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 12 million tonnes. It is used mainly in the production of phenolic, urea, melamine and acetal resins, which have wide use in the production of adhesives and binders for the wood, plastics, textiles, leather and related industries. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals, such as 1,4-butanediol and 4,4′-diphenylmethane diisocyanate (for polyurethanes and particle-board), pentaerythritol (for surface coatings and explosives) and hexamethylene tetramine (for phenol–formaldehyde resins and explosives). Formaldehyde is used as such 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. Common nonoccupational sources of exposure include vehicle emissions, some building materials, food, tobacco smoke and its use as a disinfectant. Levels of formaldehyde in outdoor air are generally below 0.001 mg/m^3 in remote areas and below 0.02 mg/m^3 in urban settings. The levels of formaldehyde in the indoor air of houses are typically 0.02–0.06 mg/m^3; average levels of 0.5 mg/m^3 or more have been measured in 'mobile homes' constructed with particle-board or in houses with urea–formaldehyde insulation, but the levels have declined in recent years as a result of changes in building materials.

It is estimated that several million people are exposed occupationally to formaldehyde in industrialized countries alone. The highest continuous exposures (frequently > 1 mg/m^3) have been measured in particle-board mills, during the varnishing of furniture and wooden floors, in foundries, during the finishing of textiles and in fur processing. Short-term exposures to much higher levels have been reported occasionally. Exposure to more than 1 mg/m^3 also occurs in some facilities where resins, plastics and special papers are produced. The average formaldehyde level measured in plywood mills and in embalming establishments is about 1 mg/m^3. Lower levels are encountered, for example, during the manufacture of garments, man-made mineral fibres, abrasives and rubber. Periodic occupational exposure occurs e.g. during disinfection in

hospitals and in food processing plants, in some agricultural operations and during firefighting. The development of resins that release less formaldehyde and improved ventilation have resulted in decreased exposure levels in many occupational settings, such as particle-board, plywood and textile mills and foundries.

The exposures that may occur concomitantly with formaldehyde in occupational settings vary by industry, facility and period. They include other components of formaldehyde-based glues and varnishes, solvents, wood dust, wood preservatives and textile finishing agents.

5.2 Human carcinogenicity data

Excess numbers of nasopharyngeal cancers were associated with occupational exposure to formaldehyde in two of six cohort studies of industrial or professional groups, in three of four case–control studies and in meta-analyses. In one cohort study performed in 10 plants in the United States, the risk increased with category of increasing cumulative exposure. In the cohort studies that found no excess risk, no deaths were observed from nasopharyngeal cancer. In three of the case–control studies, the risk was highest in people in the highest category of exposure and among people exposed 20–25 years before death. The meta-analyses found a significantly higher risk among people estimated to have had substantial exposure than among those with low/medium or no exposure. The observed associations between exposure to formaldehyde and risk for cancer cannot reasonably be attributed to other occupational agents, including wood dust, or to tobacco smoking. Limitations of the studies include misclassification of exposure and disease and loss to follow-up, but these would tend to diminish the estimated relative risks and dilute exposure–response gradients. Taken together, the epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases in the cohort studies.

Of the six case–control studies in which the risk for cancer of the nasal cavities and paranasal sinuses in relation to occupational exposure to formaldehyde was evaluated, three provided data on squamous-cell tumours and three on unspecified cell types. Of the three studies of squamous-cell carcinomas, two (from Denmark and the Netherlands) showed a positive association, after adjustment for exposure to wood dust, and one (from France) showed no association. Of the three studies of unspecified cell types, one (from Connecticut, United States) gave weakly positive results and two (also from the United States) reported no excess risk. The two case–control studies that considered squamous-cell tumours and gave positive results involved more exposed cases than the other case–control studies combined. In the studies of occupational cohorts overall, however, fewer cases of cancer of the nasal cavities and paranasal sinuses were observed than were expected. Because of the lack of consistency between the cohort and case–control studies, the epidemiological studies can do no more than suggest a causal role of occupational exposure to formaldehyde in squamous-cell carcinoma of the nasal cavities and paranasal sinuses.

Less information was available to evaluate the association of formaldehyde with adenocarcinoma of the nasal cavities and paranasal sinuses, and the small excess observed in one case–control study in Denmark may have been confounded by exposure to wood dust.

Neither cohort nor case–control studies showed excess risks for oropharyngeal, laryngeal or lung cancer among workers exposed to formaldehyde. The studies of industrial cohorts also showed low or no risk for lymphatic or haematopoietic cancers; however, the cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by a consistent lack of excess risk for brain cancer in the studies of industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists.

5.3 Animal carcinogenicity data

Formaldehyde was tested for carcinogenicity by inhalation in mice, rats and hamsters, by oral administration in drinking-water in rats, by skin application in mice, and by subcutaneous injection in rats. In additional studies in mice, rats and hamsters, modification of the carcinogenicity of known carcinogens was tested by administration of formaldehyde in drinking-water, by application on the skin or by inhalation.

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, usually only at the highest exposure. Similar studies in hamsters showed no evidence of carcinogenicity. Studies in mice either showed no effect or were inadequate for evaluation. In rats administered formaldehyde in the drinking-water, increased incidences were seen of forestomach papillomas in one study and of leukaemias and gastrointestinal tract tumours in another; two other studies in which rats were treated in the drinking-water gave negative results. Studies in which formaldehyde was applied to the skin or injected subcutaneously were inadequate for evaluation.

In experiments to test the effect of formaldehyde on the carcinogenicity of known carcinogens, oral administration of formaldehyde concomitantly with *N*-nitrosodimethylamine to mice increased the incidence of tumours at various sites; skin application in addition to 7,12-dimethylbenz[*a*]anthracene reduced the latency of skin tumours. 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

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 does not alter the concentration of formaldehyde in the blood.

Occupational exposure to formaldehyde results in damage to nasal tissues; however, these findings may have been confounded by concomitant exposures. No data were available on the induction of cell proliferation in humans. There are no conclusive data showing that

formaldehyde is toxic to the immune system, to the reproductive system or to developing fetuses in humans.

More than 90% of inhaled formaldehyde gas is absorbed in the upper respiratory tract of rats and monkeys. In rats, it is absorbed in the nasal passages; in monkeys, it is also absorbed in the nasopharynx, trachea and proximal regions of the major bronchi. In mice exposed to high concentrations of formaldehyde, minute ventilation is decreased by 50% throughout exposure, resulting in a lower effective dose. This occurs only transiently in rats, as the minute ventilation is rapidly restored. Formaldehyde is rapidly oxidized to formate, which is incorporated into biological macromolecules, excreted in the urine or oxidized to carbon dioxide.

Acute or subacute exposure of rats to a concentration of 2.5 mg/m^3 appears to cause no detectable damage to the nasal epithelium and does not significantly increase rates of cell turnover. Cell turnover rates in rat nose during subchronic or chronic exposures to formaldehyde do not increase at 2.5 mg/m^3, increase marginally at concentrations of 3.7–7.4 mg/m^3 and increase substantially at concentrations of 12.3–18.4 mg/m^3. Concentration is more important than length of exposure in determining the cytotoxicity of formaldehyde.

Inhalation of formaldehyde leads to the formation of DNA–protein cross-links in the nasal respiratory mucosa of rats and monkeys. Much lower levels of DNA–protein cross-links were found in the nasopharynx, trachea and carina of some monkeys, in decreasing concentrations with passage through the respiratory tract, but none were found in the maxillary sinus. The formation of DNA–protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3, and the yield of DNA–protein cross-links at a given inhaled concentration is approximately an order of magnitude lower in monkeys than in rats. Yields of DNA–protein cross-links are higher in the lateral meatus of the rat nose and lower in the medial and posterior meatuses. There is no detectable accumulation of DNA–protein cross-links during repeated exposure.

About 50% of formaldehyde-induced tumours in the nasal mucosa of rats have a point mutation in the *p53* tumour suppressor gene.

No adequate data were available on genetic effects of formaldehyde in humans. It is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents, *in vivo*. Formaldehyde given by inhalation or gavage to rats *in vivo* induced chromosomal anomalies in lung cells, micronuclei in the gastrointestinal tract and sperm-head anomalies.

Formaldehyde induced DNA–protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange and gene mutation in human cells *in vitro*. It induced cell transformation, chromosomal aberrations, sister chromatid exchange, DNA strand breaks, DNA–protein cross-links and gene mutation in rodent cells *in vitro*.

Administration of formaldehyde in the diet to *Drosophila melanogaster* induced lethal and visible mutations, deficiencies, duplications, inversions, translocations and crossing-over in spermatogonia. Formaldehyde induced mutation, gene conversion, DNA strand breaks and DNA–protein cross-links in fungi and mutation and DNA damage in bacteria.

In rodents and monkeys, there is a no-observable-effect level (2.5 mg/m^3) of inhaled formaldehyde with respect to cell proliferation and tissue damage in otherwise undamaged nasal

mucosa. These effects are considered to contribute to subsequent development of cancer. Although these findings provide a basis for extrapolation to humans, conclusive data demonstrating that such cellular and biochemical changes occur in humans exposed to formaldehyde are not available.

5.5 Evaluation[1]

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

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

Overall evaluation

Formaldehyde *is probably carcinogenic to humans (Group 2A).*

[1] For definitions of the italicized terms, see Preamble, pp. 23–27.