

FORMALDEHYDE

(Group 1)

For definitions of Groups, see Preamble Evaluation.

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5. Summary of Data Reported and Evaluation

[The text of these Summaries and Evaluations may be edited for language and clarity during the checking of the main text of the Monographs.]

5.1 Exposure data

Formaldehyde is produced worldwide on a large scale by catalytic, vapour-phase oxidation of methanol. Annual world production is about 21 million tonnes. Formaldehyde is used mainly in the production of phenolic, urea, melamine and polyacetal resins. Phenolic, urea and melamine resins have wide uses as adhesives and binders for the wood products, pulp and paper, and synthetic vitreous fibre industries and in the production of plastics and coatings and in textile finishing. Polyacetal resins are widely used in the production of plastics. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals, such as 1,4-butanediol, 4,4'-diphenylmethane diisocyanate, pentaerythritol and hexamethylenetetramine. Formaldehyde is used directly in aqueous solution (formalin) as a disinfectant and preservative in many applications.

Formaldehyde occurs as a natural product in most living systems and in the environment. In addition to these natural sources, common non-occupational sources of exposure include vehicle emissions, particle boards and similar building materials, carpets, paints and varnishes, food and cooking, tobacco smoke and the use of formaldehyde as a disinfectant. Levels of formaldehyde in outdoor air are generally below 0.001 mg/m³ in remote areas and below 0.02 mg/m³ in urban settings. The levels of formaldehyde in the indoor air of houses are typically 0.02–0.06 mg/m³. Average levels of 0.5 mg/m³ or more have been measured in 'mobile homes', but the levels have declined since the late 1980s as a result of standards requiring that building materials emit lower concentrations of formaldehyde.

Occupational exposure to formaldehyde occurs in a wide variety of occupations and industries. The highest continuous exposures (2–5 ppm) were measured in the past; during the varnishing of furniture and wooden floors, in the finishing of textiles, the garment industry, the treatment of fur and in certain jobs within manufactured board mills and foundries. Shorter-term exposures to high levels (3 ppm and higher) have been reported for embalmers, pathologists and paper workers. Lower levels have usually been encountered during the manufacture of man-made vitreous fibres, abrasives and rubber and in formaldehyde production industries. A very wide range of exposure levels has been observed in the production of resins and plastic products. The development of resins that release less formaldehyde and improved ventilation have resulted in decreased exposure levels in many industrial settings in recent decades.

5.2 Human data

Nasopharyngeal cancer

Since the last monograph on formaldehyde (in 1995) the follow-up of three major cohort studies has been extended and three new case–control studies have been published.

In the largest and most informative cohort study of industrial workers exposed to formaldehyde, there was a statistically significant excess of deaths from nasopharyngeal cancer in comparison with the US national population, with statistically significant exposure–response relationships for peak and cumulative exposure. An excess of nasopharyngeal cancer was also observed in a proportionate mortality analysis for the largest US cohort of embalmers and in a Danish study of proportionate cancer incidence among workers at companies which used or manufactured formaldehyde. In three other cohort studies of US garment manufacturers, British chemical workers and US embalmers, cases of nasopharyngeal cancer were fewer than expected, but the power of these studies to detect an effect on nasopharyngeal cancer was low and the deficits were small.

The relation of nasopharyngeal cancer with exposure to formaldehyde has also been investigated in seven case–control studies, five of which have found elevations of risk for overall exposure to formaldehyde, or in higher exposure categories, including one in which the increase in risk was statistically significant, and three (two of which have been published since the last monograph) that found higher risks in subjects with the highest probability, level or duration of exposure.

The most recent meta-analysis, which was published in 1997, included some but not all of the above studies and found an increased overall meta-relative risk for nasopharyngeal cancer.

The Working Group considered it improbable that all of the positive findings for nasopharyngeal cancer that were reported from the epidemiological studies, and particularly from the large study of industrial workers in the USA, could be explained by bias or unrecognized confounding effects.

Overall, the Working Group concluded that the results of the study of industrial workers in the USA, supported by the largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans.

Leukaemia

Excess mortality from leukaemia has been observed relatively consistently (six of seven studies) in the studies of professional workers (i.e. embalmers, funeral parlour workers, pathologists and anatomists). A recently published meta-analysis for exposure to formaldehyde among professionals and risk for leukaemia reported increased overall summary relative risk estimates for embalmers, and for pathologists and anatomists, which were found not to vary significantly between studies (i.e. results were found to be homogeneous). The excess of leukaemia seen in several studies appeared to be predominantly of a myeloid type. There has been speculation in the past that these findings might be explained by exposures to viruses experienced by anatomists, pathologists and perhaps funeral workers. However, currently there is little direct evidence that these occupations have a higher incidence of viral infections than the general population or that viruses have a causal role in myeloid leukaemia. Professionals may also be exposed to other chemicals, but they have no material exposure to known leukaemogens. Furthermore, the exposure to other chemicals would

differ between anatomists, pathologists and funeral workers which reduces the likelihood that such exposures could explain the observed increases in risk.

Until recently, the findings for leukaemia in studies of professional workers appeared to be contradicted by the lack of such findings among industrial workers. However, some evidence for an excess of leukaemia has been reported in the recent updates of two of the three major cohort studies of industrial workers. A statistically significant exposure–response relationship was observed between peak exposures to formaldehyde and mortality from leukaemia in the study of industrial workers in the USA. This relationship was found to be particularly strong for myeloid leukaemia, which was also observed in the study of anatomists and in several of the studies of embalmers. However, in the study of industrial workers in the USA, mortality from leukaemia was less than expected when comparisons were made using the general population as the referent group. This raises concerns about whether these findings are robust with respect to the choice of a comparison group. Leukaemia has been found to be associated with socioeconomic status, and industrial workers tend to have low socioeconomic status. Thus, the lack of an overall finding of an excess of leukaemia in the cohort of industrial workers in the USA might be explained by biases in the comparison between the study and referent populations. The study also failed to demonstrate an exposure–response relationship with cumulative exposure, although other metrics may sometimes be more relevant.

Mortality from leukaemia was also found to be in excess in the recent update of the study of garment workers exposed to formaldehyde in the USA. A small and statistically non-significant excess was observed for the entire cohort in comparison with rates from the general population. This excess was somewhat stronger for myeloid leukaemia, which is consistent with the findings from the study of industrial workers in the USA and several of the studies of medical professionals and embalmers. The excess was also stronger among workers with long duration of exposure and long follow-up, and who had been employed early in the study period when exposures to formaldehyde were believed to be the highest. This pattern of findings is generally consistent with what might be expected if, in fact, exposure to formaldehyde were causally associated with risk for leukaemia. The positive associations observed in many of the subgroup analyses presented in the analyses of the study of garment workers in the USA were based on a relatively small number of deaths, and were thus not statistically stable.

The updated study of British industrial workers failed to demonstrate excess mortality among workers exposed to formaldehyde. The lack of positive findings in this study is difficult to reconcile with the findings from the studies of garment workers and industrial workers in the USA and studies of professionals. This was a high-quality study with adequate size and sufficiently long follow-up to have had a reasonable chance to detect an excess of leukaemia. The British study did not include an evaluation of peak exposures, but neither did the study of garments workers in the USA or the studies of professionals. Also, the British study did not examine specifically the risk for myeloid leukaemia, which demonstrated the strongest findings in the studies of garment workers and industrial workers in the USA and in several of the studies of medical professionals and funeral workers.

In summary, there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia 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.

Sinonasal cancer

The association between exposure to formaldehyde and risk for sinonasal cancer has been evaluated in six case-control studies with a primary focus on formaldehyde. Four of these studies also contributed to a pooled analysis that collated occupational data from 12 case-control investigations. After adjustment for known occupational confounders, this analysis showed an increased risk for adenocarcinoma in both men and women and also (although on the basis of only a small number of exposed cases) in the subset of subjects who were thought never to have been occupationally exposed to wood or leather dust. Moreover, there was a dose-response trend in relation to an index of cumulative exposure. There was little evidence of an association with squamous-cell carcinoma. In one of the two other case-control studies, a positive association was found, particularly for squamous-cell carcinomas. An analysis of proportionate cancer incidence among industrial workers in Denmark also showed an increased risk for squamous-cell carcinomas.

Against these largely positive findings, no excess of sinonasal cancer was observed in other cohort studies of formaldehyde-exposed workers, including the three recently updated studies of industrial and garment workers in the USA and of chemical workers in the United Kingdom.

Most epidemiological studies of sinonasal cancer have not distinguished tumours arising in the nose from those developing in the nasal sinuses. Thus, any effect on the risk of nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk of cancer in the sinuses, making it more difficult to detect, particularly in cohort studies with relatively low statistical power. However, the apparent discrepancy between the results of the case-control as compared with the cohort studies might also reflect residual confounding by wood dust in the former. Almost all of the formaldehyde-exposed cases in the case-control studies were also exposed to wood dust, which caused a high relative risk, particularly for adenocarcinomas. Thus, there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans.

Cancer at other sites

A number of studies have found associations between exposure to formaldehyde and cancer at other sites, including the oral cavity, oro- and hypopharynx, pancreas, larynx, lung and brain. However, the Working Group considered that the overall balance of epidemiological evidence did not support a causal role for formaldehyde in relation to these other cancers.

5.3 Animal carcinogenicity data

Several studies in which formaldehyde was administered to rats by inhalation showed evidence of carcinogenicity, particularly induction of squamous-cell carcinomas of the nasal cavities. A similar study in hamsters showed no evidence of carcinogenicity. One study in mice showed no effect.

In four studies in rats, formaldehyde was administered in the drinking-water. One study in male rats showed an increased incidence of forestomach papillomas. In a second study in male and female rats, the incidence of gastrointestinal leiomyosarcomas was increased in females and in males and females combined. In a third study in male and female rats, the number of males bearing malignant tumours and the incidences of haemolymphoreticular tumours (lymphomas and leukaemias) and testicular interstitial-cell adenomas in males were increased. A fourth study gave negative results.

Skin application of formaldehyde concomitantly with 7,12-dimethylbenz[a]anthracene reduced the latency of skin tumours in mice. In rats, concomitant administration of formaldehyde and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in the drinking-water increased the incidence of adenocarcinoma of the glandular stomach. Exposure of hamsters by inhalation to formaldehyde increased the multiplicity of tracheal tumours induced by subcutaneous injections of *N*-nitrosodiethylamine.

5.4 Other relevant data

Toxicokinetics and metabolism

The concentration of endogenous formaldehyde in human blood is about 2–3 mg/L; similar concentrations are found in the blood of monkeys and rats. Exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter the concentration of formaldehyde in the blood. The average level of formate in the urine of people not occupationally exposed to formaldehyde is 12.5 mg/L and varies considerably both within and between individuals. No significant changes in urinary formate were detected after exposure to 0.4 ppm formaldehyde for up to 3 weeks in humans. More than 90% of inhaled formaldehyde is absorbed in the upper respiratory tract. In rats, it is absorbed almost entirely in the nasal passages; in monkeys it is also absorbed in the nasopharynx, trachea and proximal regions of the major bronchi. Absorbed formaldehyde can be oxidised to formate and CO₂ or be incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Formaldehyde has a half-life of about 1 min in rat plasma. Rats exposed to ¹⁴C formaldehyde eliminate about 40% of the ¹⁴C as CO₂, 70% in urine and 5% in faeces. After dermal application of aqueous [¹⁴C] formaldehyde approximately 7% of the dose was excreted in urine in rodents and 0.2% in monkeys. After oral dosing about 40% of the [¹⁴C] formaldehyde was excreted as CO₂, 10% in urine and 1% in faeces within 12 h.

Toxic effects in humans

There are many studies of the health effects of formaldehyde inhalation in humans. Most are in unsensitised subjects, where there is consistent evidence of irritation of the eyes, nose and throat. Symptoms are rare below 0.5 ppm, and become increasingly prevalent in exposure chamber studies as concentrations increase. Exposures to formaldehyde of up to 3 ppm are unlikely to provoke asthma in an unsensitized individual.

Nasal lavage studies show increased eosinophils and protein exudation following exposures to formaldehyde at 0.5 mg/m³. Bronchial provocation testing has confirmed occupational asthma due to formaldehyde in small numbers from several centres. The mechanism is likely to be due to hypersensitivity as the reactions are often delayed, there is a latent period of symptomless exposure and similar non-exposed asthmatic do not react at the same concentrations. There is one report of pneumonitis in a worker with 2 h of exposure sufficient for his breath to smell of formaldehyde. High levels of formaldehyde are likely to cause asthmatic reactions by an irritant mechanism. Formaldehyde is one of the commoner causes of contact dermatitis and is thought to act as a sensitizer on the skin.

Toxic effects in animals

Formaldehyde is a well documented irritant causing mild inflammation to severe ulceration. Formaldehyde caused direct toxicity in the upper respiratory system in concentration- and location-specific manner. There is evidence that formaldehyde can induce irritation to the forestomach after high-dose oral exposure. Formaldehyde is also a sensory irritant which results in a decrease in respiratory rate in rodents; mice are more sensitive than rats, as measured by respiratory depression. This respiratory depression is thought to be secondary

to stimulation of the trigeminal nerve. Formaldehyde can also result in pulmonary hyperactivity through a transient bronchoconstriction. It can also act as a skin contact sensitizer via a type IV hypersensitivity reaction. Formaldehyde does not cause haematological effects.

In-vitro toxicity

Formaldehyde exerts dose-dependent toxicity in cell cultures. Cytotoxicity involves loss of glutathione, altered Ca^{2+} -homeostasis and impairment of mitochondrial function. Thiols, including glutathione, and metabolism through ADH3, act in a protective manner.

Reproductive and developmental effects

Eleven epidemiological studies are available that have evaluated directly or indirectly the reproductive effects of occupational exposures to formaldehyde. The outcomes examined in these studies have included spontaneous abortions, congenital malformations, birth weights, infertility and endometriosis. Inconsistent reports of higher rates of spontaneous abortion and lowered birth weights were reported among women occupationally exposed to formaldehyde. Studies of inhalation exposure to formaldehyde in animal models have evaluated the effects of formaldehyde on pregnancy and fetal development. Such effects have not been clearly shown to occur at exposures below maternally toxic doses.

Genetic and related effects

There is evidence that formaldehyde is genotoxic in multiple in-vitro models and in exposed humans and laboratory animals. Studies in humans revealed increased DNA–protein cross-links in workers exposed to formaldehyde. This is consistent with studies in laboratory animals, in which inhaled formaldehyde reproducibly caused DNA–protein cross-links in rat and monkey nasal mucosa. There is a single study reporting cytogenetic abnormalities in the bone marrow of rats that inhaled formaldehyde, while other studies did not report effects in bone marrow.

Mechanistic considerations

The current data indicate that both genotoxicity and cytotoxicity play important roles in the carcinogenesis of formaldehyde in nasal tissues. DNA–protein cross-links provide a potentially useful marker of genotoxicity. The concentration–response curve for the formation of DNA–protein cross-links is bi-phasic, with the slope increasing at formaldehyde concentrations of about 2–3 ppm in Fischer 344 rats. Similar results are found in rhesus monkeys, although the dose–response curve for DNA–protein cross-links is less well defined in this species. Cell proliferation, which appears to amplify greatly the genotoxic effects of formaldehyde, is increased considerably at concentrations of formaldehyde of about 6 ppm, resulting in a marked increase in the occurrence of malignant lesions in the nasal passages of rats at concentrations above this level.

Several possible mechanisms were considered for the induction of human leukaemia, such as clastogenic damage to circulatory stem cells. The Working Group was not aware of any good rodent models for acute myeloid leukaemia in humans. Therefore, based on the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans.

5.5 Evaluation

There is *sufficient evidence* in humans for the carcinogenicity of formaldehyde.

There is *sufficient evidence* in experimental animals for the carcinogenicity of formaldehyde.

Overall evaluation

Formaldehyde is *carcinogenic to humans (Group 1)*.

For definitions of the italicized terms, see Preamble evaluation.

Previous evaluations: Suppl. 7 (1987) (p. 211); Vol. 62 (1995) (p. 217)

Synonyms

- BFV
- FA
- Fannoform
- Floguard 1015
- FM 282
- Formaldehyde, gas
- Formalin
- Formalin 40
- Formalith
- Formic aldehyde
- Formol
- Fyde
- Hoch
- Ivalon
- Karsan
- Lysoform
- Methaldehyde
- Methyl aldehyde
- Methyl oxide
- Methylene oxide
- Morbicid
- Oxomethane
- Oxymethylene
- Paraform
- Superlysoform

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