

Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens

Why Did the National Research Council Do This Study?

In 1981, the National Toxicology Program (NTP) listed formaldehyde in the 2nd Report on Carcinogens (RoC) as “reasonably anticipated to be a human carcinogen”. In 2011, NTP upgraded the listing of formaldehyde in the 12th RoC to “known to be a human carcinogen”. Following the new listing, Congress directed the Department of Health and Human Services to arrange for the National Academy of Sciences to independently review formaldehyde’s substance profile and listing in the 12th RoC. This report presents the findings and conclusions of the committee formed in response to the congressional request.

Key Finding

Because there is sufficient evidence of carcinogenicity from studies in humans that indicates a causal relationship between exposure to formaldehyde and at least one type of human cancer, the committee concludes that formaldehyde should be listed in the RoC as “known to be a human carcinogen”.

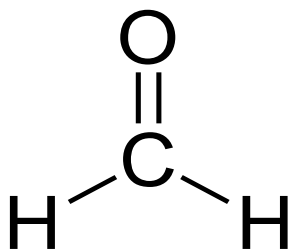


Figure 1. The structure of the formaldehyde molecule.

HOW DID THE COMMITTEE CARRY OUT ITS TASK?

The National Research Council committee approached its statement of task by first conducting a review of the substance profile for formaldehyde as presented in the 12th Report on Carcinogens (RoC), considering literature published by June 10, 2011 (the date of publication of the 12th RoC). The committee then conducted its own independent assessment of the formaldehyde literature, extending its review to include literature published through 2013. The committee concluded by making its own listing recommendation for formaldehyde.

WHAT IS THE REPORT ON CARCINOGENS?

Since 1980, the National Toxicology Program (NTP) has published the RoC, a cumulative summary of substances that have been nominated for review and judged to meet two conditions: that a significant number of people living in the United States are exposed to the substance and that the substance is known or reasonably anticipated to be a human carcinogen on the basis of the RoC listing criteria. The assessment of chemicals for listing in the RoC constitutes a hazard assessment, not a risk assessment.

WHAT IS THE DIFFERENCE BETWEEN A HAZARD ASSESSMENT AND A RISK ASSESSMENT?

Hazard indicates whether a substance can harm human health; risk indicates whether or not that harm is likely under specific exposure circumstances. A hazard assessment focuses on the identification of substances that may pose a hazard to human health, and it makes a classification regarding toxicity, for example, whether a chemical is “carcinogenic to humans” or “likely to be carcinogenic to humans”. A risk assessment focuses on the likely degree of damage and requires much more information, including completion of a hazard identification, dose–response analysis, exposure quantification, and characterization of risk. The committee thus approached its assessment of formaldehyde as an evaluation of hazard, not risk. It evaluated measures of association in a population (such as risk ratios, odds ratios, and incidence ratios) from epidemiology studies to inform its assessment of formaldehyde, but it did not identify exposure scenarios that could pose cancer risk as part of a full risk assessment.

WHAT IS FORMALDEHYDE?

Formaldehyde is an organic chemical. People can be exposed to exogenous formaldehyde (that is, formaldehyde produced outside of the body) from environmental sources (for example, combustion processes, building materials, and tobacco smoke) and in occupational settings (for example, the furniture, textile, and construction industries). People are also exposed to endogenous formaldehyde (that is, formaldehyde produced inside of the body), because the substance is produced naturally in the human body as part of the processes of cell metabolism.

Scientists have studied formaldehyde for decades to determine whether exogenous formaldehyde may be associated with cancer in humans. Much of the focus has been on cancers of the upper respiratory tract because those tissues were thought to be the most biologically plausible targets. However, there is increasing interest in the relationship between formaldehyde exposure and some lymphohematopoietic cancers (for example, leukemia).

WHAT DID THE REPORT FIND?

Peer Review

The committee found that NTP's background document for formaldehyde described the strengths and weaknesses of relevant studies in a way that is consistent and balanced. The substance profile appropriately cited studies showing positive associations that support the listing. However, the substance profile would be more complete if it included more discussion on why weaker, uninformative, inconsistent, or conflicting evidence did not alter NTP's conclusions. Although the committee identified that as a limitation in the substance profile, it would not likely alter NTP's final conclusions as presented in the substance profile for formaldehyde.

The committee's review was guided by the RoC listing criteria (see Box 2). The committee's task stated that "the NRC's assignment does not also include a separate review of the National Toxicology Program's listing criteria." Although the report does not contain an evaluation of the listing criteria, the committee did clarify several pertinent issues related to the application of the listing criteria to the assessment of formaldehyde.

The committee found the RoC listing criteria to be clear about the information needed to fulfill the criteria of sufficient evidence in experimental animals. The listing criteria were less clear about the information needed to meet the requirement of limited evidence or sufficient evidence of carcinogenicity from

Box 1 *What is the National Toxicology Program?*

The National Toxicology Program (NTP) is an interagency program of the National Institute of Environmental Health Sciences, the administrative lead and a part of the National Institutes of Health; the National Institute for Occupational Safety and Health, a part of the Centers for Disease Control and Prevention; and the National Center for Toxicological Research, a part of the Food and Drug Administration. The National Institutes of Health, the Food and Drug Administration, and the Centers for Disease Control and Prevention are all agencies under the U.S. Department of Health and Human Services.

How Does the National Toxicology Program Report on Carcinogens Differ from U.S. Environmental Protection Agency (EPA) Integrated Risk Information System (IRIS)?

There are inherent differences between EPA's IRIS assessments and NTP's RoC. IRIS assessments are comprehensive human health assessments that evaluate cancer and noncancer end points and include hazard and dose-response assessments that are used to derive toxicity values (that is, reference values and unit risk values). NTP qualitatively weighs evidence of carcinogenicity and compiles lists of substances that it classifies as known human carcinogens or reasonably anticipated human carcinogens to produce the RoC.

studies in humans. Therefore, the committee used its expert scientific judgment to interpret and apply the listing criteria to the human evidence evaluated in the report. It established a set of evaluation attributes and made judgments on the strength of each of the epidemiology studies it reviewed; studies were judged to be strong, moderately strong, or weak.

Limited evidence was defined as evidence from two or more strong or moderately strong studies with varied study designs and populations that suggested an association between exposure to formaldehyde and a specific cancer type, but alternative explanations such as chance, bias, or confounding factors could not be adequately ruled out because of limitations in the studies, and so a causal interpretation could not be accepted with confidence.

Sufficient evidence was defined as consistent evidence from two or more strong or moderately

strong studies with varied study designs and populations that found an association between exposure to formaldehyde and a specific cancer type and for which chance, bias, and confounding factors could be ruled out with reasonable confidence because of the study methodology and the strength of the findings.

The committee concludes that NTP comprehensively considered available evidence and applied the listing criteria appropriately in reaching its conclusion. The 12th RoC states that “formaldehyde is known to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in humans and supporting data on mechanisms of carcinogenesis.” The committee agrees with NTP’s conclusion, which is based on evidence published by June 10, 2011, that formaldehyde is a known human carcinogen.

Independent Assessment

The second part of the committee’s task was to conduct an independent assessment of formaldehyde. The committee identified and evaluated relevant, publicly available, peer-reviewed literature on formaldehyde, and it summarized human, experimental-animal, and mechanistic information on nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia. Other kinds of cancer were not summarized in this report because of a lack of strong evidence that formaldehyde exposure causes other types of cancer

in humans. On the basis of the RoC listing criteria (Box 2) and the definitions of limited evidence and sufficient evidence described above, the committee made its independent determinations as follows:

- There is sufficient evidence of carcinogenicity from studies of humans based on consistent epidemiologic findings on nasopharyngeal cancer, sinonasal cancer, and myeloid leukemia for which chance, bias, and confounding factors can be ruled out with reasonable confidence.
- There is sufficient evidence of carcinogenicity in animals based on malignant and benign tumors in multiple species, at multiple sites, by multiple routes of exposure, and to an unusual degree with regard to type of tumor.
- There is convincing relevant information that formaldehyde induces mechanistic events associated with the development of cancer in humans, specifically genotoxicity and mutagenicity, hematologic effects, and effects on gene expression.

Because there is sufficient evidence of carcinogenicity from studies in humans that indicates a causal relationship between exposure to formaldehyde and at least one type of human cancer, the committee concludes that formaldehyde should be listed in the RoC as “known to be a human carcinogen”.

Box 2 Report on Carcinogens Listing Criteria

Known To Be Human Carcinogen:

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

Reasonably Anticipated To Be Human Carcinogen:

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

or

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

or

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

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

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The National Academies appointed the above committee of experts to address the specific task requested by the Department of Health and Human Services. The members volunteered their time for this activity; their report is peer-reviewed and the final product signed off by both the committee members and the National Academies. This report brief was prepared by the National Research Council based on the committee's report.

For more information, contact the Board on Environmental Studies and Toxicology at (202) 334-1434 or visit <http://dels.nas.edu/best>. Copies of *Review of the Formaldehyde Assessment in the National Toxicology Program 12th Report on Carcinogens* are available from the National Academies Press, 500 Fifth Street, NW, Washington, D.C. 20001; (800) 624-6242; www.nap.edu.

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