Formaldehyde Council

November 17, 2005

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3118
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Formaldehyde – Proposed Nomination for Review in the 12th Report on Carcinogens

Dear Doctor Jameson,

The Formaldehyde Council, Inc. (FCI) appreciates the opportunity to submit comments to the National Toxicology Program (NTP) on its proposed nomination of formaldehyde to the 12th Report of Carcinogens (RoC). 70 Fed. Reg. 60549 (Oct. 18, 2005). FCI members have invested considerable resources in advancing the understanding of formaldehyde toxicology, which gives FCI a comprehensive view of the science surrounding formaldehyde, particularly formaldehyde toxicology and applicable risk assessment models.[1]

NTP's *Federal Register* notice indicates that formaldehyde's nomination rested on the decision by the International Agency for Research on Cancer (IARC) to change the classification for formaldehyde from Group 2A ("probable human carcinogen") to Group 1 ("known human carcinogen"). FCI's comments provide a summary of important subsequent developments. **In sum, FCI recommends that NTP defer its review of formaldehyde until the National Cancer Institute (NCI) completes an ongoing update of the key epidemiological study (Hauptmann et al. 2004) in 2006.** In addition, the U.S. Environmental Protection Agency (EPA) is actively reviewing formaldehyde for its Integrated Risk Information System (IRIS) database and is awaiting the update of the Hauptmann study. It also may be appropriate for NTP to delay its review of formaldehyde until EPA completes its review. This would assure appropriate scientific coordination between the two Federal agencies in their decisions regarding the carcinogenicity of formaldehyde. Finally, IARC has not published the new monograph for formaldehyde, and has indicated that it will not be available until July 2006 at the earliest. This means that members of the public have not had the benefit of reviewing IARC's monograph or a meaningful opportunity to prepare comments in response to NTP's *Federal Register* notice.

I. Recent Developments

There are more than 40 epidemiologic studies on the potential carcinogenicity of formaldehyde. Prior to the three most recent studies, three meta-analyses have been undertaken. Two of

[1] FCI is a trade association of leading producers and users of formaldehyde that is dedicated to promoting the responsible use and benefits of formaldehyde and ensuring its accurate scientific evaluation. For a list of members and additional information, please see http://www.formaldehyde.org.

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these analyses (Blair et al. 1990 and Partanen et al. 1993) concluded that there was a weakly significant increase in nasopharyngeal cancer (NPC) in workers with substantial exposure to formaldehyde compared to those with low or moderate exposures. A third meta-analysis (Collins et al. 1997) did not find a significant association between formaldehyde exposure and NPC. This last analysis differed from the previous two meta-analyses in that it was the only one to include expected numbers of NPCs from studies that did not report any NPCs, thus avoiding a reporting bias.

In 2004, IARC concluded that formaldehyde is carcinogenic to humans (Group 1), on the basis of sufficient evidence in humans and sufficient evidence in experimental animals. The principal basis for IARC's determination that exposure to formaldehyde may cause nasopharyngeal cancer in humans rests on a study (Hauptmann et al. 2004) conducted by the National Cancer Institute (NCI), which reported an increase in NPC.[2] It is important to note that two other recent, large, epidemiological studies of occupationally exposed workers (Pinkerton et al. 2004, Coggon et al. 2003) did not find any increased risk of NPC.[3]

Hauptmann et al. (2004) involved more than 25,000 workers at 10 plants where there was occupational exposure to formaldehyde. Of the 8 exposed cases of NPC, six exposed cases came from one of the 10 plants with the other two exposed cases distributed among nine plants.[4] This is not the expected pattern from an occupational carcinogen, but suggests causes other than formaldehyde exposure at the single plant where the six NPC cases were observed. In fact, a separate study of this plant found no credible association with formaldehyde exposure and NPC and the authors suggested some other factor(s) must have been involved (Marsh et al. 2002).

A. NCI Cohort Update

On October 12, 2004, NCI Director Andrew C. von Eschenbach, M.D., announced that NCI is extending the mortality follow-up of the Hauptmann et al. (2004) study by an additional eight years, updating exposure histories, and conducting a preliminary review of work histories to determine whether to undertake further quantitative exposure assessments. The update is expected to be completed in the summer of 2006.[5]

By updating the NCI study, additional cancer deaths occurring within the study group over the past eight (1995-2002) years are expected to nearly double the number of deaths and expected cancers in the study, thereby making risk estimates more precise (narrowing the confidence levels). Until this update is completed and more definitive assessment of the risks of NPCs can

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[2] IARC also observed that the Hauptmann et al. (2003) and Pinkerton et al. (2004) studies provided "strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde." We address leukemia thoroughly in Section IV.

[3] Coggon et al. (2003) involved a study of more than 14,000 British workers with formaldehyde exposures likely greater than in the NCI study, but there was no evidence of NPC. Coggon et al. (2003) concluded that the evidence for formaldehyde carcinogenicity in humans was unconvincing. This finding was consistent with Pinkerton et al. (2004), a study by the National Institute of Occupational Safety and Health (NIOSH) of more than 11,000 garment workers, which reported no increase in NPC.

[4] The Hauptmann et al. (2004) study reports 10 cases of NPC (6 at plant 1) and 4 distributed among plants 2-10. However, two of the NPC deaths at plants 2-10 occurred among workers *unexposed* to formaldehyde. Marsh and Youk (2005) at Table 2.

[5] A copy of NCI's revised research protocol is attached.

be made, the Hauptmann et al. (2004) study should not be viewed as a sound basis for assessing NTP risk from formaldehyde exposure.

B. EPA Postponement of IRIS Review

EPA is in the process of updating its IRIS database on formaldehyde, and the Hauptmann et al. (2004) cohort study is likely to play a large role in EPA's review. In November 2004, EPA announced its plan to await findings from the updated NCI study before finalizing its review of formaldehyde under the IRIS program. In the attached letter from EPA to NCI, EPA Assistant Administrator Paul Gilman notes:

> We certainly recognize that the update you are planning with an additional eight years of data could be valuable in further clarifying the previous results of the study group. If the NCI can carry out this further follow-up in the 12-18 months you have suggested, we will be able to incorporate your findings into our update as we have other ongoing work that will likely take that amount of time to be completed.

Like EPA, FCI believes that the update is crucial to the overall understanding of the carcinogenicity of formaldehyde and supports the agency's decision to postpone finalizing its review of formaldehyde under the IRIS program until the NCI update is completed. For the reasons stated above, we believe NTP's agenda pertaining to formaldehyde similarly would benefit from more precise findings from this formaldehyde study.

II. NTP Listing Criteria and the Current State of the Science of Formaldehyde

Formaldehyde is currently classified in the NTP category of "reasonably anticipated to be a Human Carcinogen." According to NTP's criteria for listing a known human carcinogen, there must be "sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer." In the October 18 *Federal Register*, NTP stated that formaldehyde was "nominated for reconsideration based on the 2004 IARC review which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans." 70 Fed. Reg. 60549 (Oct. 18, 2005).

The principal basis for IARC's determination that there was sufficient evidence that formaldehyde causes nasopharyngeal cancer in humans is the Hauptmann et al. (2004) study, which is currently being updated by NCI and should be completed in the near term. Because Hauptmann et al. (2004) was the main underpinning for the IARC decision and the update is intended to resolve the numerous critiques and uncertainties pertaining to this study, the NTP listing criteria for a nomination of a substance do not appear to be met in this instance and/or may be substantially undermined depending on the outcome of the NCI update. Consequently, any decision to review the carcinogenicity of formaldehyde without the benefit of the completed NCI update of the Hauptmann study would be premature.

III. Recent Reanalysis of Nasopharyngeal Cancer Data

FCI views the status of the NCI update of Hauptmann et al. (2004) as a compelling basis for deferring NTP's review of formaldehyde. Following IARC's decision in 2004, subsequent reanalysis of the key studies upon which IARC relied casts further doubt on the wisdom or propriety of an NTP review based on IARC's unpublished monograph. For this reason, the remainder of these comments summarizes the more recent reviews and reanalyses of the NPC and leukemia data.

Because the three major epidemiology studies published in 2003 and 2004 (Hauptmann et al. 2004, Pinkerton et al. 2004 and Coggon et al. 2003) reported inconsistent results and a clear lack of consensus on reported findings, a detailed reanalysis of the NCI study (i.e., Hauptmann et al. 2004) was conducted by Marsh and Youk (2005). The objective of the reanalysis was to determine whether NCI's suggestion of a causal association between formaldehyde exposure and mortality from NPC was robust with respect to using alternative methods of data analysis and categorizations of formaldehyde exposure.

Marsh and Youk (2005) obtained the cohort data from the NCI authors and computed U.S. and local county (regional) rate-based standardized mortality ratios (SMRs) and internal cohort rate-based relative risks (RR) by categories of four formaldehyde exposure metrics (highest peak, average intensity, cumulative, and duration of exposure), using both NCI categories and an alternative categorization based on tertiles of all NPC deaths among exposed subjects. Marsh and Youk (2005) also computed SMRs and RRs for each of 10 study plants and by plant group.

As a result of the reanalysis, Marsh and Youk (2005) demonstrated that 6 of 8 NPC deaths among exposed workers occurred in only one plant (Plant 1) and the remaining 2 deaths occurred individually in the other nine plants studied. A large, statistically significant, regional rate-based NPC SMR of 10.32 (95% CI 3.79–22.47) among formaldehyde-exposed workers in Plant 1 contrasted sharply with a 35% deficit in NPC deaths (SMR 0.65, 95% CI 0.08–2.33) among exposed workers in Plants 2–10 combined. The statistically significant exposure–response relationship with formaldehyde and NPC reported in the NCI study for highest peak exposure was driven entirely by a large, statistically significant excess NPC risk in Plant 1 for the highest peak exposure category (4+ ppm). For the remaining nine plants, RRs for all non-baseline highest peak exposure categories were less than 1.0, and there was no evidence of an exposure–response relationship. Most of the observed NPC excesses for the non-baseline categories of the other exposure metrics (average intensity, cumulative, and duration of formaldehyde exposure) were concentrated in Plant 1, and by contrast to the NCI findings, none of the corresponding exposure–response relationships was statistically significant.

Marsh and Youk (2005) concluded that there was little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from NPC. NCI's conclusion of a possible causal association was driven heavily by anomalous findings in one study plant (Plant 1). An independent and more rigorous study of Plant 1 by Marsh et al. (2004) concluded that the NPC excess was not associated with formaldehyde exposure. These findings cast additional uncertainty regarding the validity of NCI's suggested causal association.

Because studies like Hauptmann et al. (2004) are complicated, there are legitimate grounds for differences of opinion on how the data are interpreted and indeed, in addition to the reanalysis by Marsh and Youk (2005), this study generated a number of letters-to-the-editor critical of the original findings suggesting that the reported findings of NPC were spurious. The consistency and logic of the skepticism is difficult to ignore.

IV. Recent Reanalysis of Leukemia Cancer Data

The OECD's 2002 SIDS Formaldehyde Initial Assessment Profile states that, "In some studies increased risks of various non-respiratory tract cancers . . . have been observed, but without any consistent pattern and without evidence of a causal relationship with formaldehyde exposure. Since kinetic studies indicate that most inhaled formaldehyde is deposited within the upper respiratory tract, available evidence for tumours at sites other than the respiratory tract does not fulfill criteria of causality (e.g. consistency, biological plausibility)."

During its 2004 review, IARC observed that two of the key studies (i.e., Hauptmann et al. 2003 and Pinkerton et al. 2004) provided "strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde." This conclusion was tempered since IARC "could not identify a mechanism for leukaemia induction." As detailed below, IARC's observations were further undermined by another critical reanalysis of Hauptmann et al. (2003) by Marsh and Youk (2004), which revealed methodological problems casting serious doubt on the reported findings of leukemia. In addition, as correctly suspected by IARC, there is no biologically plausible mechanism through which formaldehyde would trigger chemically-induced leukemia (Golden, et al. 2005, Cole and Axten 2004, Heck and Casanova 2004, Collins and Lineker 2004). Simply stated, based on an abundance of data, chemically-induced leukemia is generated in the bone marrow. Inhaled formaldehyde is only known to act on the upper respiratory tract and not at distant sites in the body. Because it is so rapidly metabolized, formaldehyde does not enter the blood and therefore is not transported to the bone marrow, and shows no evidence of bone marrow toxicity (much less leukemia) in the numerous studies in which animals have been exposed to high concentrations via inhalation. Thus, an association between formaldehyde and leukemia is not thought to be probable based on the current scientific understanding of the biology of how formaldehyde acts in the body in conjunction with an understanding of chemically-induced leukemia.

A. Marsh and Youk reanalysis brings new light to leukemia findings

The NCI study reported increased mortality from leukemia concluding that it was associated with exposure to formaldehyde (Hauptmann et al. 2004). Using the NCI data, a separate critical reanalysis of these findings revealed methodological problems casting serious doubt on the reported findings (Marsh and Youk 2004). In epidemiological studies, the mortality from whatever disease endpoints are being investigated in the exposed population is compared to mortality from the same disease in an unexposed population (i.e., controls). A determination is typically then made if there is a significant difference (i.e., increase) in the exposed population. Obviously, if the mortality experience in the control population is lower than expected, a comparison could suggest a significant effect in the exposed population that was spurious, thus making it appear that there was a significant exposure-related effect when in reality the results were an artifact of the unusual mortality experience of the controls. In fact, as the reanalysis clearly demonstrated, there was a substantial deficit in leukemia in the internal control population in the NCI study. When the leukemia mortality was compared to that in the local population, the significant findings disappeared.

In addition, Marsh and Youk (2004) also noted that the latency pattern for leukemia reported in the NCI study was not consistent with a considerable database on chemically-induced leukemia that shows a typical latency period of 10-20 years. By "counting" leukemia deaths that occurred 20 to 40 or more years after subjects had reached their highest peak exposure category, the NCI study may have overestimated leukemia deaths purportedly due to formaldehyde exposure.

In the Pinkerton et al. (2004) study of more than 11,000 garment workers, likely exposed to less formaldehyde than in the NCI study, no increases in leukemia in comparison with the U.S. population were reported, although they did find increases in individuals employed in the early years when exposures to formaldehyde were likely even higher. These findings are limited since the study did not include any measures of individual exposure to formaldehyde. As noted earlier in these comments, the planned update of the NCI study - and its consideration of the discrepancy involving the internal vs. external control population and the latency issue - should serve to resolve whether the earlier reported findings pertaining to leukemia are, in fact, valid.

B. The ability of formaldehyde to trigger chemically-induced leukemia is biologically implausible

Chemically-induced leukemia is a well-studied phenomenon with numerous chemicals demonstrating this capability. To assess whether formaldehyde would be hypothetically capable of causing leukemia, it is necessary to consider the biological basis for leukemogenesis as it is presently understood. For example, abundant *in vitro* and *in vivo* data in animals and humans demonstrate that exposure to sufficient doses of benzene can initiate a cascade of events leading to hematopoietic toxicity and the subsequent development of acute myelogenous leukemia (AML). While the mechanism responsible for benzene-induced leukemia is not completely understood, it has been established that several benzene metabolites are likely responsible for bone marrow toxicity followed by mutation of precursor hematopoietic stem cells with subsequent development of leukemia (Snyder and Hedli 1996, Medinsky et al. 1996, Snyder 2000).

Other chemicals have also been associated with the induction of leukemia in humans and animals. These include a number of alkylating agents (i.e., cyclophosphamide, chlorambucil, Myleran), and topoisomerase inhibitors (i.e., etoposide, teniposide and doxorubicin). All of these leukemogenic exposures exert documented bone marrow toxicity and also demonstrate a range of positive effects in a variety of *in vitro* tests for hematopoietic toxicity. In other words, all of these substances or exposures share a commonality of biological plausibility as support for their demonstrated leukemogenic properties.

In June 2004, IARC was unable to identify a specific mechanism for leukemia induction as a consequence of exposure to formaldehyde. The lack of corroborating mechanistic data renders the interpretation of the epidemiological evidence somewhat equivocal. Based on the well-studied etiology of chemically-induced leukemia, a number of critiques have challenged the validity of the NCI findings for leukemia and myeloid leukemia and concluded that it is biologically implausible that formaldehyde could cause this disease (Golden, et al. 2005, Cole and Axten 2004, Heck and Casanova 2004, Collins and Lineker 2004). For example, this topic is the subject of a recent paper by Golden, et al. (2005), which states:

> Chemically-induced leukemia is a well-studied phenomenon with benzene and a number of cancer chemotherapeutic drugs recognized as capable of causing this effect. Abundant *in vitro* and *in vivo* data in animals and humans demonstrate that exposure to sufficient doses of these recognized leukemogens can initiate a cascade of events leading to hematopoietic toxicity and the subsequent development of leukemia. This review addresses the biological plausibility that formaldehyde might be capable of causing any type of leukemia by providing a broad overview of the scientific data that must be considered in order to support or refute a conclusion that a particular substance might be leukemogenic. Data on benzene and selected chemotherapeutic cancer drugs are used as examples and are briefly summarized to demonstrate the similar biological events thought to result in leukemogenesis. These data are compared and contrasted with the available data on formaldehyde in order to judge whether they fulfill the criteria of biological plausibility that formaldehyde would be capable of inducing leukemia as suggested by the epidemiological data. Based on the epidemiological data, it is reasonable to expect that, if formaldehyde were capable of inducing leukemia *in vivo* and *in vitro,* the data would offer supporting evidence for biological plausibility. In particular, there is (1) no evidence to suggest that formaldehyde reaches any target organ beyond the site of administration including the bone marrow, (2) no indication that formaldehyde is toxic to the bone marrow/hematopoietic system in *in vivo* or *in vitro*

studies, and (3) no credible evidence that formaldehyde induces leukemia in experimental animals. As discussed in this review, based on the key biological events that occur in the process of chemically-induced leukemia, there is inadequate biological evidence currently available to corroborate existing weak epidemiological associations. This provides an insufficient database to conclude that there is a causal relationship for formaldehyde and leukemia risk.

C. Bone marrow involvement

The conclusions of the above authors are further supported by an analysis of experimental models for leukemia, in conjunction with the consistent evidence in the scientific and medical literature that bone marrow alterations/damage play a fundamental and key role in the development of secondary leukemia, particularly as induced by alkylating agent chemotherapy. Formaldehyde's well-studied pharmacokinetics and metabolic pathways demonstrate the inability to enter the blood following inhalation exposure and the absence of bone marrow involvement. This leads to the inescapable conclusion that formaldehyde does not fit the model for chemically-induced leukemia.

There are no data demonstrating leukemogenic transformation via a process not involving direct bone marrow toxicity. In this regard it is worthwhile to note that rats have bone marrow stem cells that move into and out of the circulation. It is, therefore, reasonable to expect that such stem cells could be "mutated" as blood flowed through the lungs with subsequent transport back to the bone marrow in the numerous high dose inhalation bioassays with formaldehyde. The lack of leukemia or any evidence of bone marrow toxicity in any of these studies suggests that the above hypothesized sequence of events does not occur. The involvement of the bone marrow in patients with chemotherapy-induced leukemia is demonstrated by the presence of various refractory cytopenias (anemia, thrombocytopenia and leukopenia) as well as frequent reports of more severe pancytopenia as early presenting signs (Larson et al. 1996, Pedersen-Bjergaard et al. 1984, Pedersen-Bjergaard et al. 1995, Rowley et al. 1977, and Vardiman et al. 1983). There is also ample direct evidence of bone marrow damage in the clinical literature on cytotoxic drug-induced secondary leukemia (Michels et al. 1985, Levine and Bloomfield 1986, Giles and Koeffler 1994, Park and Koeffler 1996). In fact, hypocellular or hypercellular marrow has been reported to occur in as many as 90% of secondary leukemias evaluated in some series and patients with secondary leukemia often present a clinical picture virtually indistinguishable from myelodysplastic syndrome (MDS), a primary bone marrow disease (Larson et al. 1996, Levine and Bloomfield 1986). Therefore, even if transformation of a peripheral bone marrow stem cell could hypothetically occur, bone marrow involvement is still a likely prerequisite for secondary leukemia development. A transformed cell in the periphery could not rationally account for all reported morphological features of secondary leukemia.

In summary, there is no scientific support for any possible speculation that chemically-induced leukemogenic transformation can occur outside the bone marrow (extramedullary). In contrast, a diverse set of experimental and clinical data provide compelling evidence that chemically-induced leukemia is a bone marrow-derived disease. Finally, any theory or hypothesis that formaldehyde might be capable of causing leukemia via a mode of action different from all known chemical leukemogenic substances (i.e., bone marrow toxicity, leukemogenic transformation of stem cells and confirmation in a rodent model), such as mutation of circulating stem cells with subsequent transport to the bone marrow, should be capable of being experimentally validated.

D. Soffritti et al. (1989)

Of the many carcinogenicity studies on formaldehyde, the only one that has reported a carcinogenic effect at a site distant from the point of administration (i.e., nasal passages or gastric mucosa) was by Soffritti et al. (1989). In this study, male and female Sprague-Dawley rats of different ages were exposed to formaldehyde in drinking water at concentrations of 0, 10, 50, 100, 500, 1000, 1500 and 2500 mg/l for up to 104 weeks. As reported by Soffritti et al., there was an increase in what was described as leukemia at doses >500 mg/l, although the lack of any statistical analysis of the data precludes the ability to accurately assess these results. Additionally, while bone marrow was one of the tissues specifically mentioned as part of routine histopathology, there was no mention of findings from this tissue.

In reviewing the results of Soffritti et al. (1989), ATSDR (1999) expressed the following skepticism:

> Another limitation to the strength of the evidence for formaldehyde-induced leukemia is the lack of a consistent dose-response relationship in the Soffritti et al. study . . . the second part of the Soffritti et al. (1989) study found no statistically increased incidence of leukemia in groups of breeding pairs of rats or their offspring exposed for life to the higher dose level of 313 mg/kg/day. A further limitation is the absence of corroborating evidence for effects at sites distant from portals-of-entry in the other drinking water rat studies, and in inhalation-exposure animal studies.

Further, the Cancer Assessment Committee of the Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration (FDA), reviewed the study of Soffritti et al. (1989) and concluded that the data reported were "unreliable" due to "a lack of critical detail . . . questionable histopathological conclusions, and the use of unusual nomenclature to describe the tumors." Consequently, FDA "determined that there is no basis to conclude that formaldehyde is a carcinogen when ingested" (U.S. FDA, 1998).

The ability of formaldehyde to cause leukemia in animals exposed either by inhalation or ingestion must be judged in the context of all available data. Only Soffritti et al. (1989) has reported an increased incidence of leukemia and the conclusions are either highly questionable or completely invalid. Leukemia was not reported in any other of seven inhalation bioassays with formaldehyde nor was it detected in three other drinking water studies in which rats were exposed to doses as high as 1.9 g/L or 5 g/L (Takahashi et al. 1986, Tobe et al. 1989, Til et al. 1989). Given the limitations and inconsistencies as reported by the Soffritti et al. (1989) study and the critiques by ATSDR and FDA, it is difficult to reconcile the reported findings of leukemia with the rest of the peer-reviewed literature and the reported findings should not play any role in the assessment of formaldehyde carcinogenicity.

E. Conclusions on leukemia

The data on benzene and several classes of cancer chemotherapeutic drugs demonstrate a sequence of events that must occur prior to the development of leukemia in either animals or humans. First, there must be evidence that a particular suspect leukemogen can reach the bone marrow following exposure. Second, there needs to be a demonstrable toxic effect on bone marrow cells that is related to leukemia pathways. Third, current models of leukemogenesis indicate that the leukemogen must be genotoxic. These key fundamental aspects of the mode of action for leukemogenic substances, such as benzene and some cancer therapeutic drugs are simply not fulfilled by the extensive data on formaldehyde. With the

exception of high experimental exposures that would not occur in any of the human settings where epidemiological studies have been conducted, there is no evidence to suggest that formaldehyde exposure results in target organ exposure beyond the site of administration, such as the bone marrow. Furthermore, with the same caveat, there is no indication that formaldehyde is toxic to the bone marrow/hematopoietic system in *in vitro* studies.

The position of the International Programme on Chemical Safety (IPCS 1999) on this issue is virtually identical. Based on the epidemiological data, it is reasonable to expect that if formaldehyde were capable of inducing leukemia in exposed workers, the abundant *in vivo* and *in vitro* data on this chemical would offer some supporting evidence of the biological plausibility of this effect consistent with other known leukemogenic chemicals. However, based on an understanding of the biological events involved in the process of chemical leukemogenesis, it is biologically implausible that formaldehyde exposure is capable of inducing leukemia in animals or humans. This conclusion is further supported by an in-depth review by Heck and Casanova (2004), who observed that:

> [T]he abundance of negative evidence . . . is undisputed and strongly suggests that there is no delivery of inhaled formaldehyde to distant sites. Combined with the fact that formaldehyde naturally occurs throughout the body, and that multiple inhalation bioassays have not induced leukemia in animals, the negative findings provide convincing evidence that formaldehyde is not leukemogenic.

The lack of a relevant mode of action when compared to proven leukemogenic substances does not support a conclusion that it is biologically plausible that formaldehyde is capable of causing leukemia in animals, much less in humans. Consequently, there are insufficient data to conclude that there is a biologically plausible relationship between formaldehyde exposure and leukemia risk.

V. Conclusion

The Formaldehyde Council appreciates NTP's consideration of these comments on the nomination of formaldehyde for consideration for the 12th Report on Carcinogens, based on the 2004 IARC review of formaldehyde. Hauptmann et al. (2004) was the primary basis for the IARC decisions on both nasopharyngeal cancer and leukemia. However, the NCI is now updating that study, and that update will nearly double the number of deaths and expected cancers in the study, thereby making risk estimates more precise and allowing a validation of the original conclusions of the study.

Therefore, FCI views the ongoing update of the Hauptmann study as a compelling basis for deferring NTP's review of formaldehyde. In addition, subsequent reanalysis of the Hauptmann study has cast further doubt on the published results, and the update of the study should help resolve these issues as well. Finally, the fact that the IARC monograph is not yet published and therefore unavailable in its final form to NTP reviewers and the public, raises serious questions about the wisdom or propriety of an NTP review of formaldehyde at this time. FCI therefore recommends that NTP defer its review of formaldehyde until the National Cancer Institute completes it update of the Hauptmann study and IARC has published its monograph.

Because the Environmental Protection Agency is actively reviewing formaldehyde for its IRIS database but is also awaiting the update of the Hauptmann study, it may also be appropriate for NTP to delay its review of formaldehyde until EPA completes its review, thereby assuring appropriate scientific coordination between the two Federal agencies in their decisions regarding the carcinogenicity of formaldehyde.

Should you have any questions, please do not hesitate to contact us. We would be happy to provide further elaboration on these issues or copies of any of the referenced studies.

Respectfully submitted,
[Redacted]

Betsy Natz
Executive Director

Attachments:

(1) Update of the NCI cohort of workers in formaldehyde industries (September 8, 2005)
(2) Letter of October 12, 2004, from Andrew C. von Eschenbach, NCI to Stephen L. Johnson, EPA
(3) Letter of November 19, 2004 from Paul Gilman, EPA, to Andrew C. von Eschenbach, NCI
(4) Marsh, GM, Youk, AO (2004) Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. Regul Toxicol Pharmacol 40(2):113-24.
(5) 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):275-83.
(6) Marsh, GM, Youk, AO, Buchanich, JM, Cassidy, LD, Lucas, LJ, Esmen, NA, Gathuru, IM (2002) Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde. Toxicol Ind Health. 18(6):257-68.

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Update of the NCI cohort of workers in formaldehyde industries

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1 Abstract

Formaldehyde is an important industrial product; approximately 2.1 million U.S. workers were exposed to formaldehyde in 1995. Formaldehyde exposure has been associated with cancer of the nasal cavities, nasopharynx, prostate, lung, and pancreas among industrial workers in some studies. Interpretation of excess risks of brain tumors and leukemia in medical workers and other professionals exposed to formaldehyde is difficult since studies in industrial workers, thought to have higher exposures, have shown inconsistent associations. We have recently evaluated cancer mortality through 1994 in the largest cohort to date of 25,619 formaldehyde-exposed workers contributing 865,736 person-years of observation and 8,486 deaths, with exposure information up to 1980, and found a statistically significant exposure-response relationship for leukemia, particularly myeloid leukemia, and for nasopharyngeal cancer (NPC), but not for malignant brain tumors or cancer of the prostate, lung and pancreas.

The numbers of deaths for leukemia and NPC were small (69 and 9, respectively). Therefore, we propose to update mortality using a National Death Index (NDI) search for the 9 years from 1995–2003, which is estimated to add 5,246 deaths and 129,710 person-years for a total of 13,732 deaths and 995,446 person-years. This will increase the number of deaths by 144 for a total of 322 hematolymphopoietic malignancies, by 49 for a total of 118 leukemias, by 21 for a total of 51 myeloid leukemias, by 1 for a total of 10 NPC, and by 25 for a total of 104 brain tumors, based on projections using U.S. mortality rates. The updated cohort will allow a more powerful evaluation of formaldehyde exposure and mortality.

2 Background

Formaldehyde (CH_2O) is a flammable and colorless gas with a worldwide production of approximately 12 million tons in 1992 [1]. It is used in the production of resins, molding compounds, photographic film, decorative laminates, and plywood, and as a bactericide and tissue preservative. The Occupational Safety and Health Administration (OSHA) estimated that in 1995, approximately 2.1 million workers in the U.S. were exposed to formaldehyde [2]. The general population is exposed during release from combustion (e.g., from cigarettes, motor vehicle exhaust, and cooking) and emission from some building materials, such as pressed wood [3].

Formaldehyde causes acute health effects by irritation of the eye and upper airway mucosa, with an irritation threshold of about 0.5–1 ppm [3]. Inhalation exposure to formaldehyde for two or more years caused squamous cell carcinomas of the nasal cavity in rats and mice [4, 5]. However, formaldehyde can also induce effects away from the site of exposure. Increased frequencies of micronuclei [6, 7, 8], sister chromatid exchanges (SCE) [8, 9, 10, 11], chromosomal aberrations [8, 12], and DNA-protein crosslinks [10, 13] have been found in peripheral lymphocytes of humans exposed to formaldehyde. Other studies found some, but not all of these anomalies [14, 15, 16, 17, 18]. In rats, long-term inhalation of formaldehyde vapor at low concentrations of 0.6 and 1.8 ppm caused dose-related bone marrow cytotoxicity (chromosome

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aberrations and aneuploidy) [19], although the association was not found with shorter exposures at higher concentrations [20]. A significant dose-related increase of leukemia incidence was observed in Sprague-Dawley rats administered 10–1,500 ppm formaldehyde in drinking water for two years [21], but not in Wistar rats [22, 23]. A recent study found evidence for an association of formaldehyde exposure and mutant p53 protein expression in humans [24]. Mutations in the p53 tumor-suppressor gene are commonly observed in solid cancers ($> 60\%$) and less frequently in hematolymphopoietic malignancies (10–20%), but p53 mutations in hematolymphopoietic malignancies seem to be associated with poor prognosis [24].

Formaldehyde exposure has been associated with cancer of the nasal cavities, nasopharynx, prostate, lung, and pancreas in some studies of industrial workers [3]. However, these associations were inconsistent and remain controversial. Leukemia and brain cancer have been reported in studies among medical workers and other professionals exposed to formaldehyde, but results in studies of industrial workers are mixed [3].

3 Objectives

To evaluate the association between occupational exposure to formaldehyde and mortality, with a specific focus on deaths from hematolymphopoietic malignancies, NPC and brain tumors, in a cohort of 25,619 workers in 10 U.S. formaldehyde-producing or -using facilities, we propose to extend the current mortality follow-up for the cohort by 9 years from 1/1/1995 through 12/31/2003 using a NDI search for those 17,133 workers not known to be deceased by 12/31/1994. In addition to the diseases of primary interest mentioned above, we will evaluate mortality from other cancer and non-cancer outcomes including cancer of the pancreas, prostate, lung, bone, and salivary gland, and chronic nephritis and emphysema, and we will evaluate mortality from all other causes of death.

4 Rationale

The NCI formaldehyde cohort is the largest cohort of workers exposed to formaldehyde. The proposed update of mortality will increase the number of deaths by approximately 60% and will thereby allow a more detailed and more powerful evaluation of the important findings from the current follow-up. Updating mortality now for the years 1995–2003 is justified because the estimated added number of deaths (over 5,000) will be substantial due to the advanced age of cohort members. For comparison, the previous mortality update included years 1980–1994 and yielded about 4,000 deaths [25].

Further, several agencies are currently updating their formaldehyde risk assessment or plan to do so in the near future, including the U.S. EPA and the Scientific Committee on Occupational Exposure Limits (SCOEL) within the European Agency for Safety and Health at Work. The information obtained from the analysis of the updated mortality data is crucial for these regulatory agencies. Finally, providing more definitive information on the possible formaldehyde-leukemia association is important because current judgements on epidemiological findings are largely based on nasopharyngeal cancer, and leukemia is a much more frequent tumor.

5 Key considerations

The proposed study investigates formaldehyde, a common occupational and environmental exposure. Large numbers of individuals are exposed to formaldehyde, which makes the carcinogenicity of formaldehyde an important public health concern. Because of these aspects, the proposed study is consistent with the mission of DCEG in particular and the NCI in general.

We have assembled a Working Group of experienced extramural investigators to provide advice regarding the design of the study, analysis of the data, and interpretation of the results. We anticipate that this group would meet twice, once to review and discuss the protocol and a second time to discuss the results. Dr. Elizabeth Fontham (Louisiana State University), Dr. Michael Thun (American Cancer Society), and Dr. Noah Seixas (University of Washington) have agreed to serve as the Working Group. Drs. Fontham and Thun are past members of the Board of Scientific Counselors. Dr. Seixas is an industrial hygienist experienced in assessing exposures in industrial settings.

6 Preliminary data

We have recently updated cancer mortality in a cohort of 25,619 workers in 10 U.S. formaldehyde-producing or -using facilities through 1994 [26, 27], Table 1. Compared with the U.S. population, mortality was lower for all cancers (376 deaths observed vs. 494.7 expected among nonexposed, and 1,723 vs. 1,914.4 among exposed), all hematolymphopoietic malignancies (17 deaths observed vs. 27.4 expected among nonexposed, and 161 vs. 201.3 among exposed), and all leukemias (4 deaths observed vs. 10.5 expected among nonexposed, and 65 vs. 76.5 among exposed) but higher for nasopharyngeal cancer (2 deaths observed vs. 1.3 expected among nonexposed, and 8 vs. 3.8 among exposed). Quantitative estimates of formaldehyde exposure up to 1980 were constructed based on job titles, tasks, site visits by study industrial hygienists, discussions with workers and plant managers, and monitoring data. We found a statistically significant association between peak exposure to formaldehyde and leukemia (69 deaths), particularly myeloid leukemia (30 deaths), and some indication of an association for average exposure intensity, Table 2. RRs for Hodgkin's disease also increased with formaldehyde exposure, Table 2, but interpretation is problematic since this association has not been seen previously. We observed exposure-response patterns for nasopharyngeal cancer (9 deaths) for average, cumulative, peak and duration of exposure to formaldehyde, Table 2. We did not find an association for malignant brain tumors; however, we observed significantly elevated RRs for unspecified brain tumors among exposed workers, Table 2.

We lacked information on tobacco use for most of the cohort, but evidence suggests that smoking is not a confounder since there was no consistent excess or deficit for tobacco-related diseases, including lung cancer, bladder cancer, emphysema, and ischemic heart disease. Information on smoking habits obtained from medical records for a small sample of workers from two plants (63 subjects with cancer and 316 age-matched controls) revealed no major differences in smoking prevalence by level of cumulative formaldehyde exposure.

Our findings can be compared with recent results from the extended follow-up of two other cohort studies of formaldehyde-exposed workers. Among 14,014 men employed in the British formaldehyde industry, no excess of leukemia overall (31 deaths versus 34.1 expected) or in high exposure jobs (8 deaths versus 11.3 expected) was found nor was there an excess of nasopharyngeal cancer or brain tumors [28]. The design of this study was similar to ours, including the development of quantitative estimates of formaldehyde exposure from production of urea and melamine formaldehyde resins. However, our study had more than twice the number of leukemia deaths, and peak exposure and average exposure intensity were not evaluated in the British study. A cohort study of 11,039 textile workers with potential exposure to formaldehyde conducted by the National Institute for Occupational Safety and Health found an increase in myeloid leukemia mortality among workers with longer duration of exposure (standardized mortality ratio SMR=2.19, based on 8 deaths), earlier calendar year of first exposure (SMR=1.61, based on 11 deaths), and longer time since first exposure (SMR=1.91, based on 13 deaths) [29]. No excesses were observed for cancer of the nasopharynx or the brain.

The recent evaluation of cancer mortality in the NCI cohort of workers in the formaldehyde industry was included in the decision of a working group of the International Agency for Research on Cancer (IARC) to upgrade formaldehyde from probably carcinogenic (group 2A) to carcinogenic (group 1) for humans based on sufficient evidence for nasopharyngeal cancer. The working group also noted that there was strong but not sufficient evidence for leukemia [3, 30, 31]. Further, our study has been subjected to re-analyses [32, 33], has been included in several meta-analyses [34, 35], and has been critically discussed [36, 37, 38, 39, 40, 41, 42, 43]. The U.S. Environmental Protection Agency (EPA) is currently updating its assessment of formaldehyde within the Integrated Risk Information System (IRIS).

7 Approach

7.1 Study design

The previous mortality follow-up of a cohort of 25,619 workers in 10 formaldehyde-producing or -using facilities in the U.S. ended in 1994. We will extend the mortality follow-up through 12/31/2003 using a NDI search of all workers not known to be deceased by 12/31/1994.

Among the 25,619 workers in the cohort, as of 12/31/1994, 8,486 deaths occurred with 866 workers lost to follow-up. The NDI search will therefore be done for 17,133 subjects. The median age of those workers in 1994 was 64 years. We project an NDI search for the time 1/1/1995–12/31/2003 to add 5,246 deaths and 129,710 person-years for a total of 13,732 deaths and 995,446 person-years. With respect to specific cancer

sites, we expect 144 additional deaths from hematolymphopoietic malignancies (including 49 deaths from leukemia and 21 deaths from myeloid leukemia), one death from NPC and 25 deaths from brain tumors, based on projections using U.S. mortality rates, Table 3. The total number of deaths in the updated cohort is therefore expected to be 322 for hematolymphopoietic malignancies (leukemia: 118, myeloid leukemia: 51), 10 for NPC and 104 for brain tumors (malignant: 84, benign: 6, unspecified: 14).

The exposure assessment ceased in early 1980 and we do not plan to update the exposure assessment. This could cause an underestimation of exposure for individuals working after 1980. Although the median age in 1980 among subjects alive in 1980 was only 51 years, the impact of the exposure underestimation would be minimal for three reasons. First, only a small proportion of individuals was likely exposed after 1980. Considering as likely exposed after 1980 those workers who were younger than 65 years in 1980 and who were in an exposed job at the end of 1979, some exposure could be missed for an estimated 11% of all cohort subjects, and the years of missing exposure represent an estimated 6% of all person-years. Second, levels of missed exposure were probably considerably lower after 1980 than in earlier years due to substantial regulatory changes around 1985. In order to substantiate the assumption that exposures decreased after 1980, we have requested relevant OSHA monitoring data. Third, we have estimated the expected number of leukemia deaths until the end of 2003 by exposure category, using U.S. population mortality rates, under two different scenarios, assuming (a) no exposure occurred after 1980, and (b) workers in exposed jobs during 1979 continued to be exposed at that level until the earliest of age 70 years, death[1] or the end of follow-up (12/31/2003). For categories of exposure as in Table 2, ratios of expected numbers of leukemia deaths according to scenario (b) versus (a) were 1.00, 1.01, 0.98, 0.99 for average intensity and 1.00, 0.99, 0.98, 1.06 for cumulative exposure. This indicates that exposure category-specific SMRs for leukemia calculated under both scenarios would differ by less than 6%. The peak metric, i.e., highest peak exposure category ever experienced in the past, does not increase over time unless peak levels higher than previously occur. Therefore, the expected numbers of deaths by peak exposure category are identical under both scenarios.

7.2 Case definition

The diseases of primary interest are malignancies of the hematopoietic and lymphatic system, the nasopharynx and the brain. With respect to malignancies of the hematopoietic and lymphatic system, we will focus particularly on leukemia, including subtypes. As an alternative to the grouping of hematolymphopoietic disorders in the International Classification of Diseases, we will consider a grouping which reflects the lymphatic or myeloid origin of the diseases. Such a grouping would distinguish malignancies of lymphoid origin, including reticulum-cell sarcoma, lymphosarcoma, Hodgkin's disease, lymphatic leukemia, and multiple myeloma, from those originating from multipotential progenitor cells (CFU-GEMM), including myeloid and monocytic leukemia, polycythemia vera, and myelofibrosis.

Cause of death information from death certificates is not ideal to evaluate subtypes of hematolymphopoietic malignancies. Based on almost 60,000 deaths in 1985 and 1986, Percy et al. [44] calculated the confirmation rate as the proportion of death certificates with a certain cancer as underlying cause of death for which medical records confirmed such a diagnosis. Based on over 50,000 cancers diagnosed in 1974 and 1975, Percy et al. also calculated the detection rate as the proportion of all subjects diagnosed with a certain cancer for which that cancer later appeared on their death certificate as underlying cause of death. For subtypes of malignancies of lymphoid origin, confirmation and detection rates were 81–97% and 77–97%, respectively. For subtypes of malignancies originating from multipotential progenitor cells, confirmation and detection rates were 50–86% and 49–77%, respectively. Percy et al. also state that 50% of unspecified leukemias were myeloid leukemias and 15% were lymphocytic. Polycythemia vera and myelofibrosis were not evaluated. We will explore possibilities to further assess the completeness and detail of the death certificate information for the analysis of cancer subtypes.

We will also follow-up on the association between formaldehyde exposure and Hodgkin's disease observed in the previous analysis. This association is difficult to interpret because it has not been seen in any other epidemiologic study.

In addition to the diseases of primary interest, we will evaluate mortality from cancers at other sites and from relevant non-malignant diseases. This evaluation will particularly focus on diseases for which an association has been suggested either in other studies and/or in the previous analysis of the NCI cohort

[1] Since mortality in 1995-2003 is currently unknown, we estimated age at death for subjects alive at the end of 1994 as age at the end of 1994 plus half the difference between that age and 88, so that the total number of person-years contributed in 1995-2003 equals that estimated from U.S. mortality rates.

(cancer of the pancreas, prostate, lung, bone, and salivary gland, and chronic nephritis and non-cancer pulmonary disorders including emphysema).

In the 1994 follow-up, analyses were not feasible for polycythemia vera (one death) and myelofibrosis (five deaths) due to small numbers. No association with formaldehyde exposure was observed for other diseases of blood cells in the bone marrow, including seven deaths from anemia of which four were aplastic, one was hypochromic with iron loading, one was specified as other, and one was unspecified, and three deaths from agranulocytosis. We will evaluate these diseases in the proposed update. The larger numbers of cases thereby obtained would allow a more meaningful interpretation of the results.

7.3 Statistical analysis

The primary analysis will be similar to the previous analysis of the 1994 follow-up data [26, 27], i.e., Poisson regression based on the time-dependent categorical and continuous values of metrics of formaldehyde exposure, while adjusting for other occupational exposures associated with these workplaces. Analyses will be stratified by factors including pay category, sex, and ethnicity. Analyses will also address

- the shape of the exposure-response curve, e.g., using flexible semi-parametric methods such as fractional polynomials or splines,
- cross-classifications of exposure metrics,
- effect modification between exposure metrics,
- effect modification by other factors, e.g., age or time since exposure,
- latency,
- subgroups of the study population (e.g., white males, workers exposed to particulates, short-term versus long-term workers).

The toxicology literature does not provide much indication of a preference of one exposure metric over another. We will evaluate several quantitative metrics of formaldehyde exposure, including average intensity, highest peak exposure category, cumulative exposure, and duration of exposure. We will view these metrics as attempts to characterize delivered dose under different potential biologic scenarios. Duration is considered the least useful metric because it assumes constant exposure levels over time and across different work locations, which is unrealistic. Cumulative exposure, the product of duration and average intensity, describes delivered dose well if duration and intensity of exposure contribute equally to risk. This metric has been successfully used in many occupational cohort studies. Highest peak exposure would characterize delivered dose better if the target tissue is most affected by exposures exceeding a certain level, e.g., tissue defense mechanisms that work well at lower levels could be overwhelmed at higher levels. In such a situation, risk would be expected to increase with frequency and duration of high peak exposures. Average intensity of exposure is a time-weighted average of all intensity levels experienced and is therefore intermediate between cumulative exposure and highest peak exposure. We will also explore other metrics.

We will evaluate how changes of the exposure-response association for a particular outcome between the previous and the proposed follow-up occurred over follow-up time, i.e., whether they occurred relatively smoothly or suddenly, by adding small increments of follow-up time, i.e., moving forward the study end-date by a year at a time, and evaluating exposure-response gradients [45]. Because occupational formaldehyde exposure among industrial workers is assumed to have decreased with calendar time after about 1980, a smooth decrease of formaldehyde-related risk with calendar time, i.e., follow-up time, would be consistent with a causal association. However, a relatively sudden decline in the strength of an association would be more difficult to interpret.

We will assess the sensitivity of the results with respect to the uncertainty about unknown post-1980 exposures by dropping out individuals still exposed in 1979 to see if the results were similar to the analyses using the entire cohort. Further, we will impute reasonable and extreme levels of exposure based on the exposure distribution in the cohort before 1980 to determine how these various levels affect the results.

We will compare the mortality of the updated cohort with the mortality in the general U.S. population by calculating SMR. To investigate the low leukemia mortality in the cohort, particularly among the nonexposed, compared with the U.S. population, we will evaluate whether the plants are located in areas that have unusual

leukemia rates, whether established risk factors for leukemia vary by the geographic locations of the plants, and how SMRs changed over time with improving leukemia diagnoses. We will also determine whether the proportion of white collar jobs was higher among the nonexposed than the exposed.

If the additional numbers of deaths from the proposed follow-up allow, we will consider analyses by plant or by groups of plants with similar exposures. In addition, adjusting analyses for plant will be considered to control for occupational differences.

7.4 Statistical power

Based on the estimated number of deaths in the updated cohort, we will have 80% power to detect relative risks of about 1.5, 3.7, 1.9, 2.5, and 2.0 or larger for all hematolymphopoietic malignancies, Hodgkin's disease, all leukemia, myeloid leukemia, and malignant brain tumors, respectively, between high and low levels of exposure estimated by average intensity ($\geq$1.0 ppm versus >0–<0.5 ppm), cumulative exposure ($\geq$5.5 ppm-years versus >0–<1.5 ppm-years), and highest peak exposure ($\geq$4.0 ppm versus >0–<2.0 ppm).

7.5 Personnel

All collaborators on the study are investigators in the intramural program of the National Cancer Institute and are located in Rockville, Maryland.

7.6 Human subjects protection

The proposed project will not contact study participants. The National Institutes of Health Office of Human Subjects Research has reviewed the activity and has determined that it is exempt from review by the institutional review board (OSHR No. 2856). Approval will be obtained from the NDI and state institutional review boards, where necessary, to obtain death certificates.

7.7 Timeline

For the NDI search, the initial approval process takes about 2 months, and the NDI search should take between 1–2 weeks. A rough outline of the time frame for the proposed study is given below.

- February–August 2005 – protocol development and approval
  - review and approval of the project by NCI
  - sharing of the protocol by the Formaldehyde Council, companies and unions
  - review of the protocol by external Working Group
- October/November 2005 – return of data from the NDI
- July 2006 – manuscript developed

8 Project funding justification

This is a comparably inexpensive and straight-forward project which can be completed within a relatively short period of time. The only major costs occur for the NDI search.

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Table 1: Demographic characteristics of the formaldehyde workers cohort

Demographic characteristic	Number of subjects	%
Ethnicity and sex		
White men	20,658	81
Black men	1,835	7
White women	3,100	12
Black women	26	<1
Year of entry into cohort		
$\leq$ 1945	3,105	12
1946–55	11,200	44
1956–65	11,314	44
Age at entry, years		
$\leq$ 30	16,900	66
31–40	5,140	20
41–50	2,603	10
51–60	848	3
$\geq$ 61	192	1
Duration of follow-up, years		
$\leq$ 30	8,273	32
31–35	5,092	20
36–40	5,109	20
$\geq$ 41	7,145	28
Vital status as of 12/31/1994		
Alive	16,267	64
Deceased	8,486	33
Unknown	866	3
Total	25,619	100

Table 2: Selected results based on the 1994 mortality follow-up by different measures of exposure to formaldehyde

Cause (ICD[a]) of death	Relative risk[b] (# deaths)				p trend[c]
	Peak exposure[d] (ppm)				
	0	> 0 – < 2.0[e]	2.0 – < 4.0	≥ 4.0	
Hematolymphopoietic malignancies (200–209)	1.08 (17)	1.00 (48)	1.71[f] (49)	1.87[f] (64)	0.002
Hodgkin's disease (201)	0.51 (1)	1.00 (5)	3.45 (7)	3.35 (8)	0.042
Leukemia (204–207)	0.78 (4)	1.00 (16)	2.04[f] (20)	2.46[f] (29)	0.004
Lymphatic leukemia (204)	– (0)	1.00 (6)	1.51 (6)	1.39 (7)	0.559
Myeloid leukemia (205)	0.67 (2)	1.00 (6)	2.43 (8)	3.46[f] (14)	0.009
Other/unspecified leukemia (207)	1.92 (2)	1.00 (4)	2.33 (6)	2.47 (7)	0.154
Brain tumors (191, 192, 225, 238)					
Malignant (191-192)	1.64 (19)	1.00 (18)	1.06 (14)	0.74 (11)	(0.405)
Benign (225)	0.14 (1)	1.00 (3)	– (0)	0.45 (1)	(0.303)
Unspecified (238)	1.95 (3)	1.00 (1)	4.62 (3)	9.40[f] (5)	0.015
Nasopharyngeal cancer (147)	1.00[g] (2)	– (0)	– (0)	1.83 (7)	< 0.001
	Average intensity[d] (ppm)				
	0	> 0 – < 0.5[e]	0.5 – < 1.0	≥ 1.0	
Hematolymphopoietic malignancies (200–209)	0.91 (17)	1.00 (81)	1.63[f] (42)	1.50[f] (38)	0.062
Hodgkin's disease (201)	0.46 (1)	1.00 (7)	4.70[f] (8)	3.12 (5)	0.031
Leukemia (204–207)	0.56 (4)	1.00 (32)	1.52 (16)	1.68 (17)	0.242
Lymphatic leukemia (204)	– (0)	1.00 (9)	1.56 (5)	1.43 (5)	0.632
Myeloid leukemia (205)	0.41 (2)	1.00 (14)	1.15 (5)	2.49[f] (9)	0.088
Other/unspecified leukemia (207)	1.27 (2)	1.00 (9)	1.69 (5)	0.98 (3)	(0.710)
Brain tumors (191, 192, 225, 238)					
Malignant (191-192)	1.84 (19)	1.00 (23)	1.07 (9)	1.19 (11)	0.631
Benign (225)	0.18 (1)	1.00 (3)	– (0)	0.90 (1)	0.285
Unspecified (238)	0.89 (3)	1.00 (3)	2.01 (2)	3.66 (4)	0.013
Nasopharyngeal cancer (147)	1.00[g] (2)	– (0)	0.38 (1)	1.67 (6)	0.066
	Cumulative exposure[d] (ppm-yr)				
	0	> 0 – < 1.5[e]	1.5 – < 5.5	≥ 5.5	
Hematolymphopoietic malignancies (200–209)	0.74 (17)	1.00 (94)	0.79 (29)	1.03 (38)	0.202
Hodgkin's disease (201)	0.29 (1)	1.00 (12)	1.35 (5)	1.17 (3)	0.045
Leukemia (204–207)	0.48 (4)	1.00 (35)	0.90 (13)	1.14 (17)	0.235
Lymphatic leukemia (204)	– (0)	1.00 (10)	0.72 (3)	1.20 (6)	0.476
Myeloid leukemia (205)	0.32 (2)	1.00 (17)	0.57 (4)	1.02 (7)	0.157
Other/unspecified leukemia (207)	1.37 (2)	1.00 (8)	1.60 (5)	1.28 (4)	(0.783)
Brain tumors (191, 192, 225, 238)					
Malignant (191-192)	1.71 (19)	1.00 (27)	1.02 (9)	0.86 (7)	0.886
Benign (225)	0.23 (1)	1.00 (2)	0.97 (1)	1.06 (1)	0.738
Unspecified (238)	0.56 (3)	1.00 (5)	0.67 (1)	2.90 (3)	(0.806)
Nasopharyngeal cancer (147)	2.40 (2)	1.00 (3)	1.19 (1)	4.14 (3)	0.025

[a] 8th revision codes of the International Classification of Disease (ICD)

[b] Relative risk from Poisson regression stratified for calendar year, age (both in 5-year intervals), sex, and race (black/white), and adjusted for pay category (salary/wage)

[c] Likelihood ratio test (1 degree of freedom) of zero slope for continuous formaldehyde exposure among exposed person-years only; parentheses indicate negative slope estimate

[d] Formaldehyde exposure calculated using a 2-year lag interval for hematolymphopoietic malignancies and a 15-year lag interval for nasopharyngeal cancer and brain tumors

[e] Reference category for all categories

[f] 95% confidence interval does not include 1.00

[g] Reference category for this site due to no cases in the low exposed category

Table 3: Observed numbers of deaths before 1995 and projected numbers of deaths in 1995–2003 for selected causes of death

	Number of deaths		
Cause (ICD[a]) of death	Before 1995	1995–2003[b]	Total
Hematolymphopoietic malignancies (200-209)	178	144	322
Hodgkin's disease (201)	21	2	23
Leukemia (204-207)	69	49	118
Myeloid leukemia (205)	30	21	51
Other (200, 202-203, 208-209)	88	93	181
Brain tumors (191-192, 225, 238)	79	25	104
Malignant (191-192)	62	22	84
Benign (225)	5	1	6
Unspecified (238)	12	2	14
Nasopharyngeal cancer (147)	9	1	10
Total	266	170	436

[a] 8th revision codes of the International Classification of Disease (ICD)

[b] Projected deaths 1/1/1995-12/31/2003

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

OCT 12 2004

Mr. Stephen L. Johnson
Deputy Administrator
U.S. Environmental Protection Agency
Ariel Rios Building, 1102A
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Dear Mr. Johnson:

It has been brought to my attention that the Environmental Protection Agency (EPA) will soon issue a report on formaldehyde. The purpose of this message is to inform you that the National Cancer Institute (NCI) plans to initiate further follow-up of the NCI cohort of workers in the formaldehyde industry in fiscal year 2005. We plan to extend the mortality follow-up, update exposure histories, and conduct a preliminary review of work histories to determine whether to undertake further quantitative exposure assessments. This work would be conducted over a 12-18 month period, beginning in January 2005, followed by preparation and submission of a manuscript for publication. The realization of these plans will be conditional on scientific review and approval and availability of funds.

The staff of the NCI Division of Cancer Epidemiology and Genetics has already been in contact with Dr. Peter Preuss, Director of EPA's National Center for Environmental Assessment, and with Mr. David Bayliss, of that group, and have informed them of our plans. I wanted to make sure you were also aware of NCI's planned efforts.

Please let me know if you need any further information.

[Redacted]

Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

NOV 19 2004

OFFICE OF
RESEARCH AND DEVELOPMENT

Andrew C. von Eschenbach, M.D.
Director
National Cancer Institute
National Institutes of Health
Building 31, Room 11A48
31 Center Drive
Bethe[Redacted]

Dear [redacted] h:

Thank you for your letter to Deputy Administrator Stephen Johnson regarding the plans of the National Cancer Institute (NCI) to institute further follow-up on the NCI cohort of workers exposed to formaldehyde. I have been asked to reply on his behalf.

We are in the process of updating our analysis of the health effects of formaldehyde. As part of that activity we have been considering the results of NCI's most recent analysis of this study group involving more than 25,000 workers in industrial facilities throughout the United States, published this past spring. The authors reported a statistically significant increase in several types of cancers. Other recent studies of garment workers published by the National Institute of Occupational Safety and Health and industrial workers in the United Kingdom have reported increases in some cancers associated with formaldehyde exposures. The reports of increased nasopharyngeal cancers were especially important in the decision of the International Agency for Cancer Research to classify formaldehyde as a known human carcinogen at their meeting this past summer.

We certainly recognize that the update you are planning with an additional eight years of data could be valuable in further clarifying the previous results of the study group. If the NCI can carry out this further follow-up in the 12-18 months you have suggested, we will be able to incorporate your findings into our update as we have other ongoing work that will likely take that amount of time to be completed. I have asked Dr. Peter Preuss, Director of our National Center for Environmental Assessment to contact the staff of your Division of Cancer Epidemiology and Genetics in order to monitor the progress of their success in obtaining funding for the follow-up study. If the NCI cannot identify sufficient funds for this update, then we will use the best available science to update our health assessment of formaldehyde.

Thank you for your help in this important matter.

Sincerely,

[Redacted]

Paul Gilman, Ph.D.
Assistant Administrator

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Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute

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Abstract

Objective. To determine whether the National Cancer Institute's (NCI) recent suggestion of a causal association between formaldehyde exposure and mortality from leukemia and myeloid leukemia (ML) is robust with respect to alternative characterizations and categorizations of formaldehyde exposure and to alternative methods of data analysis.

Methods. The original authors provided the cohort data. We computed US and local county rate-based standardized mortality ratios (SMRs) and internal cohort rate-based relative risks (RR) by categories of four formaldehyde exposure metrics (highest peak, average intensity (AIE), cumulative, and duration), using both NCI categories and an alternative categorization based on tertiles of deaths from all leukemia among exposed subjects. For highest peak exposure, we computed RRs by the duration of time worked in the highest peak category and the time since highest peak exposure. For AIE, we computed RRs by the duration of exposure and the time since first exposure.

Results. Our external comparisons revealed that the elevated leukemia and ML RRs and associated trends reported by NCI for highest peak and AIE occurred because null (or slight) to moderate mortality excesses were compared with statistically significant baseline category deficits in deaths. Our alternative categorization of AIE yielded leukemia and ML SMRs close to 1.0 in the highest exposure category, and revealed weaker evidence of a trend in RRs for leukemia and ML. We corroborated NCI's finding of no association for cumulative and duration of formaldehyde exposure. We found no consistent evidence that leukemia or ML risks increased with increasing duration of time spent in a given highest peak exposure (or for AIE, duration of exposure in a given AIE category). We also found no consistent evidence that leukemia or ML risks were greater in the more relevant shorter (less than 20 years) versus longer (20+ years) periods of time from the first highest peak exposure (or for AIE, first exposure).

Conclusions. Our reanalysis provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from leukemia and ML. NCI's key findings for highest peak exposure and AIE do not adequately account for the inordinately large deficits in deaths in the categories used as the baselines for internal rate-based RRs. The NCI findings also do not adequately account for the duration of time subjects spent in the highest peak category (or for AIE, duration of exposure) or the time since their first peak exposure (or for AIE, time since first exposure). Our finding that NCI's suggestion of a causal association is not robust with respect to alternative categorizations of formaldehyde exposure and methods of data analysis casts considerable additional uncertainty regarding the validity of this suggested association.
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Keywords: Formaldehyde; Leukemia; Myeloid leukemia; Cohort mortality study

1. Introduction

Hauptmann et al. (2003) recently reported results from an updated 1994 follow-up of the National Cancer Institute's (NCI) cohort mortality study of workers exposed to formaldehyde (Blair et al., 1986; Blair et al., 1990; Stewart et al., 1987). Key findings included an unexpected suggestion of a causal association between formaldehyde exposure and mortality from leukemia, particularly myeloid leukemia (ML). The suspected associations for leukemia and ML were based exclusively on internal mortality rate comparisons (via relative risks (RR)) and were observed for only two of four

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formaldehyde exposure metrics considered, namely, peak formaldehyde exposure, and to a lesser extent, average intensity of formaldehyde exposure (AIE). NCI's internal analyses showed no relationship of the risk of leukemia or of ML with cumulative formaldehyde exposure or with duration of formaldehyde exposure.

Several recent publications, including an expert panel report, on which one of the current authors (GM) contributed, have challenged the validity of the NCI's findings for leukemia and ML on the grounds of biological implausibility and inadequate or questionable methodology for exposure assessment and statistical analysis (Casanova et al., in press; Cole and Axten, in press; Collins and Lineker, in press; Heck and Casanova, in press). Major shortcomings of the statistical analysis methods, in particular, included reliance on internal mortality comparisons, failure to reconcile unusually large leukemia mortality deficits among workers in the baseline categories of the exposure–response analyses, and incomplete or inappropriate analyses of peak formaldehyde exposure. We report here our reanalysis of the relationship between formaldehyde exposure and mortality from leukemia and ML using the NCI formaldehyde cohort data.

2. Objective

The main objective of our reanalysis was to determine whether NCI's suggestion of a causal association between formaldehyde exposure and mortality from leukemia and ML is robust with respect to alternative categorizations of formaldehyde exposure and alternative methods of data analysis. To this end, our current reanalysis focused on two of the major methodological issues noted in the Casanova et al. (in press) report, as described below.

2.1. Issue 1—Baseline for exposure–response analysis

The assessment of exposure–response in the NCI study was based exclusively on internal cohort rate comparisons, which differed from the previous assessment of the cohort. Such comparisons can be misleading if workers included in the baseline category (i.e., least exposed) have different underlying cancer risks than workers in the exposed groups. NCI observed a borderline statistically significant *62% deficit* in deaths from leukemia among workers unexposed to formaldehyde. Using the RRs in Tables 3 and 4 of Hauptmann et al. (2003), we previously roughly estimated US rate-based standardized mortality ratios (SMRs) of 0.49 and 0.69 for workers in the baseline categories (lowest exposure) of NCI's analysis of leukemia in relation to peak and average intensity of formaldehyde exposure, respectively (Casanova et al., in press). This finding suggested that the elevated RRs and associated trends for leukemia and ML by peak and AIE reported by NCI arose spuriously because smaller deficits or slight mortality excesses were compared to a large deficit.

2.2. Issue 2—Analysis of peak exposure and AIE

NCI's suggestion of a causal relationship between formaldehyde exposure and leukemia was driven heavily by their exposure–response analysis of peak exposure and to a lesser extent by their analysis of AIE. The authors essentially treated peak exposure (more accurately, highest peak exposure) as a monotonically increasing, time-dependent variable. That is, as subjects moved through age group- and time period-specific person-time counts, persons and person-years were also allocated to the highest peak exposure category experienced up to that time. Unless the subject subsequently works in a job associated with a higher peak exposure, all subsequent person-years are allocated to the highest peak category attained previously. For example, consider a subject who reached their highest peak exposure during the first job, and then for the remainder of their work history, worked in jobs associated with low-level or no peak exposures. If this subject subsequently died of leukemia, the observed death would be assigned to the initial highest peak category. Conversely, consider a subject who worked for most of their employment history in jobs associated with low-level or no peak exposures, and then worked briefly in a job associated with the same highest peak exposure as the subject in the first example. This subject's subsequent leukemia death would be included in the same highest peak category as the person in the first example. As illustrated in Fig. 1, many different patterns of peak exposure are possible that would result in a given leukemia death being assigned to the same highest peak category.

We believe that equating these exposure scenarios when evaluating the impact of peak exposure is not appropriate, as this approach accounts for neither the duration of time spent in the highest peak exposure category nor the relevant latent period between the date of the first highest peak formaldehyde exposure and death from leukemia or ML. The induction-latency period for the onset of leukemia after chemical exposures is thought to be shorter than for solid tumors especially for acute nonlymphocytic leukemia (Linet and Cartright, 1996). Infante et al. (1977) suggested that the increased risk for benzene exposure induced leukemia is observed in latency periods less than 20 years following first exposure, and in another NCI study, Hayes et al. (1997) found that benzene exposure within the previous 10 years was associated with ML. Thus, if there is a causal association between highest peak formaldehyde exposure and leukemia or ML, one would expect the greatest mortality risks to occur in the period up to 10–19 years from the first highest

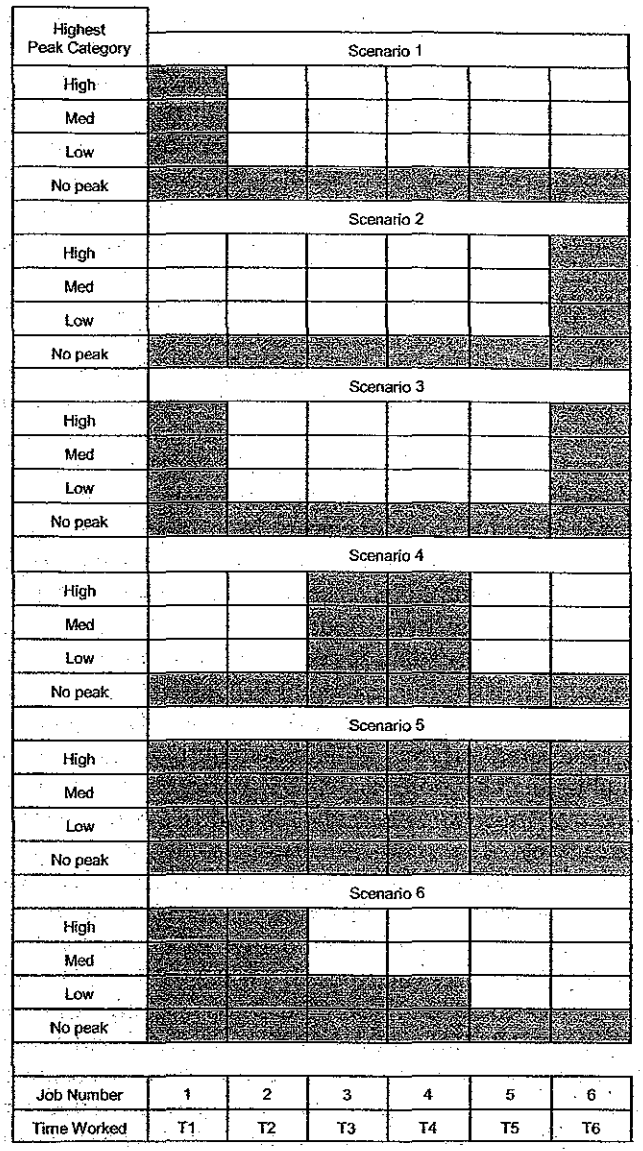

Fig. 1. Some of the possible work history scenarios in NCI study leading to an observed leukemia death being assigned to highest peak exposure category, "High."

peak exposure and the risks to increase with increasing time spent in the highest peak exposure category.

NCI also treated AIE as a time-dependent variable, but unlike highest peak exposure, AIE does not necessarily increase monotonically. That is, with AIE it is possible for a subject to move from lower to higher categories and vice versa. While this obviates some of the exposure scenario incompatibility associated with highest peak exposure, it also fails to account for either the duration of exposure or the relevant latent period between the date of the first formaldehyde exposure and death from leukemia or ML. The 2-year exposure lag period used by NCI would do little to account for discrepant exposure patterns, duration of exposure or the relevant latency period. This is particularly true given that the current follow-up period of the NCI study is 14 years beyond the date formaldehyde exposures were last estimated from subjects' work histories (through 1980). Moreover, the origin of the 2-year lag period, which was also used in the NCI study of benzene and acute myeloid leukemia (Hayes et al., 1997), seems to have come from a clinical investigation of patients with chemotherapy-related myelocytic leukemia (Park and Koeffler, 1996), which is probably not relevant for workers exposed to other agents, particularly formaldehyde.

Finally, NCI categorized their formaldehyde exposure metrics using as cutpoints the approximate 60th and 80th percentiles of the distribution of the respective metric in exposed subjects who died of any form of cancer. For each metric considered, this led to an uneven distribution of deaths for all leukemia deaths and ML among exposed subjects and consequently, NCI's exposure category-specific risk estimates are associated with varying levels of precision.

3. Methods

3.1. Cohort data

We obtained a copy of the NCI formaldehyde cohort study data from the authors. This file included individual demographic, work history, and formaldehyde exposure data for 25,619 workers first employed at one of 10 industrial plants before January 1, 1966. All event dates (e.g., birth, hire, termination, and death) were limited to month and year to protect subject confidentiality. NCI followed the cohort through 1994 for vital status and cause of death. Further details about the NCI study are provided in Blair et al. (1986) and Hauptmann et al. (2003). We first reformatted the NCI cohort data file to enable analysis with the OCMAP-Plus cohort analysis program (Marsh et al., 1998) and estimated all event days by the mid-month value 15. We subsequently performed extensive cross-checks and replicated key NCI analyses to establish the comparability of the two files. Our total person-year count differed by only 30.0 or 0.003% of the total person-years reported by NCI.

3.2. Statistical analysis

3.2.1. Issue 1—Alternative exposure–response analysis via SMRs

Using first the exposure class intervals of the NCI study, we computed both US and local county rate-based SMRs and their 95% confidence intervals by each of the four formaldehyde metrics (highest peak, average intensity, cumulative, and duration). SMRs were standardized for race/ethnicity, sex, age group, and time period. Local county area mortality rates for each of the 10 plants in the NCI study were obtained from the

Mortality and Population Database System (MPDS) maintained at the University of Pittsburgh (Marsh et al., 2003). For each study plant, the local county area was defined as the county or group of counties surrounding the plant from which most of the work force was drawn. Table 1 shows the plant code, plant location, the counties comprising the regional rate and the 1990 total populations (N) of the regional areas. Because MPDS rates are not available before 1950, we applied 1950–54 rates to previous observation periods for plants that started before 1950. This approximation should have negligible effect on SMRs, as only 3.3% of the total person-years at risk in the cohort occurred before 1950 (Table 1).

Except for highest peak exposure, where the NCI data were pre-coded into fixed categories, we also repeated the above analysis for leukemia and ML using an alternative categorization of formaldehyde exposure, namely, approximate tertiles of formaldehyde exposure among all leukemia deaths in exposed workers. Unlike the approximate 60th and 80th percentile cutpoints used by NCI, our categorization produces an almost even distribution of all leukemia deaths among the exposed categories and consequently produces risk estimates with similar precision.

3.2.2. Issue 2—Alternative analyses of peak exposure and AIE via RRs

In the NCI study, Poisson regression was used to examine exposure–response relationships by comparing internal cohort rates for leukemia and ML. Alternatively, we used relative risk (RR) regression modeling to investigate the dependence of the internal cohort rates (modeled as time to death) for leukemia and ML on combinations of the categorical formaldehyde metrics, with adjustment for potential confounding factors through matching or stratification. Study data from the entire 1934–94 period were modeled. Risk sets were explicitly constructed from the cohort data file with age as the primary time dimension, using the RISKSET program module in OCMAP-Plus (Marsh et al., 1998). To adjust for year of birth ("cohort" or time period) effects, risk sets were caliper-matched within one year on date of birth. Regression models included terms for race/ethnicity (white/black), sex and payroll category (wage, salary) to adjust for these potential confounding factors. Trends in RRs relative to the exposure measures considered were based on likelihood ratio tests using either exposed workers or unexposed and exposed workers.

To help account for the incomparable highest peak exposure scenarios possible in the NCI study, we also examined leukemia and ML mortality risks among subjects within each highest peak exposure category (excluding the unexposed baseline category) by three levels of duration of time spent in the highest peak exposure category (<1, 1–9, and 10+ years) and three levels of the time since reaching the highest peak formaldehyde exposure (<10, 10–19, and 20+ years). We used the fixed highest peak exposure categories constructed by NCI, (unexposed, 0.1–1.9, 2.0–3.9, and 4.0+ ppm). We also examined leukemia and ML mortality risks among subjects within each AIE category (excluding the unexposed baseline category) by three levels of duration of exposure (<1, 1–9, and 10+ years) and by three levels of the time since first formaldehyde exposure (<10, 10–19, and 20+ years). For AIE we used the categories in the NCI study (unexposed, >0–0.49, 0.50–0.99, and 1.0+), and the alternative categories used in the SMR analyses (unexposed, >0–0.23, 0.24–0.73, and 0.74+). In these analyses, we did not formally evaluate trends in RRs due to the inverse collinearity that exists between the duration and latency related stratifying variables. That is, because the median latency period for the onset of leukemia is considered to be between 10–19 years after chemical exposure (Hayes et al., 1997; Infante et al., 1977; Linet and Cartright, 1996), exposures

Table 1
Reanalysis of NCI formaldehyde study counties used in the regional rate comparison, 1990 population of county area and time period specific person-years by plant

NCI plant No. (Old plant No.)	Plant location	Counties used in the regional rate comparison	1990 Population of county area	<1950 Person-years	1950+ Person-years
1 (1)	Wallingford, CT	CT: Middlesex, New Haven	947,415	5080	139,061
2 (2)	Bishop, TX	TX: Kleberg, Nueces	321,419	684	28,003
3 (3)	Orangeburg, SC	SC: Orangeburg	84,803	141	70,223
5 (4)	Parlin, NJ	NJ: Middlesex, Monmouth, Ocean	1,658,107	0	53,875
6 (5)	Rochester, NY	NY: Monroe	713,968	0	24,563
7 (6)	Cincinnati, OH	OH: Butler, Clermont, Hamilton, and Warren	1,421,803	0	171,676
8 (7)	N. Tonawonda, NY	NY: Niagra	220,756	11,086	146,035
10 (8)	Sheboygan, WI	WI: Sheboygan	103,877	3630	55,015
11 (9)	Dallas, TX	TX: Dallas	1,852,810	0	58,163
12 (10)	Springfield, MA	MA: Hampden, Hampshire	602,878	6876	91,632
Total			7,927,836	27,497	838,245

received after 10 years may not be relevant to the causation of disease.

In addressing Issues 1 and 2, we calculated all formaldehyde exposure metrics using the same 2-year lag period used by NCI. As noted above, we do not support the use of the 2-year lag in this investigation, but used it only to standardize the comparison of our findings with those of NCI.

4. Results

4.1. Issue 1—Baseline for exposure–response analysis

Tables 2–5 show for all leukemia and ML, observed deaths, RRs reported by NCI, our RRs based on our alternative categorization of exposure, and our US and regional external rate-based SMRs by each of four formaldehyde exposure metrics (highest peak, AIE, cumulative, and duration), respectively. For highest peak exposure (Table 2), we observed statistically significant 50–63% deficits in leukemia mortality for unexposed subjects and subjects in the lowest exposure category (>0–1.9 ppm), which NCI used as the baseline category for RRs. US and regional SMRs in NCI's middle exposure category (2.0–3.9 ppm) are essentially null (SMRs = 1.00 and 1.04, respectively) and only moderately elevated in the highest exposure category (4.0+ ppm) (SMRs = 1.24 and 1.31, respectively). We observed a similar pattern of SMRs for ML although the values associated with the highest exposure category are slightly larger than those for all leukemia combined (SMRs = 1.42 and 1.49, respectively). Thus, the elevated RRs for leukemia and ML and associated trends for highest peak formaldehyde exposure reported by NCI occurred because null values or moderate mortality excesses were compared to large, statistically significant deficits in deaths.

Our findings in Table 3 for average intensity of formaldehyde exposure are similar to those found for highest peak exposure. For all leukemia, we observed slightly smaller 29–30% deficits in deaths among subjects in NCI's RR baseline category (>0–0.4 ppm), but these deficits remain statistically significant or nearly significant. The largest excess for all leukemia was the regional rate-based SMR of 1.22 observed in NCI's highest exposure category (1.0+ ppm). Our alternative categorization of AIE in Table 3 produced smaller US and regional SMRs, especially in the highest exposure category (SMRs = 1.00 and 1.07, respectively). This also produced weaker evidence of a trend in RRs based on the UPitt exposure categories.

For ML, Table 3 shows US and regional SMRs using NCI categories are less than 1.00 for all but the highest exposure category, where we observed 45 and 59% excesses, respectively. Our alternative exposure categorization essentially eliminated the elevated SMRs in NCI's highest exposure category and produced moderate excesses in the second highest category. Our alternative

Table 2
Observed deaths, internal rate-based rate ratios[a] (RR) and standardized mortality ratios (SMR) using US and regional rates, for all leukemia and myeloid leukemia by NCI categories[c] of highest peak formaldehyde exposure[b] (ppm)

Categorization	Observed deaths	NCI internal rate analysis		UPitt external rate analysis			
				US rates		Regional rates	
		RR	95% CI	SMR	95% CI	SMR	95% CI
All leukemia							
NCI categories[c]		Trend $p^f = .001$					
		Trend $p^g = .004$					
Unexposed	4	.78	.25–2.43	.37*	.10–.96	.38*	.10–.97
>0–1.9	16	1.00[d]	—	.49*	.28–.80	.50*	.28–.81
2.0–3.9	20	2.04	1.04–4.01	1.00	.61–1.54	1.04	.63–1.60
4.0+	29	2.46	1.31–4.62	1.24	.83–1.78	1.31	.88–1.89
Myeloid leukemia							
NCI categories[c]		Trend $p^f = .003$					
		Trend $p^g = .009$					
Unexposed	2	.67	.12–3.61	.45	.06–1.63	.42	.05–1.50
>0–1.9	6	1.00[d]	—	.43*	.16–.94	.41*	.15–.89
2.0–3.9	8	2.43	.81–7.25	.94	.41–1.85	1.01	.43–1.98
4.0+	14	3.46	1.27–9.43	1.42	.78–2.38	1.49	.81–2.50

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] Peak exposures lagged 2 years.
[c] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed.
[d] Baseline category for RRs.
[e] Not possible to regroup fixed categories.
[f] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among unexposed and exposed workers.
[g] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among exposed workers.
* $p < .05$.

Table 3
Observed deaths, internal rate-based rate ratios[a](RR) and standardized mortality ratios (SMR) using US and regional rates, for all leukemia and myeloid leukemia, by NCI, and UPitt categories of average intensity of exposure to formaldehyde[b](ppm)

Categorization	Observed deaths	Internal rate analysis		UPitt external rate analysis			
				US rates		Regional rates	
		RR	95% CI	SMR	95% CI	SMR	95% CI
All leukemia							
NCI categories[c]		Trend $p^f = .193$					
		Trend $p^g = .242$					
Unexposed	4	.56	.19–1.66	.37*	.10–.96	.38*	.10–.97
>0–0.4	32	1.00[e]	—	.70*	.48–.98	.71	.49–1.01
0.5–0.9	16	1.52	.83–2.79	1.10	.63–1.78	1.15	.66–1.78
1.0+	17	1.68	.91–3.08	1.13	.66–1.81	1.22	.71–1.95
UPitt categories[d]		Trend $p^f = .145$					
		Trend $p^g = .141$					
Unexposed	4	.57	.19–1.72	.37*	.10–.96	.38*	.10–.97
>0–0.23	22	1.00[e]	—	.68	.42–1.02	.69	.43–1.05
0.24–0.73	22	1.42	.78–2.96	1.00	.63–1.52	1.04	.65–1.57
0.74+	21	1.47	.79–2.73	1.00	.62–1.52	1.07	.66–1.63
Myeloid leukemia							
NCI categories[c]		Trend $p^f = .086$					
		Trend $p^g = .088$					
Unexposed	2	.41	.08–1.95	.46	.06–1.66	.43	.05–1.55
>0–0.4	14	1.00[e]	—	.71	.31–1.20	.70	.38–1.17
0.5–0.9	5	1.15	.41–3.23	.81	.26–1.89	.85	.28–1.97
1.0+	9	2.49	1.03–6.03	1.45	.66–2.75	1.59	.73–3.02
UPitt categories[d]		Trend $p^f = .092$					
		Trend $p^g = .081$					
Unexposed	2	.52	.10–2.64	.46	.06–1.66	.43	.05–1.55
>0–0.23	8	1.00[e]	—	.58	.25–1.14	.56	.24–1.09
0.24–0.73	11	1.95	.76–4.96	1.17	.58–2.09	1.20	.60–2.15
0.74+	9	2.01	.75–5.40	1.02	.47–1.94	1.11	.51–2.10

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] All exposures lagged 2 years.
[c] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed.
[d] UPitt categories based on tertiles of formaldehyde exposure among leukemia deaths who were exposed.
[e] Baseline category for RRs.
[f] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among unexposed and exposed workers.
[g] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among exposed workers.
* $p < .05$.

categorization of AIE also produced weaker evidence of a trend in RRs for ML. None of the RR trends in Table 3 was statistically significant.

Our SMR and RR findings in Table 4 for cumulative formaldehyde exposure in relation to leukemia and ML corroborate the corresponding findings of no association reported by NCI. While NCI reported a "weak" association between duration of formaldehyde exposure and leukemia, our findings in Table 5 revealed no evidence of an association with leukemia or with ML.

4.2. Issue 2—Analysis of peak exposure and AIE

For leukemia deaths within each highest peak exposure category, Fig. 2 shows the relationship between duration of time worked in the category and the time since the highest peak exposure. For each highest peak category, most deaths occurred 20–40 or more years after subjects had reached their highest peak exposure category. Thus, most observed latent periods exceed the expected latency periods (less than 10 or 20 years) for leukemia. For all leukemia and ML, Table 6 shows that RRs did not increase with increasing duration of time worked in the corresponding highest peak exposure category. Also, mortality risks were generally greater among subjects who worked the least amount of time (less than 1 year) within a given highest peak exposure category. The pattern of leukemia and ML risks relative to the time since first highest peak exposure was inconsistent. For some highest peak categories, such as 2.0–3.9 ppm, the greatest risks occurred 20 or more years since the highest peak and in others the greatest risk occurred before 20 years.

Table 4
Observed deaths, internal rate-based rate ratios[a] (RR) and standardized mortality ratios (SMR) using US and regional rates, for all leukemia and myeloid leukemia, by NCI and UPitt categories of cumulative exposure to formaldehyde[b] (ppm-years)

Categorization	Observed deaths	Internal rate analysis		UPitt external rate analysis			
				US rates		Regional rates	
		RR	95% CI	SMR	95% CI	SMR	95% CI
All leukemia							
NCI categories[c]		Trend $p^f = .183$					
		Trend $p^g = .235$					
Unexposed	4	.48	.16–1.42	.37*	.10–.96	.38*	.10–.97
>0–1.4	35	1.00[e]	—	.80	.56–1.12	.84	.58–1.16
1.5–5.4	13	0.90	.47–1.73	.79	.42–1.35	.82	.43–1.39
5.5+	17	1.14	.63–2.07	1.08	.63–1.73	1.14	.67–1.83
UPitt categories[d]		Trend $p^f = .182$					
		Trend $p^g = .302$					
Unexposed	4	.62	.20–1.90	.37*	.10–.96	.38*	.10–.97
>0–0.77	22	1.00[e]	—	.62*	.39–.94	.64*	.40–.97
0.78–2.96	22	1.86	1.01–3.42	1.28	.80–1.93	1.32	.83–2.00
2.97+	21	1.29	.69–2.39	.92	.57–1.41	.97	.60–1.48
Myeloid leukemia							
NCI categories[c]		Trend $p^f = .123$					
		Trend $p^g = .157$					
Unexposed	2	.32	.07–1.51	.46	.06–1.66	.43	.05–1.55
>0–1.4	17	1.00[e]	—	.92	.53–1.46	.91	.53–1.46
1.5–5.4	4	.57	.19–1.73	.58	.16–1.50	.59	.13–1.51
5.5+	7	1.02	.40–2.55	1.07	.43–2.20	1.12	.45–2.30
UPitt categories[d]		Trend $p^f = .860$					
		Trend $p^g = .865$					
Unexposed	2	.37	.08–1.83	.46	.06–1.66	.43	.05–1.55
>0–0.77	12	1.00[e]	—	.78	.40–1.37	.78	.40–1.36
0.78–2.96	8	1.22	.48–3.09	1.12	.48–2.20	1.12	.48–2.21
2.97+	8	.94	.36–2.40	.84	.36–1.66	.88	.38–1.72

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] All exposures lagged 2 years.
[c] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed.
[d] UPitt categories based on tertiles of formaldehyde exposure among leukemia deaths who were exposed.
[e] Baseline category for RRs.
[f] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among unexposed and exposed workers.
[g] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among exposed workers.
* $p < .05$.

Tables 7 and 8 show a similar pattern of results as Table 6 for AIE using either NCI categories or our alternative categorization, respectively. That is, leukemia and ML risks were generally greater among subjects who worked the least amount of time within a given AIE category, and most leukemia deaths occurred 20 or more years since first formaldehyde exposure. For most AIE categories in Tables 7 and 8, leukemia and ML risks were greater in the period less than 20 years from first exposure.

5. Discussion

One approach we followed to test the robustness of NCI's findings for leukemia and ML was to examine the appropriateness of the baseline category used in their exposure–response analyses, which were based exclusively on internal study group comparisons. The strengths of the internal study group comparison are that it will usually reduce the healthy worker effect (Pearce et al., 1986), and it allows direct comparison of relative risk across strata. However, internal comparisons can be unstable when the study population is small (producing wider confidence limits), and may be misleading if workers included in the baseline category (i.e., least exposed) have different underlying cancer risks than workers in the exposed groups. On the other hand, external comparisons based on regional rates have the strengths of being able to adjust for geographic variability in social, cultural, and economic factors related to disease (Doll, 1985) and are generally very stable. The disadvantages of the external comparison group are an inability to adjust for the healthy worker effect and a difficulty in comparing standardized mortality ratios

Table 5
Observed deaths, internal rate-based rate ratios[a](RR) and standardized mortality ratios (SMR) using US and regional rates, for all leukemia, and myeloid leukemia by NCI and UPitt categories of duration of exposure to formaldehyde[b](years)

Categorization	Observed deaths	Internal rate analysis		UPitt external rate analysis			
				US rates		Regional rates	
		RR	95% CI	SMR	95% CI	SMR	95% CI
All leukemia							
NCI categories[c]		Trend p^f = .214					
		Trend p^g = .465					
Unexposed	4	.55	.18–1.66	.37*	.10–.96	.38*	.10–.97
>0 4.9	30	1.00[e]	—	.70	.47–1.00	.73	.49–1.04
5–14.9	13	1.16	.59–2.26	.94	.50–1.62	.99	.53–1.69
15+	22	1.39	.78–2.49	1.16	.73–1.75	1.20	.75–1.82
UPitt categories[d]		Trend p^f = .564					
		Trend p^g= .902					
Unexposed	4	.43	.14–1.35	.37*	.10–.96	.38*	.10–.97
>0–1.03	22	1.00[e]	—	.83	.52–1.25	.85	.53–1.29
1.04–17.21	22	.72	.39–1.34	.67	.42–1.02	.71	.44–1.07
17.22+	21	1.27	.67–2.42	1.29	.80–1.97	1.33	.82–2.04
Myeloid leukemia							
NCI categories[c]		Trend p^f = .423					
		Trend p^*= .911					
Unexposed	2	.34	.07–1.67	.46	.06–1.66	.43	.05–1.55
>0–4.9	15	1.00[e]	—	.82	.46–1.35	.82	.46–1.36
5–14.9	3	.49	.14–1.73	.53	.11–1.56	.54	.11–1.58
15+	10	1.35	.56–3.24	1.25	.60–2.30	1.26	.60–2.31
UPitt categories[d]		Trend p^f = .731					
		Trend p^*= .351					
Unexposed	2	.23	.04–1.19	.46	.06–1.66	.43	.05–1.55
>0–1.03	12	1.00[e]	—	1.04	.54–1.82	1.06	.54–1.84
1.04–17.21	7	.37	.14–1.00	.51	.21–1.06	.52	.21–1.07
17.22+	9	1.02	.39–2.71	1.31	.60–2.48	1.31	.60–2.49

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] All exposures lagged 2 years.
[c] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed.
[d] UPitt categories based on tertiles of formaldehyde exposure among leukemia deaths who were exposed.
[e] Baseline category for RRs.
[f] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among unexposed and exposed workers.
[g] Likelihood ratio test (1 degree of freedom) for continuous formaldehyde exposure among exposed workers.
* $p < .05$.

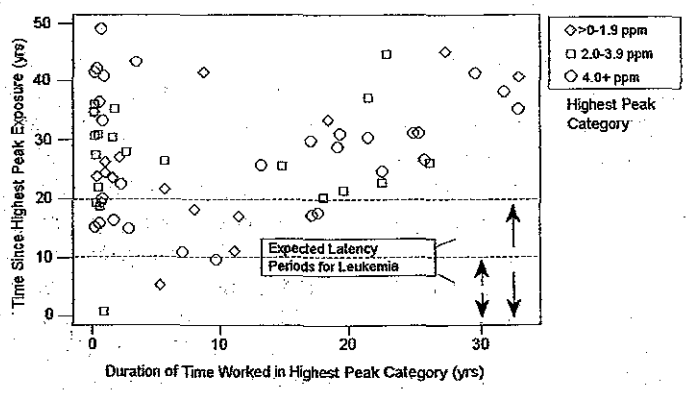

Fig. 2. Leukemia deaths ($N = 65$) in NCI study by duration of time worked in highest peak category and time since highest peak exposure within each highest peak exposure category (with NCI 2-year exposure lag).

Table 6
Observed deaths and internal rate-based rate ratios[a] (RR) for all leukemia and myeloid leukemia, by NCI categories of highest peak formaldehyde exposure[b] (ppm), and by duration of time worked in highest peak and time since first highest peak

	Highest peak formaldehyde exposure (ppm) (NCI categories)[c]							
	Unexposed		>0–1.9[d]		2.0–3.9		4.0+	
	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)
All leukemia								
All subjects	4	.78 (.25–2.43)	16	1.00 (–)	20	2.04 (1.04–4.01)	29	2.46* (1.31–4.62)
Duration of time worked in highest peak category	n/a							
< 1 year			5	1.00	9	1.00	9	1.00
1–9			6	1.25 (.37–4.23)	4	.49 (.14–1.64)	6	.37 (.12–1.16)
10+			5	1.02 (.26–3.93)	7	.46 (.15–1.40)	14	.52 (.21–1.25)
Time since highest peak exposure	n/a							
< 10 years			1		1		1	
10–19			4	1.00[e]	2	1.00[e]	7	1.00[e]
20+			11	.81 (.18–3.66)	17	2.98 (.57–15.42)	21	.44 (.12–1.60)
Myeloid leukemia								
All subjects	2	.67 (.12–3.61)	6	1.00 (–)	8	2.43 (.81–7.25)	14	3.46* (1.27–9.43)
Duration of time worked in highest peak category	n/a							
<1 year			2	1.00	4	1.00	6	1.00
1–9			3	1.48 (.22–9.68)	2	.53 (.09–3.14)	1	.05 (.005–.60)
10+			1	.52 (.04–7.63)	2	.28 (.04–2.00)	7	.23 (.06–.82)
Time since highest peak exposure	n/a							
<10 years			0		1		0	
10–19			1	1.00[e]	1	1.00[e]	5	1.00[e]
20+			5	1.23 (.10–14.53)	6	2.40 (.20–28.61)	9	.24 (.04–1.52)

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] All exposures lagged 2 years.
[c] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed.
[d] Baseline category for RRs.
[e] Baseline category for RRs is <20 years.
* $p < .05$.

between groups when their confounder distributions differ (Checkoway et al., 2004).

When we used external comparisons of the surrounding regional populations of each study plant, we consistently observed deficits in leukemia and ML deaths among unexposed subjects and among subjects in the lowest exposure category (NCI's baseline category for RRs). For highest peak formaldehyde exposure and average intensity of formaldehyde exposure, the baseline category deficits were statistically significant or nearly significant. For these two exposure metrics, the baseline category deficits compared with null values (SMR = 1.00) or slight to moderate excesses in deaths among subjects in the second highest and highest exposure categories. Thus, the elevated RRs in the higher exposure categories and trends for highest peak and average intensity of formaldehyde exposure reported by NCI for leukemia and ML occurred because null values or moderate mortality excesses were compared with statistically significant baseline category deficits in deaths.

There are at least two possible explanations for the differences in leukemia and ML risks in this study population when internal or external comparison rates are used. The first is that internal comparisons produce more valid results because selection bias stemming from the "healthy worker effect" can reduce the putative effect

Table 7
Observed deaths and internal rate-based rate ratios[a] (RR) for All leukemia, and myeloid leukemia, by NCI categories of average intensity of exposure to formaldehyde[b] (ppm) and by duration of exposure and time since first exposure

	Average intensity of formaldehyde exposure (ppm) (NCI categories)[c]							
	Unexposed		>0–0.49[d]		0.50–0.99		1.0+	
	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)
All Leukemia								
All subjects	4	.56 (.19–1.66)	32	1.00 (–)	16	1.52 (.83–2.79)	17	1.68 (.91–3.08)
Duration of exposure	n/a							
< 1 year			5	1.00	6	1.00	10	1.00
1–9			11	1.92 (.65–5.69)	4	.55 (.15–2.06)	3	.40 (.10–1.53)
10+			16	2.03 (.69–5.93)	6	.68 (.20–2.29)	4	.85 (.24–2.97)
Time since first exposure	n/a							
<10 years			2		0		0	
10–19			5	1.00[e]	3	1.00[e]	4	1.00[e]
20+			25	.99 (.30–3.21)	13	1.20 (.19–7.81)	13	.59 (.06–5.38)
Myeloid leukemia								
All subjects	2	.41 (.08–1.95)	14	1.00 (–)	5	1.15 (.41–3.23)	9	2.49* (1.03–6.02)
Duration of exposure	n/a							
<1 year			2	1.00	4	1.00	5	1.00
1–9			6	2.25 (.43–11.82)	0	–	1	.25 (.03–2.40)
10+			6	1.92 (.34–10.90)	1	.18 (.02–1.79)	3	1.13 (.22–5.78)
Time since first exposure	n/a							
<10 years			1		0		0	
10– 19			3	1.00[e]	2	1.00[e]	2	1.00[e]
20+			10	.74 (.16–3.38)	3	.56 (.01–24.84)	7	.18 (.02–1.74)

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] All exposures lagged 2 years.
[c] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed.
[d] Baseline category for RRs.
[e] Baseline category for RRs is <20 years.
* $p < .05$.

of high exposure to formaldehyde when external comparison rates are used. However, a strong overall healthy worker effect is not evident in the NCI cohort based on their reported all cause SMRs for unexposed (SMR = 0.77, 95% CI = 0.72–0.82) and exposed (SMR = 0.95, 95% CI = 0.93–0.97) workers. Moreover, the selection for workers who are healthy at time of hire is usually more relevant for cardiovascular and non-malignant respiratory diseases than leukemia or ML, which can have a relatively sudden onset, short survival time, and high case-fatality rate (Enterline, 1976).

A second explanation is that the external comparisons produce more valid results because the least exposed group has different underlying leukemia or ML mortality risks than the exposed groups. The risk in the highest peak or AIE categories when internal comparisons are used may be the result of an unusually low leukemia or ML death rate among workers in the least exposed baseline category (e.g., for peak exposure the local rate-based SMR for leukemia was 0.50, 95% CI = 0.28–0.81, $p < .05$). In fact, had the death rates for leukemia or ML among the least exposed workers been closer to or equal to those of the general regional populations from which the eight plant workforces were drawn, the internal RRs for the two more highly exposed peak or AIE categories would probably have been only slightly to moderately elevated.

The unusually low SMRs for leukemia and ML among unexposed workers and workers in the least exposed baseline category used by NCI are puzzling given that we used regional standard population rates. As regional rates can help adjust for the social, cultural, and economic factors related to diseases such as leukemia and ML, it is difficult to postulate what non-occupational factors may have had such a profound influence on the leukemia and ML mortality experiences of this cohort. Chance alone does not appear to be an explanation for the leukemia and ML deficits among unexposed and least exposed workers in the NCI study, as the deficits were consistently ob-

Table 8
Observed deaths and internal rate-based rate ratios[a] (RR) for all leukemia and myeloid leukemia, by UPitt categories of average intensity of exposure to formaldehyde[b] (ppm) and by duration of exposure and time since first exposure

	Average intensity of formaldehyde exposure (ppm) (UPitt categories)[c]							
	Unexposed		>0–0.23[d]		0.24–0.73		0.74+	
	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)	Obs	RR (95% CI)
All leukemia								
All subjects	4	.57 (.19–1.72)	22	1.00 (–)	22	1.42 (.78–2.60)	21	1.47 (.79–2.73)
Duration of exposure	n/a							
<1 year			5	1.00	6	1.00	10	1.00
1–9			6	1.11 (.33–3.75)	8	.87 (.29–2.66)	4	.52 (.17–1.76)
10+			11	1.85 (.57–5.96)	8	.51 (.17–1.57)	7	1.25 (.45–3.47)
Time since first exposure	n/a							
<10 years			2		0		0	
10–19			3	1.00[e]	5	1.00[e]	4	1.00[e]
20+			17	1.18 (.27–5.14)	17	.88 (.22–3.64)	17	.73 (.11–4.81)
Myeloid leukemia								
All subjects	2	.52 (.10–2.64)	8	1.00 (–)	11	1.95 (.76–4.96)	9	2.01 (.75–5.40)
Duration of exposure	n/a							
<1 year			2	1.00	4	1.00	5	1.00
1–9			4	1.66 (.29–9.66)	2	.16 (.02–1.46)	1	.24 (.03–2.16)
10+			2	1.05 (.12–9.32)	5	.41 (.10–1.75)	3	.79 (.16–3.97)
Time since first exposure	n/a							
<10 years			1		0		0	
10–19			1	1.00[e]	4	1.00[e]	2	1.00[e]
20+			6	.85 (.09–8.30)	7	.56 (.10–3.23)	7	.18 (.02–1.75)

[a] NCI categories and RR estimates taken from Hauptmann et al. (2003).
[b] All exposures lagged 2 years.
[c] UPitt categories based on tertiles of formaldehyde exposure among leukemia deaths who were exposed.
[d] Baseline category for RRs.
[e] Baseline category for RRs is <20 years.

served across the four formaldehyde exposure categories considered, and for peak and AIE the deficits were statistically significant. Also, the quality of the follow-up and cause of death ascertainment in the NCI study rule out under-ascertainment of leukemia or ML deaths as a reason for the deficits.

Given the absence of a viable explanation derived from the available study data, what remains is the possibility that some heretofore unknown selection factors for low leukemia and ML incidence were operating on members of the NCI cohort, or that some type of protective effect for these malignancies arose from a particular exposure or combination of exposures encountered at the study plants. Clearly, without further formal investigation of the NCI cohort, the reason(s) for the marked deficits in leukemia and ML will remain unknown. We observed a similar pattern of unusually low SMRs for lung cancer among baseline category subjects in our reanalysis of the NCI acrylonitrile worker cohort (Marsh et al., 2001).

We also found that the NCI reported associations between leukemia and ML in relation to average intensity of formaldehyde exposure were only weakly robust with respect to the categorization of this metric. Our alternative categorization, which balanced the precision of the exposure category-specific risk estimates, yielded leukemia and ML SMRs close to 1.0 in the highest exposure category, and revealed weaker evidence of a trend in RRs for leukemia and for ML. We believe that because our alternative categorization of exposure is as least as relevant as that used by NCI, the corresponding weaker evidence of a trend argues against a causal relationship between leukemia or ML and average intensity of formaldehyde exposure. Likewise, NCI's findings of a weak association between leukemia and duration of exposure were even less robust with respect to our categorization, which produced no evidence of an association. We were unable to check the robustness of the NCI findings for peak exposure as the NCI peak exposure data were pre-coded into fixed categories.

Our second approach to testing the robustness of NCI's findings for leukemia and ML involved stratified analyses and alternative characterizations of the highest peak and AIE variables that heavily influenced NCI's suggestion of a causal association for formaldehyde and leukemia. In our stratified analyses, we found no consistent evidence that leukemia or ML risks increased with increasing duration of time spent in a given highest peak exposure (or for AIE, duration of exposure in a given AIE category). We also found no consistent evidence that leukemia or ML risks were greater in shorter (less than 20 years) versus longer (20+ years) periods of time from the first highest peak exposure (or for AIE, first exposure). If a causal association between formaldehyde exposure and leukemia was true and based on highest peak or AIE, as suggested by NCI, one would expect risks to increase with increasing duration of exposure (at least up to 10 years of exposure) within a given highest peak exposure category and also to be greater within the latency period relevant for these malignancies (i.e., less than 20 years from first exposure).

6. Conclusions

Our reanalysis provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from leukemia and ML. NCI's key findings for highest peak exposure and AIE do not adequately account for the inordinately large deficits in deaths in the categories used as the baselines for internal rate-based RRs. The NCI findings also do not adequately account for the duration of time subjects spent in the highest peak category (or for AIE, duration of exposure) or the time since their first peak exposure (or for AIE, time since first exposure). Our finding that NCI's suggestion of a causal association is not robust with respect to alternative categorizations of formaldehyde exposure and methods of data analysis casts considerable additional uncertainty regarding the validity of this suggested association.

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Reevaluation of mortality risks from nasopharyngeal cancer in the formaldehyde cohort study of the National Cancer Institute

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Abstract

Objective: To determine whether the National Cancer Institute's (NCI) recent suggestion of a causal association between formaldehyde exposure and mortality from nasopharyngeal cancer (NPC) is robust with respect to alternative methods of data analysis and alternative categorizations of formaldehyde exposure.

Methods: The original authors provided the cohort data. We computed U.S. and local county (regional) rate-based standardized mortality ratios (SMRs) and internal cohort rate-based relative risks (RR) by categories of four formaldehyde exposure metrics (highest peak, average intensity, cumulative, and duration of exposure), using both NCI categories and an alternative categorization based on tertiles of all NPC deaths among exposed subjects. We computed SMRs and RRs for each of 10 study plants and by plant group (Plant 1 ($n = 4261$) vs. Plants 2–10 ($n = 21{,}358$)).

Results: Six of 10 NPC deaths observed in the NCI study occurred in only one plant (Plant 1) and the remaining four cases occurred individually in four of the other nine plants studied. A large, statistically significant, regional rate-based NPC SMR of 10.32 (95% CI = 3.79–22.47) among formaldehyde-exposed workers in Plant 1 contrasted sharply with a 35% deficit in NPC deaths (SMR = .65, 95% CI = .08–2.33) among exposed workers in Plants 2–10 combined. The statistically significant exposure–response relationship with formaldehyde and NPC reported in the NCI study for highest peak exposure was driven entirely by a large, statistically significant excess NPC risk in Plant 1 for the highest peak exposure category (4+ ppm). For the remaining nine plants, RRs for all non-baseline highest peak exposure categories were less than 1.0, and we observed no evidence of an exposure–response relationship. Most of the observed NPC excesses for the non-baseline categories of the other exposure metrics (average intensity, cumulative, and duration of formaldehyde exposure) were concentrated in Plant 1, and by contrast to the NCI findings, none of the corresponding exposure–response relationships was statistically significant.

Conclusions: Overall, our reanalysis provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from NPC. NCI's conclusion of a possible causal association was driven heavily by anomalous findings in one study plant (Plant 1). An independent and larger study of Plant 1 by the current authors concluded the NPC excess was not associated with formaldehyde exposure. Our findings cast considerable additional uncertainty regarding the validity of NCI's suggested causal association.
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1. Introduction

In 2003 and 2004, Hauptmann et al. reported results from an updated 1994 follow-up of the National Cancer Institute's (NCI) cohort mortality study of workers exposed to formaldehyde (Blair et al., 1986, 1990; Stewart et al., 1987). The 2003 report, which focused on lymphohematopoietic malignancies, included an unexpected suggestion of a causal association between formaldehyde exposure and mortality from leukemia, particularly myeloid leukemia. Several subsequent publications,

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including our reanalysis of leukemia mortality risks in the NCI cohort study (Marsh and Youk, 2004(4)), have questioned the validity of the association of formaldehyde with leukemia and myeloid leukemia on the grounds of biological implausibility and the methods applied to the exposure assessment and statistical analysis (Casanova et al., 2004; Cole and Axten, 2004; Collins and Lineker, 2004; Heck and Casnova, 2004).

In their 2004 report, which focused on solid tumors, Hauptmann et al. suggested a possible causal association between formaldehyde exposure and cancer of the nasopharynx (NPC). As with leukemia, the NCI exposure–response findings for formaldehyde and NPC were based exclusively on internal mortality rate comparisons and statistically significant exposure–response relationships were observed for only two of four formaldehyde exposure metrics considered, in this case, peak formaldehyde exposure and cumulative formaldehyde exposure. NCI's internal analysis showed no statistically significant exposure–response relationship of the risk of NPC with average intensity of formaldehyde exposure or with duration of formaldehyde exposure.

Although Hauptmann et al. (2004) acknowledged that the majority of the NPCs examined in their exposure–response analyses (five of nine) were observed in one plant (Plant 1) and reported results of plant-adjusted internal cohort analyses, they may not have conveyed clearly the extent to which their suggestion of a causal association with formaldehyde and NPC was driven by the results of Plant 1. This limitation was also noted recently by Tarone and McLaughlin, (in press). The heavy influence of Plant 1 must be viewed carefully when drawing conclusions about NPC from the NCI study, particularly considering that Marsh et al. (1994a, 1996, 2002(4)) found little evidence of an association between formaldehyde and NPC in their independent cohort and case–control studies of Plant 1.

We report here our reanalysis of the relationship between formaldehyde exposure and mortality from NPC using the NCI formaldehyde cohort data. We focused on plant-specific analyses and the heavy influence of Plant 1 in the NCI findings for NPC.

2. Methods

2.1. Data preparation

We obtained a copy of the NCI formaldehyde cohort study data from the authors. This file included individual demographic, work history, and formaldehyde exposure data for 25,619 workers first employed at one of 10 industrial plants before January 1, 1966. All event dates (e.g., birth, hire, termination, and death) were limited to month and year to protect subject confidentiality. NCI followed the cohort through 1994 for vital status and cause of death. Further details about the NCI study are provided in Hauptmann et al. (2003) and Blair et al. (1986). We first reformatted the NCI cohort data file to enable analysis with the OCMAP-Plus cohort analysis program (Marsh et al., 1998) and estimated all event days by the mid-month value 15. We subsequently performed extensive cross-checks and replicated key NCI analyses to establish the comparability of the two files. Our total person-year count differed by only 30.0 or 0.003% of the total person-years reported by NCI.

All of our NPC analyses were based on the total of 10 NPC deaths reported in the NCI study. Unlike Hauptmann et al. (2004), we did not omit from our exposure–response analyses the one NPC death in Plant 1[1] that had been recoded to oropharyngeal cancer based on findings of a medical record confirmation reported by Lucas (1994). Because Lucas (1994) limited medical record confirmation to the original four Plant 1 NPC cases reported by Blair et al. (1986), the possibility of identifying other NPC cases among the remaining Plant 1 decedents was ruled out. An unbiased assessment of diagnostic misclassification must detect classification errors in both directions. Moreover, adjustments to the distribution of cause-specific deaths, whether they be one or two-directional, invalidate the comparison of observed numbers of deaths (or death rates) between the study population and any standard population in which the adjustments were not performed in an identical fashion (Marsh et al., 1994b).

2.2. Statistical analyses-external mortality comparisons

For NPC, we computed both U.S. and regional (local county) rate-based SMRs and their 95% confidence intervals (CI) by each of the 10 plants in the NCI study and by two plant groups (Plant 1 vs. Plants 2–10). SMRs were standardized for race/ethnicity, sex, age group, and time period. Local county area mortality rates for each of the 10 plants in the NCI study were obtained from the Mortality and Population Database System (MPDS) maintained at the University of Pittsburgh (Marsh et al., 2005). MPDS includes detailed underlying cause death data obtained from the National Center for Health Statistics. For each study plant, the local county area was defined as the county or group of counties surrounding the plant from which most of the work force was drawn (Marsh and Youk, 2004). Because MPDS rates are not available before 1950, we applied 1950–1954 rates to previous observation periods for plants that started before 1950. This approximation should have negligible effect on SMRs, as only 3.3% of the total person-years at risk in the cohort occurred before 1950 (Marsh and Youk, 2004). The proportional contribution of expected NPC

[1] Plant 1 included six of the 10 NPC deaths and 19 of the 69 leukemia deaths observed in the NCI study.

deaths is likely to be even smaller because these early person-years are associated with relatively young age groups.

We also computed regional rate-based SMRs and 95% CIs for NPC by each of the four formaldehyde metrics (highest peak, average intensity, cumulative, and duration) used in the NCI study. We used the NCI exposure categories for highest peak exposure (the NCI data were pre-coded into fixed categories) and an alternative categorization for the remaining metrics (approximate tertiles of formaldehyde exposure among all NPC deaths in exposed workers). Unlike the approximate 60th and 80th percentile cutpoints used by NCI, our categorization produces a more even distribution of NPC deaths among the exposed categories.

2.3. Statistical analyses-internal mortality comparisons

In the NCI study, Poisson regression was used to examine exposure–response relationships by comparing internal cohort rates for NPC. Alternatively, we used relative risk (RR) regression modeling to investigate the dependence of the internal cohort rates (modeled as time to death) for NPC on combinations of the categorical formaldehyde metrics, with adjustment for potential confounding factors through matching or stratification. Study data from the entire 1934–1994 period were modeled. Risk sets were explicitly constructed from the cohort data file with age as the primary time dimension, using the RISKSET program module in OCMAP-Plus (Marsh et al., 1998). To adjust for year of birth ("cohort" or time period) effects, risk sets were caliper-matched within one year on date of birth. Regression models included terms for race/ethnicity (white/black), sex, and payroll category (wage, salary) to adjust for these potential confounding factors. Trends in RRs relative to the exposure measures considered were based on likelihood ratio tests using either exposed workers or unexposed and exposed workers.

Relative risk regression models were fit using exact conditional logistic regression in LogXact Version 6.0 (Cytel Software Corporation, 2002). The internal comparisons used the same exposure metric categorization scheme described for the external comparisons. All formaldehyde exposure metrics in the external and internal mortality comparisons incorporated the same 15-year lag period used by NCI.

3. Results

Table 1 shows for each of the 10 NCI study plants, selected demographic and formaldehyde characteristics and findings from the external mortality comparisons. We refer to plants by the sequential (UPitt) plant number rather than the numbering scheme used by NCI (Table 2). More than 90% of workers were exposed to formaldehyde in Plants 2–4, 6, 8, and 10, while only 64.4% and 81.8% were exposed in Plants 5 and 7, respectively. The percent of workers ever in the NCI highest peak formaldehyde exposure (4.0+ ppm) ranged from 0% for Plant 3 to 91.6% for Plant 2. The average intensity of formaldehyde exposure (AIE) (based on the median value of AIE among exposed workers) exceeded 1.0 ppm for only two plants (Plants 1 and 2). The AIE for Plant 1 (1.023 ppm) is about 10 times greater than the

Table 1
Selected characteristics and findings for 10 plants in NCI formaldehyde cohort study

UPitt (NCI) Plant No.	1 (1)	2 (2)	3 (3)	4 (4)	5 (5)	6 (7)	7 (8)	8 (10)	9 (11)	10 (12)
Entry year	1943	1945	1949	1958	1957	1951	1938	1934	1956	1941
No. Subjects	4261	784	2375	1692	744	5248	4228	1679	1933	2675
Formaldehyde exposure										
% Subjects ever exposed	87.7	99.9	92.9	93.5	64.4	91.1	81.8	99.3	88.2	94.9
% Subjects ever in highest peak category	46.1	91.6	0	72.9	20.4	2.0	0.4	1.1	9.3	69.7
Median AIE (ppm)[a]	1.023	2.799	.112	.234	.196	.233	.080	.382	.400	.543
(5–95%-tile)	.310–1.417	.300–3.927	.010–.222	.100–.596	.029–1.132	.033–.868	.020–.250	.100–2.000	.100–1.615	.216–1.124
Median Cum (ppm-years)[a]	.9	19.0	.1	2.2	1.9	.7	.1	.6	.3	1.3
(5–95%-tile)	.1–17.2	.4–86.5	.01–2.1	.06–11.9	.08–27.5	.01–16.3	.01–3.5	.03–12.0	.03–5.9	.05–16.4
Median Dur (years)[a]	1.0	11.3	1.1	9.7	16.7	3.6	1.0	1.0	.8	2.3
(5–95%-tile)	.1–24.4	.3–30.7	.1–20.3	.4–29.5	1.0–34.4	.1–31.3	.1–28.0	.1–25.0	.09–16.5	.1–29.2
Observed and expected deaths and SMRs for NPC										
Obs	6	1	1	0	0	0	1	0	0	1
SMR-US (Exp)	6.62** (.9)	5.35 (.2)	1.99 (.5)	0 (.3)	0 (.2)	0 (.8)	1.06 (.9)	0 (.3)	0 (.2)	1.44 (.7)
(95% CI)	2.43–14.40	.13–29.83	.05–11.08	0–11.84	0–21.28	0–4.36	.03–5.89	0–11.41	0–19.22	.04–8.05
SMR-local (Exp)	7.39** (.8)	6.74 (.1)	4.18 (.2)	0 (.4)	0 (.1)	0 (1.2)	1.31 (.8)	0 (0)	0 (.2)	1.10 (.9)
(95% CI)	2.71–16.08	.17–37.56	.10–23.28	0–8.48	0–26.61	0–3.12	.03–7.28	0–128.00	0–15.35	.03–6.15

[a] Based on exposed jobs only with no lag.
** $p < .01$.

Table 2
Selected characteristics and findings for Wallingford and all other plants combined in NCI formaldehyde cohort study

Characteristic/finding	Plant 1 (Wallingford)	Plants 2–10 (all other plants)
Entry year	1943	1934–58
No. subjects	4261	21,358
Formaldehyde exposure		
% Subjects ever exposed	87.7	89.9
% Subjects ever in highest peak category	46.1	20.1
Median AIE (ppm)[a]	1.023	0.366
(5–95%-tile)	(.310–1.417)	(.052–1.257)
Median Cum (ppm-years)[a]	0.9	3.2
(5–95%-tile)	(0.1–17.2)	(.06–23.5)
Median Dur (years)[a]	1.0	13.1
(5–95%-tile)	(0.1–24.4)	(.3–32.1)
Observed deaths and SMRs		
All workers		
Observed deaths	6	4
SMR-US (expected deaths)	6.62** (0.9)	.96 (4.2)
(95% CI)	(2.43–14.40)	(.26–2.45)
SMR-local (expected deaths)	7.39** (0.8)	.98 (4.1)
(95% CI)	(2.71–16.08)	(.27–2.51)
Exposed workers		
Observed deaths	6	2
SMR-US (expected deaths)	9.13** (0.7)	.64 (3.1)
(95% CI)	(3.35–19.88)	(.08–2.30)
SMR-local (expected deaths)	10.32** (0.6)	.65 (3.1)
(95% CI)	(3.79–22.47)	(.08–2.33)
Unexposed workers		
Observed deaths	0	2
SMR-US (expected deaths)	–(0.2)	1.93 (1.0)
(95% CI)	(0–14.77)	(.23–6.98)
SMR-local (expected deaths)	–(0.2)	1.98 (1.0)
(95% CI)	(0–15.98)	(.24–7.45)

[a] Based on exposed jobs only with no lag.
** $p < .01$.

corresponding AIE obtained in the independent exposure reconstruction reported by Marsh et al. (1996). The AIE for Plant 2 (2.799 ppm) is inordinately high and suggests that formaldehyde exposures in this plant may have been overestimated.

Table 1 shows that NPC SMRs based on regional rates were generally higher than those based on U.S. rates. Six of the 10 NPC deaths occurred in Plant 1 yielding statistically significant ($p < .01$) 6.62-fold and 7.39-fold excesses based on the U.S. and regional comparisons, respectively. The remaining four deaths were scattered individually across four plants (Plants 2, 3, 7, and 10), yielding not statistically significant regional rate-based mortality excesses ranging from 1.10-fold (Plant 10) to 6.74-fold (Plant 2). No NPC deaths were observed in Plants 4–6, 8, or 9.

Table 2 presents similar data as Table 1 for two plant groups (Plant 1 and Plants 2–10). While the median average intensity of formaldehyde exposure is greater in Plant 1 than Plants 2–10 combined (1.023 vs. 0.366 ppm), the multi-plant group is associated with a higher median cumulative exposure (3.2 vs. 0.9 ppm-years) and duration of formaldehyde exposure (13.1 vs. 1.0 years). The four NPC deaths combined in Plants 2–10 yield a 2% regional rate-based deficit in NPC deaths compared to the statistically significant 7.39-fold excess in Plant 1. An even greater difference in NPC regional rate-based SMRs was observed between formaldehyde-exposed workers in Plant 1 (SMR = 10.32, 95% CI = 3.79–22.47) and Plants 2–10 (SMR = 0.65, 95% CI = .08–2.33), and the NPC SMR among unexposed workers in Plants 2–10 (SMR = 1.98, 95% CI = .24–7.45) was about three times larger than the NPC SMR among the exposed workers.

Table 3 shows regional rate-based NPC SMRs for each of the four NCI exposure metrics overall and by the two plant groups (Plant 1 and Plants 2–10). Because of the small numbers of NPC deaths within the exposure categories considered, corresponding SMRs are associated with wide confidence limits and must be interpreted carefully. For all plants combined, SMRs are elevated for nearly all unexposed and exposed categories of each metric considered and are statistically significant for the highest exposure categories of highest peak exposure, average intensity of exposure, and cumulative exposure (UPitt analysis only). Many SMRs in the baseline (unexposed) categories exceeded those in the corresponding non-baseline categories. SMRs differ between the NCI and UPitt analyses due to the inclusion of 9 vs. 10 NPCs, respectively, and the alternative UPitt categorizations used for all but highest peak exposure.

The pattern of NPC SMRs for Plant 1 is similar to those reported in the independent study of Plant 1 (Marsh et al., 1996, 2002), namely, very large and often statistically significant excesses in NPC across all non-baseline exposure categories, but little evidence of consistent exposure–response relationships across the formaldehyde exposure metrics considered. All NPC deaths in Plant 1 occurred among exposed workers. For highest peak exposure in Plant 1, all six NPC deaths occurred in the greatest exposure category (4+ ppm) yielding a statistically significant ($p < .01$) SMR of 17.04 (95% CI = 6.25–37.08). In contrast, for Plants 2–10 combined, two of the four NPC deaths occurred among workers unexposed to formaldehyde yielding a near 2-fold or greater NPC excess in each of the four baseline categories. For two metrics (highest peak and duration of exposure) the baseline NPC SMR exceeded that observed among the most highly exposed workers.

Table 4 shows the results of the internal NPC mortality comparisons in the same format as Table 3. Consistent with the NCI analysis, we used as the baseline category for the relative risk (RR) estimates the lowest exposure category unless that category included zero deaths, in which case, the unexposed category was used as baseline. As with the SMRs, the estimated RRs

Table 3
NCI HCHO cohort, summary of standardized mortality ratio (SMR) analysis[e] for nasopharyngeal cancer (NPC), local county (Regional) comparisons, by plant group

Metric[c,d]	Highest peak category[a]			Average intensity of exposure (AIE)[b]			Cumulative exposure (Cum)[b]			Duration of exposure (Dur)[b]		
	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI	Obs	SMR	95% CI
All plants												
NCI Cats.												
Unexposed	2	2.22	.27–8.00	2	1.62	.20–5.84	2	1.62	.20–5.84	2	1.62	.20–5.84
Exp Cat 1	0	0	0–2.46	0	—	0–1.77	3	1.36	.28–3.97	4	1.8	.49–4.62
Exp Cat 2	0	0	0–3.47	1	1.17	.03–6.50	1	1.25	.03–6.98	1	1.07	.03–5.96
Exp Cat 3	7	4.84**	1.94–9.97	6	8.36**	3.07–18.21	3	4.57	.94–13.37	2	3.94	.48–14.25
UPitt Cats.												
Unexposed	2	2.22	.27–8.00	2	1.62	.20–5.84	2	1.62	.20–5.84	2	1.62	.20–5.84
Exp Cat 1	0	—	0–2.46	3	0.99	.20–2.90	3	1.69	.35–4.94	3	2.88	.40–8.43
Exp Cat 2	0	—	0–3.47	2	7.6	.92–27.46	2	1.3	.16–4.68	2	1.49	.18–5.38
Exp Cat 3	8	5.53**	2.39–10.90	3	8.06*	1.66–23.55	3	8.80*	1.82–25.73	3	2.35	.48–6.86
Plant 1												
UPitt Cats.												
Unexposed	0	0	0–24.59	0	—	0–15.97	0	—	0–15.97	0	—	0–15.97
Exp Cat 1	0	—	—	2	7.46	.90–26.94	3	11.70**	2.41–34.18	3	12.79**	2.64–37.37
Exp Cat 2	0	—	0–13.54	2	13.96*	1.69–50.44	2	7.21	.87–26.04	2	9.01*	1.09–32.54
Exp Cat 3	6	17.04**	6.25–37.08	2	11.78*	1.43–42.57	1	21.18	.53–118.03	1	8.03	.20–44.75
Plants 2–10												
UPitt Cats.												
Unexposed	2	2.66	.32–9.60	2	1.99	.24–7.18	2	1.99	.24–7.19	2	1.99	.24–7.18
Exp Cat 1	0	—	0–2.46	1	0.36	.01–2.02	0	—	0–2.43	0	—	0–4.58
Exp Cat 2	0	—	0–4.66	0	—	0–30.78	0	—	0–2.92	0	—	0–3.29
Exp Cat 3	2	1.83	.22–6.60	1	4.94	.12–27.50	2	6.81	.82–24.61	2	1.73	.21–6.26

[a] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed. Includes only 9/10 deaths.
[b] University of Pittsburgh categories based on approximate tertiles of formaldehyde exposure among NPC deaths who were exposed. Include 10 deaths.
[c] All exposures lagged 15 years as in NCI study.
[d] NCI exposure category cutpoints: highest peak (>0–1.9, 2.0–3.9, and 4.0+ ppm); average intensity of exposure (>0–<.5, .5–<1.0, and 1.0+ ppm); cumulative exposure (>0–1.5, 1.5–<5.5, and 5.5+ ppm-years); duration of exposure (>0–<5.0, 5.0–<15.0, and 15.0+ years). UPitt exposure category cutpoints: highest peak (same as NCI) (>0–1.9, 2.0–3.9, and 4.0+ ppm); average intensity of exposure (<1.046, 1.046–1.177, and 1.178+ ppm); cumulative exposure (<.734, .734–10.150, and 10.151+ ppm-years); duration of exposure (<.617, .617–2.258, and 2.259+ years).
[e] All SMRs adjusted for sex, race, age group, and time period.
* $p < .05$.
** $p < .01$.

are associated with wide confidence intervals and must be interpreted carefully. For highest peak formaldehyde exposure, the UPitt model based on all 10 NPC deaths yielded a risk estimate of 1.80 (95% CI = .28–20.81) in the highest peak category that included eight of 10 deaths. Our estimate is nearly equal to the corresponding RR = 1.83 (based on seven deaths, no CI available) reported in the NCI study. Our plant group analysis revealed that six of the eight NPC deaths in the largest highest peak exposure category occurred in Plant 1, yielding a similar RR = 1.95 (95% CI = .20–∞).

Of the remaining four NPC deaths in Plants 2–10, Table 4 shows that two were among unexposed workers and two were among workers in the largest highest peak exposure category. The risk estimates for each of the non-baseline categories of highest peak exposure in Plants 2–10 were less than 1.0. Because of the very sparse NPC data, the plant group analyses for highest peak formaldehyde exposure produced median unbiased estimates (MUE) based on exact conditional logistic regression (Hirji et al., 1989). As evident in the very wide confidence intervals, the MUE's are relatively unstable and should be interpreted with caution. While trend tests for the highest peak exposure analyses are shown in Table 4, and are often statistically significant, their meaning is limited as none of the exposure–response analyses contained non-zero observations for more than two categories.

For the other formaldehyde exposure metrics considered in Table 4, the UPitt alternative categorizations based on approximate tertiles of all NPC deaths among exposed workers (all plants combined) coupled with the addition of all 10 NPC deaths often produced different patterns of RRs compared with the corresponding NCI results. For example, the UPitt RRs for workers in the highest average intensity and cumulative exposure categories were greater than NCI's while

Table 4
NCI HCHO cohort, summary of relative risk (RR) analysis[j] for nasopharyngeal cancer (NPC), by plant group

Metric[c, d]	Highest peak category[a]			Average intensity of exposure (AIE)[b]			Cumulative exposure (Cum)[b]			Duration of exposure (Dur)[b]		
	Obs	RR	95% CI	Obs	RR	95% CI	Obs	RR	95% CI	Obs	RR	95% CI
All plants												
		$p^f = .044$			$p^f = .126$			$p^f = .029$			$p^f = .206$	
NCI Cats.[i]		$p^g < .001$			$p^g = .066$			$p^g = .025$			$p^g = .147$	
Unexposed	2	1.00[h]	—	2	1.00[h]	—	2	2.40	NA	2	1.77	NA
Exp Cat 1	0	NA	NA	0	NA	NA	3	1.00[h]	—	4	1.00[h]	—
Exp Cat 2	0	NA	NA	1	0.38	NA	1	1.19	NA	1	0.83	NA
Exp Cat 3	7	1.83	NA	6	1.67	NA	3	4.14	NA	2	4.18	NA
		$p^f = .039$			$p^f = .062$			$p^f = .170$			$p^f = .893$	
UPitt Cats.		$p^g = <.001$			$p^g = .111$			$p^g = .137$			$p^g = .781$	
Unexposed	2	1.00[h]	—	2	3.34	.24–35.37	2	2.11	.15–21.80	2	1.50	.11–15.66
Exp Cat 1	0	.20[e]	−∞–2.74	3	1.00[h]	—	3	1.00[h]	—	3	1.00[h]	—
Exp Cat 2	0	.24[e]	−∞–3.27	2	5.73	.47–50.56	2	0.99	.08–8.67	2	.69	.05–6.11
Exp Cat 3	8	1.80	.28–20.81	3	4.29	.57–32.44	3	6.44	.84–49.20	3	1.42	.19–10.85
Plant 1												
		$p^f = .052$			$p^f = .871$			$p^f = .833$			$p^f = .999$	
UPitt Cats.		$p^g = .033$			$p^g = .510$			$p^g = .771$			$p^g = .999$	
Unexposed	0	1.00[h]	—	0	1.24[e]	−∞–18.21	0	.93[e]	−∞–10.37	0	.97[e]	−∞–11.03
Exp Cat 1	0	Degen	NA	2	1.00[h]	—	3	1.00[h]	—	3	1.00[h]	—
Exp Cat 2	0	Degen	NA	2	1.24	.09–17.36	2	0.82	.07–7.34	2	.97	.08–8.54
Exp Cat 3	6	1.95[e]	.20–∞	2	1.12	.08–15.82	1	3.80	.06–56.52	1	1.17	.02–16.04
Plants 2–10												
		$p^f = .999$			$p^f = .329$			$p^f = .765$			$p^f = .810$	
UPitt Cats.		$p^g = .079$			$p^g = .202$			$p^g = .013$			$p^g = .238$	
Unexposed	2	1.00[h]	—	2	.40	.51–∞	2	1.00[h]	—	2	1.00[h]	—
Exp Cat 1	0	.14[e]	−∞–2.04	1	1.00[h]	—	0	.14[e]	−∞–1.96	0	.22[e]	−∞–3.24
Exp Cat 2	0	.26[e]	−∞–3.67	0	37.11[e]	NA	0	.20[e]	−∞–2.77	0	.20[e]	−∞–2.86
Exp Cat 3	2	.42[e]	.02–8.00	1	7.63	.09–621.51	2	1.25	.06–26.24	2	0.41	.02–8.92

[a] NCI categories based on 60th and 80th percentiles of formaldehyde exposure among cancer deaths who were exposed. Includes only 9/10 deaths.
[b] University of Pittsburgh categories based on approximate tertiles of formaldehyde exposure among NPC deaths who were exposed. Include 10 deaths.
[c] All exposures lagged 15 years as in NCI study.
[d] NCI exposure category cutpoints: highest peak (>0–1.9, 2.0–3.9, and 4.0+ ppm); average intensity of exposure (>0–<.5, .5–<1.0, and 1.0+ ppm); cumulative exposure (>0–1.5, 1.5–<5.5, and 5.5+ ppm-years); duration of exposure (>0–<5.0, 5.0–<15.0, and 15.0+ years) UPitt exposure category cutpoints: highest peak same as NCI (>0–1.9, 2.0–3.9, and 4.0+ ppm); average intensity of exposure (<1.046, 1.046–1.177, and 1.178+ ppm); cumulative exposure (<.734, .734–10.150, and 10.151+ ppm-years); duration of exposure (<.617, .617–2.258, and 2.259+ years).
[e] Median unbiased estimate from exact conditional logistic regression model.
[f] Likelihood ratio test (one degree of freedom) for continuous formaldehyde exposure among unexposed and exposed workers.
[g] Likelihood ratio test (one degree of freedom) for continuous formaldehyde exposure among exposed workers.
[h] Baseline category for RRs.
[i] Data reported by Hauptmann et al. (2004).
[j] NCI results based on Poisson regression models. RRs stratified by age, calendar year, sex, race, and pay category UPitt results based on relative risk regression models. RRs adjusted for age, calendar year, sex, race, and pay category. Degen, degenerative estimate from exact conditional regression model. NA, not available.
* $p < .05$.
** $p < .01$.

the RR for duration of exposure was less. However, compared with the NCI analyses, none of the trend tests for these measures was statistically significant in the UPitt alternative analyses. Table 4 also shows that most of the elevated RRs observed in the UPitt analyses were associated with Plant 1 alone. Due to sparse data, we were unable to fit RR models that included the variable plant to assess its main effects and to quantify the effect modification evident in our plant group analyses.

4. Discussion

Industry-wide historical cohort studies, such as the NCI cohort study of formaldehyde-exposed workers reanalyzed here, often involve geographically diverse plant sites associated with diverse patterns of potential confounding factors (e.g., co-exposures). If all the plants in NCI formaldehyde study had similar formaldehyde exposure and no other confounding factors, then the NCI analysis considering all plants as a single

group would be appropriate. However, evidence exists that some workers from at least one of the 10 NCI formaldehyde plants (Plant 1) had possible occupational or non-occupational exposures to potential NPC risk factors outside of the plant (Marsh et al., 1996, 2002(4)). Moreover, our experience with other multi-plant studies, such as our study of man-made mineral fiber workers (Marsh et al., 2001a) and our reanalysis of the NCI cohort study of acrylonitrile-exposed workers (Marsh et al., 2001b) has found that one or more sites with unique confounding exposures are heavily influencing the exposure–response analysis. When such plant-specific, potential confounding exposures are present, a detailed evaluation of single plants is essential to a full understanding of the exposure–response relationship (or lack thereof) in question, and hence, was a major focus of our reanalysis.

The findings of our reanalysis of the NCI formaldehyde cohort data do not support the causal association between formaldehyde exposure and nasopharyngeal cancer suggested by Hauptmann et al. (2004). First, six of the 10 NPC deaths observed in the NCI study occurred in only one plant (Plant 1) and the remaining four cases occurred individually in four of the other nine plants studied. The statistically significant, greater than 10-fold excess risk for NPC among formaldehyde-exposed workers in Plant 1 contrasts sharply with a 35% deficit in NPC deaths among exposed workers from the remaining study plants (Plants 2–10) where the median duration of formaldehyde exposure and median cumulative formaldehyde exposures were greater than those in Plant 1.

Second, as illustrated clearly in Fig. 1, we found that the statistically significant exposure–response relationship with formaldehyde and NPC reported by Hauptmann et al. (2004) for highest peak exposure was driven entirely by the large, statistically significant excess NPC risk observed for Plant 1 in the highest peak exposure category (4+ ppm). For the remaining nine study plants (Plants 2–10), which comprise 21,358 workers or 80% of the NCI cohort, there is no evidence of an exposure–response relationship using NCI's highest peak exposure metric. In fact, the RRs for all non-baseline exposure categories of highest peak exposure were less than 1.0. We also observed that most of the observed NPC excesses for the non-baseline categories of the remaining exposure metrics (average intensity, cumulative, and duration of exposure) were associated with Plant 1, and that none of the exposure–response relationships in our reanalyses of these metrics was statistically significant.

Three other historical cohort studies have evaluated NPC mortality risks among industrial workers exposed to formaldehyde and none has produced evidence of a possible causal association (Coggan et al., 2003; Pinkerton et al., 2004; Marsh et al., 2002(4)). Coggan et al. (2003) reported only one death from NPC compared to 2.0 expected in a study of 14,014 men employed after 1937 at six British factories where formaldehyde was used or produced. The one death occurred among a man whose exposure to formaldehyde was classified as low

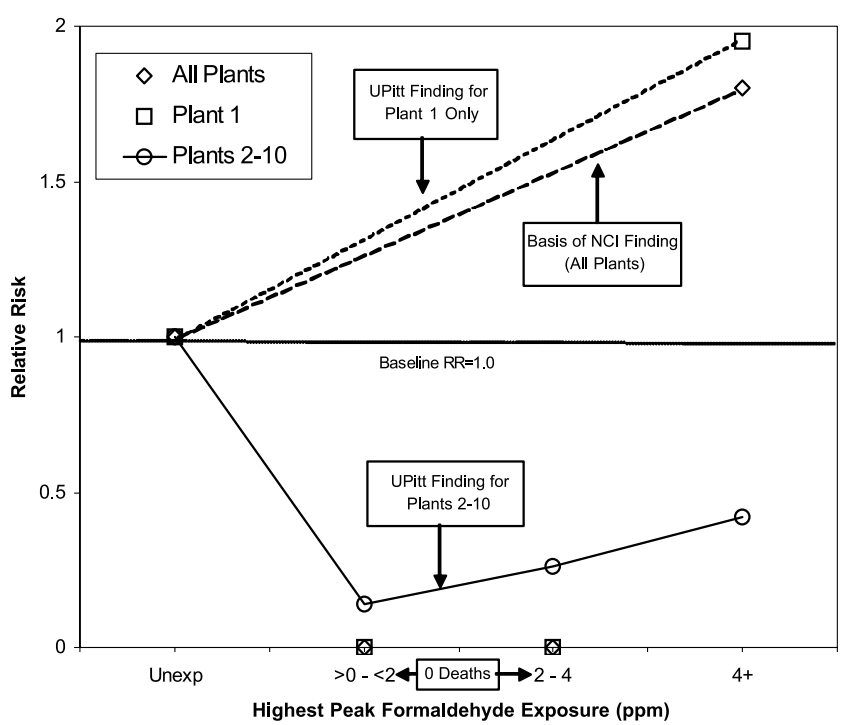

Fig. 1. Relative risks (RR) for nasopharyngeal cancer (NPC) by highest peak formaldehyde exposure and plant group

(time-weighted average exposure 0.1–1.5 ppm). A study of 11,039 workers exposed to formaldehyde for three months or more in three U.S. garment plants (Pinkerton et al., 2004), found no NPC deaths compared to 0.96 expected. As noted by Tarone and McLaughlin (in press), the combined experience of formaldehyde-exposed workers in Plants 2–10 of the NCI study, the British industrial cohort and the U.S. garment workers cohort has yielded three observed NPC deaths compared with 6.11 expected (SMR = 0.5, 95% CI = 0.1–1.4). Thus, the only cohort study-based evidence to date of a possible association with formaldehyde exposure and NPC risk comes from a single plant (Plant 1) in the NCI cohort study.

The anomalous findings for Plant 1 regarding NPC risk were noted in the original NCI cohort follow-up (Blair et al., 1986) and led to several subsequent investigations (Blair et al., 1987; Collins et al., 1987, 1988), including the independent and larger cohort study of 7328 workers from Plant 1 reported by Marsh et al. (1994a, 1996, 2002(4)). In the latest 1998 follow-up, which included a new nested case–control study of NPC, (Marsh et al. (2002(4))) reported a regional rate-based NPC SMR of 5.00 (95% CI = 2.01–10.30) based on seven deaths (the six deaths reported in the NCI study plus one death among a male worker who was not eligible for the NCI cohort[2]). However, a comprehensive exposure–response analysis for Plant 1, which accounted for quantified co-exposures to product and non-product particulates and qualitative exposures to pigments with adjustment for confounding by smoking, revealed no consistent evidence that NPC mortality risks were related to formaldehyde exposure. Further evidence against an association was the observation that only three of the seven NPC cases were exposed to formaldehyde longer than one year and each case had low average intensity of exposure (0.03–0.60 ppm)(Marsh et al., 2002(4)).

We do not feel that the unique findings for NPC in Plant 1 are due simply to chance. Chance was a more likely explanation of the original NCI findings (i.e., that four of seven NPC deaths in the NCI cohort occurred in Plant 1 (Blair et al., 1986)), but became much less likely when the statistically significant NPC excess was maintained (and three additional NPC cases were observed) in an independent and expanded (and subsequently updated) cohort study of Plant 1 (Marsh et al., 1994a, 1996, 2002(4)). We believe that occupational or non-occupational exposures to potential NPC risk factors outside of Plant 1 may have contributed to the unique findings for this plant. For example, the area around Plant 1 has been associated with leather, wood, and metal manufacturing industries that may have contributed dust or fume exposures. In fact, as we reported previously (Marsh et al., 1994a, 1996, 2002(4)), three of the original four NPC cases in Plant 1 were employed before their work at the plant in jobs involving exposure to metal fumes or dust, two potential risk factors for NPC. Moreover, the average age at hire of the seven NPC cases at Plant 1 was 29 years, thereby providing ample opportunity for prior exposures in such industries.

We also attempted to garner additional detailed information about potential exposures to NPC risk factors outside of Plant 1 in our nested case–control study of pharyngeal cancer (Marsh et al., 2002(4)), however, poor or incomplete recall by the respondents (mostly next-of-kin of the decedents) rendered the available data insufficient for statistical analysis. Further intensive investigations of subjects from Plant 1 may help elucidate the reasons for the inordinately elevated risk for NPC among workers in this one plant.

5. Conclusions

Overall, our reanalysis provided little evidence to support NCI's suggestion of a causal association between formaldehyde exposure and mortality from NPC. NCI's conclusion of a possible causal association was driven heavily by anomalous findings in one study plant (Plant 1). Our findings of no excess NPC mortality risk in Plants 2–10 of the NCI cohort study coupled with the absence of NPC risk in two other industrial cohort studies support the conclusion of our independent and larger study of Plant 1; namely, that the large, persistent NPC mortality excesses in Plant 1 were not associated with formaldehyde exposure, and may reflect the influence of non-occupational risk factors or of occupational risk factors associated with employment outside of Plant 1. The findings of our reanalysis cast considerable additional uncertainty regarding the validity of NCI's suggested association of formaldehyde and NPC.

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Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde

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Objectives: To assess the possible relationship between formaldehyde exposure and mortality risk from pharyngeal cancer (PC), in particular nasopharyngeal cancer (NPC). **Methods:** Subjects were 7328 workers employed at a plastics-producing plant (1941–1984). Vital status for 98% of the cohort and cause of death for 95% of 2872 deaths were determined. Reconstructed exposures to formaldehyde, particulates and pigment were used to compute several exposure measures. Standardized mortality ratios (SMRs) were computed for several demographic, work history and formaldehyde exposure variables. In a nested case-control study, seven cases of NPC and 15 cases of other PC were matched on race, sex, age and year of birth to four controls from the cohort. Among interviewed subjects, lifetime smoking history was determined using respondents or proxies for all but one control subject. **Results:** Statistically significant 2.23-fold and fivefold excesses for PC and NPC, respectively, were observed. Fivefold range NPC excesses were observed for both short (< 1 year) and long-term workers and were concentrated among workers hired during 1947–1956. Only three NPC cases were exposed to formaldehyde for longer than one year, and each had low average intensity of formaldehyde exposure (0.03–0.60 ppm). Only a few exposure measures revealed some evidence of an association with all PC or NPC. For all PC combined, adjustment for smoking and year-of-hire in the case-control study generally corroborated findings from the cohort study. **Conclusions:** Overall, the pattern of findings suggests that the large, persistent nasopharyngeal and other PC excesses observed among the Wallingford workforce are not associated with formaldehyde exposure, and may reflect the influence of nonoccupational risk factors or occupational risk factors associated with employment outside the Wallingford plant. *Toxicology and Industrial Health* 2002; **18:** 257–268.

Key words: *case-control study; chemical workers; cohort study; formaldehyde; nasopharyngeal cancer; occupational diseases; particulates; pharyngeal cancer; pigment*

Introduction

Since the early 1980s, when inhalation studies in laboratory animals showed that exposure to formaldehyde could cause nasal cancer in rats (Swenberg *et al.*, 1980; Albert *et al.*, 1982), the

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carcinogenic potential of formaldehyde in humans has been the subject of extensive research and controversy. While one review and two meta-analyses of the available epidemiologic evidence concluded that nasopharyngeal cancer (NPC) is associated with formaldehyde exposure (International Program on Chemical Safety, 1989; Blair *et al.*, 1990; Partanen, 1993), a recent meta-analysis of 47 studies concluded that the available studies do not support a causal association (Collins *et al.*, 1997). Other reviews have concluded that insufficient evidence exists for a causal relation between formaldehyde exposure and cancer risk (Purchase and Paddle, 1989; McLaughlin, 1994). The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a 'probable' (2A) human carcinogen based on limited human evidence and sufficient animal evidence (International Agency for Research on Cancer, 1995).

Our study involves workers from a plastics producing facility in Wallingford, CT, operated by Cytec Industries, Inc., since 1941. It is one of ten formaldehyde using or producing plants in the US included in an ongoing National Cancer Institute (NCI) cohort mortality study (Blair *et al.*, 1986). In 1987, the University of Pittsburgh, Department of Biostatistics (UPitt) began an independent, extended investigation of total and cause-specific mortality among a cohort of Wallingford workers hired between 1941 and 1984 to examine possible associations between exposures to formaldehyde and/or particulates and pigment and cancers of the lung and pharynx, which were elevated in the NCI study (Blair *et al.*, 1986; 1987). In particular, four of seven NPC deaths identified in the combined ten-plant NCI study occurred among white male Wallingford workers, resulting in a statistically significant 3.18-fold excess based on standardized comparisons with US mortality rates (Blair *et al.*, 1986).

In 1994, we confirmed the mortality excess for NPC based on the same four cases reported by NCI (Blair *et al.*, 1986) and found no new NPC cases in the extended 1980–1984 follow-up period (Marsh *et al.*, 1994). Using historical exposure estimates derived from an independent exposure assessment of the Wallingford plant, we also examined the association between selected cancer sites (NPC and lung cancer) and exposure to formaldehyde alone or in combination with particulates or pigment (Marsh *et al.*, 1996). These analyses revealed little evidence of a causal association between formaldehyde exposure and lung cancer or NPC.

Subsequent 1995 and 1998 follow-ups of the Wallingford cohort focused on NPC and other cancers of the upper respiratory tract and included the updating of work histories and associated formaldehyde exposure. The 1998 follow-up also included a new nested case-control study of NPC and other pharyngeal cancers (PCs). We report here results of the 1998 follow-up.

Methods

Historical cohort study

Study population

Our original study population included 7359 workers employed at Wallingford between 1941 and 1984. The 1984 follow-up focused on 6040 white males at risk during 1945–1998 (Marsh *et al.*, 1996). This 1998 follow-up included all Wallingford workers at risk during 1945–1998 ($n = 7328$ or 99.6% of the total population). Table 1 shows the cohort consists mostly of white males (82%), and the majority (54%) worked less than one year. More than 1300 workers (18%) were employed for ten or more years, and more than 60% of the total cohort has now been followed for 30 or more years. The year of hire categories in Table 1 reflect four distinct phases of the plant's history that are roughly correlated with exposure levels to formaldehyde and particulates (1941–1946 highest, 1966–1984 lowest) (Marsh *et al.*, 1996).

Exposure assessment

The work histories of all study members actively employed beyond the 1984 follow-up were updated through 1995, as were exposures to formaldehyde, particulates (product and nonproduct) and pigment using the historical exposure reconstruction methods used in the original study (Marsh *et al.*, 1996). Work histories and exposures were not updated beyond 1995 for the 1998 update. In brief, the exposure estimation was based on an examination of the available sampling data and job descriptions, as well as on verbal descriptions of jobs and tasks by plant personnel, including the plant industrial hygienist. A total of 4332 job titles were classified

Table 1. Selected demographic and work history characteristics of Wallingford cohort.

Characteristic	Number	Percent
Race/Sex		
White male	6040	82.4
White female	819	11.2
Nonwhite male	415	5.7
Nonwhite female	54	0.7
Total	7328	100.0
Year of hire		
1941–1946	1112	15.2
1947–1956	3050	41.6
1957–1965	1338	18.3
1966–1984	1828	24.9
Age at entry into study		
< 25	3287	44.9
25–34	2272	31.0
35–44	1124	15.3
45+	645	8.8
DOE		
< 1 month	1069	14.6
1–11.9 months	2905	39.6
1–9 years	2022	27.6
10–19 years	656	9.0
20+ years	676	9.2
TSFE (years)		
< 10	441	6.0
10–19	880	12.0
20–29	1437	19.6
30+	4570	62.4
Vital status (12/31/98)		
Alive	4341	59.2
Deceased	2872	39.2
with cause of death	2735	(95.2)
without cause of death	137	(4.8)
Unknown	115	1.6

into 235 groups by similarity of tasks performed and the likelihood for potential exposures as previously described (Esmen, 1979; Corn and Esmen, 1979). The available sampling data were sporadic measurements between 1965 and 1987. Exposures were initially assigned to each job and task on a ranked scale between background (or zero) exposure and high exposure to formaldehyde and particulate matter. Supporting documentation on use of personal protection equipment were used in developing the rankings. These rankings provided seven classes for formaldehyde, and nine classes for product particulate and nonproduct particulate. A range of exposures for each ranking was then assigned to the job categories. For formaldehyde, the classification scheme chosen maximized comparability with that developed in the NCI study (Blair *et al.*, 1986). Pigment exposure was assessed as presence or absence of any pigment.

Our exposure assessment revealed that the median average intensity of exposure (AIE) to formaldehyde for the 5665 exposed workers (0.138 ppm) was lower than the current Occupational Safety and Health Administration (OSHA) standard of 0.75 ppm (OSHA, 1992). The median formaldehyde AIE was slightly higher for the 5104 workers exposed to formaldehyde in jobs with nonproduct particulate exposure (0.20 ppm) and among the 2523 workers exposed to formaldehyde in jobs with pigment exposure (0.20 ppm). Slightly higher proportions of short- rather than long-term workers were exposed to each of the formaldehyde, product particulate and nonproduct particulate, and the combined formaldehyde/(product particulate or nonproduct particulate). However, for each of these measures, the median AIE of long-term workers was at least twice as high as that for short-term workers.

As noted earlier (Marsh *et al.*, 1996), our estimates of median AIE to formaldehyde with and without coexposure to particulates are more than ten times lower than corresponding values estimated for the same Wallingford workers in the NCI study (Blair *et al.*, 1986). This difference may be explained by the fact that the NCI used data from several facilities to estimate exposures in a single facility, including Wallingford, whereas our assessment was based exclusively on Wallingford exposure data. Our lower median AIE is also supported directly by our observation that only nine of 298 available eight-hour time-weighted average (TWA) exposure measurements from Wallingford were greater than 1 ppm and only one of the nine was greater than 3 ppm. The average of this highest measurement and the four other TWA measurements for the same job was less than 1 ppm.

Vital status tracing and cause of death ascertainment

All study members without a confirmed cause of death at the end of the 1984 follow-up were traced for deaths through December 31, 1998, utilizing the protocol of Schall *et al.* (Schall *et al.*, 1997; 2001). Underlying cause of death codes were obtained from the National Death Index Plus system or from death certificates obtained from state health departments. Death certificates were coded to the underlying cause of death by a nosologist using the

International Classification of Diseases (ICD) rules in effect at time of death. Table 1 shows that 2872 or 39% of the cohort was identified as deceased and cause of death was obtained for 2735 or 95%. Only 115 or 1.6% of the cohort remains untraced.

Statistical analyses

Analysis of general mortality patterns

Mortality analyses were limited to malignant neoplasms of the upper and lower respiratory tract and were performed using the Occupational Cohort Mortality Analysis Program (OCMAP-PLUS) (Marsh *et al.*, 1998). Person–years at risk contributed by each study member were jointly classified by race, sex, age group, calendar time, year of hire, duration of employment (DOE) and the time since first employment (TSFE).

We computed expected numbers of deaths, using as standard populations the total US and the local two county area (Middlesex and New Haven Counties) from which the Wallingford workforce was largely drawn. Population-weighted county rates were obtained from the Mortality and Population Data System (MPDS) maintained by the University of Pittsburgh (Marsh *et al.*, 2000). To account for geographic variability, the analyses focused primarily on the local county comparisons (Doll, 1985). Standardized Mortality Ratios (SMRs) and their 95% confidence intervals (CI) were computed for the Wallingford cohort and selected subgroups. Statistically significant deviations of the SMR below and above 1.00 were identified using Poisson probabilities (Breslow and Day, 1987).

Analysis in relation to occupational exposure

For all PC combined and the subcategory NPC, we computed SMRs by occupational exposure to formaldehyde through 1995 (the latest available data) with and without considering coexposures to particulates and pigment. Quantitative formaldehyde exposure measures included duration of exposure, AIE, and cumulative exposure. Other exposure measures considered were: 1) exposure to formaldehyde occurring in the same job, but not necessarily simultaneously, with particulates or pigment; 2) duration of formaldehyde exposure in jobs with average mean formaldehyde exposure, i) greater than 0.2 ppm; and ii) greater than 0.7 ppm.[1] Methodological details of the exposure measures considered are described elsewhere (Marsh *et al.*, 1996).

Nested case-control study of NPC and other PC

During the 1945–1998 study period, 22 PC deaths were identified among the Wallingford cohort and included as cases in the nested case-control study. These deaths included the specific sites: oropharynx ($n=5$), nasopharynx ($n=7$) and hypopharynx ($n=3$), as well as deaths coded to the residual category, 'pharynx, unspecified' ($n=7$). Nineteen cases were white males, two were nonwhite males and one was a white female. All seven NPC cases were white males. Although NPC is the site of primary *a priori* interest, other pharyngeal sites were included as cases because: 1) these sites are anatomically contiguous to the nasopharynx, and therefore they are potential target sites of formaldehyde and/or particulate exposures; and 2) mortality excesses for these sites were observed in the NCI study (Blair *et al.*, 1986; 1987) and our 1995 update. Sinonasal cancer deaths were not included as cases because: 1) the sinonasal region of the upper respiratory tract may not be a target site for formaldehyde exposure (Collins *et al.*, 1997; Heck *et al.*, 1989); and 2) the histologic, preneoplastic and etiologic features of sinonasal cancer are distinct from those head and neck cancers arising in contiguous sites (i.e., PC) (Roush, 1996).

Each case was matched on race, sex, age and year of birth (within two years) to four controls from the remaining living and deceased members of the cohort. We attempted to obtain information on lifetime smoking history and relevant exposures outside of Wallingford through structured telephone interviews with the respondent or a knowledgeable informant (usually a surviving family member). We successfully interviewed 15 or 68% of the 22 PC cases, including five (71%) of the seven NPC cases and ten (67%) of the 15 'other PC' cases. Interviews were obtained for 76% of 88 targeted

[1]Our previous Wallingford exposure assessment assigned formaldehyde exposure levels to 162 homogeneous department/job title combinations. Assigned exposures were the geometric means from one of eight formaldehyde exposure categories (Marsh *et al.*, 1996). 0.2 and 0.7 ppm are the geometric means of the two exposure categories close to the current OSHA standard of 0.75 ppm (OSHA, 1992).

controls, including 17 (61%) of 28 targeted NPC controls and 50 (83%) of 60 targeted 'other PC' controls. Among subjects with interview data, basic information on cigarette smoking history (ever/never smoking – all forms of tobacco) was obtained for all but one 'other PC' control. All 15 interviewed PC cases were reported as 'ever' smokers compared with 48 (71.6%) of the 67 interviewed controls. Information on relevant non-Wallingford exposures was limited by a large percentage of 'unknown' responses.

The statistical analysis of the case-control data included multivariate modeling of estimated odds ratios (OR) using exact conditional logistic regression (Breslow and Day, 1980; Cytel Software, 1993). Due to sparse data, modeling was not performed separately for NPC. For ORs showing a positive monotonic or nearly monotonic trend with increasing level of formaldehyde exposure, we computed trend test P-values. Because work history and exposure data were available at the cohort level, models included all 22 cases and 88 matched controls. For smoking history, we formed a separate category ('unknown') for subjects who were not contacted or were contacted but responded 'unknown'. Other variables were categorized as in the cohort analysis (Table 4). The 'unexposed' category was used as the baseline of the OR if the number of observed cases was at least five, otherwise, the unexposed and lowest exposure categories were combined to construct a more stable baseline category. Due to the small number of cases in some subcategories of the variables considered, certain risk sets (a case and its matched controls) for a given study factor were uninformative for estimating ORs. This contributed to some P-values close to 1.0 and/or very large 95% CIs for ORs. In the presence of many uninformative risk sets, the OR was estimated using a less robust 'median unbiased estimator (MUE)' approach (Cytel Software, 1993).

Results

Cohort study

Table 2 presents for the combined 1945–1998 study period, observed deaths and US and local rate-based SMRs for subcategories comprising the upper and lower respiratory tracts. Based on local county rates, a statistically significant 1.52-fold excess was observed for the combined buccal cavity and pharynx category. This includes a statistically significant 2.23-fold excess for PC combined and a statistically significant fivefold excess based on seven deaths for NPC, the primary site of *a priori* interest.[2] Similar, though not statistically significant, excesses of 1.80-, 1.52- and 1.89-fold were observed for cancers of the oropharynx, hypopharynx and 'pharynx-unspecified site', based on five, three and seven deaths, respectively.

For the combined respiratory system cancer category, Table 2 shows a statistically significant 1.22-fold excess (county comparison) based on 278 observed deaths. A not statistically significant 3.06-fold excess based on three deaths was observed for sinonasal cancer, including a statistically significant 10.96-fold excess based on two deaths for the subcategory 'other specified sinus' (includes the ethmoid, frontal and sphenoidal sinuses) and a statistically significant 1.21-fold excess based on 262 deaths for cancer of the bronchus, trachea, lung. US rate-based SMRs for the buccal cavity and PC categories were generally higher than those based on local rates; those for respiratory system cancer were generally lower. SMRs in the 1985–1998 update period were generally similar to those observed in the previous 1945–1984 period.

Table 3 shows county rate-based SMRs for all PC and NPC according to selected work history and formaldehyde exposure measures. Short- and long-term workers experienced similarly elevated SMRs for both cancer categories. Most PC and NPC cases occurred among workers hired between 1947 and 1956, resulting in the largest and statistically significant SMRs of 3.24 and 8.13, respectively. SMRs for neither PC nor NPC were associated with DOE, while SMRs for all PC increased with increasing TSFE. Twenty of the 22 PC cases and all seven NPC cases had some exposure to formaldehyde, resulting in statistically significant SMRs of 2.42 and 6.03, respectively.

[2]During the 1985–1998 update period, we observed an additional three deaths from NPC and six deaths from 'other PC'. The 1985–1998 SMR for NPC was 4.89 (based on 0.61 expected deaths) and statistically significant. In the previous 1945–1984 follow-up, a similar, statistically significant SMR for NPC of 5.08 was observed (four observed versus 0.79 expected deaths).

Table 2. Observed deaths and SMRs for selected cancer site categories, Wallingford Cohort, 1945–1998, US and local county comparisons (no. at risk = 7328, person–years = 240997).

Cause of death (ICDA 9th revision codes)	Observed	United States		Local County	
		SMR	95% CI	SMR	95% CI
All malignant neoplasms (140–208)	757	1.08	1.00–1.15	1.06	0.99–1.14
Buccal cavity and pharynx (140–149)	31	1.80**	1.22–2.55	1.52*	1.03–2.15
Lip (140)	1	3.23	0.08–18.00	7.75	0.19–43.19
Tongue (141)	3	0.76	0.16–2.22	0.61	0.13–1.78
Major salivary glands (142)	0	–	0–3.18	–	0–3.06
Gum and other mouth unspecified (143, 145)	3	1.20	0.25–3.51	1.01	0.21–2.95
Floor of the mouth (144)	2	2.07	0.25–7.48	1.48	0.18–5.35
Pharyngeal (146–149)	22	2.63**	1.65–3.98	2.23**	1.40–3.38
Oropharynx (146)	5	2.17	0.71–5.07	1.80	0.58–4.19
Nasopharynx (147)	7	4.94**	1.99–10.19	5.00**	2.01–10.30
Hypopharynx (148)	3	2.25	0.46–6.58	1.52	0.31–4.43
Pharynx, unspecified (149.0)	7	2.11	0.85–4.35	1.89	0.76–3.89
Respiratory system (160–165)	278	1.12	0.99–1.26	1.22**	1.08–1.38
Sinonasal (160)	3	3.10	0.64–9.07	3.06	0.63–8.93
Nose (internal) and nasal cavities (160.0)	0	–	0–33.42	–	0–47.99
Eustachian tube and middle ear (160.1)	0	–	0–148.66	–	0–128.04
Maxillary Sinus (160.2)	0	–	0–8.01	–	0–7.97
Other specified sinus (160.3, 160.4, 160.5, 160.8)	2	16.94*	2.05–61.20	10.96*	1.33–39.58
Sinus site unspecified (160.9)	1	5.59	0.14–31.16	7.17	0.18–39.95
Larynx (161)	13	1.50	0.80–2.57	1.59	0.84–2.71
Bronchus, trachea, lung (162)	262	1.11	0.98–1.25	1.21**	1.06–1.36

*$P < 0.05$.
**$P < 0.01$.

Overall, for both PC and NPC, Table 3 shows little consistent evidence of increasing mortality risks with increasing levels of the measures considered. Excess deaths were observed in both the baseline and nonbaseline categories of all the measures and many are statistically significant. For PC, only DOE in jobs with formaldehyde exposures >0.2 ppm revealed limited evidence of an association with mortality risk. For NPC, we observed limited evidence of an association with increasing duration of exposure to formaldehyde, cumulative exposure to formaldehyde or DOE in jobs with formaldehyde exposures >0.2 ppm or >0.7 ppm. Our findings for formaldehyde were not materially altered when coexposures to particulates or pigment were considered (data not shown).

Case-control study

Table 4 summarizes the exact conditional logistic regression modeling results for all PC combined. Shown for each model are the observed number of cases, the estimated OR and 95% CI, and the global test P-value (test of main effect). Among the potential confounding variables considered in the univariate models, only smoking history and year of hire were statistically significant predictors of case-control status (borderline for smoking-global $P = 0.055$). The estimated OR for workers who ever smoked was 8.03, which is higher than the risks observed for PCs in other case-control studies. (Blot *et al.*, 1998; Yu *et al.*, 1996). The 7.62-fold risk for the 'unknown' category suggests that most of these subjects were probably smokers. Year of hire showed the strongest association (global $P = 0.026$) with PC, with workers hired in 1947–1956 having a 10.07-fold risk of PC compared with workers hired 1941–1946.

Table 4 reveals limited evidence of an increasing trend in ORs for PC with increasing levels of DOE in jobs with formaldehyde exposure greater than 0.2 ppm (Dur (formaldehyde >0.2 ppm)) (trend test $P = 0.210$). Only one of the formaldehyde exposure variables considered in the univariate models (cumulative exposure to formaldehyde in the presence of pigment) was a statistically significant predictor (global $P = 0.012$) of PC risk; however, there was no evidence of a trend in risk with increasing exposure (data not shown).

Most of the models adjusted for smoking and year of hire yielded similar OR estimates as the corresponding unadjusted models suggesting generally weak confounding effects of smoking and year of hire. Adjusted models revealed some evidence of an increasing trend in ORs with

Table 3. Observed deaths and SMRs for all PC and NPC, total Wallingford cohort, 1945–1998, local county comparison, by selected work history and formaldehyde exposure indicators.

Work history/exposure indicator	All pharyngeal cancer ($n = 22$)			Nasopharyngeal cancer ($n = 7$)		
	Observed	SMR	95% CI	Observed	SMR	95% CI
Short-term workers (< 1 year)[a]	12	2.35*	1.22–4.11	4	5.35*	1.46–13.71
Long-term workers (1+ years)	10	2.10*	1.01–3.86	3	4.59	0.95–13.42
Year of hire						
1941–1946	1	0.46	0.01–2.56	0	–	0–13.10
1947–1956	18	3.24*	1.92–5.12	6	8.13**	2.98–17.69
1957+	3	1.41	0.29–4.12	1	2.63	0.07–14.64
DOE (years) (all workers)						
< 1	12	2.34*	1.21–4.09	4	5.33*	1.45–13.64
1–9	5	1.89	0.61–4.42	1	2.62	0.06–14.57
10+	5	2.36	0.76–5.50	2	7.49	0.91–27.06
TSFE (years)						
< 20	4	1.41	0.38–3.61	2	5.01	0.61–18.08
20–29	7	2.32	0.93–4.78	3	8.72*	1.80–25.48
30+	11	2.75*	1.37–4.92	2	3.04	0.37–11.00
Formaldehyde exposure measures						
Exposure to formaldehyde						
Unexposed	2	1.24	0.15–4.49	0	–	0–15.41
Exposed	20	2.42**	1.48–3.74	7	6.03**	2.42–12.42
Duration of exposure to formaldehyde (years)						
Unexposed	2	1.24	0.15–4.49	0	–	0–15.41
> 0– < 1	11	2.35*	1.17–4.21	4	5.84*	1.59–14.94
1–9	4	1.81	0.49–4.63	1	3.17	0.08–17.68
10+	5	3.65*	1.18–8.52	2	12.46*	1.51–45.02
Cumulative exposure to formaldehyde (ppm – years)						
Unexposed	2	1.24	0.15–4.49	0	–	0–15.41
> 0– < 0.004	6	3.31	1.22–7.21	1	3.97	0.10–22.10
0.004–0.219	7	2.06	0.83–4.24	3	5.89*	1.22–17.22
0.22+	7	2.30	0.92–4.73	3	7.51*	1.55–21.93
AIE to formaldehyde (ppm)						
Unexposed	2	1.24	0.15–4.49	0	–	0–15.41
> 0– < 0.03	6	2.02	0.74–4.40	1	2.41	0.06–13.44
0.03–0.159	7	3.82**	1.54–7.88	4	15.27**	4.16–39.10
0.16+	7	2.03	0.82–4.19	2	4.13	0.50–14.91
Formaldehyde > 0.2 or > 0.7 ppm measures						
Exposure to formaldehyde > 0.2 ppm						
Unexposed	8	1.72	0.74–3.39	2	3.01	0.36–10.87
Exposed	14	2.68**	1.46–4.49	5	6.79**	2.21–15.85
Duration of exposure to formaldehyde > 0.2 ppm (years)						
Unexposed	8	1.72	0.74–3.39	2	3.01	0.36–10.87
> 0– < 1	6	2.19	0.80–4.77	2	4.81	0.58–17.37
1–9	3	1.68	0.34–4.90	1	4.04	0.10–22.51
10+	5	7.35**	2.39–17.16	2	27.61**	3.34–99.73
Exposure to formaldehyde > 0.7 ppm						
Unexposed	16	2.12**	1.21–3.45	4	3.64	0.99–9.31
Exposed	6	2.55	0.94–5.56	3	9.98**	2.06–29.17
Duration of exposure to formaldehyde > 0.7 ppm (years)						
Unexposed	16	2.12**	1.21–3.45	4	3.64	0.99–9.31
< 1	4	2.58	0.70–6.61	2	9.51*	1.15–34.37
1+	2	2.50	0.30–9.03	1	11.07	0.28–61.67

[a] Does not include short-term experience of long-term workers.

increasing duration of exposure to formaldehyde (trend test $P = 0.434$), and increasing duration of exposure to formaldehyde > 0.2 ppm (trend test $P = 0.163$). The findings for formaldehyde in the adjusted models were not materially altered when coexposures to particulates or pigment were con-

Table 4. Case-control study: estimated OR for all PC, univariate and bivariate models[a].

Variable[b]	Observed cases	Univariate (no adjustments)		Adjusted for smoking and year of hire	
		OR (95%CI)	*P*-value[c]	OR (95%CI)	*P*-value[c]
Smoking status					
Never smoker	0	1.00			
Ever smoker	15	8.03[d] (1.22–∞)	–	–	
Unknown or not contacted	7	7.62[d] (1.01–∞)	0.055	–	–
Year of hire					
1941–1946	1	1.00			
1947–1956	18	10.07 (1.04–511.07)		–	–
1957+	3	2.55 (0.09–201.06)	0.026		
Worker type					
Short-term workers (< 1 year)[a]	12	1.00		1.00	
Long-term workers (1+ years)	10	0.86 (0.28–2.53)	0.811	1.01 (0.30–3.24)	0.999
DOE (years)					
< 1	12	1.00		1.00	
1–9	5	0.82 (0.20–2.87)		0.91 (0.22–3.22)	
10+	5	0.93 (0.21–3.54)	0.951	1.37 (0.20–8.86)	0.934
TSFE (years)					
< 20	4	1.00		1.00	
20–29	7	0.85 (0.16–5.78)		0.23 (0.01–2.68)	
30+	11	0.74 (0.11–5.86)	0.999	0.24 (0.003–5.69)	0.474
Formaldehyde exposure measures					
Exposure to formaldehyde					
Unexposed	2	1.00		1.00	
Exposed	20	1.88 (0.38–18.51)	0.524	3.04 (0.36–145.58)	0.433
Duration of exposure to formaldehyde (years)					
< 1	13	1.00		1.00	
1–9	4	0.86 (0.17–3.32)		1.01 (0.19–4.42)	0.615
10+	5	1.52 (0.34–6.23)	0.745	2.23 (0.34–14.97)	(0.434)
Cumulative exposure to formaldehyde (ppm – years)					
< 0.004	8	1.00		1.00	
0.004–0.219	7	0.71 (0.20–2.43)		0.89 (0.22–3.56)	
0.22+	7	0.79 (0.18–3.20)	0.824	0.81 (0.13–4.34)	0.999
AIE to formaldehyde (ppm)					
< 0.03	8	1.00		1.00	
0.03–0.159	7	1.71 (0.47–6.10)		1.80 (0.45–7.47)	
0.16+	7	0.99 (0.27–3.55)	0.549	0.86 (0.17–3.74)	0.509
Formaldehyde > 0.2 or 0.7 ppm exposure measures					
Exposure to formaldehyde > 0.2 ppm					
Unexposed	8	1.00		1.00	
Exposed	14	1.35 (0.45–4.25)	0.625	1.27 (0.35–4.88)	0.776
Duration of exposure to formaldehyde > 0.2 ppm (years)					
Unexposed	8	1.00		1.00	
> 0– < 1	6	1.02 (0.26–3.79)		1.13 (0.24–5.29)	
1–9	3	1.19 (0.17–6.26)	0.422	1.38 (0.18–9.03)	0.287
10+	5	3.28 (0.56–20.45)	(0.210)	9.49 (0.55–701.35)	(0.163)
Exposure to formaldehyde > 0.7 ppm					
Unexposed	16	1.00		1.00	
Exposed	6	1.60 (0.15–9.77)	0.633	1.30 (0.08–21.59)	0.999
Duration of exposure to formaldehyde > 0.7 ppm (years)					
Unexposed	16	1.00		1.00	
< 1	4	0.76 (0.17–2.69)		0.52 (0.08–2.45)	
1+	2	1.48 (0.14–9.42)	0.787	1.11 (0.06–11.31)	0.639

[a] Controls individually matched to cases on exact age, year of birth (±2 years), race and sex; controls sampled from risk sets derived from cohort.
[b] If unexposed category of exposure variable included < 5 cases, the baseline category and lowest exposure category were combined.
[c] Global test *P*-value of main effect; trend test *P*-value shown in parentheses if ORs display a positive monotonic (or nearly monotonic) trend.
[d] Estimate based on less robust MUE.

sidered (data not shown). In unadjusted and adjusted models, workers who had some exposure to formaldehyde had an elevated PC risk compared with unexposed workers, but long-term workers (≥ 1 year) showed a reduced or nearly equal risk compared to short-term workers.

Discussion and conclusions

The Wallingford historical cohort study provides an important epidemiological resource for evaluating long-term health effects of occupational exposure to formaldehyde, alone or in combination with exposures to particulates and pigment. It also offers a valuable contrast to the larger ten-plant NCI study, which produced much larger exposure formaldehyde estimates for the Wallingford plant (Blair *et al.*, 1986). Strengths of the Wallingford cohort study include a large cohort with a high proportion of older workers, long observation period and sufficient statistical power to detect meaningful excesses for many cause of death categories. Other strengths include excellent follow-up and cause of death ascertainment rates, and the availability of detailed work histories linked to quantitative and qualitative historical exposure estimates for individual workers. A particular strength of this latest update was the new nested case-control study, which enabled risk estimates for all PC combined to be adjusted for potential confounding by smoking history, an unmeasurable variable at the cohort level.

The Wallingford study also has several limitations that impact on the interpretation of the results. One limitation of the cohort study is that more than 50% of the cohort worked at Wallingford for less than one year, which increases the likelihood that unmeasureable, non-Wallingford occupational exposures may have confounded exposure–response relationships in this study. Also, the cohort and nested case-control studies were limited by the small number of PC cases, in particular, NPC cases, which led to low statistical power to detect other than large mortality excesses. The nested case-control study was also limited by the inability to acquire information on potential confounding factors, such as exposure to relevant occupational or nonoccupational risk factors outside the Wallingford plant (Hildesheim and Levine, 1993).

As in the original cohort study (Marsh *et al.*, 1996), this latest update of the Wallingford cohort and case-control studies provides evidence both for and against a possible association between formaldehyde exposure and mortality risks from PC. This contrasting evidence is discussed below and summarized in Table 5. The evidence that supports a possible association includes: 1) Three additional NPC cancers and six other PC deaths were observed in the 1985–1998 update period; 2) the excess mortality risk for NPC remains in the update period and overall at a statistically significant fivefold level. Excesses of this magnitude are unlikely to be related solely to uncontrolled potential confounding factors, and the use of local county rates reduces the likelihood of bias due to uncontrolled geographic variations in NPC mortality rates; 3) excess risks for other PC sites remain in the 1.5–2.0-fold range; 4) in the cohort and case-control studies, mortality risks for all PC combined (and for NPC in the cohort study) were highest among workers hired during the 1947–1956 period when formaldehyde exposures were known to be higher than later periods. This may reflect the influence of occupational factors at the Wallingford plant that were present at that time or in earlier time periods; alternatively, other factors not accounted for may also be operating; 5) the cohort and case-control studies revealed some evidence of increasing risks for all PC combined with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 ppm; and 6) the cohort study revealed some evidence of increasing NPC risks with increasing duration and cumulative exposure to formaldehyde with and without the presence of particulates, and with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 or 0.7 ppm.

Evidence in this latest update that does not support a possible association includes: 1) For most of the many formaldehyde exposure variables considered in the cohort study, elevated SMRs for all PC combined and NPC were observed in the unexposed and lower exposure categories, as well as the higher exposure categories. Similarly, the case-control analysis of all PC combined revealed elevated ORs for both the lower and higher exposure categories of the same exposure variables; 2) SMRs for all PC combined and NPC were greater among short-term (< 1 year) than long-term workers, a possible reflection of relevant

Table 5. Summary of epidemiological evidence for and against an association between formaldehyde exposure and mortality risks from PC, including NPC.

Evidence for an association	Evidence against an association
Three additional NPC cancers and six other PC deaths were observed in the 1985–1998 update period.	For most of the formaldehyde exposure variables considered in the cohort and case-control studies, elevated SMRs for all PC combined and NPC were observed in the unexposed and lower exposure categories as well as the higher exposure categories.
The excess mortality risk for NPC remains in the update period and total study period at a statistically significant, fivefold level	The limited evidence that supports a possible association was not observed consistently across the many formaldehyde exposure measures considered.
Excess risks for other PC sites remain in the 1.5–2.0-fold range.	SMRs for all PC combined and NPC were greater among short-term (< 1 year) than long-term workers, a possible reflection of relevant exposures received before or after employment at Wallingford.
In the cohort and case-control studies, mortality risks for all PC combined (and for NPC in the cohort study) were highest among workers hired during the 1947–1956 period when formaldehyde exposures were known to be higher than later periods.	The patterns of findings relative to year of hire (mortality risks for PC and NPC highest among workers hired 1947–1956) may reflect the influence of occupational factors associated with employment before the Wallingford plant.
The cohort and case-control studies revealed some evidence of increasing risks for all PC combined with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 ppm.	For most of the 22 PC cases, the very brief periods of Wallingford employment afforded little opportunity for etiologically relevant exposures.
The cohort study revealed some evidence of increasing NPC risks with increasing duration and cumulative exposure to formaldehyde with and without the presence of particulates, and with increasing DOE in jobs with average formaldehyde exposure greater than 0.2 ppm or 0.7ppm.	A manual review of time period-specific job codes for the 22 PC cases revealed no unusual pattern of jobs compared with a similar review of job codes for the controls used in the case-control study

Conclusion: The short employment periods of most of the cases coupled with patterns of findings relative to year of hire suggests that the NPC and other PC excesses may reflect the influence of occupational factors associated with employment outside the Wallingford plant and/or to non-occupational factors such as those associated with the unknown responses in the case-control study.

exposures received before or after employment at Wallingford; 3) for most of the 22 PC cases, the very brief periods of Wallingford employment afforded little opportunity for etiologically relevant exposures. Only three of the seven NPC cases and six of the 13 other PC cases were exposed to formaldehyde longer than one year, and each had low average intensity of formaldehyde exposure (ranging from 0.02 to 0.60 ppm); 4) the limited evidence that supports a possible association was not observed consistently across the many exposure measures considered; 5) a manual review of time period–specific job codes for the 22 PC cases revealed no unusual pattern of jobs compared with a similar review of job codes for the controls used in the case-control study; and 6) the short employment periods of most of the cases coupled with patterns of findings relative to year of hire suggests that the NPC and other PC excesses may reflect the influence of occupational factors associated with employment before the Wallingford plant and/or to nonoccupational factors, such as those associated with the unknown responses in the case-control study. As noted earlier (Marsh *et al.*, 1996), three of the four original NPC cases were employed before their work at Wallingford in jobs involving exposure to metal fumes or dust, two potential risk factors for NPC (Blot *et al.*, 1998).

In conclusion, although the latest update of the Wallingford cohort study and the new nested case-control study revealed some evidence that supports a possible association between formaldehyde exposure and PC risk, this evidence is outweighed by more compelling evidence that does not support such an association. Overall, the pattern of findings suggests that the large, persistent nasopharyngeal and other PC excesses observed among the Wallingford workforce may reflect the influence of nonoccupational risk factors or occupational risk factors associated with employment outside the Wallingford plant.

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