

## **Formaldehyde and Human Health <sup>1</sup>**

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### Introduction

Formaldehyde – a simple organic chemical made of hydrogen, oxygen and carbon -- is a widespread and natural constituent of all living systems, from bacteria and fish to rodents and humans. In fact, formaldehyde is one of the most abundant organic compounds in the universe. In outer space, measurements of methyl formate – a product of alcohol and formaldehyde – in the swirling dust clouds of the Milky Way suggest that if the gas condensed into liquid form, a typical dust cloud would contain a thousand trillion trillion (1 with 27 zeros after it) gallons of formaldehyde. The National Academy of Sciences (NAS) reported in 2004 that formaldehyde also is given off by vegetation, forest fires and animal waste and is a natural component of fruits and other foods. <sup>2</sup>

As life evolved on earth, formaldehyde became an important part of the process because it is one of the simplest biological forms of carbon. Even the most primitive organisms relied on formaldehyde as a building block for the synthesis of more complex molecules. Due

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<sup>1</sup> This backgrounder is based in large measure on a paper entitled "Formaldehyde: Overview of Current Issues and Challenges for the Future," prepared by Robert Golden, Ph.D., science advisor to the Formaldehyde Council, Inc., Arlington, Va., for the International Nonwovens Technical Conference, Sept. 19-22, 2005.

<sup>2</sup> Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants (2004), National Academy of Sciences.

to its importance in various metabolic processes, formaldehyde is naturally present in the human body with concentrations of approximately one to two parts per million (ppm) in blood. Because it is volatile, formaldehyde is exhaled in human breath.

Because formaldehyde has existed since the beginning of life, the evolutionary process had to include a way to ensure that formaldehyde's inherent toxicity could be controlled. Certain enzymes evolved as the control system; among the most prevalent families of enzymes in all living systems is one known as aldehyde dehydrogenases (ADHs). While many forms of ADH exist, they all have the same function – to convert formaldehyde that is formed continuously in various biological processes to formate, which is less reactive and, therefore, less toxic than formaldehyde.

These highly efficient detoxification systems are found in all species and in most tissues. Their role is simple – to keep formaldehyde from reaching concentrations that are toxic to cells. Clearly, the role of these enzymes must be considered in any evaluation of formaldehyde and human health.

### Formaldehyde: Used Widely and Studied Extensively

In addition to being a building block in biological synthesis, formaldehyde is an important industrial chemical, used in the manufacture of numerous products. And manmade formaldehyde is no different from formaldehyde that occurs naturally. Important products that benefit from formaldehyde include resins used as adhesives in the production of particleboard, fiberboard and plywood, certain types of plastics, insulation, fertilizers, fungicides, biocides, corrosion inhibitors, embalming

fluids, disinfectants and household cleaners<sup>3</sup>.

Against this backdrop, it should come as no surprise that formaldehyde is one of the most studied chemicals used today. In fact, hundreds of studies have been conducted on metabolism, toxicity and effects in animals and humans.

With the discovery in 1979 that formaldehyde caused nasal cancer in laboratory rats following lifetime exposure to very high levels, an extensive effort was undertaken – and continues – to better understand the potential for effects in humans. Concerns about formaldehyde are based on its irritant properties along with its cancer-causing potential in humans.

The aforementioned NAS report noted that irritation of the eyes and upper respiratory tract is the primary human health effect of concern for setting exposure limits for both short- and long-term inhalation exposures to formaldehyde. “Risk of cancer and other chronic health effects appears to be negligible at concentrations that do not produce chronic irritation and overt target tissue damage,”<sup>2</sup> the report states.

In fact, formaldehyde is so irritating to the nasal passages of humans at levels that produce tumors in laboratory animals that humans simply cannot tolerate it -- even for a few minutes --. But questions remain concerning formaldehyde and human cancer. This background examines those questions in light of the latest scientific evidence.

### Formaldehyde and Human Cancer

The NAS reports<sup>2</sup> that a large number of studies (including more than 40 human studies) have examined the carcinogenic potential of formaldehyde in animals and humans. In June 2004, the International Agency for Research on Cancer (IARC) – part of the World Health Organization – evaluated those studies and classified formaldehyde as “carcinogenic to humans.” IARC based its decision primarily on findings from a National Cancer Institute (NCI) study of workers indicating that formaldehyde causes nasopharyngeal cancer (NPC) in humans. NPC is a very rare form of cancer that occurs where the rear of the nasal cavity meets the throat.

This study involved more than 25,000 workers at 10 plants where occupational exposure to formaldehyde occurred. Of 10 total cases of NPC, six occurred at one of the 10 plants (referred to by epidemiologists as Plant 1) and the other four cases were distributed randomly over the other nine plants. This situation is not the expected pattern from an occupational carcinogen, but rather suggests causes other than formaldehyde exposure at the single plant where most of the cases were observed. In fact, a separate study in 2002 of this one plant found no credible association with formaldehyde, and the authors suggested some other factor(s) must have been involved.<sup>4</sup> A 2007 study by University of Pittsburgh biostatistician and epidemiologist Dr. Gary Marsh concluded that the nasopharyngeal cancer mortality excess found at Plant 1 may not be due to formaldehyde exposure but rather reflects the influence of external employment in the ferrous and non-ferrous metal industries of the local area. Employment in these industries entailed possible exposures to several suspected risk factors for upper

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<sup>3</sup> More information concerning formaldehyde's benefits may be found in “Formaldehyde: A Brief History and Its Contributions to the Economy and Society,” available upon request from the Formaldehyde Council, Inc., email [smacedo@formaldehyde.org](mailto:smacedo@formaldehyde.org)

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<sup>4</sup> Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde by G. M. Marsh et al., *Toxicology & Industrial Health*, 2002, 18(6):257-68.

respiratory system cancer such as sulfuric acid mists, mineral acid, metal dusts and heat.<sup>5</sup>

It is important to understand that IARC judges the scientific evidence based exclusively on the hazard posed by a particular chemical, not the risk. Risk is evaluated on the basis of exposure level and dose in combination with hazard. IARC classifications do not cover exposure and dose, while classifications by regulatory agencies such as the U.S. Environmental Protection Agency (EPA) generally do.

IARC concluded that two studies provided “strong but not sufficient evidence for a causal association between leukemia and occupational exposure to formaldehyde.” One of these studies was also from the NCI and was a companion to the NCI study that reported NPC. However, IARC’s conclusion about leukemia was tempered since they “...could not identify a mechanism for leukaemia (British spelling) induction.” This statement was an important cautionary note since subsequent to IARC’s skepticism, a number of peer-reviewed critical evaluations have concluded that, based on a substantial body of information about chemical-induced leukemia, it is biologically implausible that formaldehyde would be capable of causing this disease.

In 2006 scientists within the EPA’s National Center for Environmental Assessment presented a mode of action theory whereby inhaled formaldehyde is alleged to induce leukemia in humans. Further, this theory postulates that formaldehyde may induce all cancers of the blood and bone marrow. This mode of action theory lacks supporting data. Formaldehyde does not fit the toxicological profile of a chemical capable of inducing leukemia in humans. There is no existing

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<sup>5</sup> Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers by G. M. Marsh et al., *Regulatory Toxicology and Pharmacology* 48 (2007) 308-319

evidence that formaldehyde reaches the bone marrow and therefore leukemogenic transformation due to formaldehyde is biologically implausible. Existing scientific evidence and understanding indicates that leukemias arise from the bone marrow.

Shortly after the NCI studies were published in 2003 and 2004 in the peer-reviewed *Journal of the National Cancer Institute*, the FCI commissioned two independent reviews by biostatisticians Gary Marsh, Ph.D., and Ada Youk, Ph.D., of the University of Pittsburgh. Their reviews -- one on NPC and the other on leukemia -- were based on a critical reanalysis of the original NCI data. One of these reviews was published in 2004 and the other in 2005 in the peer-reviewed *Journal of Regulatory Toxicology and Pharmacology*<sup>6</sup>; they indicate that NCI’s findings pertaining to both NPC and leukemia were highly questionable.

Because studies of the type published by NCI are complicated, there can be legitimate grounds for differences of opinion on how the data are interpreted. However, in addition to the two reviews by Marsh and Youk, a number of letters to the editor also have been published and the consistency of the criticisms of the NCI results is noteworthy. Even though the NCI studies were published only in 2003 and 2004, the federal institute has already agreed and is close to completing an update, adding an additional ten years of already-available data to the evidence. This update may help determine whether or not the relationships between occupational exposures to formaldehyde and increased risk of cancer are stronger or weaker. This update is likely to be finalized in late 2007 or early 2008.

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<sup>6</sup> Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute, *Regulatory Toxicology and Pharmacology* 40 (2004) 113-124, and Reevaluation of mortality risks from nasopharyngeal cancer in the formaldehyde cohort study of the National Cancer Institute, *Regulatory Toxicology and Pharmacology* 42 (2005) 275-283.

We are unaware of any government regulatory agencies which classify formaldehyde as a known human carcinogen at this time. The EPA, which currently classifies formaldehyde as a probable carcinogen, is awaiting the results of the NCI update before proceeding with a reconsideration of formaldehyde's cancer classification under its Integrated Risk Information System (IRIS) program.

*What is the Public to Make of this Confusing Situation?*

Every human has formaldehyde from various natural and manmade sources in his or her body. It has been estimated that the body produces about 50 grams (one-and-three-quarter ounces) of formaldehyde a day<sup>7</sup>. The human body has extraordinary capabilities of detoxifying formaldehyde which suggests that people are not likely to be harmed by typical levels of formaldehyde found in normal indoor and outdoor environments.

Concern about formaldehyde's potential to cause cancer at typical levels of exposure has fallen steadily as more and more is understood about how formaldehyde acts within the body. Whether it is formaldehyde that our bodies make naturally or the low levels typically found in the air we breathe, it is well known that our bodies metabolize and detoxify formaldehyde rapidly. All of the available and emerging human health research data is demonstrating that if formaldehyde exposure is kept below levels that produce chronic irritation and overt target tissue damage, the risk of cancer is essentially zero.

The FCI is spearheading a research program to further supplement the scientific understanding concerning this versatile chemical. The results of this research, in

combination with findings from the EPA's IRIS evaluation, should further clarify the level of understanding regarding the safety of formaldehyde for consumers and formaldehyde industry workers so they can continue to make wise choices and derive the vast benefits of this simple, widely used chemical.

The FCI is an Arlington, Va.-based trade association established by the formaldehyde industry in late 2003 to promote the responsible use and benefits of formaldehyde and work to ensure its accurate scientific evaluation. For more information about FCI research or other initiatives, call 703-741-5750 or email [lrose@formaldehyde.org](mailto:lrose@formaldehyde.org); for information on formaldehyde, visit [www.formaldehyde.org](http://www.formaldehyde.org).

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<sup>7</sup> Formaldehyde Fact Sheet, MFL Occupational Health Centre, Winnipeg, Manitoba, Canada, <http://www.mflohc.mb.ca/>