involve all the major histones and are a dominant form of formaldehyde-induced DNA damage (Quievryn and Zhitkovich 2000). Lu *et al.* (2008a) isolated histone 4 with post-translational modification from calf thymus tissues. Unmodified human recombinant histone 4 was purified after expression in *E. coli* cells. Both proteins had identical sequences. Formaldehyde was reacted with histone 4 and analyzed by liquid chromatography-mass spectrometry. All the lysine residues located in both the histone *N*-terminal tail and the globular fold domain were identified as binding sites for formaldehyde. Formaldehyde could only bind to lysine residues without post-translational modification, thus, post-translational modification of lysine blocks the reaction with formaldehyde. However, formaldehyde reactions with unmodified lysine residues resulted in the formation of methylol groups followed by the formation of Schiff bases. Formaldehyde-induced Schiff bases inhibited post-translational modifications of lysine *in vitro*. Therefore, formaldehyde could alter epigenetic regulation by impairing the post-translational modification pattern and possibly disturb subsequent protein

recruitment and trigger a series of abnormal cascade effects. Furthermore, the balance between histone acetylation and deacetylation (which is important for normal cell growth) could be disturbed. An imbalance of acetylation in promoter regions could induce the deregulation of gene expression and affect carcinogenesis and cancer progression. The authors noted that they used a simplified *in vitro* model and that further testing in cells or tissues would be needed to demonstrate that such effects would occur *in vivo*.

5.8.4 Glutathione depletion and oxidative stress

5.8.4.1 In vitro *studies*

Ku and Billings (1984) reported that the metabolism and toxicity of formaldehyde in isolated rat hepatocytes was dependent upon the intracellular glutathione concentration. Hepatocytes depleted of glutathione were more susceptible to formaldehyde toxicity (loss of membrane integrity and lipid peroxidation). Cells treated with L-methionine had increased concentrations of glutathione and were protected from formaldehyde toxicity. Cells treated with antioxidants also showed a dose-related protection against toxicity suggesting that formaldehyde toxicity in glutathione-depleted cells may be mediated by a free radical mechanism.

Grafström (1990) studied the ability of formaldehyde and acrolein to cause various effects associated with carcinogenesis in cultured human bronchial cells. These included cell viability, differentiation and growth, membrane integrity, thiol and ion homeostasis, and genetic damage. Concentrations of formaldehyde associated with 50% inhibition were as follows: 0.4 mM (colony-forming efficiency), 0.2 mM (clonal growth rate), and 2 mM (membrane integrity measured by trypan blue exclusion). Free cytosolic Ca^{2+} in bronchial fibroblasts was increased by 50% at 0.5 mM. In addition, 0.2 mM formaldehyde decreased glutathione content to 80% of controls and increased the percentage of crosslinked envelopes, a marker for squamous differentiation, to 12% compared with 2% for controls. Grafström *et al.* (1996) also reported toxic effects of formaldehyde in cultured human bronchial epithelial cells under defined serum- and thiol-free exposure conditions. Formaldehyde was associated with the formation of thiohemiacetal, but not with overt oxidative stress; however, active reduction of oxidized glutathione by glutathione reductase might have masked an oxidant effect. Loss of membrane integrity coincided with extensive loss of intracellular glutathione. Formaldehyde-induced growth inhibition may be explained by decreased glutathione levels because decreased glutathione levels are known to inhibit cell growth. These authors also noted that genetic damage may be responsible for some of the cytotoxic action of formaldehyde because inhibition of DNA repair occurred in bronchial cells exposed to 0.1 to 0.3 mM formaldehyde. Thus, loss of enzyme function (particularly enzymes that carry a thiol moiety in their active site) might be an essential aspect of formaldehyde toxicity.

Nilsson *et al.* (1998) investigated the role of exogenous and endogenous thiols in formaldehyde toxicity in human oral fibroblasts and epithelial cells. Formaldehyde decreased the colony-forming efficiency of both cell types in a concentration-dependent manner, but was more toxic to fibroblasts than to epithelial cells. The difference in

toxicity was attributed to the comparatively lower cellular levels of thiols (glutathione and cysteine) in fibroblasts.

Teng *et al.* (2001) also investigated the cytotoxic effects of formaldehyde in isolated rat hepatocytes. Hepatocytes were treated with 2, 4, or 10 mM formaldehyde. Dose-dependent effects included a decrease in mitochondrial membrane potential, inhibition of mitochondrial respiration that was accompanied by formation of reactive oxygen species, glutathione depletion, and lipid peroxidation. Cells depleted of glutathione were much more susceptible to the cytotoxic effects of formaldehyde. Cytotoxicity was associated with a decrease in metabolism and an increase in lipid peroxidation.

Tyihák *et al.* (2001) exposed human HT-29 colon carcinoma and HUV-EC-C endothelial cell cultures to formaldehyde concentrations of 0.1 to 10 mM. Cultures were evaluated at 24, 48, and 72 hours after treatment. The cell cultures exposed to the high dose were completely eradicated. At 1 mM, enhanced apoptosis and reduced mitosis were observed in cultures of both cell types, while at the low dose (0.1 mM), enhanced cell proliferation and decreased apoptotic activity occurred. Tumor cells were more responsive than endothelial cells at the low-dose level. The authors proposed that low doses of exogenous or intrinsic formaldehyde may increase cell proliferation and inhibit apoptosis leading to neoplasia, whereas at high doses, formaldehyde may cause damage to endothelial, epithelial, or other cells by inducing apoptosis, and inhibiting repair.

Saito *et al.* (2005) investigated the cytotoxic effects exerted by formaldehyde in the presence or absence of reactive oxygen species. Jurkat E6-1 cells from a human T-leukemia cell line were cultured with variable concentrations of formaldehyde (< 1 to 100 mM) for 3 hours. There was a concentration-dependent decrease in cell viability with significant decreases at concentrations greater than 1 mM. Cells cultured with the water-soluble radical initiator, 2,2′-azobis-[2-(2-imidazolin-2-yl)propane] dihydrochloride (AIPH) at concentrations up to 8 mM showed no decrease in viability. However, cell viability was significantly decreased at AIPH concentrations of more than 3 mM in the presence of 1 mM formaldehyde. Further analysis indicated that cell death resulted from necrosis rather than apoptosis. Cell death was preceded by a significantly increased cellular level of reactive oxygen species. Total cellular glutathione was reduced to about 60% of the control value in cells treated with 1 mM formaldehyde for 2 hours, while 6 mM AIPH reduced glutathione levels to about 5% of the control value. Glutathione was completely depleted in cell cultures treated with both formaldehyde and AIPH. These results indicate a synergistic interaction of formaldehyde and free radicals.

5.8.4.2 In vivo *studies*

In vitro studies (discussed above) indicated that formaldehyde exposure resulted in the formation of reactive oxygen species, glutathione depletion, and lipid peroxidation and that antioxidants had a protective effect (Ku and Billings 1984, Teng *et al.* 2001). Several *in vivo* studies have examined oxidative stress in rats exposed to formaldehyde. These studies show that formaldehyde exposure can cause oxidative stress in the rat liver, plasma, lymphocytes, heart, and brain.

Söğüt *et al.* (2004) investigated the oxidant/antioxidant status of albino Wistar rats exposed to 0-, 10-, or 200-ppm formaldehyde 8 hours/day, 5 days/week for 4 weeks. Glutathione levels in liver tissues were significantly reduced at both exposure levels. Xanthine oxidase levels were reduced in the high-dose group. There were no significant changes in malondialdehyde or nitric oxide levels. Thus, the authors suggested that the antioxidant system of liver tissue is moderately impaired by excessive formaldehyde exposure. The authors also concluded that glutathione depletion from subacute exposures to formaldehyde may increase susceptibility to oxidative damage.

Gurel *et al.* (2005) investigated the biochemical and histopathological changes occurring in the frontal cortex and hippocampal tissue of the rat brain after formaldehyde exposure. Male Wistar rats were divided into three groups of six rats each. One group received intraperitoneal injections of 10 mg/kg b.w. formaldehyde (37% solution) for 10 days. The second group received intraperitoneal injections of formaldehyde and vitamin E, and the third group was untreated (controls). The animals were killed at the end of the treatment period, and the frontal cortex and hippocampal tissues were removed. Malondialdehyde and protein carbonyl levels were significantly increased in these tissues, while superoxide dismutase and catalase enzyme activities were decreased in the formaldehyde-only treatment group compared with controls. Rats treated with both formaldehyde and vitamin E showed lower malondialdehyde and protein carbonyl levels with no inhibition of superoxide dismutase or catalase. The authors concluded that formaldehyde caused oxidative damage to tissues in the brain, which was likely mediated through the production of free radicals.

Gülec *et al.* (2006) evaluated the oxidant/antioxidant status and lipid peroxidation in the hearts of rats exposed to formaldehyde. Groups of 10 adult Wistar rats (sex was not identified) were placed in inhalation chambers and exposed to 0-, 10-, or 20-ppm formaldehyde 8 hours/day, 5 days/week for 4 or 13 weeks. The animals were checked daily and body weights were recorded weekly. At the end of the experiment, the animals were necropsied, and examined grossly for pathological changes, and heart tissues were prepared for biochemical analysis. Superoxide dismutase levels were increased in all exposed groups compared with controls. Catalase activity was significantly decreased at both exposure levels in groups exposed for 4 weeks but not at 13 weeks. Thiobarbituric acid-reactant substances were measured as an index of lipid peroxidation and were slightly increased in exposed groups compared with controls, but the differences were not significant. Nitric oxide levels were not affected. The authors concluded that subacute and subchronic exposure to formaldehyde might stimulate oxidative stress in cardiac cells and tissues. The increased superoxide dismutase activity was thought to be secondary to decreased catalase activity, as a compensatory mechanism, thus protecting heart tissue from damage.

Im *et al.* (2006) evaluated the effects of formaldehyde exposure on rat plasma proteins. Male Sprague-Dawley rats (10 per group) were exposed to 0-, 5-, or 10-ppm formaldehyde 6 hours/day, 5 days/week for 2 weeks in an inhalation chamber. Lipid peroxidation and protein oxidation levels in plasma, lymphocytes, and liver were determined using the malondialdehyde assay and carbonyl spectrometric assay. The comet assay was used to evaluate DNA damage (see Section 5.6.3). Lipid peroxidation

and protein oxidation were dose-dependently increased in plasma, lymphocytes, and liver of exposed rats. In addition, a proteomic analysis identified 19 up-regulated and 13 down-regulated proteins as biomarkers of formaldehyde exposure. These included proteins involved in apoptosis, transportation, signaling, energy metabolism, and cell structure and motility.

Kum *et al.* (2007a) measured oxidative stress in the adult and developing rat liver after inhalation exposure to formaldehyde and xylene. Four age groups (embryonic day 1, 1 day old, 4 weeks old, and adults), each containing 24 female Sprague-Dawley rats were used. Each age group was further divided into four experimental groups of 6 rats each. In addition to the control group, rats were exposed to 6-ppm formaldehyde, 300-ppm xylene, or xylene + formaldehyde for 8 hours/day for 6 weeks. Body and liver weights were measured, and superoxide dismutase, catalase, glutathione, and malondialdehyde levels were determined. Body and liver weights were decreased in all exposure groups compared with controls in the embryonic day 1 group compared with controls. Body and liver weights were significantly decreased in the xylene + formaldehyde exposure groups of 1-day-old rats, but not in the xylene + formaldehyde combined exposure group. Liver weights were significantly higher in the xylene and xylene + formaldehyde combined exposure groups of 4-week-old rats. There were no significant differences in body or liver weights in the adult rat exposure groups compared with controls. Superoxide dismutase levels were significantly decreased in the formaldehyde-exposed group of 4-week-old rats. Glutathione levels were significantly decreased in the xylene and xylene + formaldehyde combined exposure groups of 1-day-old rats. Malondialdehyde levels were not significantly different from controls in any of the formaldehyde or xylene + formaldehyde combined exposure groups. Catalase activity was slightly increased in the xylene + formaldehyde combined exposure group of embryonic rats. The authors concluded that these data suggested that the developing rat liver is more susceptible to the toxic effects of formaldehyde and xylene than the adult rat liver.

5.8.5 Nasal tumors

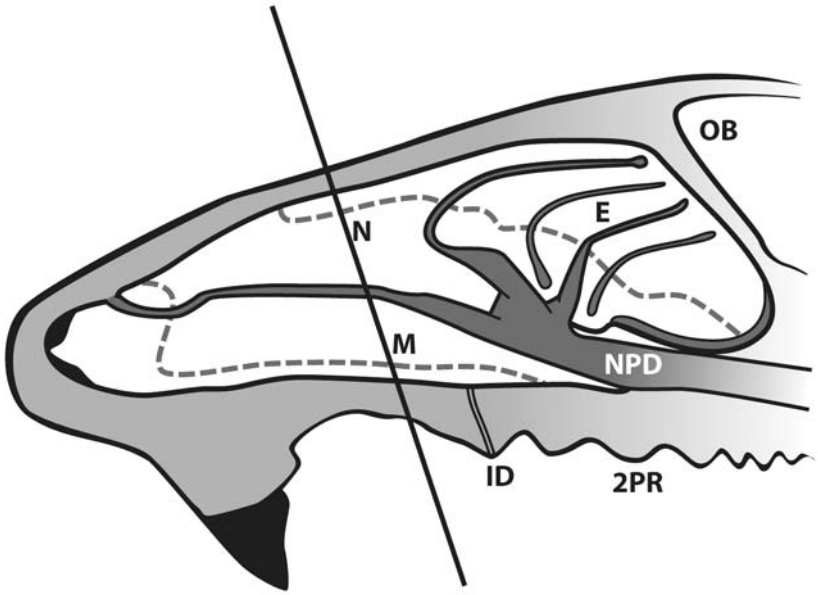
Increased incidences of nasal tumors were found in studies in experimental animals (see Section 4). In addition, oral administration of formaldehyde to rats resulted in increased incidences of gastrointestinal tract cancers. There is considerable evidence that airway deposition, genotoxicity, cytotoxicity, and cell proliferation are important factors in nasal tumor formation (IARC 2006). A number of studies have investigated the underlying mechanisms of the nasal tumor response (reviewed by Heck *et al.* 1990, Morgan 1997). In parallel with the mechanistic studies, anatomically accurate three-dimensional computation fluid dynamics (CFD) models have been developed to provide high resolution predictions of nasal air flow and regional flux of inhaled formaldehyde (see Section 5.2) into adjacent nasal tissue. CFD models also have been used to predict crosslink formation, and, when combined with a two-stage clonal growth model, to link crosslink and regenerative cellular proliferation with tumor formation (Conolly *et al.* 2000, 2003, 2004).

5.8.5.1 Airway deposition models and predictions

Morgan (1997) considered that although the nasal passages of rats and humans are fundamentally identical biological target organs, minor differences could be critically important. Regional deposition of inhaled gases and tissue susceptibility are the two major factors that influence the distribution of lesions in the respiratory tract. Tissue susceptibility is frequently related to differences in local enzyme-mediated biotransformation to a toxic species or to local doses that exceed detoxification thresholds. Keller *et al.* (1990) conducted a histochemical analysis of formaldehyde dehydrogenase (the primary metabolizing enzyme for formaldehyde) and reported that regional differences were insufficient to account for the localized toxicity of formaldehyde in the rat nose, which would indicate that nasal airflow and intranasal uptake patterns of formaldehyde were important. CFD models have allowed researchers to investigate interspecies differences in airflow patterns, formaldehyde flux and absorption, and effects on the upper respiratory tract, and to gain a better understanding of mechanisms and modes of action.

Studies with formaldehyde-exposed rats and rhesus monkeys show site- and species-specific patterns for both carcinogenic and noncarcinogenic lesions in the upper respiratory tract (Casanova *et al.* 1994, Monticello *et al.* 1996, Kimbell *et al.* 1997). The nasal vestibule in rats, monkeys, and humans is lined with squamous epithelium; however, areas posterior to the nasal vestibule are lined with respiratory, transitional, and olfactory epithelia (Kimbell *et al.* 1997). Inhaled formaldehyde does not result in lesions in the nasal vestibule, but a common response in other epithelia is conversion to the squamous form (i.e., squamous metaplasia). This observation suggests that squamous epithelium is resistant to formaldehyde toxicity and that squamous metaplasia may be an adaptive response. Further, squamous epithelium may be protective by absorbing less formaldehyde than other epithelial types. Kimbell *et al.* (1997) compared CFD model predictions and observed squamous metaplasia incidence in the area of the rat nose (lateral meatus and mid-septum) where squamous-cell carcinoma occurred in chronic inhalation studies (Figure 5-3). Regional formaldehyde flux was correlated with the distribution of formaldehyde-induced squamous metaplasia in rats exposed to 10- or 15-ppm formaldehyde. Kepler *et al.* (1998) conducted a similar study in the rhesus monkey. Simulated airflow patterns showed good agreement with experimental observations.

A)



B)

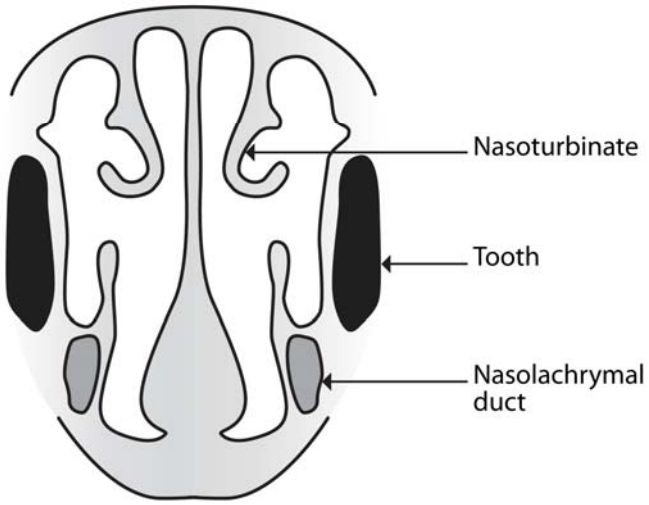


Figure 5-3. Sagittal (A) and cross- (B) section through the rat nose

Source: adapted from Kerns *et al*. 1983a and Mery *et al.* 1994. (Illustration prepared by Donna Jeanne Corcoran, Image Associates, Durham, N.C.)

A) Sagittal section through the rat nose. The curved dashed lines indicate the junction of the squamous/transitional and respiratory epithelia (anterior line) and the respiratory and olfactory epithelia (posterior line). N = nasoturbinates, M = maxilloturbinates, E = ethmoturbinates, ID = incisive duct, NPD = nasopharyngeal duct, OB = olfactory bulb, 2PR = second palatal ridge.

B) Cross section through the rat nose at the level indicated by the slanted line in panel A.

Kimbell *et al.* (2001a) predicted formaldehyde flux in the entire nasal passages of rats, monkeys, and humans, estimated flux in specific sites for correlation with formaldehyde-induced cell proliferation data, and compared the flux values predicted for the three species. Regions of the nasal passages in rats and monkeys that had similar cell proliferation rates also had similar predicted flux values with a rat to monkey ratio of 0.98 for the highest site-specific flux values. Simulations using the human CFD model predicted that flux values in an anterior portion of the human nose were similar to fluxes predicted in a region of high tumor incidence in the rat nose. The authors concluded that proliferative and carcinogenic responses could be expected to occur in humans under conditions similar to those inducing these effects in rats and monkeys. Kimbell *et al.* (2001b) further refined the CFD models to obtain quantitative descriptions of nasal uptake patterns. Their simulations indicated a decreasing gradient of flux values from anterior to posterior regions of the nasal cavity in all three species with steeper gradients in rats and monkeys than in humans. Nasal flux patterns in humans shifted posteriorly, and the overall nasal uptake decreased as inspiratory flow rate increased. The authors noted that these results are consistent with an increased airflow pushing inhaled gas further into the respiratory tract.

Cohen-Hubal *et al.* (1997) conducted the first quantitative demonstration of the role of site-specific formaldehyde flux and crosslink formation. These authors used a CFD model to link dosimetry predictions with measured tissue deposition. Crosslink predictions compared well with experimentally measured data. Conolly *et al.* (2000) expanded on the work of Cohen-Hubal *et al.* and used an improved CFD model to predict regional flux of formaldehyde and crosslink formation in the respiratory and olfactory mucosa of the rat, monkey, and human. Simulated formaldehyde concentrations ranged from 0.1 to 20 ppm over a 3-hour exposure. Good fits to the rat and monkey crosslink data were obtained. Differences in the predictions between regions of the nasal mucosa were accounted for by site-specific tissue thickness and flux estimates. The predicted crosslink dose response for the human case was compared with the rat and monkey and was similar for all three species even though there were significant interspecies differences in nasal anatomy, breathing rates, and parameter estimates.

Georgieva *et al.* (2003) also developed a mathematical model that linked airflow-driven formaldehyde uptake and crosslink formation in regions of the rat nose with high and low tumor incidence. A CFD model was integrated with a physiologically based mathematical model that incorporated tissue thickness, formaldehyde diffusion, formaldehyde removal by enzymatic and nonenzymatic processes, DNA distribution in the nasal mucosa, and the reversible conversion of formaldehyde to methylene glycol. Parameter values where taken from the literature or estimated using published correlations. The model simulations had a very good fit for the experimentally measured crosslink data in both high- and low-tumor-incidence regions of the nose.

Conolly *et al.* (2003) described biologically motivated quantitative modeling of the exposure-tumor response continuum in the rat using a CFD model linked with a two-stage clonal growth model. Regenerative cell proliferation was used as a surrogate for cytolethality. The average division rate constants were based on labeling index data reported by Monticello *et al.* (1991, 1996). A time-weighted unit length labeling index

was calculated for the entire 78 weeks of exposure. The calculated rate constants were plotted against formaldehyde concentrations and resulted in a J-shaped exposure-response curve. The probability of mutation per cell generation (a function of the tissue crosslink concentration and the rate of cell division) was used in the clonal growth model to predict tumor yield. A sensitivity analysis indicated that the directly mutagenic pathway had little influence and that the tumor outcome was due primarily to regenerative cellular proliferation.

Conolly *et al.* (2004) extended the approach used by Conolly *et al.* (2003) to humans. The primary objective was to maximize the use of relevant mechanistic data in predicting human cancer response to inhaled formaldehyde. The only structural difference between the rat and human tumor-response models was that the human model included the entire respiratory tract to provide the capability for predicting tumor risk associated with oronasal breathing at higher exertion levels. The human clonal growth model used three sets of baseline parameters for nonsmokers, smokers, and a mixed population of nonsmokers and smokers in order to estimate human respiratory tract tumor incidences not explicitly related to formaldehyde exposure. Cancer risk predictions were based on J-shaped and hockey stick-shaped dose-response curves and included 18 exposure scenarios involving continuous (80-year environmental exposure), and light or heavy working occupational scenarios. Predicted risks for smokers were about an order of magnitude higher than for nonsmokers. Their data indicated that excess risk for continuous environmental exposure to formaldehyde at concentrations below 1 ppm (J-shaped dose-response model) or 0.2 ppm (hockey-stick dose-response model) were *de minimis* ($< 10^{-6}$). Breathing rate changes based on various activity levels did not result in large changes to the calculated risk.

Results from Conolly *et al.* (2003, 2004) were later challenged by Subramaniam *et al.* (2007, 2008) and Crump *et al.* (2008). These authors identified sources of uncertainty in the CFD models and modified selected features to examine the sensitivity of the predicted dose response to select assumptions. They found that the dose-response predictions below the range of exposures where tumors were observed were highly sensitive to the choice of control data. In contrast to the results reported by Conolly *et al.* (2003), their reanalysis indicated that up to 74% of the added tumor probability could be attributed to formaldehyde's mutagenic action. Furthermore, slight numerical perturbations in the assumptions regarding the effects of formaldehyde on the division rates and death rates of initiated cells resulted in risk estimates that were up to 10,000 times those reported by Conolly *et al.* (2004).

5.8.5.2 Cytotoxicity and cellular proliferation in experimental animals

At high concentrations formaldehyde is highly irritating and cytotoxic, causing loss of cilia and cell death in the nasal cavity (Conaway *et al.* 1996). IARC (2006) provided a comprehensive review of formaldehyde-induced cytotoxicity and cell-proliferation studies. Increased cell proliferation is believed to contribute to carcinogenesis by providing additional cell divisions, thus increasing the probability of spontaneous or chemically induced mutations (Monticello and Morgan 1997).

Studies in rats and mice show species differences in the cytotoxicity of inhaled formaldehyde to the respiratory epithelium (Chang *et al.* 1983, Monticello *et al.* 1991, Monticello *et al.* 1996). The sequence of effects, which are more severe in the rat, include rhinitis, epithelial dysplasia, squamous metaplasia and hyperplasia, and squamous-cell carcinoma. Mice were able to compensate for increased concentrations of formaldehyde by reducing minute ventilation, thus reducing deposition and subsequent tissue damage. Eighteen hours after a single 6-hour exposure to 15-ppm formaldehyde, cell proliferation increased 13-fold in rats and 8-fold in mice compared with controls. Cell proliferation was not evident until exposure concentrations exceeded 6 ppm following acute, subchronic, or chronic exposures; however, histopathological effects and a sustained increase in cell proliferation did not occur at concentrations less than 2 ppm, regardless of the exposure duration.

A sustained increase in cellular proliferation subsequent to epithelial-cell toxicity is believed to be an important determinant of neoplastic progression associated with formaldehyde exposure (Liteplo and Meek 2003). Monticello *et al.* (1996) examined the proliferative response in various regions of the rat nose following exposures to formaldehyde concentrations of 0, 0.7, 2, 6, 10, or 15 ppm for up to 24 months (6 hours/day, 5 days/week). Animals were sacrificed at 3, 6, 12, 18, and 24 months. The incidence of regional formaldehyde-induced nasal tumors was correlated with the population-weighted unit length labeling index (i.e., the product of the S-phase nuclei per millimeter of basement membrane and the total number of cells per site) at 3 months. Thus the weighted labeling index incorporates both the cell replication rate and the number of cells at the specific site. A sustained increase in the labeling index was observed only at exposure concentrations that yielded significant numbers of nasal tumors (10 and 15 ppm) (Table 5-30). The authors concluded that target-cell population size, cell proliferation, and local dosimetry play a significant role in the concentration-response curve for formaldehyde-induced nasal cancer in rats.

Table 5-30. Formaldehyde exposure, cell proliferation, and nasal tumor incidence

Exposure (ppm)	Cell proliferation (population-weighted S-phase nuclei/mm basement membrane × 10^6)[a]			Tumor incidence (%)		
	ALM	PLM	AMS	ALM	PLM	AMS
0	9.9	3.9	1.2	0/90	0/90	0/90
0.7	10.3	4.0	1.5	0/90	0/90	0/90
2	9.6	5.7	2.3	0/90	0/90	0/90
6	15.4	4.9	0.8	1/90 (1)	0/90	0/90
10	74.9	7.8	7.2	12/90 (13)	2/90 (2)	0/90
15	91.0	30.2	13.9	17/147 (12)	9/147 (6)	8/147 (5)

Adapted from Monticello *et al.* 1996.
ALM = anterior lateral meatus; PLM = posterior lateral meatus; AMS = anterior mid-septum.
[a]Calculated as the product of the unit length labeling index and the total number of nasal epithelial cells at each site. [These data were presented in Figure 8 of Monticello *et al.* (1996); however, the paper incorrectly reported the value as 10^7. The correct value is 10^6.]

Woutersen *et al.* (1989) studied the role of cell proliferation in formaldehyde carcinogenesis (see Section 4.1.2). These authors reported that compound-related degenerative, inflammatory, and hyperplastic changes of the nasal respiratory and olfactory mucosa were observed when rats with undamaged noses were exposed to 10-ppm formaldehyde for 3 months but not when exposed to 0.1 or 1 ppm. These effects were increased in similarly exposed rats that had severe injury to the nasal mucosa from electrocoagulation. Furthermore, nasal tumors were observed in rats with damaged noses exposed to 10-ppm formaldehyde for 28 months but not in rats with undamaged noses. The authors suggested that tissue damage followed by epithelial regeneration may contribute to formaldehyde-induced carcinogenesis.

McGregor *et al.* (2006) reviewed the carcinogenicity and toxicity data of formaldehyde and glutaraldehyde. Although inhalation of these compounds caused similar effects in the nasal epithelium of rats and mice, only formaldehyde induced a dose-related increase in nasal tumors. The postulated mode of action for the carcinogenicity of formaldehyde is that prolonged exposure above a critical concentration induces sustained cytotoxicity and cell proliferation. Genetic changes, occurring secondary to the cytotoxicity, metaplasia, and hyperplasia, result in neoplasia. This mode of action is supported by observations of a consistent, nonlinear dose-response relationship for three key events (sustained cell proliferation, DNA-protein crosslink formation, and tumors) and concordance of these effects across regions of the nasal passages. The nonlinearity of the response may be explained by saturation of glutathione-mediated detoxification at concentrations above 4 ppm. However, key events postulated in the mode of action for formaldehyde (cytotoxicity, cell proliferation, and DNA-protein crosslink formation) have been demonstrated with glutaraldehyde exposure without causing nasal tumors in rats and mice. A possible explanation for this discrepancy is that the dialdehyde function of glutaraldehyde may inhibit the macromolecules from further reaction. If these macromolecules are proteins involved in maintenance of survival, then their inhibition may be more likely to lead to cell death instead of a change in the differentiation state. If glutaraldehyde reacts with DNA, then repair of these lesions may be more difficult. This is consistent with the conclusions of Hester *et al.* (2005) (see Section 5.6.5) based on a comparison of gene-expression profiles, DNA repair, and apoptosis following exposures to formaldehyde or glutaraldehyde, which found that glutaraldehyde had increased apoptosis, greater mitochondrial damage and decreased DNA repair compared with formaldehyde.

5.8.6 Other tumors

Other potential tissue target sites include lymphohematopoietic tumors in humans, such as leukemia and myeloid leukemia (see Section 3) and experimental animals (hemolymphoreticular tumors, see Section 4), and malignant mammary-gland tumors, testicular interstitial-cell adenoma, and gastrointestinal leiomyosarcoma in experimental animals (see Section 4.2). No studies were identified evaluating potential mechanisms for mammary-gland, gastrointestinal, or testicular tumors although toxic effects on the testes have been reported in experimental animals (see Section 5.4.3). In contrast, numerous review articles or commentaries were identified that discussed the association between lymphohematopoietic cancers and formaldehyde exposure. This section briefly reviews

lymphohematopoietic cancer, and arguments supporting and against the biological plausibility of formaldehyde-induced leukemia.

In humans, the bone marrow is the source of all blood cells in the circulation by the time of birth (Kumar *et al.* 2010). The blood cells arise from a common pluripotent progenitor cell (stem cell). In the bone marrow, this stem cell forms two multipotent progenitor cells, the common myeloid stem cell and the common lymphoid stem cell. These cells in turn form committed stem cell lines that form fully differentiated blood cells. The myeloid series forms eosinophils, monocytes, polymorphonuclear leukocytes, platelets, erythrocytes, and basophils, whereas the lymphoid series forms plasma cells (B cells), natural killer (NK) cells, and T cells (see Figure 5-4). Hematopoietic progenitor cells have been identified outside of the bone marrow in the peripheral circulation (Fritschi and Siemiatycki 1996), lymph, and in lymphoid tissue and can circulate back to the bone marrow.

Malignant blood diseases (leukemia, lymphomas, and myeloma) are a heterogenous group of neoplasms that arise from stem cells at different hierarchical levels of hematopoietic and lymphoid cell development (Greaves 2004). The hierarchical cell population structure includes different stages of stem cells, which are associated with different types of malignancies. Mutations can occur at any stem cell level, and stem cells at any one level undergoing mutations and clonal expansion can produce a variety of different types of neoplasms. The type of neoplasm depends on the target cell undergoing transformation and the phenotype produced as a result of the different genetic abnormalities (Greaves 2004). Examples of lymphoid neoplasms are chronic lymphocytic leukemia, multiple myeloma, Hodgkin's lymphoma, and non-Hodgkin's lymphoma. The terms lymphocytic leukemia and lymphoma are used to describe the usual tissue distribution of the disease (bone marrow and peripheral blood vs. discrete mass in lymphoid tissue) at the time of clinical presentation, but both types of neoplasms can be present in bone marrow, circulating blood, and lymphoid tissues. Acute myelogenous leukemia (AML) (myeloid leukemia) is a heterogeneous group of neoplasms that primarily involve the bone marrow. Some lymphatic tumors, especially non-Hodgkin's lymphoma, appear to originate outside the bone marrow (Pyatt *et al.* 2008).

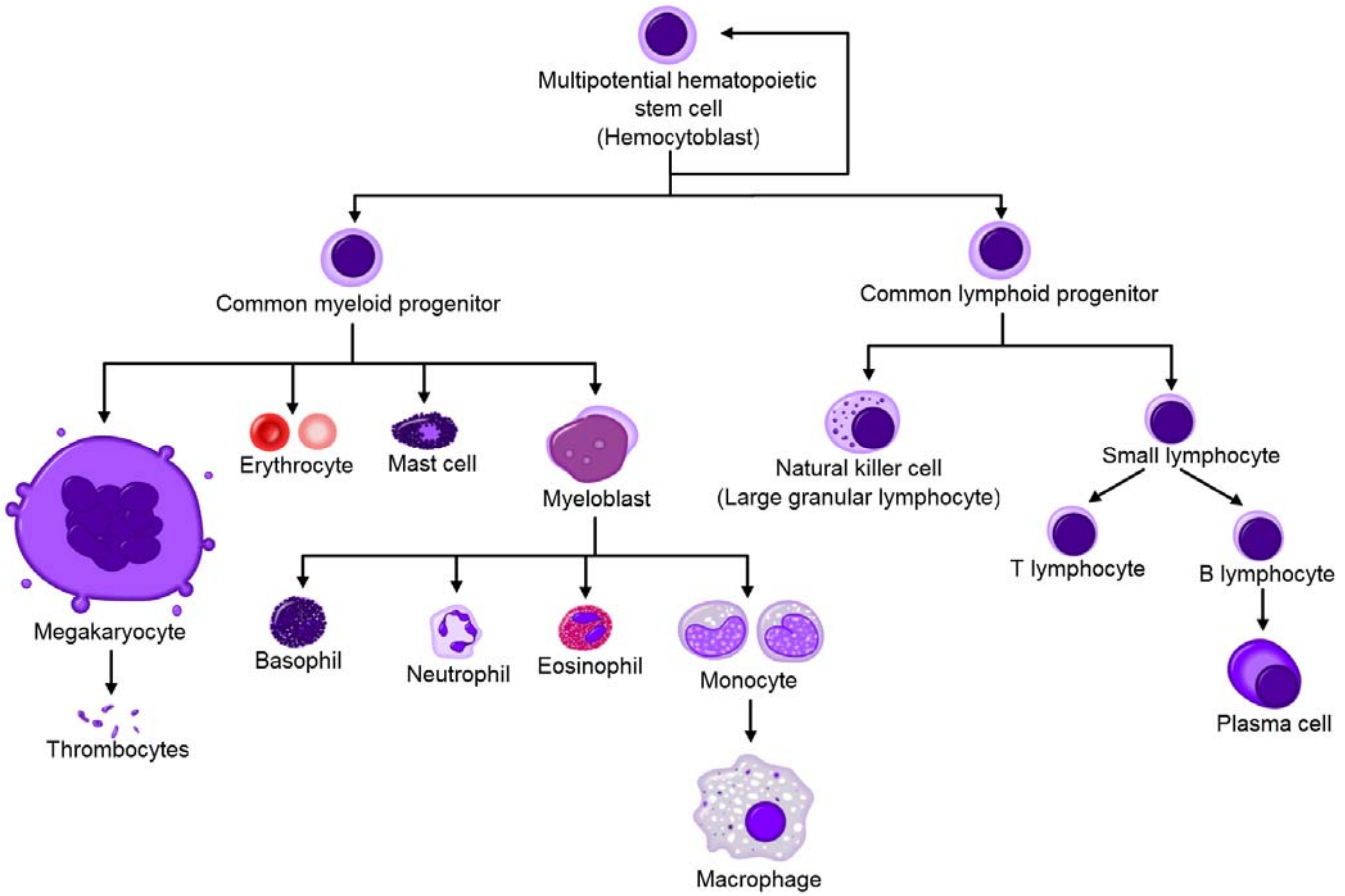


Figure 5-4. Hematopoietic system
Source: Wikipedia (http://en.wikipedia.org/wiki/Haematopoiesis)

Chromosomal translocations (two-way or reciprocal) are present in the majority of white cell neoplasms, and gene deletion and mutations are also common. Chromosomal translocations in blood neoplasm may arise from disruption of the normal processors of DNA double-strand breakage repair or rearrangements (Greaves 2004).

Two groups of researchers have proposed potential mechanisms for formaldehyde-induced leukemia: (1) Zhang *et al.* (2009a) and (2) the Environmental Protection Agency (EPA) (Note that the EPA did not publish their proposed mechanism in the peer-reviewed literature, but the major points are discussed in a criticism published by Pyatt *et al.* (2008).) The basic concepts of these proposed mechanisms are similar.

Zhang *et al.* (2009a,b) identified three potential mechanisms for formaldehyde-induced leukemia: (1) direct damage to stem cells in bone marrow, (2) damage to circulating hematopoietic stem/progenitor cells in the blood, or (3) damage to pluripotent stem cells present within the nasal turbinates and/or olfactory mucosa. Although the biological plausibility of the first model has been questioned (discussed below), these authors suggested that absorbed formaldehyde would dissolve in the blood and be converted to its hydrated form (methanediol) and could be transported to bone marrow in this form. However, if formaldehyde is not able to reach bone marrow in sufficient quantities to damage stem cells, the two alternate mechanisms involving damage to circulating stem/progenitor cells that travel to bone marrow and become initiated leukemic cells are plausible. Thus, the critical DNA or macromolecular binding occurs in the blood, and when the affected cells proliferate, unrepaired lesions could lead to mutations and cellular toxicity. The initiated stem cell could be re-incorporated into the bone marrow, and eventually lead to leukemia. The authors cited the detection of DNA-protein crosslinks and cytogenetic damage in circulating lymphocytes of exposed workers as supporting evidence. The same type of damage would be expected to occur in circulating hematopoietic stem cells.

The third mechanism is similar to the second but involves pre-mutagenic or mutagenic damage to primitive pluripotent stem cells that reside in the oral or nasal passages. Damaged stem cells could be released from the nasal passages, perhaps enhanced by formaldehyde-induced cytotoxicity, circulate through the blood, and eventually be incorporated into the bone marrow. Supporting evidence for this mechanism includes toxicity and DNA-protein crosslinks in the nasal passages of laboratory animals exposed to formaldehyde, reports of increased micronuclei in the nasal and oral mucosa of formaldehyde-exposed humans, and a study (Murrell *et al.* 2005) that showed that olfactory epithelial cells obtained from rat nasal passages contained hematopoietic stem/progenitor cells. These cells were shown to re-populate the hematopoietic tissues of irradiated rats and to form hematopoietic stem/progenitor cells of multiple lineages *in vivo*. Data relevant for evaluating the hypothesis that formaldehyde could induce leukemias through interaction with lymphoid cells in the nose could include the finding of chloromas (myeloid tumor cells) in the nasal cavity. Chloromas, also called granulocytic sarcomas or myeloid sarcomas, are rare tumors that can occur almost anywhere in the body, including the head and neck (Prades *et al.* 2002). Occurrence of these tumors in the nasal passages has been reported in a few instances (Sanford and Becker 1967, Scully *et al.* 1990, Prades *et al.* 2002).

Tang *et al.* (2009) reviewed eight studies conducted in China on hematological parameters among formaldehyde-exposed humans. The authors concluded that most of the studies showed that long-term exposure can decrease the number of white blood cells, and possibly lower platelet numbers and hemoglobin concentration (see Section 5.4.2). One case report was identified of a previously healthy woman diagnosed with pancytopenia (decreased levels of all formed elements in the blood) shortly after moving into a newly remodeled apartment. Zhang *et al.* (2010) reported that formaldehyde-exposed workers had significantly lower counts of total white blood cells, granulocytes, platelets, red blood cells, and lymphocytes and a 20% decrease in colony formation from circulating progenitor cells compared with controls. Statistically significantly higher frequencies of monosomy of chromosome 7 ($P = 0.0039$) and trisomy of chromosome 8 were found in a subset of 10 highly exposed subjects.

According to Pyatt *et al.* (2008), the EPA-proposed mode of action relies on the following assumptions: (1) many lymphoid malignancies arise outside of the bone marrow, (2) lymphoid tissue present at the portal of entry represents a target cell in nasal-associated lymph tissue, (3) circulating stem cells or hematopoietic progenitor cells can be exposed to formaldehyde in the lungs or nasal passages, (4) formaldehyde has been reported to cause leukemia or lymphomas in rats and mice exposed by inhalation[5] and oral routes, (5) formaldehyde is genotoxic, and (6) some epidemiological studies suggest an association between formaldehyde exposure and lymphohematopoietic malignancies.

Several authors have questioned the biological plausibility of an association of formaldehyde and systemic tumors (primarily leukemia) because of formaldehyde's reactivity and lack of evidence for bone marrow toxicity (Cole and Axten 2004, Heck and Casanova 2004, Golden *et al.* 2006, Pyatt *et al.* 2008). Evidence that suggests that formaldehyde would not be a leukemogen includes the following: (1) normal metabolic processes prevent formaldehyde from entering the systemic circulation as formaldehyde is rapidly metabolized by circulating erythrocytes, and blood concentrations of formaldehyde did not increase in humans exposed to 1.9 ppm for 40 minutes, in rats exposed to 14.4 ppm for 2 hours, or in rhesus monkeys exposed to 6 ppm for 4 weeks, (reviewed by Golden *et al.* 2006); (2) formaldehyde does not cause overt bone marrow toxicity or pancytopenia at high doses, a common feature of known leukemogens; (3) there is no credible evidence that formaldehyde induces leukemia in experimental animals; and (4) epidemiological studies provide limited evidence that occupational exposure to formaldehyde is associated with leukemia. Pyatt *et al.* (2008) concluded that all known leukemogenic chemicals cause dose-related hematotoxicity, induce bone marrow hypoplasia and dysplastic morphological changes in the bone marrow, and produce hematopoietic neoplasias in rodents. Lapidot *et al.* (1992) described a model for transplantation of human bone marrow into severe combined immunodeficient (SCID)

[5] Pyatt *et al.* (2008) stated that the EPA proposal cited the unpublished Batelle data (which is the inhalation study reported by Kerns *et al.* [1983]) as showing a significant increase (and dose-response) in lymphomas in female mice and leukemia in female rats but that the author's review of the data does not support the EPA conclusion.

mice that could serve as an animal model of human hematopoietic diseases (such as leukemia), but no studies using this model with exposure to formaldehyde or other potential leukemogens were identified.

Both EPA (as reviewed by Pyatt *et al.* 2008) and Zhang *et al.* (2009a,b) stated that their proposed mechanisms are supported by human studies demonstrating increased micronuclei in nasal and buccal epithelial cells; by the presence of DNA crosslinks, micronuclei, chromosomal aberrations, and SCE in lymphocytes of formaldehyde-exposed workers or students; and by animal studies showing increased micronuclei and SCE in pulmonary lavage cells of formaldehyde-exposed rats. Pyatt *et al.* (2008) argued that the human studies lack consistency, genotoxic effects in animals are limited to local effects, and an *in vitro* study by Schmid and Speit (2007a) found that DNA crosslinks are repaired before lymphocytes begin to replicate. Further, non-Hodgkin's lymphoma is not associated with formaldehyde exposure in human studies, which would argue against nasal tissue as a target of formaldehyde mutagenic effects.

5.9 Summary

5.9.1 Adsorption, distribution, metabolism, and excretion

Formaldehyde is a metabolic intermediate that is essential for the biosynthesis of purines, thymidine, and some amino acids. The metabolism of formaldehyde is similar in all mammalian species studied. Differences in distribution following inhalation exposure can be related to anatomical differences. For example, rats are obligate nose breathers while monkeys and humans are oronasal breathers. Thus, in humans, some inhaled formaldehyde will bypass the nasal passages and deposit directly into the lower respiratory tract. The endogenous concentrations in the blood of humans, rats, and monkeys are about 2 to 3 μg/g and do not increase after ingestion or inhalation of formaldehyde from exogenous sources (Casanova *et al.* 1988, Heck *et al.* 1985, Heck and Casonova 2004). Although formaldehyde is rapidly and almost completely absorbed from the respiratory or gastrointestinal tracts, it is poorly absorbed from intact skin. When absorbed after inhalation or ingestion, very little formaldehyde reaches the systemic circulation because it is rapidly metabolized by glutathione-dependent formaldehyde dehydrogenase and *S*-formyl-glutathione hydrolase to formic acid, which is excreted in the urine or oxidized to carbon dioxide and exhaled (IARC 2006). Formaldehyde reaching the circulation is rapidly hydrated to methanediol, which is the predominant form in the circulation (Fox *et al.* 1985). Although the metabolic pathways are the same in all tissues, the data indicate that the route of absorption does affect the route of elimination. When inhaled, exhalation is the primary route of elimination; however, when ingested, urinary excretion as formate is more important. Unmetabolized formaldehyde reacts non-enzymatically with sulfhydryl groups or urea, binds to tetrahydrofolate and enters the single-carbon intermediary metabolic pool, reacts with macromolecules to form DNA and protein adducts, or forms crosslinks primarily between protein and single-stranded DNA (Bolt 1987).

5.9.2 Toxic effects

Formaldehyde is a highly reactive chemical that causes tissue irritation and damage on contact. Formaldehyde concentrations that have been associated with various toxic

effects in humans show wide interindividual variation and are route dependent. Symptoms are rare at concentrations below 0.5 ppm; however, upper airway and eye irritation, changes in odor threshold, and neurophysiological effects (e.g., insomnia, memory loss, mood alterations, nausea, fatigue) have been reported at concentrations ≤ 0.1 ppm. The most commonly reported effects include eye, nose, throat, and skin irritation. Other effects include allergic contact dermatitis, histopathological abnormalities (e.g., hyperplasia, squamous metaplasia, and mild dysplasia) of the nasal mucosa, occupational asthma, reduced lung function, altered immune response, and hemotoxicity (IARC 2006). Some studies of Chinese workers suggest that long-term exposure to formaldehyde can cause leucopenia, and one study reported that a significantly higher percentage of formaldehyde-exposed workers had blood cell abnormalities (leucopenia, thrombocytopenia, and depressed serum hemoglobin levels) compared with unexposed controls (reviewed by Tang *et al.* 2009). Zhang *et al.* (2010) reported that Chinese factory workers exposed to high levels of formaldehyde had significantly lower counts of white blood cells, granulocytes, platelets, red blood cells and lymphocytes than unexposed controls. *In vitro* studies indicated that formaldehyde exposure caused a significant, dose-related decrease in colony forming progenitor cells (Zhang *et al*. 2010). Other studies have shown that formaldehyde exposure affects changes in the percentage of lymphocyte subsets (Ying *et al.* 1999, Ye *et al.* 2005). Higher rates of spontaneous abortion and low birth weights have been reported among women occupationally exposed to formaldehyde (IARC 2006, Saurel-Cubizolles *et al.* 1994). Oral exposure is rare, but there have been several apparent suicides and attempted suicides in which individuals drank formaldehyde. These data indicate that the lethal dose is 60 to 90 mL (Bartone *et al.* 1968, Yanagawa *et al*. 2007). Formaldehyde ingestion results in severe corrosive damage to the gastrointestinal tract followed by CNS depression, myocardial depression, circulatory collapse, metabolic acidosis, and multiple organ failure.

The toxic effects of formaldehyde in experimental animals include irritation, cytotoxicity, and cell proliferation in the upper respiratory tract, ocular irritation, pulmonary hyperactivity, bronchoconstriction, gastrointestinal irritation, and skin sensitization. Other reported effects include oxidative stress, neurotoxicity, neurobehavioral effects, immunotoxicity, testicular toxicity, and decreased liver, thyroid gland, and testis weights (IARC 2006, Aslan *et al*. 2006, Sarsilmaz *et al*. 2007, Golalipour *et al*. 2008, Özen *et al.* 2005, Majumder and Kumar 1995).

In vitro studies have demonstrated that formaldehyde is directly cytotoxic and affects cell viability, cell differentiation and growth, cell proliferation, gene expression, membrane integrity, mucociliary action, apoptosis, and thiol and ion homeostasis (IARC 2006). Since metabolism of formaldehyde is glutathione-dependent, cells depleted of glutathione are more susceptible to formaldehyde toxicity (Ku and Killings 1984).

5.9.3 Carcinogenicity of metabolites and analogues

Formic acid (formate + H^+), the major metabolite of formaldehyde, has not been tested for carcinogenic effects. Acetaldehyde, an analogue of formaldehyde, is listed as *reasonably anticipated to be a human carcinogen* by the NTP (2004). Acetaldehyde induced respiratory tract tumors in rats (adenocarcinoma and squamous-cell carcinoma of

the nasal mucosa) and laryngeal carcinoma in hamsters. In addition, epidemiological studies have reported increased risks of cancers of the upper digestive tract (esophagus, oral cavity, and pharynx) and upper respiratory tract (larynx and bronchi) in humans (Salaspuro 2009).

Glutaraldehyde and benzaldehyde have also been tested for carcinogenicity in 2-year bioassays by the NTP. Glutaraldehyde was not considered to be carcinogenic in rats or mice, and benzaldehyde was not considered to be carcinogenic in rats. The NTP concluded that there was some evidence of carcinogenicity for benzaldehyde in mice based on an increased incidence of squamous-cell papilloma and hyperplasia in the forestomachs of male and female mice (NTP 1999).

5.9.4 Genetic and related effects

Formaldehyde is a direct-acting genotoxic compound that affects multiple gene expression pathways, including those involved in DNA synthesis and repair and regulation of cell proliferation. Most studies in bacteria were positive for forward or reverse mutations without metabolic activation and for microsatellite induction (Mu and Harris 1988). Studies in non-mammalian eukaryotes and plants also were positive for forward and reverse mutations, dominant lethal and sex-linked recessive lethal mutations, and DNA single-strand breaks (Conaway *et al.* 1996, IARC 2006). *In vitro* studies with mammalian and human cells were positive for DNA adducts, DNA-protein crosslinks, DNA-DNA crosslinks, unscheduled DNA synthesis, single-strand breaks, mutations, and cytogenetic effects (chromosomal aberrations, sister chromatid exchange, and micronucleus induction).

In *in vivo* studies in rats, formaldehyde caused DNA-protein crosslinks (in the nasal mucosa and fetal liver but not bone marrow) (Casanova-Schmitz *et al.* 1994a, Wang and Liu 2006), DNA strand breaks (lymphocytes and liver) (Im *et al.* 2006, Wang and Liu 2006), dominant lethal mutations (Kitaeva *et al.* 1990, Odegiah 1997), chromosomal aberrations (pulmonary lavage cells and bone marrow in one of two studies) (Dallas *et al.* 1992, Kitaeva *et al.* 1990), and micronucleus induction in the gastrointestinal tract (Migliore *et al*. 1989). However, it did not induce sister chromatid exchange or chromosomal aberrations in lymphocytes or micronucleus formation in peripheral blood (Kilgerman *et al.* 1984, Speit *et al.* 2009). Mutations in the *p53* gene were detected in nasal squamous-cell carcinomas from rats (Recio *et al.* 1992). Inhalation exposure to formaldehyde also induced DNA-protein crosslinks in the nasal turbinates, nasopharynx, trachea, and bronchi of rhesus monkeys (Casanova *et al.* 1991). In mice, formaldehyde exposure did not cause dominant lethal mutations (Epstein *et al.* 1972, Epstein and Shafner 1968), micronucleus induction (Gocke *et al.* 1981), or chromosomal aberrations (Fontignie-Houbrechts 1981, Natarajan *et al.* 1983) when exposed by intraperitoneal injection or induce micronuclei by intravenous or oral exposure (Morita *et al.* 1997), but did induce heritable mutations when exposed by inhalation (Liu *et al.* 2009b).

In studies of lymphocytes from health professional workers exposed to formaldehyde, higher levels of formaldehyde-albumin adducts were found in workers exposed to relatively high concentrations compared with workers exposed to lower concentrations (Pala *et al.* 2008) and higher levels of DNA-protein crosslinks, strand breaks, and

pantropic p53 protein levels were found in exposed workers compared with unexposed workers (Shaham *et al*. 2003). Wang *et al.* (2009) found higher levels of DNA adducts (N^6-hydroxymethyldeoxyadenosine [N^6-HOMe-dAdo]) among smokers compared with non-smokers; however, the source of formaldehyde is not clear (for example, it could be formaldehyde in tobacco or a metabolite of a tobacco-specific compound). Numerous studies have evaluated chromosomal aberrations and sister chromatid exchange in lymphocytes and micronucleus induction in lymphocytes, or nasal or oral epithelial cells from humans exposed to formaldehyde (primarily health professionals, but also industrial workers, volunteers and subjects exposed from environmental sources). Among formaldehyde-exposed subjects, statistically significant increased frequencies (compared with unexposed, low exposure or pre- exposure vs. post-exposure) of cytogenetic damage in lymphocytes were observed for chromosomal aberrations in 7 of 12 reviewed studies, sister chromatid exchanges in 6 of 12 studies and micronuclei induction in 5 of 7 studies reviewed. In addition to these studies, Zhang *et al.* (2010) reported that lymphocytes from workers exposed to high levels of formaldehyde had statistically increased frequency of monosomy of chromosome 7 and trisomy of chromosome 8. Statistically significant increased frequencies of micronuclei were also observed in the buccal cavity or oral epithelium in four of five reviewed studies and in the nasal epithelium in all five available studies (Note that findings from two studies, Suruda *et al.* [1993] and Tikenko-Holland *et al.* [1996], evaluating the same study participants are treated as one study in this count). In addition to these studies, a review of cytogenetic studies in the Chinese literature on formaldehyde-exposed workers reported increased incidences of chromosomal aberrations in lymphocytes (one study) and micronuclei in lymphocytes and nasal epithelial cells (one study each); however, two studies did find increases in sister chromatid exchanges in lymphocytes.

Regulation of gene expression by formaldehyde was investigated in eight studies. Formaldehyde exposure increased expression of genes involved in intracellular adhesion, inflammation, xenobiotic metabolism, nucleic acid metabolism, cell-cycle regulation, apoptosis, and DNA repair. Thus, multiple biochemical pathways are affected by formaldehyde exposure.

5.9.5 Mechanistic considerations

Although the biological mechanisms associated with formaldehyde-induced cancer are not completely understood, it is important to recognize that chemicals can act through multiple toxicity pathways and mechanisms to induce cancer or other health effects (Guyton *et al.* 2009). Potential carcinogenic modes of actions for formaldehyde include DNA reactivity (covalent binding), gene mutation, chromosomal breakage, aneuploidy, and epigenetic effects.

Studies evaluating nasal tumors in rats have shown that regional dosimetry, genotoxicity, and cytotoxicity are believed to be important factors. Computational fluid dynamics models have been developed to predict and compare local flux values in the nasal passages of rats (Kimbrell *et al*. 1993, 1997), monkeys (Kepler *et al.* 1998), and humans (Subramaniam *et al.* 1998). Regions of the nasal passages with the highest flux values are the regions most likely affected by formaldehyde exposure. Similar flux values were predicted for rats and monkeys for regions of the nasal passages with elevated cell

proliferation rates, thus providing support for the hypothesis that formaldehyde flux is a key factor for determining toxic response. Furthermore, DNA-protein crosslinks and cell-proliferation rates are correlated with the site specificity of tumors (Pala *et al.* 2008). Cell proliferation is stimulated by the cytotoxic effects of formaldehyde. Increased cell proliferation may contribute to carcinogenesis by increasing the probability of spontaneous or chemically induced mutations. The dose-response curves for DNA-protein crosslinks, cell proliferation, and tumor formation show similar patterns with sharp increases in slope at concentrations greater than 6 ppm. The observed sequence of nasal lesions is as follows: rhinitis, epithelial dysplasia, squamous metaplasia and hyperplasia, and squamous-cell carcinoma.

Biological mechanisms have been proposed for the possible association between lymphohematopoietic cancers and formaldehyde exposure. Proposed mechanisms for formaldehyde-induced leukemia are: (1) direct damage to stem cells in the bone marrow, (2) damage to circulating stem cells, and (3) damage to pluripotent stem cells present in the nasal turbinate or olfactory mucosa (Zhang *et al.* 2009a,b). Evidence in support of the potential for DNA damage to circulating hematopoietic stem cells is that DNA-protein crosslinks have been identified in the nasal passages of laboratory animals exposed to formaldehyde, and increased micronuclei have been identified in the nasal and oral mucosa of formaldehyde-exposed humans. In addition, olfactory epithelial cells obtained from rat nasal passages contain hematopoietic stem cells, which have been shown to re-populate the hematopoietic tissue of irradiated rats (Murrell *et al.* 2005). However, some authors have questioned the biological plausibility of an association between formaldehyde exposure and leukemia, because formaldehyde is rapidly metabolized, and it would not be expected to enter the systemic circulation (Cole and Axten 2004, Golden *et al.* 2006, Heck and Casanova 2004, Pyatt *et al.* 2008). They stated that formaldehyde does not cause bone marrow toxicity or pancytopenia, which are common features of known leukemogens, and that the genotoxic and carcinogenic effects in animals and humans are limited to local effects. [The recent reports of adducts in leukocytes of smokers (Wang *et al.* 2009b), albumin adducts in medical research workers (Pala *et al.* 2008), DNA-protein crosslinks measured in peripheral blood cells of hospital workers (Shaham *et al.* 2003), and the hematologic changes measured by Zhang *et al.* (2010) suggest that formaldehyde might enter the systemic circulation of humans exposed to formaldehyde.]

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Glossary of Terms

Acinar: Pertaining to one of the granular masses which constitute a racemose or compound gland such as the pancreas.

Acute lymphocytic leukemia (also called: acute lymphoblastic leukemia, acute lymphoid leukemia, acute lymphatic leukemia): A group of neoplasms composed of immature precursor B or T lymphocytes (lymphoblasts).

Acute myeloid leukemia: A leukemia characterized by accumulation of immature myeloid forms of blood cells in the bone marrow and suppression of normal hematopoiesis.

Acute: The clinical term is used for a disease having a short and relatively severe course. In rodent testing, usually pertains to administration of an agent in a single dose.

Adduct: A complex that forms when a chemical binds to a biological molecule such as DNA or a protein.

Adenocarcinoma: A cancer that develops in the lining or inner surface of an organ.

Adenoma: An ordinarily benign neoplasm of epithelial tissue in which the neoplastic cells form glands or gland-like structures in the stroma.

Adipose tissue: Fatty tissue.

Aleukemia: A condition where the leukemic cells are primarily in the bone marrow and not in the peripheral circulation; white blood cell count is normal or depressed.

Alkyd (alkyde): Any of several synthetic resins made by heating together a polybasic acid, such as phthalic or maleic acid, and a polyhydric alcohol, such as glycerin or a glycol: these resins are used in paints, varnishes, and lacquers.

Allele: Any one of a series of two or more different genes that occupy the same position (locus) on a chromosome.

Alveolar/bronchiolar: Pertaining to the alveoli or bronchi of the lungs.

Ambient air: Outdoor air to which the general public is exposed.

Ameloblastoma: A malignant jaw tumor which stems from the ameloblasts, cells which form tooth enamel.

Anemia: Lower than normal limits of circulating red blood cells.

Aneuploidy: One or a few chromosomes above or below the normal chromosome number.

Anthropogenic: Caused by humans.

Apoptosis: A mechanism of cellular suicide which occurs after sufficient cellular damage, also called programmed cell death.

Aquifer: Geologic formations containing sufficient saturated porous and permeable material to transmit water.

Aromatic hydrocarbon: An organic chemical compound formed primarily from carbon and hydrogen atoms with a structure based on benzene rings and resembling benzene in chemical behavior; substituents on the rings(s) may contain atoms other than carbon or hydrogen.

Ascites: Effusion and accumulation of serous fluid in the abdominal cavity.

Atypia: An abnormality in cells.

Bacteriostatic: Inhibiting the growth or multiplication of bacteria.

Benign tumor: An abnormal mass of tissue that does not spread and that is not life-threatening.

Betel nut: The nut of the Areca palm tree and an ingredient of betel nut quid, an addictive mix chewed in some Pacific and Asian cultures. Its use is associated with aggressive oral cancers affecting especially the inner lining of the cheeks and lips; other sites include the tongue, lower lip, tonsil and floor of the mouth.

Bilirubin: A pigment produced when the liver processes waste products.

Bioaccumulation: The process by which a material in an organism's environment progressively concentrates within the organism.

Bioassay: The determination of the potency or concentration of a compound by its effect upon animals: Isolated tissues: Or microorganisms: As compared with a chemical or physical assay.

Bioconcentrate: Accumulation of a chemical in tissues of a fish or other organism to levels greater than in the surrounding medium.

Biotransformation: The conversion within an organism of molecules from one form to another: a change often associated with change in pharmacologic activity.

Bronchiogenic carcinoma: A carcinoma originating in the bronchi of the lung.

Bronchioloalveolar: Derived from epithelium of terminal bronchioles.

Buccal cavity: The vestibule in the mouth between the teeth and the cheeks.

Calendaring: A process of smoothing or glazing paper or cloth by pressing it between plates or passing it through rollers.

Cannula: A tube for insertion into a duct or cavity.

Carcinoma: A malignant neoplasm of the epithelium.

Carina: A projection of the lowest tracheal cartilage.

Chelating agent: A substance used to reduce the concentration of free metal ion in solution by complexing it; often used to remove toxic metals from the body.

Chromosomal aberrations: Any abnormality of a chromosome's number or structure.

Chronic lymphocytic leukemia: A lymphoid leukemia arising from B-cells.

Chronic myeloid leukemia: A cancer of the blood-forming tissues associated with an increased production of terminally differentiated myeloid cells.

Chronic: Continuing for a long period time. In rodent testing, pertains to dosing schedules of greater than 3 months.

Cicatrical stricture: A scar formed in the healing of a wound that causes a decrease in the diameter of a canal, duct, or other passage.

Clastogen: Any substance which causes chromosomal breaks.

Colitis: Inflammation of the colon.

Confounding: A relationship between the effects of two or more causal factors observed in a set of data such that it is not logically possible to separate the contribution of any single causal factor to the observed effects.

Copolymers: A polymer of two or more different monomers.

Creatinine: A waste product of protein metabolism that is found in the urine.

Critical temperature: The temperature of a gas above which it is no longer possible by use of any pressure, however great, to convert it into a liquid.

Cytogenetic: The cellular constituents concerned in heredity.

Cytotoxic: An agent that is toxic to cells.

Dam: Female parent.

Dehydrogenation: The removal of one or more hydrogen ions or protons from a molecule.

Differentiated squamous-cell types: Neoplastic squamous cells similar in appearance to normal squamous cells, but are less orderly.

Diffusion coefficient: The rate at which a substance moves from an area of high concentration to an area of low concentration.

Dissociation constant (pK_a): The equilibrium constant for the breaking apart of a weak acid into its hydrogen and conjugate base in a water solution.

Dorsal: Relating to the back or posterior of a structure.

Dysplasia: An abnormality of development; in pathology, alteration in size, shape, and organization of adult cells.

Ectoparasitic infection: An infection caused by a parasite that lives on the outside of the body.

Effluents: Waste material such as water from sewage treatment or manufacturing plants discharged into the environment.

Electrocoagulation: Use of a high-frequency electric current to bring about the coagulation and destruction of tissue.

Endogenous: Originating within an organism.

Endogenously: Derived or produced internally.

Eosinophil: A granular leukocyte with a nucleus that usually has two lobes connected by a slender thread of chromatin and is readily stained by eosin.

Epidemiology: A science concerned with the occurrence and distribution of disease in populations.

Epididymis: A coiled segment of the spermatic ducts that serves to store and transport spermatozoa between the testis and the vas deferens.

Epigenetics: Changes in phenotype (appearance) or gene expression caused by mechanisms other than changes in the underlying DNA sequence.

Epithelial: Relating to or consisting of epithelium.

Epithelium: The cellular covering of internal and external surfaces of the body, including the lining of vessels and other small cavities.

Erythema: Redness of the skin produced by congestion of the capillaries.

Erythrocytes: Cells that carry oxygen to all parts of the body (red blood cells).

Esthesioneuroepithelioma: A tumor consisting of undifferentiated cells of sensory nerve epithelium.

Esthesioneuroma: (Olfactory neuroma) A nasal cavity tumor of nervous tissue from olfactory epithelium.

Eukaryote: An organism whose cells contain a limiting membrane around the nuclear material and which undergoes mitosis.

Ever hourly: Workers who had ever worked in an hourly job.

Exogenous: Developed or originating outside the body.

Extrahepatic: Outside of, or unrelated to, the liver.

Fibroblasts: Connective tissue cells.

Fibrosarcoma: A type of soft tissue sarcoma that begins in fibrous tissue, which holds bones, muscles, and other organs in place.

Flash point: The lowest temperature at which the vapor of a combustible liquid can be made to ignite momentarily in air.

Flux: The rate of mass flow across a unit area.

Follicular lymphoma: The most common form of Non-Hodgkin's lymphoma in the US.

Forestomach: A non-glandular expansion of the alimentary canal between the esophagus and the glandular stomach. Rodents have a forestomach and a glandular stomach, whereas, humans have only a glandular stomach.

Formalin: A solution of formaldehyde in water typically containing 37% formaldehyde by mass and 10% to 15% methanol as a stabilizer.

Fundus: In anatomy, a term used for the bottom or base of an organ, or the part of a hollow organ farthest from its mouth.

Gastrectomy: Surgical removal of the stomach.

Gavage: In animal experiments, the introduction of material through a tube passed through the mouth into the stomach.

Genotoxicity: The amount of damage caused to a DNA molecule.

Glandular stomach: The muscular sac between the esophagus and the small intestine containing glandular tissue. The glands of the stomach secrete mucous, hydrochloric acid and digestive enzymes.

Grana cheese: A class of hard, mature cheeses from Italy which have a granular texture and are often used for grating (e.g., Parmigiano-Reggiano or parmesan cheese).

Gray iron: A cast iron alloy with a graphitic microstructure.

Half-life: The time required for a substance to be reduced to one-half its present value through degradation or through elimination from an organism.

Healthy-worker effect: Phenomenon of workers usually exhibiting overall death rates lower than those of the general population due to the fact that the severely ill and disabled are ordinarily excluded from employment.

Hematocrit: The volume percentage of the erythrocytes in the whole blood.

Hematopoietic: Pertaining to the formation of blood or blood cells.

Hemolymphoreticular: Pertaining to the network of cells and tissues of the blood and lymph nodes found throughout the body.

Henry's law: The relationship that defines the partition of a soluble or partially soluble species between the gas and solution phases.

Hepatoblastoma: A malignant neoplasm occurring in young children, primarily in the liver, composed of tissue resembling embryonal or fetal hepatic epithelium, or mixed epithelial and mesenchymal tissues.

Hepatocellular: Pertaining to cells of the liver.

Hepatotoxic: A substance that is toxic to the liver.

Heterozygotes: An organism that has different alleles at a particular gene locus on homologous chromosomes.

Histones: The chief protein components of chromatin. They act as spools around which DNA is wound, and they play a role in gene regulation.

Hodgkin's disease: (Hodgkin's lymphoma) A form of malignant lymphoma characterized by painless progressive enlargement of the lymph nodes, spleen, and general lymphoid tissue.

Homozygotes: An organism that has the same alleles at a particular gene locus on homologous chromosomes.

Hydrolysis: A chemical reaction in which the interaction of a compound with water results in the decomposition of that compound.

Hydroxyl radicals: A particularly reactive, damaging type of free radical that is formed when superoxide radicals react with hydrogen peroxide.

Hyperkeratosis: excessive thickening of the outer layer of the skin, which contains keratin.

Hyperplasia: The abnormal multiplication or increase in the number of normal cells in normal arrangement in a tissue.

Hypertrophy: increase in volume of a tissue or organ produced entirely by enlargement of existing cells.

Hypopharynx: The lowermost section of the pharynx.

Ileitis: Inflammation of the ileum (distal portion of the small intestine extending from the jejunum to the cecum).

***In situ*:** Latin phrase meaning confined to the site of origin; a cancer that has not metastasized or invaded neighboring tissues

***In vitro*:** Biological process taking place in a test tube, culture dish, or elsewhere outside a living organism.

***In vivo*:** Biological processes taking place in a living organism.

Intraperitoneal [i.p.] injection: Injection within the peritoneal cavity, i.e., the area that contains the abdominal organs.

Intravesical: Occurring within the urinary bladder.

Isoenzymes: Any of the chemically distinct forms of an enzyme that perform the same biochemical function.

Jejunitis: Inflammation of the jejunum (a portion of the small intestine extending from the duodenum to the ileum).

Keratinizing squamous-cell types: Neoplastic squamous cells with keratin in the cytoplasm.

K_{oc} (soil organic carbon-water partitioning coefficient)**:** A measure of the tendency for organics to be adsorbed by soil and sediment which is useful in predicting the mobility of organic contaminants in soil.

Lacrimation: The production, secretion, and shedding of tears.

Large B-cell lymphomas: Types of lymphomas of the B cell lineage; a common form of non-Hodgkin's lymphoma.

Large-cell diffuse lymphoma: An aggressive B cell non-Hodgkin's lymphoma.

Larynx: Also called the voice box, it is located below the pharynx in the neck.

Latency: The time between the instant of stimulation (exposure to a substance) and the beginning of a response (disease).

LD_{50}: The dose that kills 50 percent of a group of test animals.

Leachate: The liquid produced in a landfill from the decomposition of waste within the landfill.

Leiomyosarcoma: A malignant (cancer) tumor of smooth muscle cells that can arise almost anywhere in the body, but is most common in the uterus, abdomen, or pelvis.

Leukemia: A cancer of the blood-forming tissues that is characterized by a marked increase in the number of abnormal white blood cells (leukocytes) in the peripheral blood.

Leukocyte: White blood cell.

Lipid peroxidation: The oxidative degradation of lipids by free radicals resulting in cell damage.

Lipophilicity: The affinity of a molecule or a moiety for a lipophilic (as fats) environment.

Lymphatic: A small sac or node in which lymph is stored; or pertaining to the lymph, lymph nodes, or vascular channels that transport lymph to the lymph nodes.

Lymphocyte: A mononuclear leukocyte that is primarily a product of lymphoid tissue and participates in humoral and cell-mediated immunity.

Lymphohematopoietic: Of, relating to, or involved in the production of lymphocytes and cells of blood, bone marrow, spleen, lymph nodes, and thymus.

Lymphoma: A neoplasm of the lymphatic tissue.

Lymphosarcoma: Any of various malignant neoplastic disorders of lymphoid tissue; excluding Hodgkin's disease.

Macroarray: A term for microarrays with larger and fewer spots in the array.

Macrophage: A large cell that is present in blood, lymph, and connective tissues, removing waste products, harmful microorganisms, and foreign material from the bloodstream.

Malignant: Tending to become progressively worse; life-threatening.

Meta-analysis: The process or technique of synthesizing research results by using various statistical methods to retrieve, select, and combine results from previous separate but related studies.

Metabolism: The whole range of biochemical processes that occur within living organisms, consisting both of anabolism and catabolism (the buildup and breakdown of substances, respectively).

Metabolite: A substance produced by metabolism.

Metaplasia: A change in morphology of one differentiated cell type to a differentiated cell type that does not normally occur in that tissue.

Micronuclei: Nuclei separate from, and additional to, the main nucleus of a cell, produced during the telophase of mitosis or meiosis by lagging chromosomes or chromosome fragments derived from spontaneous or experimentally induced chromosomal structural changes.

Microsatellite instability: A condition manifested by damaged DNA due to defects in the normal DNA repair process. Sections of DNA called microsatellites, which consist of a sequence of repeating units of 1 to 6 base pairs in length, become unstable and can shorten or lengthen.

Minute ventilation: The total volume (in liters) that is exhaled form the lung in one minute.

Mitogen: A substance that induces mitosis.

Monocyte: A mononuclear phagocytic leukocyte.

Monomer: A chemical subunit that is joined to other similar subunits so as to produce a polymer.

Multiple myeloma: A malignant neoplasm derived from plasma cells which can be found at several locations in the body.

Myelodysplasia: A description for hemopoietic stem cells that do not mature normally.

Myelodysplastic syndromes: A group of clonal stem cell disorders associated with ineffective hematopoiesis and associated cytopenias.

Myeloid leukemia: A heterogeneous group of neoplasms that originate from hematopoietic progenitor cells of the myeloid series (red blood cells, white blood cells, and platelets).

Nasal cavity: Air-filled space above and behind the nose.

Nasal turbinates: (nasal conchae, nasoturbinates) Scrolled spongy bones in the posterior part of the nasal cavity.

Nasopharynx: The upper part of the pharynx, posterior to the nasal cavity and above the soft palate.

Necropsy: The examination of the dead body of an animal by dissection so as to detail the effects of the disease.

Necrosis: The pathologic death of one or more cells, or of a portion of tissue or organ, resulting from irreversible damage.

Neoplasm: An abnormal mass of cells.

Neutrophil: A granular leukocyte having a nucleus with three to five lobes connected by slender threads of chromatin.

Non-Hodgkin's lymphoma: A heterogeneous group of malignant lymphomas; the only common feature being an absence of the giant Reed-Sternberg cells characteristic of Hodgkin's disease.

Nucleoside: An organic compound consisting of a purine or pyrimidine base linked to a sugar but lacking the phosphate residues that would make it a nucleotide.

Nucleotide: The molecular subunit of nucleic acids; consists of a purine or pyrimidine base, a sugar, and phosphoric acid.

Octanol-water partition coefficient (K_{ow}): A measure of the equilibrium concentration of a compound between octanol and water.

Oral cavity: The cavity of the mouth, bounded above by the hard and soft palates and below by the tongue and the mucous membrane connecting it with the inner part of the mandible.

Oronasal: Pertaining to the mouth and the nose.

Oropharyngeal: Associated with the part of the pharynx between the soft palate and the epiglottis.

Oropharynx: The part of the pharynx between the soft palate and the epiglottis; located below the nasopharynx.

Osteochondroma: A benign bone tumor consisting of projecting adult bone capped by cartilage.

Oxidation: The addition of oxygen to a compound with a loss of electrons; always occurs accompanied by reduction.

Pancytopenia: Lower than normal circulating red blood cells, white blood cells, and platelets.

Pantropic: Having an affinity for many tissues; capable of attacking derivatives of any of the three embryonic layers.

Papilloma: A benign tumor derived from epithelium that can arise from skin, mucous membranes, or glandular ducts.

Paraformaldehyde: A polymer of formaldehyde.

Paranasal sinuses: Air-filled cavities surrounding the nasal cavity. There are 4 pairs of paranasal sinuses: maxillary, frontal, ethmoid, and sphenoid.

Parenchyma: The distinguishing or specific cells of a gland or organ, contained in and supported by the connective tissue, framework, or stroma.

Percutaneous: Effected or performed through the skin.

Perirenal: Of, relating to, occurring in, or being the tissues surrounding the kidney.

Phagocyte: Any cell that ingest microorganisms or other cells and foreign particles.

Pharyngitis: Inflammation of the pharynx.

Pharynx: The passageway connecting the oral and nasal cavities to the larynx and esophagus.

Photolysis: The decomposition or separation of molecules by the action of light.

Polymer: A chemical formed by the joining together of similar chemical subunits.

Polymorphism: A variation in the DNA that is too common to be due merely to new mutation.

Polypoid: Resembling a polyp; i.e., a growth that protrudes from a mucous membrane.

Prills: Granules or pellets that flow freely and do not clump together.

Proctitis: Inflammation of the mucous membrane that lines the rectum.

Prokaryote: An organism that does not have a true nucleus (e.g., bacteria).

Pulmonary: Of or relating to the lungs.

Pyknosis: Contraction of nuclear contents to a deep staining irregular mass; a sign of cell death.

Pylorus: A small circular opening between the stomach and the duodenum.

Rales: Wet, crackly lung noises heard on inspiration which indicate fluid in the air sacs of the lungs; often indicative of pneumonia.

Resin: Any of a class of solid or semisolid viscous substances obtained either as exudations from certain plants or prepared by polymerization of simple molecules.

Rhabdomyosarcoma: A highly malignant tumor of striated muscle.

Rhinitis: Inflammation of the mucous membrane of the nose.

Rhinosinusitis: Inflammation of the nose and sinuses.

Sarcoma: A malignant tumor of connective tissue.

Seroprevalence: The overall occurrence of a disease within a defined population at one time, as measured by blood tests.

Sinonasal: Pertaining to the nasal and sinus cavities.

Sister chromatid exchange (SCE): The exchange during mitosis of homologous genetic material between sister chromatids; increased as a result of inordinate chromosomal fragility due to genetic or environmental factors.

Small-cell diffuse lymphoma: Lymphoma affecting immature B cells.

Specific gravity: The ratio of the density of a substance to the density of a standard substance. For liquids and solids the standard substance is usually water, for gases the standard substance is air.

Spelt-wheat: Hardy wheat of inferior quality, grown mostly in Europe for livestock feed.

Squamous-cell histotype: Cellular structure that is stratified.

Subacute: Between acute and chronic; denoting the course of a disease of moderate duration or severity. In rodent testing, usually pertains to a dosing schedule of less than one month.

Subchronic: In rodent testing, generally refers to a dosing schedule lasting from one to three months.

Subcutaneous injection: Injection beneath the skin.

Syngenic: Individuals or tissues that have identical genotypes (i.e., identical twins or animals of the same inbred strain, or their tissues).

Tachycardia: Abnormally rapid heart rate.

Thermosetting resin: A resin that has the property of becoming permanently hard and rigid when heated or cured.

Thoracolumbar: Pertaining to the thoracic and lumbar vertebrae.

Threshold limit value (TLV): The maximum permissible concentration of a material, generally expressed in parts per million in air for some defined period of time.

Time-weighted average (TWA): The average exposure concentration of a chemical measured over a period of time (not an instantaneous concentration).

Trioxane: A trimer of formaldehyde used as fuel and in plastics manufacture.

Ubiquitous: Present everywhere at once.

Upper respiratory tract: Consists of the nasal and oral cavities, pharynx, larynx, and trachea.

Urticaria: A vascular reaction of the skin marked by the transient appearance of smooth, slightly elevated patches (wheals) and often attended by severe itching (also called hives).

Uveal carcinoma (intraocular melanoma): A malignant tumor arising from melanocytes in the uvea (iris, ciliary body, choroid) of the eye.

Vacuolation: Creation of small cavities containing air or fluid in the tissues of an organism.

Vapor density: The ratio of the weight of a given volume of one gas to the weight of an equal volume of another gas at the same temperature and pressure.

Vapor pressure: The pressure exerted by a vapor in equilibrium with its solid or liquid phase.

Vestibulum: An anatomical cavity, chamber, or channel; vestibule.

Volatile: Quality of a solid or liquid allowing it to pass into the vapor state at a given temperature.

Xenobiotic: A pharmacologically, endocrinologically, or toxicologically active substance not endogenously produced and therefore foreign to an organism.

Z-DNA: A form of DNA in which the double helix twists in a left-hand direction, thus producing a zigzag appearance.

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