Formaldehyde

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Citation for most recent IARC review

IARC Monograph 88, 2006

Current evaluation

Conclusion from the previous Monograph:

Formaldehyde is *carcinogenic to humans (Group 1)*. There is *sufficient evidence* in humans for the carcinogenicity of formaldehyde. There is *sufficient evidence* in experimental animals for the carcinogenicity of formaldehyde.

However, on p.276 of IARC Monograph 88 with regard to the ability of formaldehyde to cause leukemia it states: "In summary, there is strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde. Increased risk for leukemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers."

The Working group concluded that the epidemiological findings provided 'strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde'. However, after reviewing the toxicological and mechanistic data available, the Group concluded that 'Based on the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans'. Several possible mechanisms were considered for the induction of human leukemia, such as clastogenic damage to circulatory stem cells. The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukemia in humans.

Exposure and biomonitoring

A number of new papers regarding exposure levels in several countries have been published since the monograph in 2006. A detailed review of exposure levels in China and elsewhere has recently been published (Tang et al., 2009). A summary of outdoor ambient concentrations worldwide was provided in Table 2 of a recent review and meta-analysis (Zhang et al., 2009).

Cancer in humans

(*adequate***,** Vol 88, 2006)

Formaldehyde has been evaluated by IARC to be a known cause of human nasal cancer, based on epidemiological and toxicological evidence. There is also strong support for a mechanism of action for nasopharyngeal carcinogenesis in which inhaled formaldehyde causes DNA-protein crosslinks in nasopharyngeal tissue.

Only one new report from an original epidemiology study in relation to leukemia induction by formaldehyde has been published since the last review. The NCI group has published a recent update of one of their studies, with an additional 10 years of follow-up, and it continues to suggest a possible link between formaldehyde exposure and mortality due to lymphohematopoietic malignancies, particularly myeloid leukemia (Beane Freeman, Blair et al., 2009).

Details are as follows: In the NCI's formaldehyde cohort, previously followed through December 31, 1979, and updated through December 31, 1994, formaldehyde exposure was associated with an increased risk for leukemia, particularly myeloid leukemia, that increased with peak and average intensity of exposure. Beane-Freeman et al. extended follow-up an additional 10 years through December 31, 2004 (median follow-up = 42 years), for 25 619 workers employed at one of 10 formaldehyde-using or formaldehyde-producing plants before 1966 (Beane Freeman et al., 2009). There were statistically significant increased risks for the highest vs. lowest peak formaldehyde exposure category ($\geq$ 4 parts per million (ppm) vs. >0 to <2.0 ppm) and all lymphohematopoietic malignancies (RR = 1.37; 95% CI = 1.03 to 1.81, *P* trend = .02) and Hodgkin lymphoma (RR = 3.96; 95% CI = 1.31 to 12.02, *P* trend = .01). Statistically nonsignificant associations were observed for multiple myeloma (RR = 2.04; 95% CI = 1.01 to 4.12, *P* trend > .50), all leukemia (RR = 1.42; 95% CI = 0.92 to 2.18, *P* trend = .12), and myeloid leukemia (RR = 1.78; 95% CI = 0.87 to 3.64, *P* trend = .13). There was little evidence of association for any lymphohematopoietic malignancy with average intensity or cumulative exposure at the end of follow-up in 2004. However, disease associations varied over time. For peak exposure, the highest formaldehyde-related risks for myeloid leukemia occurred before 1980, but trend tests attained statistical significance in 1990 only. After the mid-1990s, the formaldehyde-related risk of myeloid leukemia declined. The authors concluded that evaluation of risks over time suggests a possible link between formaldehyde exposure and lymphohematopoietic malignancies, particularly myeloid leukemia but also perhaps Hodgkin lymphoma and multiple myeloma. Observed patterns could be due to chance but are also consistent with a causal association within the relatively short induction – incubation periods characteristic of leukemogenesis.

Epidemiological issues worthy of further research include the appropriateness of the dose metric used in the NCI studies in which a significant association with hematological neoplasms was observed primarily with highest peak exposure rather than with average intensity or cumulative dose of formaldehyde. The implication of the association with highest peak exposure to both toxicological mechanisms of action as well as to the dose-response pattern appropriate to formaldehyde risk analysis would also be pertinent subjects for further research.

It should be noted that Marsh and Youk (2004) criticized the highest peak exposure metric used in the NCI studies, including pointing out that the peak exposures used in the metric were not based on actual measurements but estimated from estimated average time-weighted exposures (Marsh and Youk 2004). In their reanalysis, no association was observed between duration of time at the highest peak or the time since the first highest peak and leukemia mortality. They also suggest that some of the key methods of analysis used to evaluate the highest peak exposure metric are flawed or deficient). However, they did find that standardized mortality ratios for peak exposure categories and all leukemia and myeloid leukemia increased from deficits in the lowest exposed (e.g., 0.4 – 0.5) to excesses in the highest exposed (e.g., 1.2 – 1.4) categories (Marsh and Youk 2004).

A recent meta-analysis also used a "highest exposure" category to evaluate leukemia risk from formaldehyde exposure (Zhang et al., 2009). Using data from 19 studies, the summary relative risk (RR) for all types of lymphohematopoietic cancer combined was 1.25 (95% CI,

1.09–1.43, Shore adjusted). The summary relative risk was elevated in the 15 studies reporting data on all leukemia (RR = 1.54; 95% CI, 1.18–2.00, p < 0.001, Shore adjusted) with the highest summary relative risk seen in the six studies of myeloid leukemia (RR = 1.90; 95% CI, 1.31–2.76, p = 0.001, Shore adjusted). All six studies of myeloid leukemia had relative risks of 1.4 or higher. This new meta-analysis provides additional evidence of an association between formaldehyde exposure and human leukemia, especially for myeloid leukemia.

Based on the original data (observed deaths) in the above six studies, Zhang, Steinmaus et al. 2009 (Table 3) showed for the first time that myeloid leukemia (51%) is the primary type of leukemia observed with 19% being lymphocytic leukemia, while the remainder are unspecified. Furthermore, AML (64%, acute myeloid leukemia) is the major subtype of myeloid leukemia among leukemia deaths reported in formaldehyde-exposed individuals.

Bosetti et al. also published a quantitative analysis of pooled results from the published cohort studies through February 2007 (Bosetti, McLaughlin et al., 2008). They concluded that brain cancer and lymphohematopoietic neoplasms were modestly elevated in risk in professionals, but not in industry workers. They did not specifically examine myeloid leukemia.

Cancer in experimental animals

(*sufficient***,** Vol 88, 2006)

Mechanisms of carcinogenicity

Although the updated meta-analysis of Zhang et al. adds weight to the association between formaldehyde exposure and myeloid leukemia (Zhang, Steinmaus et al., 2009), several impediments remain to current full acceptance of formaldehyde as a cause of human myeloleukemogenesis. These include difficulty in understanding the pathway for this highly reactive inhaled agent to reach the human bone marrow; the high background levels of exposure to formaldehyde; and the recognition that it appears to have distinguishing features from other known human myeloleukemogens, including the current absence of evidence of pancytopenia in the published English literature and a relatively long latency period for AML.

It is not uncommon that epidemiological associations which are initially met with skepticism because of the absence of a perceived biological causal linkage spur the performance of basic mechanistic studies and animal toxicology that then provide the basis for confirming the causal validity of the epidemiological association. When the putative cause is an agent of major industrial importance to which exposure is common, such as formaldehyde, and for which there is an extensive toxicological data base, there is ample incentive to carefully and comprehensively investigate the potential biological linkage, as well as to replicate the epidemiological findings.

Described below are key issues related to the current issue of whether formaldehyde is a cause of human hematological cancers, and research that might help resolve the issue or at least narrow the extent of the current uncertainty. One of us co-authoring this document (MS) has been senior author of a paper containing a meta-analysis of the epidemiological literature

supporting a causal relation between formaldehyde and AML, as well as proposing biological mechanisms by which formaldehyde could cause AML. The other co-author (BG) has had a recent manuscript accepted for publication which concludes that current toxicological and hematological evidence does not support formaldehyde as a human myeloid leukemogen (Goldstein 2009).

New research related to mechanisms of formaldehyde penetrance to hematopoietic stem cells

Given the fact that formaldehyde is a highly reactive gas, the question arises as to how it reaches the blood and bone marrow to elicit toxic effects and produce leukemia. Several studies have reported increased chromosomal damage in the form of aberrations and micronuclei in circulating peripheral blood lymphocytes of workers exposed to formaldehyde (Suruda et al., 1993; Kitaeva et al., 1996; Ye et al., 2005; Yu et al., 2005; Orsiere et al., 2006). Increased levels of cytogenetic damage have also been reported in the bone marrow of exposed mice and rats, suggesting that it reaches the bone marrow in experimental animals (Kitaeva et al., 1990; Tao et al., 2004).

In aqueous solution, formaldehyde is converted mostly to oligomers of its diol form methanediol (formaldehyde hydrate, $CH_2(OH)_2$, or methylene glycol) and a dynamic equilibrium with formaldehyde is formed. The concentration of the diol oligomers versus that of formaldehyde depends on the precise conditions (temperature, pH, formaldehyde concentration) under which the reaction occurs (Walker 1964). Thus, methanediol, with a molecular weight of only 48, which can readily penetrate into tissues, may travel to the marrow through the blood where it is in equilibrium with reactive formaldehyde. The formaldehyde, once regenerated, can react with cellular macromolecules producing toxic injury (Fox et al., 1985). Further research into the generation of methanediol and its persistence in the circulation would be of value.

It is also possible that formaldehyde promotes leukemogenesis through direct induction of DNA damage and chromosome aneuploidy in hematopoietic stem or early progenitor cells in the nasal circulation or the nose. This hypothesis clearly requires additional testing and there at least two alternate mechanisms. As suggested by Zhang et al. formaldehyde may induce leukemia by damaging hematopoietic stem/progenitor cells circulating in the peripheral blood; or, by damaging the primitive pluripotent stem cells present within the nasal turbinates and/or olfactory mucosa. In these two alternate models, damaged stem/progenitor cells would then travel to the bone marrow and become initiated leukemic stem cells (Zhang et al., 2009).

New research related to the possible relation of formaldehyde leukemogenesis to known human leukemogens

Known human myeloid leukemogens are ionizing radiation, benzene and various systemic cancer chemotherapeutic agents. While the specific physicochemical processes vary greatly, common to all are mechanisms which result in the disruption of bone marrow DNA. Some act by direct alkylation of DNA; some through the action of free radicals or active states of oxygen; some through intercalating metals within the DNA structure; and some by inhibiting enzymes involved in cell division. Yet all of these agents produce pancytopenia at high doses,

which has not been described in the English literature with formaldehyde. Further, the epidemiological literature on AML associated with formaldehyde suggests a much longer latency period than usually observed with other known human myeloleukemogens (Goldstein 2009).

In their recent review Zhang et al. concluded that the published data on formaldehyde hematotoxicity are limited and inconsistent (Zhang et al., 2009). Several previous studies showed that formaldehyde altered the counts of different types of blood cells. One study reported that exposure to formaldehyde in humans reduced white blood cell counts (Kuo et al., 1997). Another recent study concluded that formaldehyde increased B cells, but decreased total T cells (CD3) and T-helper cells (CD8) in the blood of exposed workers, while T-suppressor (CD4) cells remained unchanged (Ye et al., 2005). In male rats exposed to a high dose of formaldehyde, increased monocytes, red blood cells and hemoglobin were detected, but lymphocyte counts were decreased (Vargova et al., 1993). Pancytopenia has not been a feature of classic long term safety assessment studies in which laboratory animals are exposed to the maximum tolerated dose of formaldehyde (Rusch et al., 1983; Maronpot et al., 1986; Appelman et al., 1988; Monticello et al., 1996). However, as the hematological system had not been perceived as a primary target of formaldehyde, it is perhaps possible that subtle effects were overlooked that may be observed with further study. The inconsistencies and limitations in the published studies suggest that more comprehensive studies of the hematological effects of formaldehyde in exposed populations and in laboratory animals are needed.

Recently, Tang et al. have evaluated the Chinese literature and describe eight studies conducted in China on hematological parameters in formaldehyde-exposed humans (Tang et al., 2009). These are published mainly in Chinese journals. The majority of these studies show that long-term exposure can decrease the number of white blood cells and possibly lower platelet and hemoglobin counts (see Table 9 in (Tang et al., 2009)). In a detailed study of occupationally exposed nurses, personal and area exposure data, as well as complete blood cell counts, were collected. This data was reported as a correlation matrix for complete blood count, formaldehyde concentration and work duration. The study concluded that the correlation between the decrease in WBCs and increase in formaldehyde concentration is the best indicator of exposure among the other outcomes (Kuo et al., 1997). One study of only 10 exposed subjects showed a non-significant decrease in WBC counts compared to the 10 controls (Tang et al., 2009), likely due to the small sample size. Another study reported no significant differences in WBC and Hb in individuals occupationally exposed to formaldehyde (Tang et al., 2009). Further evaluation of these Chinese studies is warranted.

Implications of the possibility that the nose is the site of formaldehyde leukemogenesis

Two inferences can be drawn from the proposal that formaldehyde may be leukemogenic through virtue of its reaction with hematopoietic stem cell precursors within the nose which would allow indirect assessment of this possibility.

A. Analysis of other nasal carcinogens and leukemia incidence in relation to formaldehyde

One inference is that other known nasal carcinogens might then be expected to be leukemogens. For chromium, a meta-analysis of 49 epidemiologic studies evaluating cancer mortality found an SMR for leukemia of only 88 (Cole and Rodu 2005). However, the major study of workers in a sulfur mustard factory showed an increase in leukemia risk (13 deaths observed; 8.51 expected) which was not statistically significant (Easton et al., 1988). This may reflect the fact that sulfur mustard is a known cause of human and laboratory animal pancytopenia – it was its pancytopenic effect observed in World War I mustard gas casualties that led to mustard derivatives being evaluated as a chemotherapeutic agent. Nickel, another known human nasal carcinogen, is not listed as causing leukemia; nor is arsenic, which may be a nasal carcinogen (Hayes 1997; Navarro Silvera and Rohan 2007). Both nickel and chromium are thought to act as carcinogens through DNA-protein cross-linking, the proposed mechanism of action of formaldehyde. Research into understanding the pathways of DNA damage of formaldehyde in relation to other know nasal carcinogens, as well as clarification of the risk of leukemia in cohorts exposed to other nasal carcinogens, would be helpful in interpreting the potential for formaldehyde leukemogenesis.

B. Analysis of the implications of the apparent rarity of chloroma formation within the nose

Another implication of the possibility that nasal tissue contains myelopoietic precursor cells is that nasal tissue would also be a location for isolated accumulations of myeloid tumor cells known as chloromas. Chloromas classically are collections of extramedullary malignant hematopoietic precursor cells that are sometimes observed prior to the development of frank AML.

Chloromas have been reported in virtually every tissue. However, if they occur at all in the nasal cavity they are relatively rare. For example, Yamauchi and Yasuda describe the site location of 102 tumor nodules in 74 patients with non-leukemic granulocytic sarcoma, i.e., chloromas that are diagnosed prior to systemic evidence of leukemia (Yamauchi and Yasuda 2002). The 23 tissues listed are skin, adipose tissue, bone, mediastinum, lymph nodes, tonsil, spleen, uterus, ovary, vagina, breast, testis, stomach, small intestine, liver, pancreas, epidural spine, meninges, brain, orbit, heart, lungs and urinary bladder – but not nasal tissue. Underdiagnosis of nasal tissue chloromas is unlikely.

Chloromas do occur in paranasal sinuses (O'Brien et al., 2008). However, based on data in the rhesus monkey penetration of formaldehyde into sinuses is restricted (Monticello et al., 1989; Kepler et al., 1998). Similarly the IARC monograph (2006), points out that the usual practice of combining cancers of the nose and nasal sinuses might dilute a true effect of formaldehyde on nasal cancers, presumably because nasal sinuses would not be an expected location for formaldehyde exposure. More research is needed, including a thorough review of the literature, to both substantiate the apparent lack of chloromas in nasal tissue, and to further understand its implications. These include the finding that chloromas preferentially have the [t(8:21)] chromosomal translocation (Byrd et al., 1997).

Pyatt et al.(Pyatt et al., 2008) have also made a series of theoretical arguments against the nose as the site of formaldehyde leukemogenesis in response to the United States Environmental Protection Agency (EPA) recently proposed mode of action (MOA) to explain

how inhaled formaldehyde (FA) might induce leukemia, lymphoma and a variety of other lymphohematopoietic (LHP) malignancies in occupationally exposed workers. As discussed above the hypothesis requires that B lymphocytes or hematopoietic progenitor cells (HPC) present at the "portal of entry (POE)" undergo sustained mutagenic change as a result of direct FA exposure. These modified cells would then migrate back to the bone marrow or primary lymphatic tissue and subsequently develop into specific LHP disease states. Chemical interaction at the POE is an absolute requirement for the hypothesized MOA as, according to Pyatt et al., and they claim there is no convincing evidence that inhaled FA causes distant site (e.g., bone marrow) toxicity. The authors further claim the available data does not support the proposed concept of "peripheral transformation" at the chemical entry site and that the existing science does not support the proposed MOA as a logical explanation for proposing that FA is a realistic etiological factor for any LHP malignancy (Pyatt et al., 2008).

Implications of the possible epidemiological association of lymphoproliferative tumors to considerations of formaldehyde as a leukemogen

Modern molecular biological tools have amply demonstrated the ability of early hematopoietic precursor cells to differentiate broadly in both myeloproliferative and lymphoproliferative directions. The recent update by the NCI (Beane Freeman et al., 2009) suggests that there may also be an increase in lymphoid tumors in this cohort. This suggests that further study of the molecular mechanisms by which formaldehyde might cause AML consider the broader implications of an effect on an early hematopoietic precursor cell capable of differentiating to lymphoid and myeloid cell types.

Research on implications of epidemiological and mechanistic findings to risk assessment

The potential for leukemogenesis is of particular importance to the quantitative assessment of formaldehyde risks and its regulation as a risk to workers and the general population. Classic risk assessment dose response models for carcinogenesis tend to use linear “one-hit” models. The findings in the NCI cohort of a relationship of leukemia with highest peak exposure rather than standard dose measures potentially has implications for the dose extrapolation model. Similarly, the implications of a mechanism model which first leads to a malignant transformation of nasal pluripotential cells, and then subsequently to dislodge these cells, also needs to be explored.

Molecular events involved in formaldehyde carcinogenesis

Ridpath et al. (Ridpath et al., 2007) reported that cells deficient in the FANC/BRCA pathway are hypersensitive to plasma levels of formaldehyde. They assessed the DNA damage response to plasma levels of formaldehyde (13 to 97 micromol/L) using chicken DT40 cells with targeted mutations in various DNA repair genes. Hypersensitivity to formaldehyde was detected in DT40 mutants deficient in the BRCA/FANC pathway, homologous recombination, or translesion DNA synthesis. Human cells deficient in FANCC and FANCG were also hypersensitive to plasma levels of formaldehyde. These results indicate that the BRCA/FANC pathway is essential to counteract DNA-protein crosslinks caused by formaldehyde. Based on the results obtained in their study, the authors proposed that endogenous formaldehyde might have an effect on highly proliferating cells, such as bone marrow cells. Further, homologous recombination induced by formaldehyde in DNA-deficient cells may lead to leukemia-inducing translocations, a possibility that should be investigated.

Recently, Swenberg and colleagues (Lu et al., 2009) have produced findings which support the idea that formaldehyde may cause cancer by altering epigenetic regulation. Using mass spectrometry, the N-terminus of histone and lysine residues located in both the histone N-terminal tail and the globular fold domain were identified as binding sites for formaldehyde. The observation that only lysine residues without post-translational modification (PTM) can be attacked by formaldehyde indicates that PTM blocks the reaction between lysine and formaldehyde. Additionally, Lu et al. found that formaldehyde-induced Schiff bases on lysine residues could inhibit the formation of PTM on histones that may affect their function in gene regulation (Lu et al., 2009).

Research needs and recommendations

More molecular epidemiological studies examining the genotoxic effects of formaldehyde are needed (Zhang et al., 2009). For example, the only human studies performed to date showing elevated DPCs in the peripheral mononuclear cells of formaldehyde-exposed workers (Shaham et al., 1996; Shaham et al., 2003), need to be replicated due to the excessively high levels of DPCs reported in the controls.

Studies showing increased CA in humans have a number of methodological weaknesses, including poor exposure assessment, non-current measurement of exposure and outcome, small sample size, etc, necessitating replication of the findings in better-designed studies (Bauchinger and Schmid 1985; Chebotarev et al., 1986; Vozenilkova et al., 1991; Kitaeva et al., 1996; He, Jin et al., 1998; Lazutka et al., 1999). Despite these limitations, many studies report positive results indicating that formaldehyde is able to cause a range of genotoxic effects in the DNA and chromosomes of lymphocytes, and possibly other bone marrow-derived cells. Recent studies have investigated the potential mechanisms underlying DNA damage (Wang et al., 2007) and the DNA repair pathways (Ridpath et al., 2007) induced by formaldehyde.

It is hypothesized that the induction of DPCs by endogenous formaldehyde plays a critical role in the initiation of progressive bone marrow failure or predisposition to malignant tumors in Fanconi anemia patients. Exposure to exogenous sources of formaldehyde could push susceptible individuals into a dangerous zone in which genotoxic levels of DPC are induced. One of the big limitations to this hypothesis is the uncertainty over whether exogenous formaldehyde can reach the bone marrow. A mouse model, such as a Fanconi anemia deficient mouse could be a useful tool to better understand whether formaldehyde causes bone morrow toxicity by inhalation. Such a model would also allow us to investigate the potential role of endogenous formaldehyde on the etiology of acute myeloid leukemia in Fanconi anemia patients.

Although leukemia arises from damaged blood stem cells, little is known about the sensitivity of blood stem cells to formaldehyde and whether formaldehyde produces mutations related to leukemia in these cells. As discussed above, some studies report that formaldehyde produces chromosome damage in circulating blood cells of exposed humans, but it is not known if it

also does so in blood progenitor/stem cells or how consistent its effects are. Studies of $CD34^+$ cells exposed to formaldehyde in culture were suggested to address these issues.

Molecular epidemiology/biomarker studies of occupationally-exposed populations should be designed to address whether formaldehyde causes hematotoxicity, as it has not been definitively shown. A biomarker discovery approach should be applied in these studies using toxicogenomic, proteomic, and metabolomic tools. Leukemia-specific markers, such as chromosome translocations, should be examined in peripheral blood leukocytes and progenitor cells. Together, the study of leukemia-specific chromosome damage in cultured $CD34^+$ cells and of hematotoxicity in human populations will strengthen the biological plausibility and help to elucidate a mode of action.

Further studies in transgenic mice with DNA repair deficiencies is one possible future research direction. The determination of whether adducts are formed in the bone marrow of mice treated with formaldehyde-generating chemicals and whether the FANC/BRCA pathway is involved in the response to such damage in the bone marrow could help to determine if exogenous formaldehyde reaches the bone marrow. The potential application of the *Pig-A* mutation assay and/or a knock-out mouse model to clarify the mechanisms of formaldehyde-induced leukemogenesis is also proposed. These various research approaches will provide lines of evidence that can be used to ascertain causality.

Finally, because few tools are available to measure formaldehyde exposure internally, chemical-specific methodologies to specifically detect adducts of formaldehyde to DNA and proteins in blood, bone marrow and other target tissues are urgently needed. The recently developed assay for the formaldehyde-DNA adduct N^6-HOMe-dAdo in leukocytes is one example. The ability to accurately measure formaldehyde exposure, particularly if the marker was linked to a potential pathway of formaldehyde carcinogenesis, would address one of the key aspects of causality judgment in risk assessment, that of biologic gradient or exposure-response relationship. According to this relationship, increasing effects associated with greater exposure strongly suggest cause and effect. Swenberg and colleagues recently demonstrated that formaldehyde can cross-link GSH with DNA by forming *S*-[1-(N^2-deoxyguanosinyl)methyl]glutathione in the test tube, and proposed utilizing this adduct as a biomarker of formaldehyde exposure and toxicity (Lu et al., 2009). Further, the authors proposed that this adduct, coupled with isotope-labeled formaldehyde, could differentiate between endogenous and exogenous origin of formaldehyde-derived adducts.

In conclusion, much of the uncertainty in the risk assessment of formaldehyde and leukemia could be limited through a concerted effort among all associated disciplines in the design of future studies. Risk assessment does not weigh one type of evidence against another, but rather weighs all of the evidence taken together. Research that strengthens the consistency, strength, specificity, exposure-response relationship, or biological plausibility of an observed association, or that provides experimental evidence in human populations, will aid in making supportable causality judgments.

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