5. Summary of Data Reported and Evaluation

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 in wood product, pulp and paper, and synthetic vitreous fibre industries, 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'-methylenediphenyl diisocyanate, pentaerythritol and hexamethylenetetramine. Formaldehyde is used directly in aqueous solution (formalin) as a disinfectant and preservative in many applications.

Occupational exposure to formaldehyde occurs in a wide variety of occupations and industries. The highest continuous exposures (2–5 ppm) [2.5–6.1 mg/m³] were measured in the past during the varnishing of furniture and wooden floors, in the finishing of textiles, in the garment industry, in the treatment of fur and in certain jobs within manufactured board mills and foundries. Shorter-term exposures to high levels (3 ppm and higher) [3.7 mg/m³ 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 levels of exposure in many industrial settings in recent decades.

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 these have declined since the late 1980s as a result of standards that require that building materials emit lower concentrations of formaldehyde.
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, a statistically significant excess of deaths from nasopharyngeal cancer was observed in comparison with the US national population, with statistically significant exposure–response relationships for peak and cumulative exposure. An excess of deaths from nasopharyngeal cancer was also observed in a proportionate mortality analysis of the largest US cohort of embalmers and in a Danish study of proportionate cancer incidence among workers at companies that 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 relationship between nasopharyngeal cancer and exposure to formaldehyde has also been investigated in seven case–control studies, five of which found elevated risks for overall exposure to formaldehyde or in higher exposure categories, including one in which the increase in risk was statistically significant; three studies (two of which have been published since the last monograph) found higher risks among subjects who had 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 in six of seven studies of professional workers (i.e. embalmers, funeral parlour workers, pathologists and anatomists). A recently published meta-analysis of exposure to formaldehyde among professionals and the risk for leukaemia reported increased overall summary relative risk estimates for embalmers, and for pathologists and anatomists, which did not vary significantly between studies (i.e. the results were found to be homogeneous). The excess incidence 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 that are experienced by anatomists, pathologists and perhaps funeral workers. However, there is currently little direct evidence that these occupations have a higher incidence of viral infections than that of the general population or that viruses play 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 deaths from 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, a finding that 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 lower 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 that of industrial workers tends to be low. Thus, the lack of an overall finding of an excess of deaths from 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 among 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 who had a 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 highest. This pattern of findings is generally consistent with what might be expected if, in fact, exposure to formaldehyde were causally associated with a risk for leukaemia. The positive associations observed in many of the subgroup analyses presented in 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 of adequate
size and with sufficiently long follow-up to have had a reasonable chance to detect an excess of deaths from leukaemia. The British study did not include an evaluation of peak exposures, but neither did the study of garments workers in the USA nor the studies of professionals. Also, the British study did not examine specifically the risk for myeloid leukaemia, which represented 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 the risk for sinonasal cancer has been evaluated in six case–control studies that primarily focused 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, a dose–response trend was observed in relation to an index of cumulative exposure. There was little evidence of an association with squamous-cell carcinoma, although 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 mortality from 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 between tumours that arise in the nose and those that develop in the nasal sinuses. Thus, any effect on the risk for nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk for cancer in the sinuses, and would thus mask its detection, particularly in cohort studies that have 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
resulted in 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 the induction of squamous-cell carcinomas of the nasal cavities. A similar study in hamsters showed no evidence of carcinogenicity, and one study in mice showed no effect.

In four studies, formaldehyde was administered in the drinking-water to rats. 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 that developed 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 adenocarcinomas of the glandular stomach. Exposure of hamsters by inhalation to formaldehyde increased the multiplicity of tracheal tumours induced by subcutaneous injections of N-nitrosodioethy lamine.

### 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 these concentrations. The average level of formate in the urine of people who are 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 in humans after exposure to 0.5 ppm [0.6 mg/m³] formaldehyde for up to 3 weeks. 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 oxidized to formate and carbon dioxide or may 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 $[^{14}\text{C}]$formaldehyde eliminated about 40% of the $^{14}\text{C}$ as exhaled carbon dioxide, 17% in the urine and 5% in the faeces; 35–39% remained in the tissues and carcass. After dermal application of aqueous $[^{14}\text{C}]$formaldehyde, approximately 7% of the dose was excreted in the urine by rodents and 0.2% by monkeys. After oral administration, about 40% of $[^{14}\text{C}]$formaldehyde was excreted as exhaled carbon dioxide, 10% in the urine and 1% in the faeces within 12 h.

**Toxic effects in humans**

Many studies have evaluated the health effects of inhalation of formaldehyde in humans. Most were carried out in unsensitized subjects and revealed consistent evidence of irritation of the eyes, nose and throat. Symptoms are rare below 0.5 ppm, and become increasingly prevalent in studies in exposure chambers as concentrations increase. Exposures to up to 3 ppm [3.7 mg/m$^3$] formaldehyde are unlikely to provoke asthma in an unsensitized individual.

Nasal lavage studies show increased numbers of eosinophils and protein exudation following exposures to 0.5 mg/m$^3$ formaldehyde. Bronchial provocation tests have confirmed the occurrence of occupational asthma due to formaldehyde in small numbers of workers from several centres. The mechanism is probably hypersensitivity, because the reactions are often delayed, there is a latent period of symptomless exposure and unexposed asthmatics do not react to the same concentrations. One case of pneumonitis was reported in a worker who was exposed for 2 h to a level that was sufficient for his breath to smell of formaldehyde. High levels of formaldehyde probably 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 that causes mild inflammation to severe ulceration. It caused direct toxicity in the upper respiratory system in a 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 that induces 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 by the irritant effect of formaldehyde. Formaldehyde can also result in pulmonary hyperactivity through transient bronchoconstriction.
It can also act as a skin contact sensitizer via a type IV T-cell mediated hypersensitivity reaction. Formaldehyde does not induce 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 alcohol dehydrogenase 3, act in a protective manner.

**Reproductive and developmental effects**

Eleven epidemiological studies have evaluated directly or indirectly the reproductive effects of occupational exposures to formaldehyde. The outcomes examined in these studies 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, which 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 laboratory studies, in which inhaled formaldehyde reproducibly caused DNA–protein cross-links in rat and monkey nasal mucosa. A single study reported 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, and the slope increases at formaldehyde concentrations of about 2–3 ppm [2.4–3.7 mg/m³] in Fischer 344 rats. Similar results are found in rhesus monkeys, although the dose–response curve 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 [7.4 mg/m³], and results 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 that simulate the occurrence of acute myeloid leukaemia 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 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).