Chapter 5.8 Formaldehyde

General description

Physical and chemical properties

Formaldehyde ($H_2C=O$) is a flammable, colourless reactive and readily polymerized gas at normal room temperature and pressure, with a relative molecular mass of 30.03 and a pungent odour. Formaldehyde is soluble in water, ethanol and diethyl ether and is used in solution or in polymerized form (paraformaldehyde). Under atmospheric conditions, formaldehyde is readily photo-oxidized in sunlight to carbon dioxide. It reacts relatively quickly with trace substances and pollutants in the air so that its half-life in urban air, under the influence of sunlight, is short. In the absence of nitrogen dioxide, the half-life of formaldehyde is approximately 50 minutes during the daytime; in the presence of nitrogen dioxide, this drops to 35 minutes (*1*). Under specific conditions, formaldehyde can react with hydrogen chloride or other inorganic chlorides to form bis(chloromethyl)ether (*2*).

Sources

Formaldehyde is formed naturally in the troposphere during the oxidation of hydrocarbons.
In the natural environment, formaldehyde is an intermediary in the methane cycle, with low background concentrations. It is one of the volatile compounds formed in the early stages of the decomposition of plant residues in the soil (*1*). The most important man-made source of formaldehyde is automotive exhaust from engines not fitted with catalytic converters. Other anthropogenic sources include direct emissions, especially from the production and use of formaldehyde. The major anthropogenic sources affecting humans are in the indoor environment. Products containing formaldehyde, such as resins, glues, insulating materials, chipboard, plywood and fabrics, are common. Other sources are cigarette smoke, heating and cooking (*1*).

Occurrence in air

Formaldehyde is the most common aldehyde in the environment. The natural background concentration is < 1 $\mu g/m^3$ with a mean of about 0.5 $\mu g/m^3$ (*2*).

In urban environments, outdoor air concentrations are more variable and depend on local conditions; annual averages are usually between 1 and 20 $\mu g/m^3$. Short-term peaks, e.g. in heavy traffic or during severe inversions, can range up to 100 $\mu g/m^3$ (*1, 2*). The levels of formaldehyde in indoor air are often higher than those in outdoor air. Major sources of formaldehyde in some dwellings are off-gassing of urea–formaldehyde foam insulation, particle board and formaldehyde-based resins. In the early 1980s, mean levels of 490 $\mu g/m^3$ were measured in mobile homes, with individual measurements as high as several mg/m^3 in new mobile homes (*2, 3*). Now formaldehyde levels in mobile homes are typically around 100 $\mu g/m^3$ or less (*2*). Mean levels in conventional homes with no urea–formaldehyde foam insulation range from 25 to 60 $\mu g/m^3$ (*2*).

Conversion factors

1 ppm = 1.25 mg/m^3

1 mg/m^3 = 0.8 ppm (at 20 °C and 1013 hPa)

Analytical methods in air

The most widely used methods for the determination of formaldehyde in air are based on spectrophotometry, with which sensitivities of 10–30 μg/m^3 can be achieved. High-performance liquid chromatography is a sensitive method, with a detection limit of 2 μg/m^3. The method of sampling and the treatment of samples before analysis are important in the accuracy of the determination. In all of these methods, other organic and inorganic chemicals, such as sulfur dioxide, other aldehydes and amines, cause interference. Table 1 provides methods for the determination of formaldehyde in air (*2*).

Table 1. Methods for the analysis of formaldehyde in air

Sample preparation	Assay procedure	Limit of detection (mg/m^3)
Draw air through impinger containing aqueous pararosaniline; treat with acidic pararosaniline and sodium sulfite	Spectrometry	0.01
Draw air through polytetrafluorethylene filter and impingers, each treated with sodium bisulfite solution; develop colour with chromotropic acid and sulfuric acid; read absorbance at 580 nm	Spectrometry	0.03
Draw air through solid sorbent tube treated with 10% 2-(hydroxymethyl) piperidine on XAD-2; desorb with toluene	Gas chromatography/flame ionization detection	0.3
	Gas chromatography/nitrogen selective detection	0.02
Draw air through impinger containing hydrochloric acid/2,4-dinitrophenyl hydrazine reagent and isooctane; extract with hexane/dichloromethane	High performance liquid chromatography/UV detection	0.002
Draw air through silica gel coated with acidified 2,4-dinitrophenylhydrazine reagent	High performance liquid chromatography/UV detection	0.002
Expose passive monitor (Du Pont Pro-Tek® Formaldehyde Badge) for at least 2 ppm-h; analyse according to manufacturer's specifications	Chromotropic acid test	0.1

Source: International Agency for Research on Cancer (*2*).

Routes of exposure

The possible routes of exposure to formaldehyde are ingestion, inhalation, dermal absorption and, rarely, blood exchange as in dialysis.

Air

Assuming a breathing volume of 20 m^3/day for an average adult, given the air levels mentioned above and making assumptions of the time spent in various environments, one can calculate inhalation exposure per day. Average time estimates lead to the conclusion that people spend 60–70% of their time in the home, 25% at work and 10% outdoors. If one assumes that normal work exposures are similar to home exposures, and the data given on the occurrence of formaldehyde in air are used, the daily exposure resulting from breathing is about 1 mg/day, with a few exposures at > 2 mg/day and a maximum of about 8 mg/day (Table 2).

Occupational exposure

Occupational exposure may contribute considerably to total exposure. For example, a high occupational exposure (e.g. in formaldehyde or resin production, or during disinfection procedures or embalming of bodies) of 1 mg/m^3 for a 25% time-weighted period during which 8 m^3 air is breathed would give an intake of about 8 mg/day (Table 2).

Smoking

Concentrations of 60–130 mg/m^3 have been measured in mainstream cigarette smoke (*4*). For a person smoking 20 cigarettes per day, this would lead to an exposure of 1 mg/day. Exposure to side-stream smoke (or environmental tobacco smoke, ETS) can be estimated from chamber measurements. When six cigarettes were smoked in a 50-m^3 test chamber with one air change per hour, formaldehyde levels were over 0.12 mg/m^3 within 15 minutes *(5)*. Weber-Tschopp and co-workers (*6*) measured the yield of 5–10 cigarettes in a 30-m^3 chamber with low air changes per hour (0.2–0.3) at 0.21–0.35 mg/m^3 , which would correspond to about 0.05–0.07 mg/m^3 at one air change per hour. This concentration is in the same range as that likely to be found in rooms of most conventional buildings without cigarette smoke (Table 2).

Table 2. Average exposure concentrations to formaldehyde and contribution of various atmospheric environments to average exposure to formaldehyde

Source	Concentration (mg/m^3)	Exposure (mg/day)
Ambient air (10% of time; 2 m^3/day)	0.001 – 0.02	0.002 – 0.04
Indoor air		
Home (65% of time; 10 m^3/day)		
– conventional	0.03 – 0.06	0.3 – 0.6
– mobile home	0.1	1.0
– environmental tobacco smoke	0.05 – 0.35	0.5 – 3.5
Workplace (25% of time; 8 m^3/day)		
– without occupational exposure [a]	0.03 – 0.06	0.2 – 0.5
– with occupational exposure	1.0	8.0
– environmental tobacco smoke	0.05 – 0.35	0.4 – 2.8
Smoking (20 cigarettes/day)	60 – 130	0.9 – 2.0 [b]

[a] Assuming the normal formaldehyde concentration in conventional buildings.

[b] Total amount of formaldehyde in smoke from 20 cigarettes.

Source: WHO Regional Office for Europe (*3*).

Drinking-water

Except for accidental contamination of water with formaldehyde, concentrations in drinking-water can be expected to be less than 0.1 mg/litre; intake from this source can therefore be considered negligible (below 0.2 mg/day) (*3*).

Food

Formaldehyde occurs naturally in foods, and foods may be contaminated as a result of fumigation (e.g. of grain), cooking (as a combustion product) and release from formaldehyde-resin-based tableware (*1*). Formaldehyde has been used as a bacteriostatic agent in some foods, such as cheese (*7*). Fruits and vegetables typically contain 3–60 mg/kg, milk and milk products about 1 mg/kg, meat and fish 6–20 mg/kg and shellfish 1–100 mg/kg. The daily intake is difficult to evaluate, but a rough estimate from the available data is in the range of 1.5–14 mg/day for an average adult, most of it in a bound and unavailable form (*1*).

Other exposures

Cosmetic products containing formaldehyde, formalin and/or paraformaldehyde may come into contact with hair (e.g. shampoos and hair preparations), skin (deodorants, bath products, skin preparations and lotions), eyes (mascara and eye make-up), oral mucosa (mouthwashes and breath fresheners), vaginal mucosa (vaginal deodorants) and nails (cuticle softeners and nail creams and lotions). Exposure from most of these sources is localized, although some formaldehyde is available for inhalation (e.g. from shaving creams). Systemic absorption, including penetration into the circulatory system, is estimated to be negligible (*1*). Contact with liquid barriers, as in the eyes and vagina, does not appear to lead to significant absorption. There have been reports of newborn infants being exposed to formaldehyde-containing disinfectants in incubators (*1*).

In certain rare events, formaldehyde in aqueous solution enters the bloodstream directly. These events are most likely to occur in dialysis or in surgery with assisted circulation, in which the dialysis machine and tubes are disinfected with formaldehyde. Formaldehyde from adsorption or backwashes can then enter the patient's bloodstream (*1*).

Relative significance of different routes of exposure

At levels to which humans may be exposed, adverse effects are most likely to be observed primarily following inhalation. It has been shown experimentally that effects on organisms (e.g. mammals) are more closely related to concentration than to the accumulated total dose; this is due to the rapid metabolism and high reactivity and water solubility of formaldehyde. Dermal exposure predominantly affects the skin itself, and little if any formaldehyde reaches the bloodstream. There is a relatively large exposure to formaldehyde from ingestion of food, but most of it is present in a bound form. Blood exchange is a critical form of exposure but is very rare, even in the very small segment of the population at risk (*2*).

Toxicokinetics

Absorption

Owing to its solubility in water, formaldehyde is rapidly absorbed in the respiratory and gastrointestinal tracts and metabolized. Over 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. Although formaldehyde or its metabolites can penetrate human skin – it induces allergic contact dermatitis in humans – dermal absorption appears to be very slight (*1, 2*).

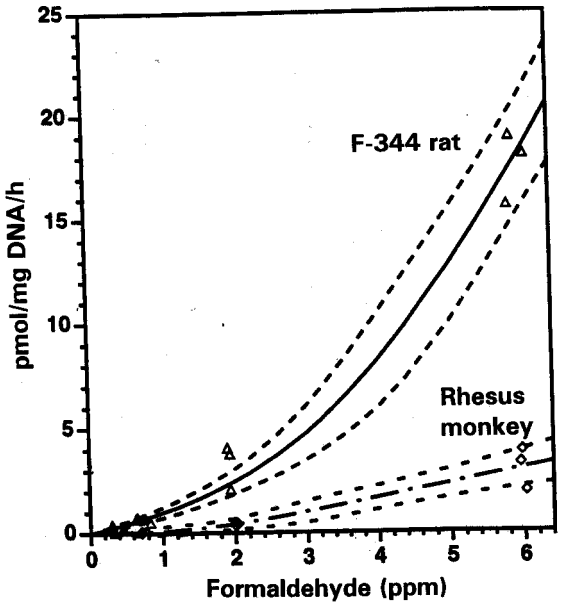
Distribution

Owing to its rapid metabolism, exposure of humans, monkeys or rats to formaldehyde by inhalation does not alter the concentration of endogenous formaldehyde in the blood, which is about 2–3 mg/litre for each of the three species. Intravenous administration of formaldehyde to dogs, cats and monkeys does not result in accumulation of formaldehyde in the blood, because of its rapid conversion to formate. In dogs, orally administered formaldehyde results in a rapid increase in formate levels in the blood. Following a 6-hour inhalation exposure of rats to ^{14}C-formaldehyde, radioactivity was extensively distributed in other tissues, the highest concentration occurring in the oesophagus, followed by the kidneys, liver, intestine and lung, indicating that absorbed ^{14}C-formaldehyde and its metabolites are rapidly removed by the mucosal blood supply and distributed throughout the body (*1*).

Metabolism and elimination

Formaldehyde reacts virtually instantaneously with primary and secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Formaldehyde acts as an electrophile and can react with macromolecules such as DNA, RNA and protein to form reversible adducts or irreversible cross-links. Absorbed formaldehyde can be oxidized to formate along three different pathways, and can be exhaled as carbon dioxide or incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways (Fig. 1). In the body, formaldehyde is produced in small quantities as a normal metabolite and also in the oxidative demethylation of xenobiotics; it may therefore be found in the liver (*2*). Formaldehyde disappears from the plasma with a half-time of about 1–1.5 minutes, most of it being converted to carbon dioxide and exhaled via the lungs. Smaller amounts are excreted in the urine as formate salts and several other metabolites (*3*).

Fig. 1. Metabolism and fate of formaldehyde

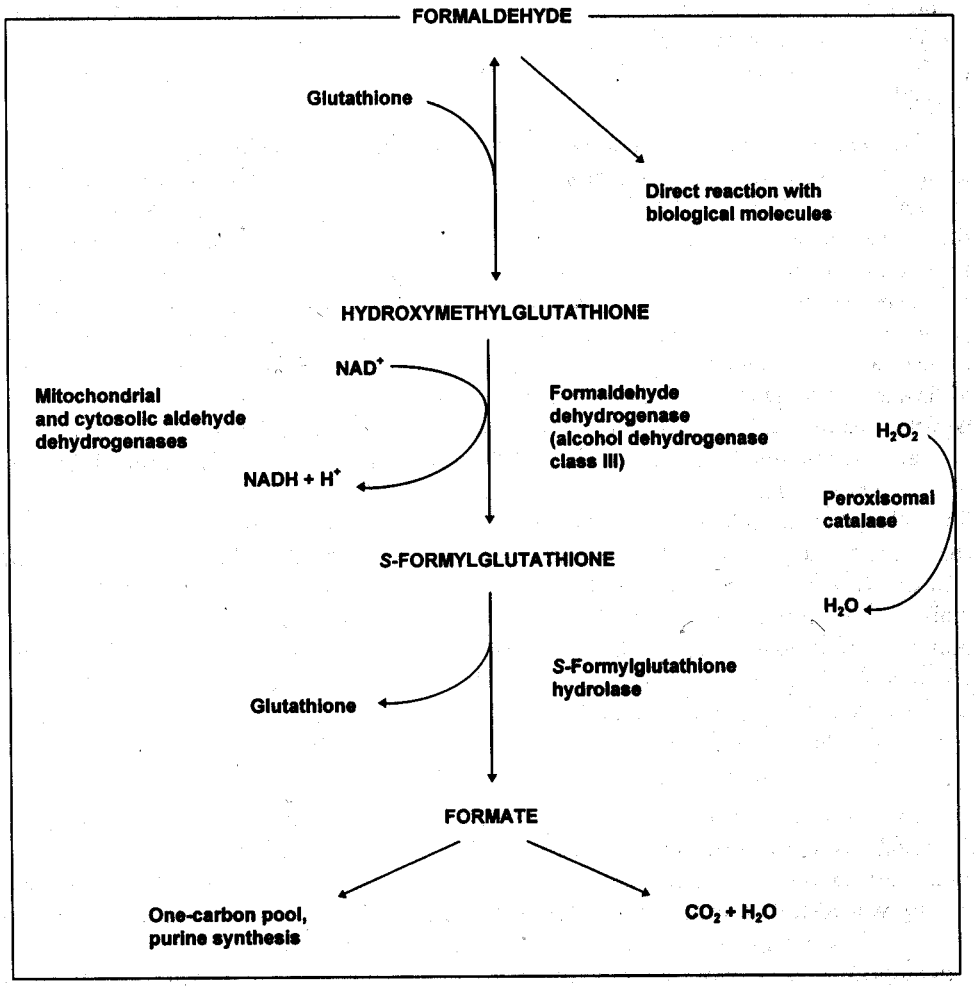


Source: International Agency for Research on Cancer (*2*).

Biomarkers of exposure

Inhalation of formaldehyde leads to the formation of DNA–protein cross-links in the nasal respiratory mucosa of rats and monkeys. The formation of these 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 (Fig. 2). There is no detectable accumulation of DNA–protein cross-links during repeated exposure. Application of a pharmacokinetic model to the data obtained in rats and monkeys indicates that the concentration of DNA–protein cross-links in the human nasal mucosa would be lower than those in rats and monkeys (*2, 8–10*). No data are available on DNA–protein cross-links in humans (*2*).

Fig. 2. Concentration of DNA–protein cross-links formed per unit time in the turbinates and lateral wall/septum of Fischer 344 rats and rhesus monkeys in relation to airborne formaldehyde concentration



Source: International Agency for Research on Cancer (*2*).

Formate in urine is not a useful biomarker for human exposure; the average baseline level of formate in the urine of unexposed subjects varies considerably (over one order of magnitude) both within and among subjects (*2*).

Health effects

Effects on experimental animals and *in vitro* test systems

Toxicological effects
Formaldehyde has been shown to be toxic *in vitro* in a variety of experimental systems, including human cells. It reduced growth rate, cloning efficiency and the ability of cells to take up neutral red and to exclude trypan blue while inducing squamous differentiation of cultured human bronchial epithelial cells (*11, 12*). These effects occurred simultaneously with elevated levels of intracellular calcium ions, decreased levels of free low-relative-molecular-mass thiols, including glutathione, and the appearance of genotoxicity (*2*).

Acute inhalation exposure of rats and mice to formaldehyde concentrations as high as 120 mg/m^3 produced salivation, dyspnoea, vomiting, spasm and death. At a concentration of 1.2 mg/m^3, acute exposure resulted in sensory irritation (decrease in breathing frequency), eye irritation, and increased airway resistance and decreased compliance in rats and mice, with mice being more sensitive than rats (*1*). Acute or subacute exposure of rats to a concentration of 2.5 mg/m^3 appeared to cause no detectable damage to the nasal epithelium and did not significantly increase rates of cell turnover. Cell turnover rates in rat nose during subchronic or chronic exposure to formaldehyde did not increase at 2.5 mg/m^3, but increased marginally at concentrations of 3.7–7.4 mg/m^3, and increased substantially at concentrations of 12.3–18.4 mg/m^3. Concentration was more important than dose (concentration × length of exposure) in determining the cytotoxic effects of formaldehyde on the nasal mucosa of rats (*1, 2*). Rhesus monkeys exposed to 7.3 $mg.m^{-3}$ formaldehyde (6 hours per day, 5 days per week) had a larger percentage of the nasal mucosa surface area affected after six weeks than after five days. Cell proliferation was increased in the nasal passages, larynx, trachea and carina, but the effects in the lower airways were minimal compared with the effects on the nasal mucosa (*13*).

Major dose-related lesions observed in rats and mice after long-term, repeated inhalation exposure (2.4, 6.7 or 17.2 mg/m^3) were dysplasia, hyperplasia and squamous metaplasia of the nasal epithelium; these lesions regressed to some extent after cessation of exposure (*1*). It also appeared that rats exposed to 1.2 mg/m^3 for 22 hours per day, 7 days per week over 26 weeks developed no detectable nasal lesions, but rats exposed to 2.4 mg/m^3 for 6 hours per day, 5 days per week for 24 months did develop mild squamous metaplasia of the nasal epithelium. Although the total dose received by the former group was 2.5 times higher than that received by the latter, no nasal lesions were seen, again demonstrating the greater importance of concentration than total dose (*2*).

Aqueous formaldehyde solution is a sensitizer for the skin of guinea pigs; nevertheless, pulmonary sensitivity was not induced when formaldehyde was administered dermally, by injection or by inhalation, and no cytophilic antibodies were detected in blood (*2*).

A number of short - and long-term oral toxicity studies with formaldehyde have been performed in rats and dogs (*2, 14*). Pathological changes in rats were essentially restricted to

gastric lesions occurring at doses ranging from 50 to 300 mg per kg body weight per day. The gastric lesions comprised ulceration and papillary hyperplasia and hyperkeratosis of the forestomach, and atrophic gastritis and ulceration and hyperplasia of the mucosa of the glandular stomach. No such gastric changes were observed in dogs (*14*).

Whether administered by inhalation, ingestion or the skin to various rodent species, formaldehyde did not exert adverse effects on reproductive parameters or fetal development (*2*).

Carcinogenic effects

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 to the skin or by inhalation (*2*).

Several carcinogenicity studies in which formaldehyde was administered to rats by inhalation produced evidence of carcinogenicity, particularly induction of squamous cell carcinomas of the nasal epithelium, usually only at the highest exposure level which ranged from about 18 to 25 mg/m^3. In one long-term inhalation study, a high incidence of nasal squamous cell carcinomas (15/58) was found in rats exposed to 12.3 mg/m^3, the nasal mucosa of which had been severely damaged by electrocoagulation before the exposure to formaldehyde started. In a comparable group of rats exposed to the same formaldehyde concentration but with an undamaged nasal mucosa, no formaldehyde-related nasal tumours were found (*2*).

In one study in mice, no statistically significantly increase in the incidence of nasal tumours was found after chronic (2-year) exposure to formaldehyde concentrations up to 17.6 mg/m^3. Similar long-term studies in hamsters showed no evidence of carcinogenicity (*2*).

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 through the drinking-water gave negative results. Studies in which formaldehyde was applied to the skin or injected subcutaneously were inadequate for evaluation (*2*).

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 (*2*).

Genotoxic effects

Formaldehyde induces DNA–protein cross-links in mammalian cells *in vitro* and *in vivo* (*2*). The precise nature of these cross-links is unknown. They are removed from normal cells with

a half-time of 2–3 hours; the removal rates were similar at nontoxic and toxic concentrations of formaldehyde (*15*).

DNA–protein cross-links were measured in the mucosa of several regions of the respiratory tract of rats exposed by inhalation to 0.4, 0.9, 2.4, 7.3 or 12.2 mg/m^3 ^{14}C-formaldehyde, and of rhesus monkeys exposed by inhalation (mouth-only) to 0.9, 2.4 or 7.3 mg/m^3 ^{14}C-formaldehyde for 6 hours. The concentration of cross-links increased non-linearly with the airborne concentration in both species. The concentrations of cross-links in the turbinates and anterior nasal mucosa were significantly lower in monkeys than in rats. Cross-links were also formed in the nasopharynx and trachea of monkeys, but they were not detected in the sinus, proximal lung or bone marrow. The investigators suggested that the differences between rats and monkeys with respect to DNA–protein cross-link formation may be due to differences in nasal cavity deposition and in the elimination of absorbed formaldehyde (*9, 16*).

In addition to DNA–protein cross-links, formaldehyde induced DNA single-strand breaks, chromosomal aberrations, sister chromatid exchanges and gene mutations in human cells *in vitro*. It induced cell transformation, chromosomal aberrations, sister chromatid exchanges, DNA strand breaks, DNA–protein cross-links and gene mutations 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 mutations, gene conversion, DNA strand breaks and DNA–protein cross-links in fungi, and mutations and DNA damage in bacteria. Assays for dominant lethal mutations in rodents *in vivo* gave inconclusive results. In single studies, formaldehyde induced sperm head abnormalities in rats but not in mice (*2*).

While there is conflicting evidence that formaldehyde can induce chromosomal anomalies in the bone marrow of rodents exposed by inhalation *in vivo*, recent studies have shown that it induced cytogenetic damage in the cells of tissues that are more locally exposed, either by gavage or by inhalation. Rats given 200 mg per kg body weight formaldehyde orally were killed 16, 24 or 30 hours after treatment and examined for the induction of micronuclei and nuclear anomalies in cells of the gastrointestinal epithelium. The frequency of mitotic figures was used as an index of cell proliferation. Treated rats had significant (greater than five-fold) increases in the frequency of micronucleated cells in the stomach, duodenum, ileum and colon; the stomach was the most sensitive, with a 20-fold increase in the frequency of micronucleated cells 30 hours after treatment, and the colon the least sensitive. The frequency of nuclear anomalies was also significantly increased at these sites. These effects were observed in conjunction with signs of severe local irritation (*17*).

In another experiment, rats were exposed to 0, 0.62, 3.7 or 18.5 mg/m^3 formaldehyde for 6 hours per day on five days per week, for one and eight weeks. There was no significant increase in chromosomal abnormalities in the bone-marrow cells of formaldehyde-exposed rats relative to controls, but there was a significant increase in the frequency of chromosomal aberrations in pulmonary lavage cells (lung alveolar macrophages) from rats that inhaled 18.5 mg/m^3 formaldehyde. Aberrations, which were predominantly chromatid breaks, were seen in 7.6% and 9.2% of the scored pulmonary lavage cells from treated animals, and in 3.5% and 4.8% of the cells from controls, after one and eight weeks, respectively (*18*).

The spectrum of mutations induced by formaldehyde has been studied in human lymphoblasts *in vitro,* in *Escherichia coli*, and in naked pSV2gpt plasmid DNA (*2, 19*). About 50% of

formaldehyde-induced tumours of the nasal epithelium of rats appeared to have a point mutation in the p53 tumour suppressor gene (*20*).

Overall, formaldehyde was 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 and micronuclei, respectively, in the gastrointestinal tract (*2*).

Critical organs, tissues and effects

From the above data on the toxicity, mutagenicity and carcinogenicity of formaldehyde in experimental animals, it appears that the upper respiratory tract, particularly the nose, is the prime target organ of airborne formaldehyde. In addition to sensory irritation, in rats adverse effects are primarily found in the nasal epithelium. The effects comprise degeneration, necrosis, increased cell turnover, hyperplasia, metaplasia and squamous cell carcinoma. Except for squamous cell carcinomas (possibly induced in mice) and increased cell turnover (not measured), similar changes were also found in formaldehyde-exposed mice and hamsters.

Another critical effect of airborne formaldehyde is the induction of DNA–protein cross-links in the nasal epithelium of rats and in the nasal, nasopharyngeal and tracheal epithelium of monkeys. Two crucial observations in this respect are that the concentrations of cross-links in the nasal epithelium were an order of magnitude lower in monkeys than in rats, and that they increased exponentially with increasing exposure levels.

Thus, airborne formaldehyde is an irritant producing tissue damage and regenerative hyperplasia at the site of entry (nose), and it possesses genotoxic activity, inducing DNA–protein cross-links also at the site of entry. The combination of both properties in all likelihood is essential for the induction of nasal carcinomas in rats by formaldehyde vapour.

Interaction with other chemicals

In addition to the experiments performed to examine the effect of formaldehyde on the carcinogenicity of known carcinogens (see the section on carcinogenic effects), a number of studies has been conducted in which exposure to formaldehyde was combined with exposure to compounds such as ozone (*2, 21, 22*), acrolein, acetaldehyde, crotonaldehyde, chlorine and/or sodium chloride aerosol (*12, 23–27*), wood dust (*28*), ionizing radiation (*29, 30*), *N*-nitroso-*N*-methylurea (*29, 30*), benzo(*a*)pyrene-diol-epoxide (*31*) and carbon black particles (*32*).

Formaldehyde, acrolein, acetaldehyde and crotonaldehyde are major air contaminants, and may occur simultaneously in many indoor and outdoor environments. These chemicals are all respiratory tract irritants and, at sufficiently high concentrations, will damage the nasal epithelium in experimental animals. Studies with mixtures of formaldehyde and ozone in rats revealed interactive effects on the nasal respiratory epithelium with respect to cell proliferation (*21, 33*). Depending on exposure time and concentration, the interactions varied from antagonism to potentiation and clear synergism. To induce a synergistic effect on cell proliferation, at least one of the chemicals had to be present at a cytotoxic concentration (*33*). However, these interactive effects were not confirmed in a more recent 3-day inhalation study with mixtures of formaldehyde (4.3 mg/m^3) and ozone (0.8 mg/m^3) in rats; in this study, the effects of combined exposure on the nasal respiratory epithelium were at most additive (*22*).

Co-exposure of rats to formaldehyde and acrolein at relatively high, toxic concentrations resulted in significantly higher yields of DNA–protein cross-links in nasal epithelium than exposure to formaldehyde alone, most probably because of inhibition of the oxidative metabolism of formaldehyde due to glutathione depletion by acrolein (*23*). Nasal injury caused by formaldehyde is markedly enhanced by simultaneous exposure to sodium chloride aerosols (*24*).

A number of three-day inhalation studies in rats and *in vitro* studies, using human and rat nasal epithelial cells, have been carried out with mixtures of formaldehyde, acrolein, acetaldehyde and/or crotonaldehyde (*12*). The results of the rat studies allowed the overall conclusion that combined exposure to these aldehydes with the same target organ (nose), and exerting the same type of adverse effect (nasal irritiation/cytotoxicity), but with partly different target sites (different regions of the nasal mucosa), is not associated with increased toxicity as compared to exposure to the individual chemicals, provided the exposure levels are similar to or lower than the no-observed-adverse-effect-levels (NOAELs) of the individual chemicals i.e. 1.2 mg/m^3 formaldehyde , 0.58 mg/m^3 acrolein and 750 ppm acetaldehyde. The combined effect of these aldehydes at higher (toxic) exposure concentrations were additive or infra-additive in nature. From the *in vitro* studies it appeared that, with respect to cytotoxicity, mixtures of formaldehyde, acrolein and crotonaldehyde act in a concentration-additive manner with no convincing evidence of synergism (*12*). With respect to sensory irritation in mice, combined exposure to formaldehyde and acrolein resulted in additive effects (*25*). Also in mice, pretreatment with formaldehyde induced cross-tolerance to chlorine, acetaldehyde and acrolein with respect to sensory irritation (*26, 27*). In rats, sensory irritation to mixtures of formaldehyde, acrolein and acetaldehyde appeared to be more pronounced than the irritation caused by similar concentrations of each of the aldehydes alone, but was less than the sum of the effects of the individual aldehydes. The degree of irritation caused by the mixture could accurately be predicted by a model for competitive agonism, thus providing evidence that the combined effect of these aldehydes is basically a result of competition for a common receptor (the trigeminal nerve receptor) (*12*).

Long-term exposure (104 weeks) of rats to formaldehyde vapour (15.2 mg/m^3) plus untreated beech wood dust (25 mg/m^3) resulted in a slightly higher incidence of squamous metaplasia accompanied by dysplasia of the nasal epithelium (4/15) than was seen in rats exposed to formaldehyde (1/16) or wood dust (0/16) alone (*28*).

Using *in vitro* test systems, Grafström et al. (*29, 30*) showed that formaldehyde in submutagenic concentrations enhanced the mutagenic and cytotoxic activity of ionizing radiation and *N*-nitroso-*N*-methylurea. On the other hand, Klein-Szanto et al. (*31*) found that formaldehyde applied simultaneously or sequentially with benzo(*a*)pyrene-diol-epoxide to human infant tracheabronchial epithelium did not induce alterations different from those observed after application of formaldehyde alone.

Combined exposure of mice to formaldehyde (3 or 6 mg/m^3) and carbon black particles (3.5 or 10 mg/m^3) did not alter the susceptibility of the lung to respiratory infection (*Staphylococcus aureus*) and did not impair alveolar macrophage phagocytosis as compared with the responses to formaldehyde alone (*32*).

Effects on humans

Toxicological effects

Predominant signs of short-term exposure to formaldehyde in humans are irritation of the eyes, nose and throat, together with concentration-dependent discomfort, lachrymation, sneezing, coughing, nausea, dyspnoea and finally death (Table 3). Symptoms are often more severe at the start of exposure than after minutes or hours, when they gradually diminish.

A series of pulmonary function studies has been conducted in healthy nonsmokers and asthmatics exposed to formaldehyde vapour; generally, lung function was unaltered. Fifteen healthy nonsmokers and 15 asthmatics were exposed to 2.4 mg/m^3 formaldehyde for 40 minutes to determine whether acute exposures could induce asthmatic symptoms (*34, 35*). No significant airway obstruction, changes in pulmonary function or bronchial hyperreactivity were noted. Similar observations were made on a group of 15 hospital laboratory workers who had been exposed to formaldehyde (*36*).

Healthy nonsmokers and asthmatics were exposed to 3.7 mg/m^3 formaldehyde for 1 or 3 hours, either at rest or when engaged in intermittent heavy exercise. No significant changes in pulmonary function and nonspecific airway reactivity were observed among asthmatic subjects. Small decreases (< 5%) in pulmonary function were observed in healthy nonsmokers exposed to formaldehyde while engaged in heavy exercise. Two normal and two asthmatic subjects had decrements greater than 10% (*37–39*).

Healthy nonsmokers were exposed for 3 hours at rest to 0, 0.6, 1.2, 2.4 or 3.7 mg/m^3 formaldehyde; they were also exposed to 2.4 mg/m^3 while exercising. Nasal flow resistance was increased at 3.7 mg/m^3 but not at 2.4 mg/m^3. There was no significant decrement in pulmonary function or increase in bronchial reactivity to methacholine with exposure to 3.6 mg/m^3 at rest or to 2.4 mg/m^3 with exercise (*40*).

In a study of controlled exposure to formaldehyde, 18 subjects, 9 of whom had complained of adverse effects from urea–formaldehyde foam insulation installed in their homes, were exposed to 1.2 mg/m^3 formaldehyde, or to off-gas products of urea–formaldehyde foam insulation containing 1.5 mg/m^3 formaldehyde, for 90 minutes (*41*). No statistically or clinically significant change in pulmonary function was seen either during or 8 hours after exposure, and no evidence was obtained that urea–formaldehyde foam insulation off-gas acts as a lower airway allergen. When 15 asthmatic subjects were exposed for 90 minutes to concentrations of 0.008–0.85 mg/m^3 formaldehyde, no change in pulmonary function was seen, and there was no evidence of an increase in bronchial reactivity (*42*).

Pulmonary function has been assessed in residents of mobile and conventional homes (*43–45*) and mobile offices (*46*) exposed to concentrations of 0.007–2.0 mg/m^3. No changes were seen in pulmonary function or airway resistance.

Table 3. Effects of formaldehyde in humans after short-term exposure

Concentration range or average (mg/m^3)	Time range or average	Health effects in general population
0.03	Repeated exposure	Odour detection threshold (10th percentile) [a]
0.18	Repeated exposure	Odour detection threshold (50th percentile) [a]
0.6	Repeated exposure	Odour detection threshold (90th percentile) [a]
0.1 – 3.1	Single and repeated exposure	Throat and nose irritation threshold
0.6–1.2	Single and repeated exposure	Eye irritation threshold
0.5 – 2	3–5 hours	Decreased nasal mucus flow rate
2.4	40 minutes on 2 successive days with 10 minutes of moderate exercise on second day	Post-exposure (up to 24 hours) headache
2.5 – 3.7	– [b]	Biting sensation in eyes and nose
3.7	Single and repeated exposure	Decreased pulmonary function only at heavy exercise
5 – 6.2	30 minutes	Tolerable for 30 minutes with lachrymation
12 – 25	– [b]	Strong lachrymation, lasting for 1 hour
37 – 60	– [b]	Pulmonary oedema, pneumonia, danger to life
60 – 125	– [b]	Death

[a] Frequency of effect in population.

[b] Time range or average unspecified.

Sources: World Health Organization (*1*); International Agency for Research on Cancer (*2*); WHO Regional Office for Europe (*3*).

Lung function tests were performed on particle-board and plywood workers (*47–50*), workers using acid-hardening paints (*51, 52*), embalmers (*53, 54*), urea–formaldehyde resin producers (*47, 55*), medical students (*56*) and anatomy and histology workers (*57*). These groups were often exposed to formaldehyde in combination with other substances. The formaldehyde concentrations were <0.02 to >6 .0 mg/m^3. In most of the studies, formaldehyde alone or in combination with other agents caused transient, reversible declines in lung function, but there was no evidence that formaldehyde induces a chronic decrement in lung function.

There are a few case reports of asthma-like symptoms caused by formaldehyde, but none of these demonstrated a sensitization effect and the symptoms were considered to be due to irritation (*1*). Significantly greater prevalence rates of asthma and chronic bronchitis were found in children from houses with formaldehyde levels of 70–140 $\mu g/m^3$ than in those less exposed, especially in children also exposed to ETS (*58*). In addition, peak expiratory flow rates in children decreased linearly with the formaldehyde exposure level, the effect occurring at formaldehyde levels as low as 40 $\mu g/m^3$ and being greater in asthmatic than in healthy children.

Skin sensitization (allergic contact dermatitis) is induced only by direct skin contact with formaldehyde solutions in concentrations higher than 2%. The lowest patch test challenge concentration in an aqueous solution reported to produce a reaction in sensitized persons was 0.05% formaldehyde (*1*).

Formaldehyde is a skin irritant and can cause allergic contact dermatitis. It is difficult to distinguish between these two effects (*59*).

To determine whether specific immunoglobulin (IgE) antibodies are involved in contact dermatitis after exposure to formaldehyde, 23 patients with a history of a positive epicutaneous test to formaldehyde were studied. Fifteen (65%) showed a positive reaction on retesting. The findings do not support the hypothesis that specific IgE antibodies are active in the pathogenesis of contact sensitivity to formaldehyde, in either atopic or nonatopic patients (*60*).

Contact urticaria has also, but rarely, been associated with exposure to formaldehyde. Cases have been reported in a nonatopic histology technician (*61*), a worker exposed through contact with formaldehyde-treated leather (*62*) and a worker in a pathology laboratory (*63*).

There are no conclusive data showing that formaldehyde is toxic to the immune system. Immunological tests were performed on 23 asthmatics living in urea–formaldehyde foam-insulated homes and on four living in conventionally insulated homes. The authors concluded that long-term exposure to formaldehyde had not affected the six immune parameters measured, but that short-term acute exposure resulted in minor immunological changes (*64*).

No IgE-mediated sensitization could be attributed to formaldehyde in 86 individuals at risk of exposure to formaldehyde (*65*), and none of 63 practising pathologists had allergen-specific IgE directed against formaldehyde, although 29 subjects complained of sensitivity to formaldehyde (*66*).

The immune responses of a large number of people exposed to formaldehyde were investigated, including people living in mobile homes or working in buildings insulated with urea–formaldehyde foam, patients undergoing haemodialysis with formaldehyde-sterilized dialysers, physicians and dialysis nurses exposed to formaldehyde, histology technicians, medical and pathology students, and workers in an aircraft factory who were exposed to formaldehyde and other substances (including phenol and solvents) (*67–69*). The authors of the last paper stated that none of their studies indicated an immunological basis for respiratory or conjunctival symptoms (conjunctivitis, rhinitis, coughing, wheezing, shortness of breath) seen after exposure to gaseous formaldehyde *(69)*.

The possibility that formaldehyde induces pathological or cytogenetic changes in the nasal mucosa has been examined in people exposed either in residential environments or in occupational settings (Table 4). Damage to the nasal mucosa such as squamous cell metaplasia and mild dysplasia of the respiratory epithelium, and micronuclei in mucosal cells, has been reported (*2*). However, these findings may have been confounded by concomitant exposures, and no final conclusions can therefore be drawn. Moreover, most of the studies did not suggest an association between the nasal effects and the exposure to formaldehyde (*2*).

No data are available on the induction of increased cell proliferation in the nasal epithelium of humans. There are also no conclusive data showing that formaldehyde is toxic to the reproductive system or to developing fetuses in humans (*2*).

Table 4. Findings in nasal mucosa of people with occupational exposure to formaldehyde

Reference	Industry	Concentration of formaldehyde (mg/m^3)	No. of exposed	No. of controls	Method	Findings
Edling et al. (*70*)	Formaldehyde (laminate plant)	0.5–1.1	38	25	Nasal biopsy	Histological score: exposed 2.8, controls 1.8 (P<0.05) Four exposed men had mild dysplasia
Edling et al. (*71*)	Formaldehyde Wood dust (laminated particle board)	0.1–1.1 (peaks to 5) 0.6–1.1	75	25	Nasal biopsy	Histological score: exposed 2.9, controls 1.8 (P<0.05) Six men had mild dysplasia
Berke (*72*)	Formaldehyde (phenol?) (laminate)	0.02–2.4 (peaks to 11–18.5)	42	38	Swab smears Clinical examination	No positive correlation between exposure to formaldehyde and abnormal cytology More mucosal abnormalities in nonsmoking exposed workers (P=0.004)
Boysen et al. (*73*)	Formaldehyde (production of formaldehyde and formaldehyde resins)	0.6–>2.4	37	37	Nasal biopsy	Histological score: exposed 1.9, controls 1.7 (P<0.05) Three exposed and none of the controls had dysplasia
Holström et al. (*74*)	Formaldehyde (resins for laminate production)	0.05–0.5 (peaks to >1)	62	32	Nasal biopsy	Histological score: exposed 2.16, controls 1.56 (P< 0.05). No case of dysplasia
Ballarin et al. (*75*)	Formaldehyde Wood dust (plywood factory)	0.1–0.39 0.23–0.73	15	15	Nasal scrapes	Micronuclei in nasal mucosal cells: exposed 0.90, controls 0.25 (P<0.010) Cytological score: exposed 2.3, controls 1.6 (P<0.01) One exposed had mild dysplasia
Suruda et al. (*76*)	Mortuary	0.18–5.16	29	29	Swab smears	Micronuclei in nasal mucosal cells: pre-exposure 0.41/1000, post-exposure 0.50/1000 (P=0.26)
Titenko-Holland et al. (*77*)	Mortuary	0.18–5.16	13	13	Swab smears	Micronuclei (centromere-negative in nasal mucosal cells): pre-exposure 0.051%, post-exposure 0.096% (P=0.04)

Source: International Agency for Research on Cancer (*2*).

Table 5. Aggregated risk ratios (RR), 95% confidence intervals (95% CI) and observed (O) and expected (E) frequencies of respiratory cancers in the meta-analyses of Blair et al. *(80)* and Partanen *(81)*

Site	Level or duration of exposure to formaldehyde											
	Any				Low/medium				Substantial			
	Blair et al. *(80)*		Partanen *(81)*		Blair et al. *(80)*		Partanen *(81)*		Blair et al. *(80)*		Partanen *(81)*	
	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)	O/E	RR (95% CI)
Lung:												
– Medical professions[a]	29/89	0.3 (0.2–0.5)	54/160	0.3 (0.3–0.4)	–[c]	–-	–-	–-	–-	–-	–-	–-
– Nonmedical professions[b]	490/520	0.9 (0.9–1.0)	474/486	1.0 (0.9–1.1)	–-	–-	–-	–-	–-	–-	–-	–-
– Industrial workers	1181/1097	1.1 (1.1–1.1)	833/752	1.1 (1.0–1.2)	514/422	1.2 (1.1–1.3)	518/425	1.2 (1.1–1.3)	250/240	1.0 (0.9–1.2)	233/216	1.1 (1.0–1.2)
Nose and nasal sinuses	60/56	1.1 (0.8–1.4)	93/78	1.1 (0.8–1.5)	38/46	0.8 (0.6–1.1)	33/30	1.1 (0.7–1.8)	30/28	1.1 (0.7–1.5)	36/21	1.7 (1.0–2.8)
Nasopharynx	31/25	1.2 (0.8–1.7)	36/21	2.0 (1.4–2.9)	30/27	1.1 (0.7–1.6)	23/16	1.6 (1.0–2.7)	13/6	2.1 (1.1–3.5)	11/4	2.7 (1.4–5.6)
Other respiratory	–-	–-	69/57	1.2 (0.9–1.6)	–-	–-	52/48	1.1 (0.7–1.5)	–-	–-	23/20	1.2 (0.6–2.1)

[a] Anatomists, pathologists, forensic medicine specialists.

[b] Funeral directors, embalmers, undertakers, medicinal drug users.

[c] – = no data available.

Source: International Agency for Research on Cancer (*2*).

Carcinogenic and genotoxic effects

A series of papers on the cytogenetic effects of formaldehyde in humans has been published (*2*). The studies mostly concern occupational exposures (plywood makers, makers of wood splinter materials, morticians, paper makers and hospital autopsy service workers) and measure chromosomal anomalies, micronuclei in peripheral lymphocytes, buccal epithelium (*78*) or nasal epithelium and sperm abnormalities. Both positive and negative results were obtained, but their interpretation is difficult because of the small number of subjects studied, inconsistencies in the findings, inadequate reporting of the data, and concomitant exposure to other chemicals. No increase in urinary mutagenicity was observed in autopsy workers as compared to controls (*79*). No data are available on DNA–protein cross-links in humans. The overall conclusion is that adequate data on genetic effects of formaldehyde in humans are not available (*2*).

The relationship between exposure to formaldehyde and cancer has been investigated in over 25 cohort studies of professionals (pathologists, anatomists and embalmers) and industrial groups (formaldehyde producers, formaldehyde resin makers, plywood and particle board manufacturers, garment workers and workers in the abrasives industry). Relative risks have been estimated as standardized mortality ratios (SMRs), proportionate mortality ratios (PMRs), proportionate cancer mortality ratios (PCMRs) and standardized incidence ratios (SIRs). In some studies, exposure was not assessed but was assumed on the basis of the subject's occupation or industry; in others, it was based on duration of exposure and quantitative estimates of historical exposure levels. Mortality in several of the cohorts was followed beyond the period covered by the original report; only the latest results are reviewed below, unless there were important differences in the analyses performed or changes in the cohort definition (*2*).

Recent meta-analyses by Blair et al. (*80*) and Partanen (*81*) contain most of the available data. The International Agency for Research on Cancer (IARC) (*2*) summarized the results of the two meta-analyses in tabular form (Table 5). IARC (*2*) also systematically reviewed case-control studies of cancer of the oral cavity, pharynx and respiratory tract. Also, McLaughlin (*82*) recently published a critical review on formaldehyde and cancer.

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 of 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 gradient. 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 (*2*).

Of 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 (*2*).

The cohort studies of embalmers, anatomists and other professionals who use formaldehyde tended to show low or no risk for lymphatic or haematopoietic cancers, and excess risks for cancers of the brain, although they were based on small numbers. These findings are countered by consistent lack of excess risk for brain cancer in the studies of the industrial cohorts, which generally included more direct and quantitative estimates of exposure to formaldehyde than did the cohort studies of embalmers and anatomists (*2*).

IARC (*2*) interpreted the above data as limited evidence for the carcinogenicity of formaldehyde in humans, and classified formaldehyde as "probably carcinogenic to humans" (Group 2A).

In a recently published cohort study (*83*), a significantly increased relative risk of 3.0 (1.4–5.7; 95% confidence limits) for sinonasal cancer was found among blue-collar workers potentially exposed to formaldehyde, but with no probable exposure to wood dust, the major confounder.

Sensory effects

Formaldehyde has a pungent odour with odour detection thresholds as specified in Table 3; the odour recognition threshold is not known. Formaldehyde poses nuisance problems in indoor environments owing to its release from building materials or furnishings. Indoor air usually contains other organic compounds which, in combination with formaldehyde or by themselves, may have odorous and irritating properties causing discomfort. It has been reported that some sensitive individuals can sense formaldehyde concentrations of 0.01 mg/m^3 and perhaps even lower as a "warm" feeling on the face (*84*).

Interaction with other chemicals

A group of 24 healthy nonsmokers were exposed while engaged in intermittent heavy exercise for 2 hours to formaldehyde at 3.7 mg/m^3 or to a mixture of formaldehyde and 0.5 mg/m^3 of respirable carbon aerosol, in order to determine whether adsorption of formaldehyde on respirable particles elicits a pulmonary response. Small (<5%) decreases were seen in forced vital capacity and forced expiratory volume, but these effects were not

considered to be clinically significant (*85*). Risby et al. (*86*) and Rothenberg et al. (*87*) estimated that the amount of formaldehyde adsorbed on to carbon black or dust particles and delivered to the deep lung by particle inhalation is minuscule in relation to the amount that remains in the vapour phase and is adsorbed in the upper respiratory tract.

The industrial manufacture of furniture, plywood and particle board may entail simultaneous exposure to formaldehyde and wood dust, both being nasal carcinogens, the former in rats and the latter in humans (*2*). While the epidemiological studies in woodworkers revealed the cancer excess to be attributable to wood dust *per se* rather than to other exposures in the workplace such as formaldehyde, it is also true that exposure to wood dust is often an important confounder in epidemiological studies on formaldehyde in industrial groups (*2*), indicating that exposure to formaldehyde may enhance the nasal cancer risk associated with wood dust exposure.

Evaluation of human health risks

Exposure evaluation

The major route of exposure to formaldehyde is inhalation. Table 2 shows the contribution of the various atmospheric environments to non-occupational air levels. Indoor air concentrations are several orders of magnitude higher than levels in ambient air. Owing to the extremely high concentrations of formaldehyde in tobacco smoke, smoking constitutes a major source of formaldehyde.

Health risk evaluation

Predominant symptoms of formaldehyde exposure in humans are irritation of the eyes, nose and throat, together with concentration-dependent discomfort, lachrymation, sneezing, coughing, nausea, dyspnoea and death (Table 3).

Damage to the nasal mucosa such as squamous cell metaplasia and mild dysplasia of the respiratory epithelium have been reported in humans, but these findings may have been confounded by concomitant exposures to other substances.

There is convincing evidence of high concentrations of formaldehyde being capable of inducing nasal cancer in rats and possibly in mice. Formaldehyde has been shown to be genotoxic in a variety of *in vitro* and *in vivo* systems. There is also epidemiological evidence of associations between relatively high occupational exposure to formaldehyde and both nasopharyngeal and sinonasal cancers.

There is substantial variation in individual responses to formaldehyde in humans. Significant increases in signs of irritation occur at levels above 0.1 mg/m^3 in healthy subjects. At concentrations above 1.2 mg/m^3, a progression of symptoms and effects occurs. Lung function of healthy nonsmokers and asthmatics exposed to formaldehyde at levels up to 3.7 mg/m^3 was generally unaltered. It is assumed that in these studies the observed effects were more related to peak concentrations than to mean values.

There is some evidence of formaldehyde inducing pathological and cytogenetic changes in the nasal mucosa of humans. Reported mean exposures ranged from 0.02 mg/m^3 to 2.4 mg/m^3, with peaks between 5 mg/m^3 and 18 mg/m^3. 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. There are also epidemiological observations of an association between relatively high occupational exposures to formaldehyde and sinonasal cancer. IARC (*2*) has interpreted the available cancer data as limited evidence for the carcinogenicity of formaldehyde in humans, and classified formaldehyde in Group 2A.

Formaldehyde is a nasal carcinogen in rats. A highly significant incidence of nasal cancer was found in rats exposed to a level of 16.7 mg/m^3, but the dose–response curve was nonlinear, the risk being disproportionately low at low concentrations. It also appears that the dose–response curves were nearly identical for neoplastic changes, cell turnover, DNA–protein cross-links and hyperproliferation, when the relationship between non-neoplastic and neoplastic lesions in the nasal respiratory epithelium was analysed. This close concordance indicates an association among the observed cytotoxic, genotoxic and carcinogenic effects. It is thus likely that hyperproliferation induced by cytotoxicity plays a significant role in the formation of nasal tumours by formaldehyde.

Despite differences in the anatomy and physiology of the respiratory tract between rats and humans, the respiratory tract defence mechanisms are similar. It is therefore reasonable to assume that the response of the human respiratory tract mucosa to formaldehyde will be similar to that of the rat. Thus, if the respiratory tract tissue is not repeatedly damaged, exposure of humans to low, noncytotoxic concentrations of formaldehyde can be assumed to be associated with a negligible cancer risk. This is consistent with epidemiological findings of excess risks of nasopharyngeal and sinonasal cancers associated with concentrations above about 1 mg/m^3.

Simultaneous exposure of humans to formaldehyde and other upper respiratory tract toxicants, such as acrolein, acetaldehyde, crotonaldehyde, furfural, glutaraldehyde and ozone, may lead to additive or synergistic effects, in particular with respect to sensory irritation and possibly also regarding cytotoxic effects on the nasal mucosa.

Guidelines

The lowest concentration that has been associated with nose and throat irritation in humans after short-term exposure is 0.1 mg/m^3, although some individuals can sense the presence of formaldehyde at lower concentrations.

To prevent significant sensory irritation in the general population, an air quality guideline value of 0.1 mg/m^3 as a 30-minute average is recommended. Since this is over one order of magnitude lower than a presumed threshold for cytotoxic damage to the nasal mucosa, this guideline value represents an exposure level at which there is a negligible risk of upper respiratory tract cancer in humans.

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