



Addendum to the 12th Report on Carcinogens

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The twelfth edition of the National Toxicology Program (NTP) Report on Carcinogens (RoC) contains a change in the listing status of formaldehyde. Prior editions of the RoC had listed formaldehyde as *reasonably anticipated to be a human carcinogen*, and following a rigorous scientific review, formaldehyde is now reassigned to the category *known to be a human carcinogen*. Concurrently, the Environmental Protection Agency (EPA) prepared and released a draft Integrated Risk Information System (IRIS) assessment of formaldehyde. At the request of EPA Administrator Jackson, a National Academy of Sciences (NAS) committee was convened to conduct an independent review of the draft EPA IRIS assessment of formaldehyde. The draft EPA IRIS assessment is a comprehensive health effects assessment and provides quantitative estimates of human risks of adverse human health outcomes from specific levels of exposure to formaldehyde.

The NAS committee was not charged with performing its own health effects assessment, conducting its own literature searches, or formulating its own conclusions regarding cancer causality for formaldehyde. The charge to the NAS consisted of specific questions, one of which (Is the weight-of-evidence *narrative* in the EPA IRIS assessment scientifically supported?) was related to the hazard identification component of the IRIS document and was relevant to the IRIS formaldehyde cancer assessment; the other charge questions were specific for the risk assessment component of the IRIS document.

The NAS produced a peer-review report of the EPA IRIS assessment's justifications for its conclusions for health effects, including cancer (NRC 2011). Because the NAS document is not an independent hazard assessment, it has limited applicability to the NTP's RoC evaluation of formaldehyde. The RoC evaluation involved a multistep comprehensive assessment of the literature, and resulted in a narrative justification for the NTP's conclusions that was developed independently from the EPA IRIS assessment. Neither the NTP listing process nor the justification for the listing of formaldehyde in the RoC was reviewed by the NAS. Nonetheless, the NTP has carefully reviewed the key scientific issues raised in the NAS peer-review report for potential relevance to the NTP's conclusions on the carcinogenicity of formaldehyde.

Listing for formaldehyde in the 12th RoC

The NTP's decision to list formaldehyde in the 12th RoC as *known to be a human carcinogen* was the result of a rigorous scientific review process that included many opportunities for public involvement and comment. The NTP solicited advice from three independent review groups: a non-government expert scientific panel, a government interagency scientific panel, and a National Institute of Environmental Health Sciences (NIEHS)–NTP scientific panel.

The criterion for listing as *known to be a human carcinogen* in the RoC is “sufficient evidence of carcinogenicity from studies in humans, which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer” (see page 4 of the 12th RoC). The NTP's decision to list formaldehyde as *known to be a human carcinogen* is based on the points below and is consistent with the recommendations from each of the three independent review groups.¹ Point A alone satisfies the RoC criteria to list a substance as *known to be a human carcinogen*.

- A. Sufficient evidence of cancer from studies in humans: nasopharyngeal cancer, sinonasal cancer, and lymphohematopoietic cancer, specifically myeloid leukemia.
- B. Supporting evidence from (a) cancer studies in experimental animals (primarily tumors of the nasal cavity, but also tumors at other sites) and (b) mechanistic data, which are data that determine how a (typically) adverse health outcome occurs.

The information that the NTP used to reach a decision on the listing status for formaldehyde is presented in a publicly available Background Document, which was peer reviewed by the non-government expert panel and was discussed in detail by each of the three review groups charged with making a listing recommendation. For the purpose of listing a substance as *known to be a human carcinogen* in the RoC, the literature must provide sufficient information to establish that significant exposure to the substance occurs or has occurred in the United States, and to allow a determination of cancer causation from scientific evidence from studies in humans. Appreciation of “mode of action,” or an understanding of how exposure to a given substance might lead to cancer, is an important piece of supporting evidence, but is not a requirement for listing in the RoC. Empirical evidence of cancer causation in humans is sufficient to satisfy the listing criterion.

Causality from studies in humans is defined by the RoC listing criteria as a credible association that cannot be explained by chance, bias, or confounding. Several of the guidelines proposed by Bradford-Hill — strength of the association (e.g., magnitude

¹The expert panel's recommendation on listing status is available at http://ntp.niehs.nih.gov/ntp/roc/twelfth/2009/November/FA_PartB.pdf.

of the risk estimate, consistency across findings, exposure-response relationships, and temporality) — are used to evaluate whether an association is credible and whether chance, bias, and confounding can be ruled out (Hill 1965). Emphasis is placed on “informative studies,” which are studies of high quality with a design and methodologies to detect an effect and to rule out potential confounding from exposure to other carcinogens. Characteristics of these studies are sufficient statistical power, robust exposure assessments, evaluation of exposure-response relationships, and adequate reporting to allow a full consideration of methodological limitations.

The scientific decision to list a substance in the RoC is based on the entire body of literature, including both positive and negative studies. The evidence that supports the listing status is captured in the substance profile and includes (1) the identification of informative studies and (2) the critical findings from those studies that allow one to rule out chance, bias, and confounding, such as consistency across studies in tumor sites of interest, consistency in increased risk in different populations, statistical significance, and positive exposure-response relationships.

Conclusions of the EPA IRIS assessment regarding formaldehyde as a human carcinogen

The conclusions for formaldehyde reached by the EPA IRIS evaluation are generally consistent with those of the NTP RoC evaluation. The EPA IRIS and the NTP RoC concluded that human epidemiologic studies demonstrate that formaldehyde exposure causes nasopharyngeal cancer, sinonasal (nasal and paranasal) cancer, and myeloid leukemia.

The EPA IRIS also stated there was a causal association with all leukemias and lymphohematopoietic cancers as a group, and there was strong, but not sufficient, evidence for a causal association for other upper-respiratory tract cancers, Hodgkin’s lymphoma, or multiple myeloma. The NTP recognizes that there is scientific disagreement over whether it is appropriate to group lymphohematopoietic cancers and, therefore, evaluated data on both grouped and individual subtypes of leukemia. With regard to these cancers, the RoC’s listing of formaldehyde as a known human leukemogen is based on formaldehyde’s causal association with myeloid leukemia only, not lymphohematopoietic cancers as a group.

NAS conclusions from the committee’s review of the EPA IRIS assessment of formaldehyde

The NAS report includes the following conclusions:

- A. The NAS committee stated that the EPA narrative justifies EPA’s conclusion that formaldehyde causes cancers of the nose, nasal cavity, and nasopharynx in humans, which is consistent with the NTP’s listing of formaldehyde as *known to be a human carcinogen* in the 12th RoC.

- B. The NAS committee stated that the EPA narrative does not justify the IRIS assessment's conclusion that formaldehyde causes specific subtypes of lymphohematopoietic cancers, such as myeloid leukemia. Because the NAS committee did not conduct its own independent assessment, it did not offer an opinion on whether the evidence from studies in humans supports a causal relationship. The NTP has concluded that the scientific evidence from studies in humans is sufficient to conclude that exposure to formaldehyde causes myeloid leukemia.
- C. The NAS committee stated that the EPA narrative does justify the IRIS assessment's conclusion that formaldehyde causes genetic damage (damage to DNA and chromosomes) in exposed humans, which is a presumed mechanism by which formaldehyde causes cancer. The NTP evaluation for the 12th RoC concurs.

The NAS and RoC conclusions specific for lymphohematopoietic cancers

As mentioned above, the NAS did not specifically state an opinion on the strength of the epidemiologic evidence for an association of formaldehyde and myeloid leukemia in exposed humans. They noted that while a well-established mode of action is not required to make causal inference, they did not believe it was plausible, based on the demonstrated rapid reactivity of formaldehyde with blood components, that inhaled formaldehyde could gain direct access to the bone marrow. The NAS also disagreed with the grouping of all lymphohematopoietic cancers in the EPA IRIS assessment because they believed that they are different diseases. They commented that the narrative provided in the draft IRIS assessment did not support the EPA's determination that formaldehyde causes lymphohematopoietic cancers and recommended that the EPA clarify its arguments that support determinations of causality, including describing the criteria that were used to weigh evidence and assess causality.

The NTP used the approach described above in its hazard evaluation for myeloid leukemia for the RoC. A limitation in the body of literature of human studies on formaldehyde and lymphohematopoietic cancers is that only a subset reported risk estimates specific for myeloid leukemia. The scientific information supporting the NTP's conclusions is summarized in the RoC substance profile. The substance profile identifies the high-quality, informative studies on formaldehyde that allow one to rule out chance, bias, and confounding; describes the study populations and findings; and discusses why they were considered to be the most useful studies. The evidence supporting causality in human studies is (1) consistent findings of increased risk among the highest exposed workers across studies, (2) positive exposure-response relationships, and (3) adequacy to rule out confounding. A recent meta-analysis finding a positive association among workers with the highest exposure ($RR = 2.47$,

95% CI = 1.31 to 2.67) confirmed the consistency of the findings across studies (Schwilk *et al.* 2010).

The NAS committee, the EPA IRIS document, and the 12th RoC formaldehyde substance profile are consistent on the point that the mechanism(s) by which formaldehyde causes leukemia are not known, but agree that formaldehyde causes genetic damage in exposed humans, which is a key event in cancer formation. Most substances that cause leukemia are thought to do so by directly damaging stem cells (cells that give rise to blood and lymphoid cells) in the bone marrow. Formaldehyde is highly reactive; thus, some scientists have questioned whether it is plausible for formaldehyde inhaled through the nasal cavity to cause adverse health effects in tissues, such as bone marrow, that are far from the site of entry. The 12th RoC substance profile acknowledges the current lack of understanding of the biological mechanism(s) by which formaldehyde causes cancer at distal sites, including the evidence in laboratory animals failing to demonstrate systemic delivery. In addition, the substance profile cites direct evidence of genetic damage in circulating lymphocytes (white blood cells) and evidence of suppression of blood-forming elements in workers exposed to formaldehyde as support for the plausibility that formaldehyde causes myeloid leukemia. At the current time, it is not known how formaldehyde causes genetic damage to the stem cells, leading to hematological changes, and cancer; however, plausible hypotheses have been advanced on ways that formaldehyde might damage stem cells in the nose or blood without directly damaging the bone marrow and they are discussed in the substance profile. The mechanism(s) by which a substance listed in the RoC causes cancer are typically not known and, as noted above, mode of action is not a requirement for listing. Empirical evidence of cancer causation in humans satisfies the criterion for listing as *known to be a human carcinogen*.

Conclusion

Studies in humans have shown that formaldehyde causes nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia. The NTP's recommendation for listing formaldehyde in the 12th RoC is the result of a rigorous scientific review process that provided many opportunities for public and scientific input, including an independent assessment of the literature by external experts and peer review of the science supporting the NTP's listing decision.

Although the NAS report is an important document, it has limited applicability to the NTP review of formaldehyde, because it is a peer-review report of the EPA IRIS assessment's justifications for its conclusions on carcinogenicity and other health effects and not an independent hazard assessment of the scientific literature on formaldehyde. Nevertheless, the NAS report concurs with the EPA's conclusions that formaldehyde causes cancer of the nose, nasal cavity, and nasopharynx and genetic damage (a general mechanism by which substances are thought to cause cancer), which is supportive of the NTP's listing for formaldehyde as *known to be a human*

carcinogen. With respect to myeloid leukemia, the NAS report questioned the plausibility that formaldehyde could cause this specific type of cancer by currently known mechanism(s), but was silent on whether the epidemiologic data from cancer studies in humans show a causal relationship. The NTP acknowledges uncertainty regarding the mechanism by which formaldehyde causes myeloid leukemia. The NTP's conclusion that formaldehyde causes myeloid leukemia is based on the human epidemiologic data and is consistent with the RoC listing criterion.

References

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