Formaldehyde Expert Panel Report

Part B - Recommendation for Listing Status for Formaldehyde and Scientific Justification for the Recommendation

The Report on Carcinogens (RoC) expert panel for formaldehyde 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 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 Science 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

<u>Technical experts to the panel: (Non-voting)</u>

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

The expert panel's recommendation for listing status and the scientific justification for their recommendation follow.

Overall Evaluation

Following a discussion of the body of knowledge, the expert panel applied the RoC listing criteria and unanimously recommended by a vote of 9 yes/0 no that formaldehyde should be listed in the RoC as *known to be a human carcinogen,* based on sufficient evidence in human epidemiology studies.

The major considerations that led the panel to its recommendation are discussed below.

Because of the common industrial use of formaldehyde or formaldehyde-containing compounds and its presence in outdoor and indoor environments, it is clear that a substantial number of U.S. residents are frequently exposed to detectable concentrations of formaldehyde.

The panel identified epidemiological studies of workers exposed to formaldehyde that indicated a causal relationship between exposure to formaldehyde and cancer in humans. These studies, in a variety of unrelated occupations, found evidence of significant excess of three types of cancer with a positive dose-response relationship: nasopharyngeal carcinoma (NPC), sinonasal adenocarcinoma and myeloid leukemia. Chance, bias, and confounding are unlikely to explain the observed excess in these cancers.

Sufficient evidence of carcinogenicity of formaldehyde from animal studies was an additional major factor in our assessment. Carcinogenicity was sufficiently evident in two animal species, including multiple strains of rats at multiple sites using two routes of exposure to formaldehyde. Available evidence was not sufficient regarding development of myeloid leukemia in animals; the panel noted that evidence was not clear as to whether formaldehyde had been tested in animal models that would be appropriate for assessing myeloid leukemia.

Formaldehyde is a highly reactive chemical that readily binds with critical macromolecules such as DNA and proteins. Evidence from animal studies suggests that formaldehyde can produce cancer at the point of contact in the upper respiratory tract via a cytoxicity-induced cellular proliferation and/or a genotoxic mechanism. Regarding myeloid leukemia, there is evidence that genotoxic endpoints have been detected in peripheral lymphocytes in the blood of formaldehyde-exposed people. Animal studies involving exposure to formaldehyde via inhalation also suggest that formaldehyde can produce toxic effects at sites distal from the point of contact. These studies indicate, collectively, that it is not implausible that formaldehyde can cause tumors at distal sites, although the precise mechanisms by which this occurs are not clear.

Based on the information from the human epidemiologic studies, formaldehyde was determined to be *known to be a human carcinogen.* Animal studies support this conclusion.

The panel voted 9 yes/0 no to accept the scientific justification for formaldehyde to be listed as *known to be a human carcinogen.*

Human Exposure

Uses

Formaldehyde is a ubiquitous chemical in the environment and has wide application in industry. Because of its use in the manufacture of construction materials, foods and cosmetics, home furnishings, and clothing, virtually everyone is exposed to some level of formaldehyde; however, occupational exposures are the highest. The major uses of formaldehyde in the United States--which account for 80% of its use--are in the production of resins that are used to make adhesives and binders for wood products, pulp and paper products, plastics, synthetic fibers and textile finishing, and as a chemical intermediate. Formaldehyde is also used as a biocide and preservative in agriculture, medicine, food and cosmetics, and embalming. It is a product of combustion from organic materials such as gasoline and diesel fuels, coal, wood, and tobacco.

Population Exposed

No current data were found on the number of people in the United States who are exposed to formaldehyde; however, in the late 1980s, the U. S. 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. 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, about 84,000 at concentrations between 0.75 and 1 ppm, and about 107,000 at concentrations greater than 1 ppm.

Exposure Levels

The ranges of means of historical measurements for area samples and personal exposures in the United States reported in the literature are as follows: in formaldehyde and formaldehyde-based resin production: 0.54 – 1.37 ppm and 0.08 – 14.2 ppm, respectively; in wood-based products and paper production: 0.00 – 0.69 ppm; in the plywood and laminated veneer industry: 0.08 – 0.24 ppm; in wood-based product manufacturing: 0.11 – 2.68; in the paper products industry: 0.05 – 0.98 ppm; in the manufacture of textiles and garments: 0.07 – 1.17 ppm; in foundries: 0.38 – 0.52 ppm; in the formaldehyde-based plastic products industry: 0.33 – 38.2 ppm; in embalming or autopsies: 0.12 – 8.10 ppm; in histopathology laboratories: 0.00 – 0.33 ppm; in the construction industry: 0.02 – 1.52 ppm; in fiberglass manufacturing: 0.02 – 0.42; from combustion sources, particularly related to fire-fighters: 0.01 – 0.55 ppm; in agricultural settings: 0.00 – 2.62 ppm; and, in office buildings and non-industrial workplaces: 0.00 – 0.07 ppm.

Exposure Criteria

The U.S. OSHA has a permissible exposure limit (PEL) of 0.75 ppm (8-h TWA), an action limit of 0.5 ppm (8-h TWA), and a short-term exposure limit of 2 ppm. The National Institute for Occupational Safety and Health (NIOSH) has a recommended exposure limit (REL) of 0.016 ppm (10-h TWA) and a 15-min exposure limit of 0.1 ppm.

The American Conference of Governmental Industrial Hygienists (ACGIH) recommended a ceiling limit of 0.3 ppm.

Conclusion

Because of the common industrial use of formaldehyde and formaldehyde-containing compounds and its widespread presence in outdoor and indoor environments, it is clear that U.S. citizens are frequently exposed to detectable concentrations of formaldehyde. Occupational groups encounter the highest exposure concentrations, and exposures have been documented to exceed current exposure criteria in many settings. It is difficult to estimate the number of individuals exposed to significant formaldehyde concentrations, but it is likely that well over 2 million workers are exposed occupationally to formaldehyde. The above information supports the conclusion that a relatively large number of U.S. citizens are exposed to considerable amounts of formaldehyde.

Human Cancer Studies

Summary of Findings for Each Cancer Site:

Nasopharyngeal Cancer (NPC)

Informative Studies

Studies that are informative for evaluating the potential carcinogenicity of formaldehyde to cause NPC are listed in Table 1. For a rare cancer site such as NPC, population-based case-control studies tended to be more informative than studies nested in occupational cohorts, since the former include larger numbers of cases. The collective results of case-control studies provided the preponderance of evidence in the panel's evaluation of the potential for formaldehyde to cause NPC. The most informative case-control studies are those with a sizable number of cases, and for which risk estimates were presented for exposure metrics indicating multiple levels of exposure (i.e., those that did not simply present results for ever-exposed) using variables such as duration, intensity, or cumulative exposure. Several studies fit these criteria: Roush *et al.* (1987); West *et al.* (1993); Vaughan *et al.* (2000); and Hildesheim *et al.* (2001). The Vaughan *et al.* study from (1986) provides additional information, but is limited by its small size (27 cases). The study of Armstrong *et al*. (2000) stated that they found no differences in NPC risk associated with any of the formaldehyde exposures for which varying duration, intensity, or latency were examined, but they did not present results for these analyses.

The only cohort study that is individually informative for evaluating the potential carcinogenicity of formaldehyde is the National Cancer Institute's (NCI) cohort of workers in formaldehyde industries, for which NPC results were presented in Hauptmann *et al*. (2004). This study is informative because the authors performed a relatively detailed exposure assessment and conducted internal analyses examining exposure-response patterns. The other large cohort studies reviewed had more limited exposure assessment and most presented results as an overall standardized mortality

ratio (SMR; comparing observed to expected mortality). Hauptmann *et al*. found elevated risk estimates at the highest levels of average intensity, peak exposure, and cumulative exposure, based on 9 NPC cases. Nevertheless, interpretation of the Hauptmann *et al*. results is limited (as it is for all of the cohort studies) because their results are based on a very small number of cases.

Relevant Findings

Evidence from the case-control studies is mainly based on analyses indicating increased risk by longer exposure latency or higher exposure (e.g., longer duration or higher intensity). Three of four case-control studies that presented NPC risk by duration found the highest risk elevations with longer duration of formaldehyde exposure (Vaughan *et al.* 1986 and 2000; Hildesheim *et al.* 2001), with risk estimates ranging from 1.6 to 2.7 for 10+ years to 18+ years (versus 0 years), whereas one study did not (West *et al.* 1993).

Each of four case-control studies that presented NPC risk by exposure measures indicating average intensity or cumulative exposure found the highest risk elevations associated with the highest exposure categories, with risk estimates of 1.4 for high- versus no exposure (Roush *et al.* 1987) and risk estimates of 1.5 to 3.0 for the highest cumulative exposure versus no exposure (Vaughan *et al.* 1986 and 2000; Hildesheim *et al.* 2001). Vaughan *et al*. (2000) also classified subjects by probability of formaldehyde exposure, and found increasing risk with greater probability of exposure: OR = 1.6 (1.0 to 2.8) for possible, probable, or definite exposure; OR = 2.1 (1.1 to 4.2) for probable or definite exposure; and OR = 13.3 (2.5 to 70) for definite exposure.

Several studies also found higher magnitude risk estimates with longer latency of exposure. Roush *et al*. (1987) found a 2.3-fold increased risk of NPC for high exposure lagged by 20 years (versus no exposure), whereas the risk estimate for high exposure without a lag was 1.4. West *et al*. (1993) found a 2.9-fold increased risk of NPC associated with exposure lagged by at least 25 years, whereas there was only a small elevation (OR = 1.3) associated with exposures within the past 25 years. Hildesheim *et al*. (2001) did not find increasing risk with longer latency of exposure.

In the NCI industrial cohort, Hauptmann *et al*. (2004) observed the highest elevations of NPC mortality in internal comparisons for the highest levels of average intensity (RR = 1.67, 6 cases), peak exposure (RR = 1.83, 7 cases), and cumulative exposure (RR = 4.14, 3 cases). These results were adjusted for calendar year, age, sex, and pay category. These increases were not statistically significant due to the small numbers of cases.

Only one study examined risks specific to histologic subtypes of NPC. Vaughan *et al*. (2000) examined undifferentiated and non-keratinizing NPC (28% of all cases), differentiated squamous-cell NPC (60%), and epithelial NPC (12%). Because they did not find an association for undifferentiated and non-keratinizing NPC with ever-exposure to formaldehyde, they excluded this subtype from their main analyses. No other study examined NPC subtype-specific risks. However, the distribution of histologic subtypes differs widely between regions in which the cited studies were conducted; while

squamous-cell NPC is the most common subtype in western countries, non-keratinizing and undifferentiated NPC is the most common subtype in Asian countries. Positive associations between formaldehyde exposure and NPC were observed in epidemiologic studies from both of these regions.

Sinonasal

Informative Studies

Because of the rarity of sinonasal cancer, case-control studies played a key role in their evaluation. The most informative study with the most power to examine risks among histologic subtypes and dose-response relationships was a pooled reanalysis of 12 sinonasal case-control studies (Luce *et al.* 2002). This reanalysis included three studies described in detail in the background document, including ones conducted among the Dutch (Hayes *et al.* 1986) and the French (Luce *et al.* 1993), and in Washington state (Vaughan *et al.* 1986). Two additional studies not included in the pooled reanalysis were a Danish case-control study (Olsen and Asnaes 1986) and a Connecticut case-control study (Roush *et al.* 1987).

Although the results of many studies of occupationally exposed populations were reviewed, only one reported more than three cases: a proportionate cancer incidence analysis of Danes employed in industries using formaldehyde, which provided limited information (Hansen and Olsen 1995, 1996). The four large studies (NCI industrial cohort [Hauptmann *et al.* 2004], NCI nested case-control study of funeral industry workers [Hauptmann *et al.* 2009], U.K. cohort [Coggon *et al.* 2003], and NIOSH cohort of garment workers [Pinkerton *et al.* 2004]) were examined closely, but lacked the power to examine dose-response relationships or examine histologic subtypes.

Relevant Findings

The major support for an association between formaldehyde and sinonasal cancer is from case-control studies. The relevant results from these studies are presented in Table 2. The most informative study was a pooled analysis of 12 case-control studies by Luce and colleagues (2002), which found an increased risk of sinonasal cancer associated with increasing cumulative exposure. The study included data from three of the studies described in the background document (Hayes *et al.* 1986; Vaughan *et al.* 1986; and Luce *et al.* 1993). The authors reported that 9 of 12 studies observed an increased risk associated with formaldehyde. The findings from the studies by Hayes and colleagues (1986) and Luce and colleagues (1993) were in line with the pooled result, although Vaughan and colleagues did not observe an excess risk associated with occupational exposure to formaldehyde. Two other studies were not included in the pooled analysis. Olsen and Asnaes (1986) observed an excess risk of sinonasal cancer associated with formaldehyde in a Danish case-control study, while Roush and colleagues (1987) found no evidence of an association in a Connecticut study, except possibly in the highest exposure category (OR = 1.5 (95% CI = 0.6 to 3.9, 7 cases) for high exposure for 20 or more years).

Several studies presented results by histologic type, principally squamous-cell carcinoma (SCC), the most common pathology, and adenocarcinoma (ADC), a rarer

form, which has also been found to be associated with wood and leather dust. When the results of the pooled analysis (Luce *et al.* 2002) were examined by tumor type, the highly elevated ORs were observed for ADC, but not for SCC. Olsen and Asnaes (1986) observed excesses for both ADC and SCC. Roush and colleagues (1987) did not present their results by histologic type.

Because of the well-recognized association between wood dust and sinonasal cancer and the use of formaldehyde in some of the wood industries, wood dust exposure was considered in several of the studies. Bias due to confounding by wood dust and effect modification between formaldehyde and wood dust have been explored via adjustment and examination of separate and joint effects. A synergistic effect between exposure to wood dust and formaldehyde was observed in the Luce *et al*. (2002) pooled analysis. The French study (Luce *et al.* 1993) also observed a synergistic effect between formaldehyde and wood dust for ADC. Olsen and Asnaes (1986) observed excesses for formaldehyde alone, and formaldehyde and wood dust combined. Hayes and colleagues (1986) did not observe confounding due to wood dust.

The studies of occupationally exposed populations were generally uninformative, with one exception. The Danish population-based cohort study (Hansen and Olsen 1995), created through record linkage, reported a standardized proportionate incidence ratio (SPIR) of 3.0, based on 9 cases not exposed to wood dust. Note that there is an overlap in the cases used in this study with the Olsen and Asnaes (1986) case-control study described above. The other studies reported few or no cases. The NCI industrial cohort (Hauptmann *et al.* 2004) observed an SMR of 1.19 based on 3 cases, while the U.K. chemical industry cohort observed an SMR of 0.87 based on 2 cases (Coggon *et al.* 2003). No cases were observed in the Pinkerton *et al*. (2004) NIOSH garment industry cohort (expected = 0.16). None of the five studies of embalmers or anatomists that reported results for sinonasal cancer observed any cases (expected = 3.5).

Leukemia

Informative Studies

There are four studies (Table 3) that played a key role in this evaluation of the association between formaldehyde exposure and leukemia: a study of mortality from lymphohematopoietic cancers among workers in the U.S. funeral industry (Hauptmann *et al.* 2009); a study of mortality from lymphohematopoietic cancers among U.S. industrial workers employed at 10 formaldehyde-producing or using facilities (the NCI industrial cohort; Beane Freeman *et al.* 2009); a study of British workers employed at six chemical factories (Coggon *et al.* 2003); and a study of workers employed at three facilities in the U.S. garment industry (Pinkerton *et al.* 2004). These four studies are analyses of mortality in populations occupationally exposed to formaldehyde. These studies were judged to be particularly informative because they are relatively large studies that have drawn internal contrasts between workers assessed as having different exposure levels.

Relevant Findings

Overall, the strongest evidence for an association between formaldehyde exposure and leukemia is for myeloid leukemia. Despite the rarity of this outcome, many of the key studies are of cohort, rather than case-control study design. Those case-control studies that have addressed the association between leukemia and formaldehyde have tended to provide results that appear consistent with the cohort studies judged as principal studies for evaluation of this association.

Studies of pathologists, embalmers, and anatomists in the United States, the United Kingdom, and Canada provide major supportive evidence of a positive association between formaldehyde exposure and leukemia. The most informative of these studies is Hauptmann *et al*. (2009), which contrasted workers in the funeral industry who worked in embalming with those who did not, and quantified exposure-response associations. A positive association was reported between embalming (ever worked) and myeloid leukemia; there was little evidence of an association with lymphohematopoietic cancers of lymphoid origin. The risk of myeloid leukemia increased with duration of employment as an embalmer and peak formaldehyde exposure, and was substantially elevated among those with the highest estimated cumulative exposure to formaldehyde. Prior studies of U.S. funeral industry workers drew contrasts to the general population, reporting elevated PMRs for myeloid leukemia in the studies by Hayes *et al.* (1990), and Walrath and Fraumeni (1983, 1984). Excesses of leukemia have also been reported among Canadian undertakers and British pathologists (Hall *et al.* 1991, Levine *et al.* 1984).

The U.S. NCI has conducted a large cohort study of U.S. industrial workers employed at 10 formaldehyde-producing or using facilities. In the primary analysis of this cohort, formaldehyde exposure was assumed to have ceased in 1980. Considering follow-up through 1994, Beane Freeman *et al*. (2009) found elevated relative risks for leukemia, in particular for myeloid leukemia, when contrasting the highest to lowest groups defined on presumed levels of peak formaldehyde exposure and average intensity of formaldehyde exposure. With follow-up extended through 2004, the authors found that myeloid leukemia remained positively associated with average intensity of exposure and peak exposure; however, the magnitude of estimated associations between formaldehyde exposure and myeloid leukemia tended to diminish as follow-up of this cohort extended 15 years or more after exposure to formaldehyde was assumed to have ceased. The authors examined the impact of censoring people who remained employed in 1980 (as opposed to assuming zero exposure), which led to larger estimates of the relative risks for peak exposure and average intensity.

The U.S. NIOSH conducted a large cohort study of workers employed at three facilities in the garment industry (Pinkerton *et al.* 2004). Standardized mortality ratios were reported stratified by period of employment and duration of employment. An excess of myeloid leukemia was reported in this cohort, which was largest in magnitude for those first exposed prior to 1963 and smallest in magnitude for those first exposed in 1971 or later. SMRs for myeloid leukemia increased monotonically with employment duration for the categories examined.

In Britain, a large cohort study was conducted of workers employed at six chemical factories, at which formaldehyde was used or produced (Coggon *et al.* 2003). SMRs were calculated contrasting leukemia rates for all workers with the rates for the referent population. No excess of leukemia was observed in the overall cohort, or in the smaller subgroup of men judged ever to have had high exposure to formaldehyde. Analyses of myeloid leukemia were not reported separately.

Several other studies were reviewed but contributed less to the weight of evidence in the panel's deliberations. Most included small numbers of exposed cases and did not report results separately for myeloid leukemia. Few case-control studies are included in the reviewed literature on myeloid leukemia and formaldehyde. The results of these case-control studies appear consistent with the cohort studies. A study by Blair (2001) ascertained incident cases of chronic myeloid leukemia (CML) and acute myeloid leukemia (AML) and reported a positive association for CML but not for AML. A nested case-control study by Ott (1989) reported a positive association between non-lymphocytic leukemia and occupational exposure to formaldehyde, but included only 2 exposed cases.

Issues with Interpretation:

Statistical Power

Most cohort studies and other studies of occupationally exposed groups were too small to be very informative for either sinonasal cancer or nasopharyngeal cancer and much too small to be informative for sinonasal adenocarcinoma. Sinonasal cancer is a rare tumor and even the NCI industrial cohort with 25,619 workers followed for four decades had only 2.5 cases expected. This problem is further exacerbated because sinonasal adenocarcinoma is a rare pathology, particularly in North America. For example, there were 315 sinonasal cancer cases from the 3 American studies in the pooled re-analysis by Luce and colleagues (2002) and only 9% were adenocarcinomas. Thus, the U.S. studies have very low power to observe an excess of this type of tumor and an excess (based on very small numbers) could be obscured because of reliance on death certificates as a source of information.

Death Certificates

All the studies of occupationally exposed groups in this evaluation relied on death certificates. This is challenging for identifying both sinonasal adenocarcinomas and myeloid leukemias because death certificates do not always list the pathology. While it is common practice to code specific types of leukemia on death certificates when it is available, there is no ICD code to indicate specific pathology of solid tumors. By contrast, case-control studies have often presented results by histopathological type when the epidemiology is known to differ, as is the case for both sinonasal cancer and leukemia.

Potential Confounding Issues

Smoking

Risk estimates for associations between NPC and formaldehyde were significantly elevated after adjustment for smoking in several studies (West *et al.* 1993, Vaughan *et al.* 1986, and Vaughan *et al.* 2000). Among the studies of sinonasal cancer Vaughan *et al*. (1986) adjusted for smoking, while both Hayes *et al*. (1986) and Luce *et al*. (2002) stated that adjustment for smoking did not alter their results. While smoking is a risk factor for SCC, it is not a risk factor for ADC (Luce *et al.* 2002).

The study of workers in the U.S. funeral industry (Hauptmann *et al.* 2009) considered potential confounding by smoking; analyses directly adjusted for tobacco use (which had little impact on risk estimates). Confounding by smoking was not directly adjusted for in the NCI industrial cohort, the U.S. NIOSH study of garment workers, or in the study of British workers in the chemical industry. However, adjustment for birth cohort and pay code effects in cohort analyses provides an indirect approach to minimize potential confounding by smoking (and given the modest association between myeloid leukemia and cigarette smoking, large differences in smoking prevalence by formaldehyde exposure would be needed to result in substantial confounding).

Wood Dust

Wood dust is a known cause of NPC and sinonasal cancers, and persons working with wood are often exposed to both wood dust and formaldehyde. Several studies that found significantly increased risks of NPC associated with formaldehyde either adjusted for wood dust (West *et al.* 1993), found no association with wood dust in the study (Vaughan *et al.* 2000), or found similar formaldehyde associations within subgroups of the study population without wood exposure (Hildesheim *et al.* 2001). The correlation between wood dust exposure and formaldehyde was quite modest ($r = 0.26$ to 0.35 for different measures of exposure) in the study of Hildesheim *et al*. (2001). Wood dust does not appear to be a confounder for SNC and may possibly have a synergistic relationship for ADC.

Other Occupational Exposures

Leather dust is another potential confounding factor for SNC, particularly ADC. However, it is a relatively rare exposure and not likely to be an issue except in regions with a leather industry. The pooled sinonasal case control study by Luce and colleagues (2002) addressed the potential for confounding from leather dust in the same manner as wood dust.

In the study of workers in the U.S. funeral industry (Hauptmann *et al.* 2009) and in the study of garment workers (Pinkerton *et al.* 2004), the authors identified few other important occupational exposures that were plausible confounders for the associations between formaldehyde exposure and myeloid leukemia. Hauptmann and colleagues discussed potential confounding by benzene and ionizing radiation in the workplace; the authors concluded that there was negligible evidence of exposure to these hazards. Pinkerton *et al*. reported that industrial hygiene surveys did not identify any chemical exposures at the plants, other than formaldehyde, that were likely leukemogens.

In the NCI industrial cohort, potential confounding by benzene and other occupational hazards was directly evaluated by adjustment for potential exposure to these hazards and via adjustment for duration of employment as a chemist or laboratory technician. In the study of British workers in the chemical industry, the authors noted that workers in these factories were likely to be exposed to a variety of hazards other than formaldehyde, but these hazards were not quantified or directly adjusted for.

Exposure Misclassification

The study of workers in the U.S. funeral industry derived exposure estimates based upon information reported by next-of-kin and co-workers on dates of employment, embalming, frequency of spills of embalming fluids, and ventilation conditions at work. It is likely that some of the key determinants of exposure levels (such as spills and ventilation conditions) are poorly recollected by these informants.

In analyses of the NCI industrial cohort of workers employed at 10 formaldehyde-producing or using facilities, formaldehyde exposure was assumed to have ceased in 1980 (i.e., zero exposure was assumed after this date). Estimates of formaldehyde exposures after 1980 were not constructed due to absence of work history information after this date. The absence of work history information after 1980 likely leads to exposure misclassification after this date, which would increase with longer follow-up.

In the U.S. NIOSH study of garment workers, limited information on exposure levels was available. Measurements in the early 1980s suggested that exposure levels were similar across departments and plants; while information on historical exposure levels was not available, the authors posited that formaldehyde exposure levels were substantially higher in the earlier years of operation of these facilities than in the 1980s when measurements were made (geometric mean concentration = 0.15 ppm). Estimates of exposures (duration of employment) were truncated for the period after 1981/1982 due to absence of more recent work history information. The absence of more recent work history information is likely to lead to exposure misclassification as follow-up of this cohort is extended.

In the study of British workers employed at six chemical factories, at which formaldehyde was used or produced, it was noted that formaldehyde use at these factories dated back to the 1920s; for some factories, personnel records were judged to be complete many years after the start of work with formaldehyde. Workers were classified into one of five categories of exposure to formaldehyde based upon job title. Each job was assigned to the same exposure category for all time periods, despite the likelihood that exposure levels varied substantially over time. No information was provided on whether employment history information for this cohort was updated along with the update in the follow-up.

Indirect assessment of occupational exposures using job titles and industries in case-control studies as well as other study designs, can also introduce misclassification, but this misclassification is generally non-differential in nature and would tend to bias risk estimates toward the null.

Critiques of Nasopharyngeal Cancer in the NCI Industrial Cohort

Marsh and Youk (2005) conducted a reanalysis of the NCI industrial cohort in which SMRs for NPC were stratified by industrial plant. Five of the 9 cases reported in Hauptmann and colleagues (2004) occurred in Plant 1. The comparatively high number of cases in Plant 1 may be due to potential confounding from an unidentified agent. An alternative explanation for the high number of NPC cases observed in Plant 1 is that this plant included a large proportion of the highly-exposed persons in the NCI study (Table 4). Plant 1 comprised 17% of the cohort study population and 20% of all deaths, and had the second-highest median concentration of formaldehyde (1.1 ppm; second only to Plant 2 which had a median concentration of 3.3 ppm, but only comprised 3% of the study population and 3% of all deaths). If formaldehyde causes NPC, then we would expect to see a high proportion of cases occurring in Plant 1.

Summary of Main Findings

The panel considered the evidence for a variety of head and neck, brain, respiratory (including lung), and lymphatic and hematopoietic cancers for which there was some evidence of carcinogenicity. Their evaluation focused on three sites for which the evidence was strongest and most consistent; namely nasopharyngeal cancer, sinonasal adenocarcinoma, and myeloid leukemia. For each of these cancer types there was evidence of an exposure-response relationship with increased risk among workers classified as having the highest exposure to formaldehyde. Overall, the evidence from epidemiologic studies for each of these three sites is consistent with a causal relationship between formaldehyde and cancer in humans and the panel believed that the patterns observed could not be explained by bias, confounding, or chance.

Recommendation

There is sufficient evidence from studies in humans which indicates a causal relationship between exposure to formaldehyde and human cancer.

Table 1. Summary of studies that are informative for assessment of formaldehyde exposure and nasopharyngeal cancer

Hauptmann *et al.* 2004, NCI combined cohort of formaldehyde-exposed industrial workers	*Cohort study* NCI cohort, USA N = 25,619 Employed: 1934–66 Follow-up: 1966–94	Exposure to formaldehyde was reconstructed using work histories collected through 1980 on the basis of job titles, tasks, plant visits by industrial hygienists, information from workers and plant managers, and monitoring data	SMR: 2.10 (1.05–4.21);8 *Exposure response analyses* *(RR; number of exposed deaths)* Average intensity (ppm) 0 (ref.) 1.00; 2 > 0–< 0.5 NR; 0 0.5–< 1.0 0.38; 1 ≥ 1.0 1.67; 6 Peak exposure (ppm) 0 (ref.) 1.00; 2 > 0–< 2.0 NR; 0 2.0–< 4.0 NR; 0 ≥ 4.0 1.83; 7 P_{trend}[a] < 0.001 P_{trend}[b] 0.044[c] Cumulative exposure (ppm-yr) 0 2.40; 2 > 0–< 1.5 (ref.) 1.00; 3 1.5–< 5.5 1.19; 1 ≥ 5.5 4.14; 3	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 was subsequently re-classified as oropharynx (Marsh and Youk, 2005)
Vaughan *et al.* 1986 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

Roush *et al.* 1987 Connecticut, United States	*Population-based study* 1935–75 *Cases*: 173 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 1.0 (0.6–1.7); 21/79 Any/20-yr 1.3 (0.7–2.4); 17/51 High/none 1.4 (0.6–3.1); 9/27 High/20-yr 2.3 (0.9–6.0); 7/14	Adjusted for age and calendar period
West *et al.* 1993 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: yrs 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 medicine
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	Occupational histories and other information obtained by interview (participant and proxy) and classified by job description and industry *Exposure groups: TWA-8 h (ppm)*	*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	Adjusted for age, sex, region, smoking, proxy status, and education Exposure to wood dust did not increase the risk of NPC in this study

	digit dialing	Low < 0.10 Moderate ≥ 0.10–< 0.50 High ≥ 50	> 0.4–1.10 1.8 (0.8–4.1); 22/20 > 1.10 3.0 (1.3–6.6); 24/19 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 exposed 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 (yrs)* All subjects ≤ 10 1.3 (0.69–2.3); 31/21 > 10 1.6 (0.91–2.9); 43/20 P_{trend} 0.08 Subjects without exposure to wood (yr) ≤ 10 1.3 (NR); 23/16 > 10 1.7 (NR); 28/13 P_{trend} 0.09	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 No exposure-response with duration

NR = not reported
[a] across exposed
[b] across exposed and not exposed
[c] based on 2 values

Table 2. Summary of case-control studies investigating formaldehyde exposure and sinonasal cancer

Olsen and Asnaes 1986, Olsen *et al.* 1984 Denmark	*Population-based study* 1970–82 *Cases:* 466 (67% men) identified by Danish Cancer Registry *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 yr. of diagnosis	Employment histories obtained from national pension and population registries. Exposure to wood dust and formaldehyde classified by industrial hygienists based on 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)* SNC 1.6 (NR) ADC 2.2 (0.7–7.2); 17 SCC 2.3 (0.9–5.8); 13 *Ever exposed, not exposed to wood dust* SNC 1.8 (0.7–3.9); 5 ADC 7.0 (1.1–43.9); 1 SCC 2.0 (0.7–5.9); 4 *Exposed to both formaldehyde and wood dust* SNC 3.5 (2.2–5.6); 28 ADC 39.5 (22.0–70.8); 16 SCC 1.6 (0.8–3.3); 9	80% power to detect an OR of 2.0 for SNC Lagging exposure by 10 years did not alter results Results for SNC combined come from Olsen *et al.* 1984; results for ADC and SCC come from Olsen and Asnaes 1986
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); 15/18 Any exposure/IH_B 1.6 (0.9–2.8); 24/44 Low exposure/IH_A 2.2 (0.8–5.4): 8/11 Low exposure/IH_B 1.0 (0.4–2.5); 7/20 High exposure/IH_A 3.0 (1.0–8.7); 7/7 High exposure/IH_B 2.1 (1.1–4.1); 17/24 *SCC* Any exposure/IH_A 3.0 (1.3–6.4); 12/18 Any exposure/IH_B 1.9 (1.0–3.6); 19/44	No adjustment, but effect estimates did not change after adjustment for smoking or alcohol use; 18 cases of ADC overall

			Low exposure/IH_A 2.7 (1.0–7.2); 7/11 Low exposure/IH_B 1.4 (0.5–3.4); 6/20 High exposure/IH_A 3.1 (0.9–10.0); 5/7 High exposure/IH_B 2.4 (1.1–5.1); 13/24	
Vaughan *et al.* 1986 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	SNC 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 yr 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	SNC *Probably exposed: level/lag time* Any/none 0.8 (0.5–1.3); 21/79 Any/20-yr 1.0 (0.5–1.8); 16/51 High[c] 1.0 (0.5–2.2); 9/27 High[c]/20 yr 1.5 (0.6–3.9); 7/14	Adjusted for age and calendar period
Luce *et al.* 1993 France	*Hospital-based study* 1986–98 *Cases:* 207 male 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	Occupational histories and other information obtained by interview and exposure classified by job title and industry	SCC (men only) *Possible exposure* 0.96 (0.38–2.42); 7/35 *Probable or definite* Average level ≤ 2 0.70 (0.28–1.73); 7/49 > 2 1.32 (0.54–3.24); 9/32 Cumulative level ≤ 30 1.26 (0.54–2.94); 9/3 > 30 0.68 (0.27–1.75); 7/7	SCC: Adjusted for age and exposure to wood dust, glues, and adhesives 97 % of ADC cases were also exposed to wood dust ADC: Adjusted for age and exposure to glues and adhesives

	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 (N = 86) – lists of friends and family provided by cases and matched by sex, age, and residence		No relationship between SCC risk and average exposure, cumulative exposure, duration of exposure, and age or date of first exposure *ADC (men only) with probable or definite exposure to formaldehyde and medium or high exposure to wood dust* Possible exposure 1.28 (0.16–10.42); 4/3 <u>Average level</u> ≤ 2 4.15 (0.96–17.84); 24/8 > 2 5.33 (1.28–22.20); 43/9 <u>Duration (yr)</u> ≤ 20 1.03 (0.18–5.77); 10/7 > 20 6.86 (1.69–27.80); 57/10 <u>Cumulative level</u> ≤ 30 1.13 (0.19–6.90); 8/5 30–60 2.66 (0.38–18.70); 7/3 > 60 6.91 (1.69–28.23); 52/9 <u>Date of first exposure</u> ≤ 1944 6.02 (1.18–30.69); 26/6 ≥ 1955 4.26 (1.06–17.20); 41/11 *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	

Luce *et al.* 2002	*Pooled analysis (12 case-control studies)* *Cases:* 195(169 men, 26 women) ADC, 432 (330 men, 102 women) SSC *Controls*: 3,136 (2,349 men, 787 women)	Occupational history information collected from each study was used to develop a standardized JEM based on job titles and years of employment collected in each study 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); 43/265 Medium 1.1 (0.8–1.6); 40/266 High 1.2 (0.8–1.8); 30/211 ADC Low 0.7 (0.3–1.9); 6/265 Medium 2.4 (1.3–4.5); 31/266 High 3.0 (1.5–5.7); 91/211 *Women* SCC Low 0.6 (0.2–1.4); 6/96 Medium 1.3 (0.6–3.2); 7/53 High 1.5 (0.6–3.8); 6/25 ADC Low 0.9 (0.2–4.1); 2/96 Medium 0 cases High 6.2 (2.0–19.7); 5/25 *No or low wood dust exposure* Formaldehyde exposure No or low (ref.) 1.0 Medium 1.3 (0.5–3.3) High 2.2 (0.8–6.3) *Medium or high wood dust exposure* Formaldehyde exposure No or low (ref.) 1.0 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.

ADC = adenocarcinoma; 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 highly exposed for most of their working lives.

Table 3. Summary of principal studies of formaldehyde exposure and lymphohematopoietic cancers

Hauptmann *et al.* 2009	*Nested case-control study* Deaths identified from cohorts of Hayes *et al*. 1990, Walrath *et al.* 1983, 1984, which are studies of the National Funeral Directors Association, licensing board and state funeral directors associations, NY State Bureau of Funeral Directors and CA Funeral Directors and Embalmers. Controls randomly selected from other causes of deaths	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 levels (peak, intensity, and cumulative) were assigned to each individual using a predictive model based on the exposure-response data	*Embalming (reference never exposed)* *Ever exposed* Lymphoid 1.1 (0.5–2.1); 81 Myeloid leukemia 11.2 (1.3–95.6); 33 *Questionnaire-based metrics (P trend)* Duration (jobs with embalming) LHC 0.058 Nonlymphoid 0.046 Myeloid leukemia 0.020 No. 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 TWA-8 h (ppm) LHC 0.635 Nonlymphoid 0.256 Myeloid leukemia 0.396 Peak exposure (ppm) LHC 0.555 Nonlymphoid 0.089 Myeloid leukemia 0.036 No association of lymphoid origin LHC	Only one case of myeloid leukemia was observed in reference (never exposed) so analysis was repeated using embalmers with fewer than 500 lifetime embalmings as the reference group. The risk of myeloid leukemia was substantially elevated among those with the highest estimated cumulative exposure to formaldehyde (OR = 4.0, 95%CI = 1.2–13.2, based on 22 exposed cases).

			with any of the exposure metrics *Reference < 500 lifetime embalmings: Myeloid leukemia* RR (highest category of exposure); *P* Duration (> 34 yr) 3.9 (1.2–12.5); 0.024 No. emb. (> 3,068) 3.0 (1.0–9.2); 0.057 Cum. Exp (> 9,253) 3.1 (1.0–9.6); 0.047 Avg. Exp (> 1.9) 2.3 (0.7–7.5);NR TWA-8 (> 0.18) 2.6 (0.8–8.3); NR Peak (> 9.3) 2.9 (0.9–9.5); NR *P* for trends (among exposed) the same as trends with the reference group of non-embalmers.	
Beane Freeman *et al.* 2009 (update of Hauptmann *et al.* 2003)	NCI cohort, USA N = 25,619 *Hauptmann et al.. 2003* Follow-up 1966–94 median yr 35 Person-yrs 865,708 *Beane Freeman et al*. Follow-up 1966–2004 median yr 42 Person-yrs 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 (ppm) 0.3 (0.01–4.25) Cumulative (ppm-yr) 0.6 (0–107.4) Duration 2 yr (0–46) All workers 82.5% exposed to	Internal analysis (RR, number of cases) *All leukemia* Peak exposure 0.1–1.9 ppm 1.00; 41 2.0–3.9 ppm 0.98 (0.60–1.62); 27 ≥ 4.0 ppm 1.42 (0.92–2.18); 48 P_{trend} 0.020 Average intensity 0.1–0.4 ppm 1.00; 67 0.5–0.9 ppm 1.13 (0.71–1.79); 25 ≥ 1.0 ppm 1.10 (0.68–1.78); 24 P_{trend} 0.50 *Myeloid leukemia* Peak exposure 0.1–1.9 ppm 1.00; 14 2.0–3.9 ppm 1.30 (0.58–2.92); 11 ≥ 4.0 ppm 1.78 (0.87–3.64); 19 P_{trend} 0.07 Average intensity 0.1–0.4 ppm 1.00; 24 0.5–0.9 ppm 1.21 (0.56–2.62); 9 ≥ 1.0 ppm 1.61 (0.76–3.39); 11	Internal analysis adjusted by calendar year, age, sex, race, and pay category. For follow-up through 1994, Beane Freeman *et al*. reported elevated risks for leukemia, particularly myeloid leukemia when contrasting highest and lowest groups defined on presumed levels of peak exposure (leukemia: RR = 1.60, 95%CI = 0.9–2.92; myeloid leukemia: RR = 2.79, 95%CI = 1.08–7.21) and average intensity (leukemia: RR = 1.34, 95%CI = 0.74–2.41; myeloid leukemia: RR = 2.19, 95%CI =

		formaldehyde 4.7% employed in jobs with ≥ 2 ppm average intensity 22.6 % employed in jobs involving ≥ 4 ppm peak exposure	P_{trend} 0.40	0.92–5.25)
Coggon *et al.* 2003	British Chemical Workers Study, 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 were from the British Industrial Plastics plant	SMR analysis *Entire cohort* LH NR leukemia 0.91 (0.62–1.29); 31 *Highly exposed* Leukemia 0.71 (0.31–1.39); 8	
Pinkerton *et al.* 2004	NIOSH cohort of garment workers, USA N = 11,039 1955–98	All workers considered exposed; personal exposure levels available from plant monitoring programs *Exposure levels* 3 plants in 1981 to 1984	*SMR analysis* LH 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 disease 0.55 (0.07–1.98); 2 Reticulosarcoma/ lymphosarcoma 0.85 (0.28–1.99); 5	

		Median 8-h TWA (ppm) 0.15 (0.09–0.20) Median duration = 3.3 yr Exposures prior to the 1970s were estimated to be as high as 10 ppm	Other LH 0.97 (0.64–1.40); 28 <u>Exposure duration: 10 + years</u> Leukemia 1.53 (NR); 12 Myeloid leukemia 2.19 (NR); 8 Acute myeloid leukemia 2.02 (NR); 5 <u>Time since first exposure: 20+ yrs</u> Leukemia 1.31 (NR); 19 Myeloid leukemia 1.91* (NR); 13 Acute myeloid leukemia 1.93 (NR); 9 <u>10+ yrs duration, 20+ yr since first exposure</u> Leukemia 1.92 (1.08–3.17); 15 Myeloid leukemia 2.55 (1.10–5.03); 8	

*95% CI excludes the null value (1.0)

Table 4. Information on 10 plants included in the NCI industrial cohort

1	R, MC	4,261 (16.6)	1,679 (19.8)	0.9	1.1	90
2	MC, F	784 (3.1)	260 (3.1)	1.9	3.3	80
3	PW	2,375 (9.3)	754 (8.9)	0.2	0.1	1
4	PF	1,692 (6.6)	437 (5.1)	0.4	0.3	1
5	PF	744 (2.9)	130 (1.5)	0.5	NR	NR
6	DL	5,248 (20.5)	1,821 (21.5)	0.5	0.3	37
7	F, R, MC	4,228 (16.5)	1,179 (13.9)	0.1	0.1	0
8	R, MC, PP	1,679 (6.6)	706 (8.3)	0.5	0.7	59
9	R, MC, PP	1,933 (7.5)	350 (4.1)	0.4	0.4	21
10	F, R, MC	2,675 (10.4)	1,170 (13.8)	0.6	0.4	23
Total		25,619	8,486			38

NR = not reported
Products: R = resins; MC = molding compounds; F = formaldehyde and other products not containing formaldehyde; PW = plywood; PF = photographic film; DL = decorative laminates; PP = plastic products
[a] source: Hauptmann *et al.* 2004
[b] source: Blair *et al.* 1990
[c] source: Stewart *et al.* 1990

Note: Plant 1, from which 16% of the cohort and 20% of the deceased workers came—with the exception of Plant 2 from which only 3% of the cohort came—had the highest mean and median worker concentrations and had the highest proportion of workers (90%) with exposures greater than 0.5 ppm.

Cancer Studies in Experimental Animals

There is sufficient evidence for the carcinogenicity of formaldehyde from studies in experimental animals in two species, including multiple strains of rats at multiple sites using two routes of exposure.

Exposure by Inhalation

Formaldehyde exposure by inhalation was associated with nasal tumors in three strains of rats and one strain of mouse, predominantly squamous cell carcinomas and less commonly other benign and malignant nasal tumors. Extensive histopathology was conducted by Kerns *et al.* (1983) and Kamata *et al.* (1997). A limited histopathology examination was conducted by Sellakumar *et al.* (1985) and studies by Monticello *et al.* (1996) and Feron *et al.* (1988) only included a histopathology examination of the nasal cavity.

Squamous-cell carcinomas and other nasal tumors were observed in male (Kerns *et al.* 1983, Kamata *et al.* 1997, Monticello *et al.* 1996) and female (Kerns *et al.* 1983) Fischer 344 rats, male Sprague-Dawley rats (Sellakumar *et al.* 1985), and male Wistar rats (Feron *et al.* 1988). Tumors of the nasal cavity are rare in rats and mice. Two nasal squamous-cell carcinomas found in male $B6C3F_1$ mice (Kerns *et al.* 1983) were considered to be related to formaldehyde exposure.

Exposure by Drinking Water

Formaldehyde exposure in drinking water was associated with forestomach squamous-cell papillomas in one study in male Wistar rats (Takahashi *et al.* 1986). The exposure was for 32 weeks and the histopathology examination was reported to be limited to the stomach and other organs of the peritoneal cavity. Formaldehyde exposure was also associated with malignant tumors of the intestine in female Sprague-Dawley rats (5 leiomyosarcoma and 1 adenocarcinoma in 37 animals) exposed from gestation day 13 through 2 years of life; no intestinal tumors were observed in 49 untreated female controls (Soffritti *et al.* 1989). These malignant intestinal tumors were rare in female laboratory historical controls (leiomyosarcomas: 0.04%; adenocarcinomas: 0.11%) (Soffritti *et al.* 1989). In a second drinking water study, Sprague-Dawley rats were exposed to formaldehyde for 104 weeks beginning at 7 weeks of age and observed for life. The number of testicular interstitial-cell adenomas was significantly increased in the 1000 mg/L exposure group when compared with the methanol control group (Soffritti *et al.* 2002).

In Sprague-Dawley rats exposed to formaldehyde in drinking water for 104 weeks beginning at 7 weeks of age, a statistically significant increase in the incidence of “hemolymphoreticular neoplasias” was reported in males only at the highest dose, when compared with the methanol control group (Soffritti *et al.* 1989, 2002); no such increases were observed in female rats. This finding was not judged to be informative due to the pooling of all types of hemolymphoreticular neoplasias,

including those of different cell lineages and the lack of detail provided on the cellular origin and site. Photographic documentation of the hemolymphoreticular neoplasias provided in the 1989 publication raised additional concerns. In female rats, Soffritti *et al.* (2002) reported a statistically significant increase in malignant tumors of the mammary gland. However, the authors combined adenocarcinomas, fibrosarcomas, and liposarcomas. When liposarcomas were removed from the analysis, the mammary tumor incidence was not significantly different from the methanol control group.

Other Relevant Data

Toxicokinetics

Insofar as there are at least three cancer types associated with formaldehyde exposure in humans, namely, sinonasal adenocarcinoma, nasopharyngeal cancer, and myeloid leukemia, the toxicokinetic issues are somewhat different. For tumors occurring at the point of contact (sinonasal adenocarcinoma and nasopharyngeal cancer), it is clear that formaldehyde is absorbed at the site of contact (via inhalation) and causes damage to cells in the sinonasal-pharyngeal areas. Regarding myeloid leukemia, the toxicokinetic issues relate to distribution of formaldehyde from the nasal and pharyngeal passages to the blood and possibly to the bone marrow. The only direct evidence that formaldehyde enters the blood following inhalation is the study of Pala *et al*. (2008) who measured formaldehyde-human-serum albumin (HSA) adducts in people exposed to formaldehyde. There is also indirect evidence that formaldehyde produced formaldehyde-DNA adducts in the blood of smokers (Wang *et al.* 2009) and DNA-protein crosslinks (DPCs) in the blood of formaldehyde-exposed hospital workers (Shaham *et al.* 2003, Shaham *et al.* 1996, Shaham *et al.* 1997). It is also well recognized that formaldehyde exists in equilibrium with methanediol and with *S*-hydroxymethylglutathione, both of which offer possible mechanisms for formaldehyde to enter the blood and be transported to other tissues. The panel recognized that the endogenous levels of formaldehyde-methanediol in human blood are high (about 0.1 mM, Heck and Casanova 2004) and that this represents a significant challenge for low-dose extrapolations.

Genotoxicity Data

It is clear from studies with *in vitro* model systems involving bacterial, mammalian, and human cells that formaldehyde is genotoxic. Also, Merk and Speit (1998) reported that formaldehyde appears to act via a clastogenic mechanism (i.e., by producing chromosome aberrations rather than point mutations) in mammalian cells. Thus, inhalation of formaldehyde should exert similar effects in sinonasal-pharyngeal cells. This is supported by results from studies in rodents and primates, where all 8 inhalation bioassays of formaldehyde reported elevated levels of DPCs in cells at point of contact (rodent: nasal mucosa; Rhesus monkey: upper respiratory tract). In humans exposed to formaldehyde, elevated levels of micronuclei (MN) were reported in nasal and epithelial cells (of 6 studies, 4 showed significant increases in MN, one showed a positive but non-significant effect and one clearly showed no

effect), and buccal/oral cells (of 6 studies, 5 showed significant increases in MN and one showed a positive but non-significant effect).

Concerning the genotoxic effects of formaldehyde distal to point of contact, the data are somewhat inconsistent. There were a few rodent inhalation studies measuring cytogenetic effects in lymphocytes, most of which were negative [sister-chromatid exchanges (SCEs): neither of 2 studies was positive; chromosome aberrations (CAs): neither of 2 studies was positive]. However, there was some evidence from rodent bioassays of cytogenetic effects in bone marrow (CAs: 1 of 2 studies was positive) and pulmonary lavage cells (the only study was positive). Also, Im *et al*. (2006) reported DNA damage (comet assay) in lymphocytes and liver from rats exposed to formaldehyde. There is substantial evidence that formaldehyde caused cytogenetic effects in human peripheral blood lymphocytes (CAs: of 12 studies, 7 showed significant increases in CAs, 3 clearly showed no effect, and 2 showed a positive but non-significant effect; SCEs: of 12 studies, 6 showed significant increases in SCEs, 4 clearly showed no effect, and 2 showed a positive but non-significant effect; MN: of 7 studies, 5 showed significant increases in MN, one clearly showed no effect, and one showed a positive but not-significant effect). In addition, Costa *et al*. (2008) reported DNA damage (comet assay) in lymphocytes from formaldehyde-exposed workers; this finding is supported by the review of Chinese studies summarized by Tang *et al.* (2009). Finally, the recent study of Zhang *et al*. (in press) showed evidence of aneuploidy in human chromosomes 7 and 8 in myeloid progenitor cells from formaldehyde-exposed workers.

Overall, the evidence indicates that genotoxicity is important to the mechanism[s] of carcinogenicity of formaldehyde.

Toxicity Studies

Formaldehyde is a highly reactive chemical that readily binds with critical macromolecules, including DNA and proteins. Such reactions with cells at the site of contact, primarily in the respiratory tract, cause localized inflammation, with the associated cell proliferation and generation of reactive oxygen species and cytokines that can play roles in carcinogenicity. Cytotoxic effects of formaldehyde are well documented in the upper airways of rodents and humans. Limited evidence shows that rodents exposed to formaldehyde by inhalation have experienced toxic effects at distal sites, including liver damage [DNA damage (comet assay) and lipid peroxidation (Im *et al*. 2006)], testicular damage (serum testosterone levels, seminiferous tubule diameter, stress protein levels) (Özen *et al.* 2005), and neurological damage (decreased superoxide dismutase, decreased glutathione, increased lipid peroxidation (Lu *et al.* 2008). Recent human studies showing hematological changes in formaldehyde-exposed workers (including decreased white blood cell counts, platelet counts, and hematocrit) (Tang *et al.* 2009, Zhang *et al.* 2009), suggest possible toxicity to the hematopoietic system.

Mechanistic Data

There are two proposed mechanisms of formaldehyde carcinogenicity, namely, a cytotoxicity-induced-cell-proliferation (CICP) mechanism and a genotoxic mechanism. Regarding tumors in the sinonasal-pharyngeal regions (point of contact), evidence supports both these mechanisms in animal studies. Although inhalation of formaldehyde is clearly irritating in humans, all published human studies of upper respiratory effects of formaldehyde exposure have focused upon genotoxic endpoints. Indeed, evaluation of a CICP mechanism is impractical in humans. Nonetheless, the clear evidence of genetic damage in human sinonasal-pharyngeal cells provides a plausible mechanism for explaining the epidemiologic associations between formaldehyde exposure and sinonasal adenocarcinomas and nasopharyngeal cancers.

Regarding myeloid leukemia, there is evidence that formaldehyde causes genotoxicity in human lymphocytes, as summarized above (see Genotoxicity Data). In light of the propensity of formaldehyde to damage chromosomes in mammalian cells, it is also important to emphasize that chromosome aberrations are the only validated biomarkers of human cancer (Bonassi *et al.* 2008). Since formaldehyde is genotoxic and has been shown to damage the liver, testes, and lymphocytes following inhalation in rodents or humans, it is plausible to expect that formaldehyde would cause tumors at sites distal to point of entry. While it would be desirable to have an accepted mechanism that fully explains the association between formaldehyde exposure and distal cancers, the lack of such a mechanism should not detract from the strength of the epidemiologic evidence that formaldehyde causes myeloid leukemia.

Report Approved: Dr. McMartin Signature Redacted

Kenneth E. McMartin, Ph.D., Chair

12-16-09

Date

References

1. Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S. 2000. Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. *Int J Epidemiol* 29(6): 991-998.
2. Beane Freeman LE, Blair A, Lubin JH, Stewart PA, Hayes RB, Hoover RN, Hauptmann M. 2009. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries: the National Cancer Institute Cohort. *J Natl Cancer Inst* 101(10): 751-61.
3. Blair A, Stewart PA, Hoover RN. 1990. Mortality from lung cancer among workers employed in formaldehyde industries. *Am J Ind Med* 17(6): 683-99.
4. Blair A, Zheng T, Linos A, Stewart PA, Zhang YW, Cantor KP. 2001. Occupation and leukemia: a population-based case-control study in Iowa and Minnesota. *Am J Ind Med* 40(1): 3-14.
5. Bonassi S, Norppa H, Ceppi M, Stromberg U, Vermeulen R, Znaor A, Cebulska-Wasilewska A, Fabianova E, Fucic A, Gundy S, Hansteen IL, Knudsen LE, Lazutka J, Rossner P, Sram RJ, Boffetta P. 2008. Chromosomal aberration frequency in lymphocytes predicts the risk of cancer: results from a pooled cohort study of 22 358 subjects in 11 countries. *Carcinogenesis* 29(6): 1178-1183.
6. Coggon D, Harris EC, Poole J, Palmer KT. 2003. Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst* 95(21): 1608-1615.
7. Costa S, Coelho P, Costa C, Silva S, Mayan O, Santos LS, Gaspar J, Teixeira JP. 2008. Genotoxic damage in pathology anatomy laboratory workers exposed to formaldehyde. *Toxicology* 252(1-3): 40-8.
8. Feron VJ, Bruyntjes JP, Woutersen RA, Immel HR, Appelman LM. 1988. Nasal tumours in rats after short-term exposure to a cytotoxic concentration of formaldehyde. *Cancer Lett* 39(1): 101-111.
9. Hall A, Harrington JM, Aw TC. 1991. Mortality study of British pathologists. *Am J Ind Med* 20(1): 83-89.
10. Hansen J, Olsen JH. 1995. Formaldehyde and cancer morbidity among male employees in Denmark. *Cancer Causes Control* 6(4): 354-360.
11. Hansen J, Olsen JH. 1996. [Occupational exposure to formaldehyde and risk of cancer]. *Ugeskr Laeger* 158(29): 4191-4194.
12. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. 2003. Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *J Natl Cancer Inst* 95(21): 1615-1623.
13. Hauptmann M, Lubin JH, Stewart PA, Hayes RB, Blair A. 2004. Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol* 159(12): 1117-1130.
14. Hauptmann M, Stewart PA, Lubin JH, Beane Freeman LE, Hornung RW, Herrick RF, Hoover RN, Fraumeni JF, Jr., Blair A, Hayes RB. 2009. Mortality from lymphohematopoietic malignancies and brain cancer among embalmers exposed to formaldehyde. *J Natl Cancer Inst*(Epub).
15. Hayes RB, Raatgever JW, de Bruyn A, Gerin M. 1986. Cancer of the nasal cavity and paranasal sinuses, and formaldehyde exposure. *Int J Cancer* 37(4): 487-92.
16. Hayes RB, Blair A, Stewart PA, Herrick RF, Mahar H. 1990. Mortality of U.S. embalmers and funeral directors. *Am J Ind Med* 18(6): 641-652.
17. Heck H, Casanova M. 2004. The implausibility of leukemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regul Toxicol Pharmacol* 40(2): 92-106.

18. Hildesheim A, Dosemeci M, Chan CC, Chen CJ, Cheng YJ, Hsu MM, Chen IH, Mittl BF, Sun B, Levine PH, Chen JY, Brinton LA, Yang CS. 2001. Occupational exposure to wood, formaldehyde, and solvents and risk of nasopharyngeal carcinoma. *Cancer Epidemiol Biomarkers Prev* 10(11): 1145-1153.
19. Im H, Oh E, Mun J, Khim JY, Lee E, Kang HS, Kim E, Kim H, Won NH, Kim YH, Jung WW, Sul D. 2006. Evaluation of toxicological monitoring markers using proteomic analysis in rats exposed to formaldehyde. *J Proteome Res* 5(6): 1354-66.
20. Kamata E, Nakadate M, Uchida O, Ogawa Y, Suzuki S, Kaneko T, Saito M, Kurokawa Y. 1997. Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. *J Toxicol Sci* 22(3): 239-54.
21. Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA. 1983. Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res* 43(9): 4382-92.
22. Levine RJ, Andjelkovich DA, Shaw LK. 1984. The mortality of Ontario undertakers and a review of formaldehyde-related mortality studies. *J Occup Med* 26(10): 740-746.
23. Lu Z, Li CM, Qiao Y, Yan Y, Yang X. 2008. Effect of inhaled formaldehyde on learning and memory of mice. *Indoor Air* 18(2): 77-83.
24. Luce D, Gérin M, Leclerc A, Morcet JF, Brugère J, Goldberg M. 1993. Sinonasal cancer and occupational exposure to formaldehyde and other substances. *Int J Cancer* 53(2): 224-231.
25. Luce D, Leclerc A, Bégin D, Demers PA, Gérin M, Orlowski E, Kogevinas M, Belli S, Bugel I, Bolm-Audorff U, Brinton LA, Comba P, Hardell L, Hayes RB, Magnani C, Merler E, Preston-Martin S, Vaughan TL, Zheng W, Boffetta P. 2002. Sinonasal cancer and occupational exposures: a pooled analysis of 12 case-control studies. *Cancer Causes Control* 13(2): 147-157.
26. Marsh GM, Youk AO. 2005. Reevaluation of mortality risks from nasopharyngeal cancer in the formaldehyde cohort study of the National Cancer Institute. *Regul Toxicol Pharmacol* 42(3): 275-283.
27. Merk O, Speit G. 1998. Significance of formaldehyde-induced DNA-protein crosslinks for mutagenesis. *Environ Mol Mutagen* 32(3): 260-268.
28. Monticello TM, Swenberg JA, Gross EA, Leininger JR, Kimbell JS, Seilkop S, Starr TB, Gibson JE, Morgan KT. 1996. Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. *Cancer Res* 56(5): 1012-1022.
29. Olsen JH, Jensen SP, Hink M, Faurbo K, Breum NO, Jensen OM. 1984. Occupational formaldehyde exposure and increased nasal cancer risk in man. *Int J Cancer* 34(5): 639-644.
30. Olsen JH, Asnaes S. 1986. Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities. *Br J Ind Med* 43(11): 769-774.
31. Ott MG, Teta MJ, Greenberg HL. 1989. Lymphatic and hematopoietic tissue cancer in a chemical manufacturing environment. *Am J Ind Med* 16(6): 631-643.
32. Özen OA, Akpolat N, Songur A, Kus I, Zararsiz I, Ozacmak VH, Sarsilmaz M. 2005. Effect of formaldehyde inhalation on Hsp70 in seminiferous tubules of rat testes: an immunohistochemical study. *Toxicol Ind Health* 21(10): 249-254.
33. Pala M, Ugolini D, Ceppi M, Rizzo F, Maiorana L, Bolognesi C, Schiliro T, Gilli G, Bigatti P, Bono R, Vecchio D. 2008. Occupational exposure to formaldehyde and biological monitoring of Research Institute workers. *Cancer Detect Prev* 32(2): 121-6.
34. Pinkerton LE, Hein MJ, Stayner LT. 2004. Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med* 61(3): 193-200.

35. Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A. 1987. Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: a case-control study. *J Natl Cancer Inst* 79(6): 1221-1224.
36. Sellakumar AR, Snyder CA, Solomon JJ, Albert RE. 1985. Carcinogenicity of formaldehyde and hydrogen chloride in rats. *Toxicol Appl Pharmacol* 81(3 Pt 1): 401-406.
37. Shaham J, Bomstein Y, Meltzer A, Kaufman Z, Palma E, Ribak J. 1996. DNA--protein crosslinks, a biomarker of exposure to formaldehyde--*in vitro* and *in vivo* studies. *Carcinogenesis* 17(1): 121-125.
38. Shaham J, Bomstein Y, Melzer A, Ribak J. 1997. DNA-Protein Crosslinks and Sister Chromatid Exchanges as Biomarkers of Exposure to Formaldehyde. *Int J Occup Environ Health* 3(2): 95-104.
39. Shaham J, Bomstein Y, Gurvich R, Rashkovsky M, Kaufman Z. 2003. DNA-protein crosslinks and p53 protein expression in relation to occupational exposure to formaldehyde. *Occup Environ Med* 60(6): 403-409.
40. Soffritti M, Maltoni C, Maffei F, Biagi R. 1989. Formaldehyde: an experimental multipotential carcinogen. *Toxicol Ind Health* 5(5): 699-730.
41. Soffritti M, Belpoggi F, Lambertin L, Lauriola M, Padovani M, Maltoni C. 2002. Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann N Y Acad Sci* 982: 87-105.
42. Stewart PA, Schairer C, Blair A. 1990. Comparison of jobs, exposures, and mortality risks for short-term and long-term workers. *J Occup Med* 32(8): 703-708.
43. Takahashi M, Hasegawa R, Furukawa F, Toyoda K, Sato H, Hayashi Y. 1986. Effects of ethanol, potassium metabisulfite, formaldehyde and hydrogen peroxide on gastric carcinogenesis in rats after initiation with N-methyl-N'-nitro-N-nitrosoguanidine. *Jpn J Cancer Res* 77(2): 118-24.
44. Tang X, Bai Y, Duong A, Smith MT, Li L, Zhang L. 2009. Formaldehyde in China: Production, consumption, exposure levels, and health effects. *Environ Int*.
45. Vaughan TL, Strader C, Davis S, Daling JR. 1986. Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. *Int J Cancer* 38(5): 677-683.
46. Vaughan TL, Stewart PA, Teschke K, Lynch CF, Swanson GM, Lyon JL, Berwick M. 2000. Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. *Occup Environ Med* 57(6): 376-384.
47. Walrath J, Fraumeni JF, Jr. 1983. Mortality patterns among embalmers. *Int J Cancer* 31(4): 407-411.
48. Walrath J, Fraumeni JF, Jr. 1984. Cancer and other causes of death among embalmers. *Cancer Res* 44(10): 4638-4641.
49. Wang M, Cheng G, Balbo S, Carmella SG, Villalta PW, Hecht SS. 2009. Clear differences in levels of a formaldehyde-DNA adduct in leukocytes of smokers and nonsmokers. *Cancer Res* 69(18): 7170-4.
50. West S, Hildesheim A, Dosemeci M. 1993. Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. *Int J Cancer* 55(5): 722-727.
51. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. 2009. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Mutat Res* 681(2-3): 150-68.
52. Zhang L, Beane Freeman L, Nakamura J, Hecht S, Vandenburg J, Smith M, Sonawane B.. Formaldehyde and leukemia: Epidemiology, potential mechanisms, and implications for risk assessment. *Environ Mol Mutagen* (in press): 25 pp.