IPCS International Programme on Chemical Safety

Environmental Health Criteria 89

Formaldehyde

Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization

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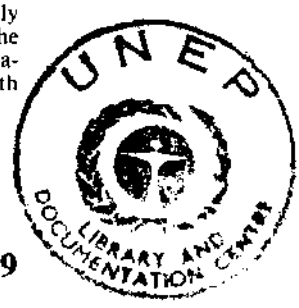

Environmental Health Criteria 89

FORMALDEHYDE

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The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the effects of chemicals on human health and the quality of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk-assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

Every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors that may have occurred to the Manager of the International Programme on Chemical Safety, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda, which will appear in subsequent volumes.

* * *

A detailed data profile and a legal file can be obtained from the International Register of Potentially Toxic Chemicals, Palais des Nations, 1211 Geneva 10, Switzerland (Telephone no. 7988400 - 7985850).

ENVIRONMENTAL HEALTH CRITERIA FOR FORMALDEHYDE

A WHO Task Group on Environmental Health Criteria for Formaldehyde met at the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany, from 9 to 13 November, 1987. Professor U. Mohr opened the meeting and welcomed the members on behalf of the host Institute, and Dr G. Vollmer spoke on behalf of the Federal Government, which sponsored the meeting. Dr D. Kello opened the meeting on behalf of the Director-General, World Health Organization, and Dr E. Smith addressed the meeting on behalf of the three cooperating organizations of the IPCS (UNEP/ILO/WHO). The Task Group reviewed and revised the draft criteria document and made an evaluation of the risks for human health and the environment of exposure to formaldehyde.

The drafts of this document were prepared by DR R.F. HERTEL and DR G. ROSNER of the Fraunhofer Institute for Toxicology and Aerosol Research, Hanover, Federal Republic of Germany. Available international and national reviews of formaldehyde were consulted during the preparation of the criteria document and are listed in the Appendix. Dr E. Smith of the IPCS Central Unit was responsible for the overall scientific contents of the document and Mrs M.O. Head of Oxford for the editing.

The efforts of all who helped in the preparation and finalization of the document are gratefully acknowledged.

* * *

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1. SUMMARY AND CONCLUSIONS

1.1 Physical and Chemical Properties, and Analytical Methods

Formaldehyde is a flammable, colourless and readily polymerized gas at ambient temperatures. The most common commercially available form is a 30-50% aqueous solution. Formaldehyde is readily soluble in water, alcohols, and other polar solvents, but has a low degree of solubility in non-polar fluids.

Methanol or other substances are usually added to the solutions as stabilizers to reduce intrinsic polymerization.

Formaldehyde decomposes at 150 °C into methanol and carbon monoxide; in general it is highly reactive with other chemicals. In sunlight, it is readily photo-oxidized to carbon dioxide. It has a very low *n*-octanol/water partition coefficient as well as a low soil-absorption coefficient. The Henry constant is relatively high at 0.02 $Pa \cdot m^3/mol$.

Chemical analysis for formaldehyde involves direct extraction from solid and liquid samples while absorption and/or concentration by active (filtration) or passive (diffusion) sampling is necessary for air samples. A variety of absorbants is available. The most widely used methods of analysis are based on photometric determination. Low concentrations in air can be detected, after appropriate absorption, by means of high performance liquid chromatography.

1.2 Sources of Human and Environmental Exposure

Formaldehyde is present in the environment as a result of natural processes and from man-made sources. It is formed in large quantities in the troposphere by the oxidation of hydrocarbons. Minor natural sources include the decomposition of plant residues and the transformation of various chemicals emitted by foliage.

Formaldehyde is produced industrially in large quantities and used in many applications. Two other important man-made sources are automotive exhaust from engines without catalytic converters, and residues, emissions, or wastes produced during the manufacture of formaldehyde or by materials derived from, or treated with it.

It has been calculated that the average rate of global production from methane in the troposphere is of the order of 4×10^{11} kg/year, while the total industrial production in recent years has been about 3.5×10^9 kg/year; the emission from automotive engines has not been quantifiable on a global basis.

Formaldehyde has a variety of uses in many industries, it has medical applications as a sterilant and is used as a preservative in consumer products, such as food, cosmetics, and household cleaning agents.

One of the most common uses is in urea-formaldehyde and melamine-formaldehyde resins. Urea-formaldehyde foam is used to insulate

buildings (UFFI); it can continue to emit formaldehyde after installation or constituting a source of persistent emission. Phenolic plastics and polyacetal plastics are also important fields of application, but are not expected to release formaldehyde.

There are several indoor environmental sources that can result in human exposure including cigarettes and tobacco products, furniture containing formaldehyde-based resins, building materials containing urea-formaldehyde resins, adhesives containing formaldehyde used for plastic surfaces and parquet, carpets, paints, disinfectants, gas cookers, and open fireplaces.

Indoor areas of special importance are hospitals and scientific facilities where formaldehyde is used as a sterilizing and preserving agent, and living spaces, such as schools, kindergartens, and mobile homes or apartments where there may be uncontrolled emissions of formaldehyde from tobacco smoking, building materials, and furniture.

1.3 Environmental Transport, Distribution, and Transformation

Air is the most relevant compartment in the formaldehyde cycle, most of the production and/or emissions, and degradation processes occurring in the atmosphere.

Photolysis and reaction with hydroxyl radicals rapidly remove formaldehyde from the atmosphere. The calculated half-life of each process is a matter of hours, according to environmental conditions. Transport of formaldehyde over distances is probably not of great importance, nevertheless some organic compounds (air pollutants or natural) from which formaldehyde can be derived are more stable and can contribute to the formation of formaldehyde over considerable distances. The compound can be dissolved in the atmosphere in cloud and rainwater and can be adsorbed as an atmospheric aerosol.

The value of the Henry constant suggests that formaldehyde in aqueous solution is less volatile than water and that volatilization from an aquatic environment is not expected under normal environmental conditions. The high water solubility and the low *n*-octanol/water partition coefficient suggest that adsorption on suspended solids and partition in sediments is not significant. In water, formaldehyde is rapidly (days) biodegraded by several species of microorganisms, provided the concentration is not too high. Formaldehyde is also readily biodegradable in the soil. Because the soil adsorption coefficient is very low, leaching occurs easily and mobility in soil is very high.

As it has a low *n*-octanol-water partition coefficient (log P_{ow}), formaldehyde is not be expected to bioaccumulate in aquatic organisms. Furthermore, aquatic organisms are able to metabolize and transform it through various metabolic pathways.

1.4 Environmental Levels and Human Exposure

Air concentrations of formaldehyde, near the ground in coastal, mountain, or oceanic areas, ranged from 0.05 to 14.7 $\mu g/m^3$, and the

majority of concentrations were within the range 0.1-2.7 $\mu g/m^3$. In the presence of man-made inputs, but away from any industrial plants, mean values ranged from 7 to 12 $\mu g/m^3$ with a few peaks up to 60-90 $\mu g/m^3$. Data from different parts of the world were in good agreement.

Rain water contains 110-174 μg/litre with peaks as high as 310-1380 μg/litre.

Emissions of formaldehyde from industrial processes vary widely according to the types of industry. A considerable amount of formaldehyde comes from the exhaust emissions of motor vehicles, but this varies greatly according to country and the grade of fuel.

There is some natural formaldehyde in raw food, levels ranging from 1 mg/kg up to 90 mg/kg, and accidental contamination of food may occur through fumigation, the use of formaldehyde as a preservative, or through cooking.

Tobacco smoke as well as urea-formaldehyde foam insulation and formaldehyde-containing disinfectants are all important sources of indoor formaldehyde.

Indoor air levels (non-workplace), measured in various countries, depended on several factors, but mainly on the age of the building and the building materials, the type of construction, and the ventilation. They varied widely with different situations, but most ranged from a minimum of 10 $\mu g/m^3$ up to a maximum of 4000 $\mu g/m^3$. In some cases, low values were found in rooms with substantial sources of formaldehyde emission. Disinfection of areas of hospitals produced the highest levels, up to 20 000 $\mu g/m^3$, but the personnel carrying out disinfection wear protective equipment and the areas are not occupied until formaldehyde levels have fallen to 1.2 mg/m^3 (1 ppm) and below. Levels in rooms in which there is tobacco smoking can exceed 100 $\mu g/m^3$.

The contributions of various atmospheric environments to the average human daily intake has been calculated to be 0.02 mg/day for outdoor air, 0.5-2 mg/day for indoor conventional buildings, < 1-10 mg/day for buildings with sources of formaldehyde, 0.2-0.8 mg/day for work places without occupational use of formaldehyde, 4 mg/day for work places using formaldehyde, and 0-1 mg/day for environmental tobacco smoke. Smoking 20 cigarettes per day corresponds to an intake of 1 mg/day through inhalation.

The formaldehyde concentration in drinking-water is generally about 0.1 mg/litre resulting in a mean daily intake of 0.2 mg/day. The quantity of formaldehyde ingested in food depends on the composition of the meal and, for an average adult, may range from 1.5 to 14 mg/day.

1.5 Kinetics and Metabolism

Formaldehyde is readily absorbed in the respiratory and gastrointestinal tracts. Dermal absorption of formaldehyde appears to be very slight. Increases in blood concentrations of formaldehyde were not detected in rats or human beings exposed to formaldehyde through inhalation, because of rapid metabolism.

The metabolites of formaldehyde are incorporated into macromolecules via one-carbon pathways or are eliminated in the expired air (CO_2) and urine. Formaldehyde that escapes metabolism can react with macromolecules at the site of entry. DNA-protein cross-links have been detected in tissues exposed directly to formaldehyde, but not in tissues remote from the absorption site.

1.6 Effects on Organisms in the Environment

Formaldehyde is used as a disinfectant to kill viruses, bacteria, fungi, and parasites, but it is only effective at relatively high concentrations.

Algae, protozoa, and other unicellular organisms are relatively sensitive to formaldehyde with acute lethal concentrations ranging from 0.3 to 22 mg/litre. Aquatic invertebrates showed a wide range of responses; some crustaceans are the most sensitive with median effective concentration (EC_{50}) values ranging from 0.4 to 20 mg/litre. In 96-h tests on several fish species, the LC_{50} of formaldehyde for adults ranged from a minimum of about 10 mg/litre to a maximum of several hundred mg/litre; most species showed LC_{50} values in the range of 50-100 mg/litre. The responses of various species of amphibians are similar to those of fish with median acute lethal concentrations (LC_{50}) ranging from 10 to 20 mg/litre for a 72-h exposure.

No data are available on long-term aquatic studies.

Eggs and larvae of some cattle parasites were killed by formaldehyde solution (1-5%) and some nematodes by a 37% solution, whereas other nematodes were unaffected. In ruminant mammals, formaldehyde protects dietary protein from microbial proteolysis in the rumen and increases the efficiency of utilization of amino acids.

Few data are available on the effects of formaldehyde on plants. However, from the agricultural use of urea-formaldehyde fertilizers, it appears that, at recommended concentrations, formaldehyde does not alter nitrogen and carbohydrate metabolism in plants, but that high doses have negative effects on soil metabolism. Formaldehyde impairs pollen germination.

1.7 Effects on Experimental Animals

Acute inhalation exposure of rats and mice to formaldehyde at very high concentrations (120 mg/m^3) produced salivation, dyspnoea, vomiting, spasms, and death. At a concentration of 1.2 mg/m^3, eye irritation, decreased respiratory rate, increased airway resistance, and decreased compliance appeared. Mice were more sensitive than rats.

Short-term, repeated exposures (7-25 mg/m^3) of rats produced histological changes in the nasal epithelium, such as cell degeneration, inflammation, necrosis, squamous metaplasia, and increased cell proliferation.

There is growing evidence that it is concentration rather than dose that determines the cytotoxic effects of formaldehyde on the nasal

mucosa of rats; concentrations below 1 mg/m^3 do not lead to cell damage and hyperplasia.

Dose-related lesions observed in long-term, repeated inhalation exposure (2.4, 6.7, or 17.2 mg/m^3) were dysplasia and squamous metaplasia of the respiratory and olfactory epithelia, which regressed to some extent after cessation of exposure.

Formaldehyde produced nasal squamous cell carcinomas in rats exposed to high concentrations (17.2 mg/m^3), which also caused severe tissue damage. The concentration - response curve was extremely non-linear with a disproportionate increase in tumour incidence at higher concentrations. A low, but not statistically significant, incidence of nasal tumours occurred at 6.7 mg/m^3. No tumours were found at other sites. Mice developed squamous cell carcinomas of the nasal cavity with long-term exposure to 17.2 mg/m^3, but this finding was not statistically significant. No tumours were found at other sites. No tumours were found in hamsters.

Long-term oral administration of formaldehyde (0.02-5% in the drinking-water) to rats was found to induce papillomas in the forestomach.

Several skin initiation/promotion studies with formaldehyde did not produce evidence of skin carcinogenicity in mice; the results with respect to promotion were either negative or inconclusive.

1.8 Effects on Man

Formaldehyde has a pungent odour detectable at low concentrations, and its vapour and solutions are known skin and eye irritants in human beings. The common effects of formaldehyde exposure are various symptoms caused by irritation of the mucosa in the eyes and upper airways. In the non-industrial indoor environment, sensory reactions are typical effects, but there are large individual differences in the normal population and between hyperreactive and sensitized people.

There are a few case reports of asthma-like symptoms caused by formaldehyde, but none of these demonstrated a sensitization effect (neither Type I nor Type IV) and the symptoms were considered to be due to irritation. Skin sensitization is induced only by direct skin contact with formaldehyde solutions in concentrations higher than 20 g/litre (2%). The lowest patch test challenge concentration in an aqueous solution reported to produce a reaction in sensitized persons was 0.05% formaldehyde.

The available human evidence indicates that formaldehyde does not have a high carcinogenic potential. While some studies have indicated an excess of cancer in exposed individuals or populations, only nasal or nasopharyngeal tumours are likely to be causally related to formaldehyde exposure.

Formaldehyde does not have any adverse effects on reproduction and is not teratogenic.

Formaldehyde *in vitro* interferes with DNA repair in human cells, but there are no data relating to mutagenic outcomes.

2. IDENTITY, PHYSICAL AND CHEMICAL PROPERTIES, ANALYTICAL METHODS

2.1 Identity

Chemical formula:	CH_2O [HCHO]
Chemical structure:	
CAS registry number:	50-00-0
RTECS registry number:	LP 8925000
UN number:	1198, 2209, 2213
EC numbers:	605-001-01 (solution 5% to < 25%) 605-001-02 (solution 1% to < 5%) 605-001-005 (solution ≥ 25%)
IUPAC name:	Methanal
Common synonyms:	formaldehyde, methanal, methylene oxide, oxymethylene, methylaldehyde, oxomethane
Common names for solutions of formaldehyde:	Formalin, Formol

Formaldehyde is a colourless gas at normal temperature and pressure, with a relative molecular mass of 30.03.

The most common commercially available form is a 30-50% aqueous solution. Methanol or other substances are usually added to the solution as stabilizers to reduce intrinsic polymerization. The concentration of methanol can be up to 15%. The concentration of other stabilizers is of the order of several 100 mg/litre. Concentrated liquid formaldehyde-water systems containing up to 95% formaldehyde are obtainable, but the temperature necessary to maintain solution and prevent separation of polymer increases from around room temperature to 120 °C as the solution concentration increases.

In solid form, formaldehyde is marketed as trioxane $(CH_2O)_3$, and its polymer, paraformaldehyde, with 8-100 units of formaldehyde. Paraformaldehyde has become technologically important.

2.2 Physical and Chemical Properties

Formaldehyde is a flammable, colourless, reactive, and readily polymerized gas at normal temperature. The heat of combustion for formaldehyde gas is 4.47 Kcal per gram. It forms explosive mixtures

with air and oxygen at atmospheric pressure. Flammability is reported to range from 12.5 to 80 volume %, a 65-70% formaldehyde-air mixture being the most readily flammable.

Formaldehyde is present in aqueous solutions as a hydrate and tends to polymerize. At room temperature and a formaldehyde content of 30% and more, the polymers precipitate and render the solution turbid.

Formaldehyde decomposes into methanol and carbon monoxide at temperatures above 150 °C, although uncatalysed decomposition is slow below 300 °C.

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 min during the daytime; in the presence of nitrogen dioxide, this drops to about 35 min (Bufalini et al., 1972).

Some physical and chemical properties of formaldehyde are presented in Table 1.

Table 1. Physical and chemical properties of formaldehyde[a]

Relative molecular mass	30.03
Relative gas density (air = 1)	1.04
Melting point (°C)	-118[b]
Boiling point (°C)	-19.2[b]
Explosivity range in air (vol %) (g/m^3)	7-73 87-910
n-octanol/water partition coefficient) (log P_{ow})	-1
Specific reaction rate (k) with OH radical (k OH)	$15 \cdot 10^{-18}$ $m^3/mol \cdot s$
Distribution water/air: Henry constant (H)	0.02 Pa· m^3/mol
Vapour pressure	101.3 kPa at -19 °C 52.6 kPa at -33 °C

[a] Modified from: BGA (1985).
[b] From: Diem & Hilt (1976) and IARC (1982).
From: Neumüller (1981) and Windholz (1983).

2.3 Conversion Factors

1 ppm formaldehyde = 1.2 mg/m^3 at 25 °C, 1066 mbar
1 mg formaldehyde/m^3 = 0.83 ppm

A number of other conversion factors have been cited but, for this draft, 0.83 has been used.

2.4 Analytical Methods

The most widely used methods for the determination of formaldehyde are based on photometric measurements. Methods for the sampling and determination are summarized in Table 2. The type of sampling depends on the medium in which the formaldehyde is to be determined.

Direct and indirect methods can be used for sampling formaldehyde in air. Indirect sampling (by means of a grab sample) is used when formaldehyde is present in extremely low concentrations or where sampling sites are removed from analytical laboratories. However, lack of preconcentration means that a very sensitive analytical technique is needed and there may also be absorption on the wall of the collecting container. Alternatively, the sample may be preconcentrated by passing air (active sampling) through an absorbing liquid. The collection efficiency of some liquids is reported in NRC (1981):

Water	80-85% (85% with ice bath)
1% aqueous bisulfite	94-100% (with ice bath)
3-methyl-2-benzothiazolene hydrazine (MBTH)	84-92%
Chromotropic acid in concentrated sulfuric acid	99%
Concentrated sulfuric acid	99%

Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). Aqueous or 50% 1-propanol solutions are used for formaldehyde sampling. For active sampling, aqueous solutions and solutions containing sulfite, 3-methyl-2-benzothiazolonehydrazone (MBTH), chromotropic acid, or 2,4-dinitrophenylhydrazine (DNPH) are generally used as the absorbing solution (Stern, 1976). For passive sampling, sodium bisulfite (Kennedy & Hull, 1986), triethanolamine (Prescher & Schönbude, 1983), and DNPH (Geisling et al., 1982) are used and sorbents such as silica gel, aluminium oxide, and activated carbon, sometimes specially pretreated, may be useful for taking samples at the work place (DFG, 1982).

In 1981, the US National Institute of Occupational Safety and Health (NIOSH) developed a solid-sorbent sampling method in which

Table 2. Sampling and analytical methods for formaldehyde[a]

Method	Sampling	Analysis	Sensitivity mg/litre (ppm)		Interferences
			15-min	long-term	
Chromotropic acid: NIOSH 3500	midget impinger	spectrophotometry	0.19 (0.16)	0.05 (0.04) (1 h)	phenol, other organic substances
Paraosaniline (original)	midget impinger	spectrophotometry	0.02 (0.02)	0.0006 (0.0005) (8 h)	sulfur dioxide
Paraosaniline (modified)	midget impinger	spectrophotometry	0.05 (0.045)	0.0012 (0.001) (8 h)	sulfur dioxide
Paraosaniline (TGM-555)	continuous	colorimetric	0.06 (0.05)	NA	sulfur dioxide
MBTH	absorber	spectrophotometry	0.12 (0.10)	0.0036 (0.003) (8 h)	
Acetylacetone spectrophotometric	midget impinger	spectrophotometry	0.12 (0.10)	---	other aldehydes, amines, Sulfur dioxide
Acetylacetone fluorimetric	midget impinger	fluorimetry	0.05 (0.04)	---	other aldehydes, amines, Sulfur dioxide
2,4-DNPH aqueous ethanol	midget impinger	HPLC	0.00007 (0.00006)	0.000018 (0.000015) (1 h)	
2,4-DNPH coated adsorbent	adsorbent tube	HPLC	1.58 (1.32)	0.12 (0.10) (3 h)	
NIOSH 3501	midget impinger	polarography	1.94 (1.62)	0.32 (0.27) (1.5 h)	other aldehydes
OSHA acidic hydrazine	midget impinger	polarography	0.12 (0.10)	0.012 (0.01) (2.5 h)	acetaldehyde

Table 2 (contd).

Method	Sampling	Analysis	Sensitivity mg/litre (ppm)		Interferences
			15-min	long-term	
NIOSH 2502	reactive adsorbent	gas chromatography	9.38 (7.82)	0.6 (0.5) (4 h)	
MIRAN	continuous	infrared	0.5 (0.4)	NA	multiple
Draeger	reactive adsorbent	visual	0.6 (0.5)	NA	
Passive monitor 3M	reactive adsorbent	spectrophotometry (CA)	3.84 (3.2)	0.12 (0.1) (8 h)	
DuPont	reactive adsorbent	spectrophotometry (CA)	9.6 (8)	0.3 (0.25) (8 h)	
Air Quality Research	reactive adsorbent	spectrophotometry (CA)	8.04 (6.7)	0.25 (0.21) (8 h)	
Envirotech	moist adsorbent	spectrophotometry (PUR)	0.86 (0.72)	0.07 (0.06) (8 h)	other aldehydes

[a] Modified from: Consensus Workshop on Formaldehyde (1984).

samples collected can be stored for at least 14 days, at room temperature, before analysis, without loss of the analyte (Blade, 1983).

A method for the specific and sensitive determination of formaldehyde and other aldehydes and ketones in air has been described by Binding et al. (1986). The specificity is based on subsequent high performance liquid chromatographic separation. In air samples of 5 litres, the detection limit is 0.05 ml/m^3. The method is suitable for determining 5-min short-term values, as well as for continuous sampling over a whole work shift.

A sensitive method for the determination of formaldehyde is based on the Hantzsch reaction between acetylacetone (2,4-pentanedione) ammonia and formaldehyde to form 3,5-diacetyl-1,4-dihydrolutidine. Formaldehyde concentration can be determined colorimetrically (Nash, 1953) or, more sensitively, by fluorimetry (Belman, 1963). The method is subject to interference by oxides of nitrogen, sulfur dioxide and ozone but is less subject to interference by phenol than the chromotropic acid method.

Photometric assay, using the sulfite-pararosaniline or the chromotropic acid method, is usually applied to determine formaldehyde in air. Automated analytical equipment has been developed.

Suitable analytical methods for monitoring air in the work-place environment have been developed and recommended by the German Research Society, DFG (1982) and by NIOSH (1984).

Menzel et al. (1981) described a special continuously-operating measuring device, developed for determining formaldehyde in particle boards for classification purposes; equipment for continuous measurements using the pararosaniline method is available (Lyles et al., 1965).

A simple colour reaction for the identification of urea formaldehyde resins and diisocyanates, carried out on the surface of wood-based panels, has been described by Schriever (1981). This is based on the reaction with *p*-dimethyl-aminocinnamaldehyde (DACA), resulting in a red colour for both the resins and diisocyanates. The reaction of purpald with formaldehyde is used to distinguish between urea formaldehyde resins and diisocyanates and it is possible to identify diisocyanates when mixed with urea formaldehyde resins.

Water sampling may be by means of grab samples. Where water or individual effluents are not homogeneous several subsamples may be collected at different times from different sampling locations and combined for analysis. If sample storage is necessary it should be frozen or at least kept at 4 °C to prevent biological or chemical degradation of formaldehyde. An organic solvent is used for extraction of formaldehyde prior to analysis.

Concentrations of formaldehyde in the air in the range of 0.05-40 mg/m^3 can be determined by the use of gas-detector tubes which contain a colour reagent (Leichnitz, 1985). They cannot be relied upon in the presence of other substances, e.g., tobacco smoke or below a concentration of 0.05 mg/m^3.

Formaldehyde can be extracted from foods using a solvent, such as isopetane, or by steam distillation and extraction with ether. Before extraction foodstuffs may be pulverized or homogenized.

The Association of Official Analytical Chemists (AOAC, 1984) recommends the Helmer-Fulton Test (registration No. 20.081) for the determination of formaldehyde in food and a spectrophotometric method (Nash's reagent B; registry no. 31203) for the determination of formaldehyde in maple syrup.

3. SOURCES IN THE ENVIRONMENT

3.1 Natural Occurrence

Formaldehyde is naturally formed in the troposphere during the oxidation of hydrocarbons. These react with OH radicals and ozone to form formaldehyde and/or other aldehydes as intermediates in a series of reactions that ultimately lead to the formation of carbon monoxide and dioxide, hydrogen, and water (Zimmermann et al., 1978; Calvert, 1980).

Of the hydrocarbons found in the troposphere, methane occurs in the highest concentration (1.18 mg/m^3) in the northern hemisphere. Thus, it provides the single most important source of formaldehyde (Lowe et al., 1981).

Terpenes and isoprene, emitted by foliage, react with the OH radicals, forming formaldehyde as an intermediate product (Zimmermann et al., 1978). Because of their short life-times, this potentially important source of formaldehyde is only important in the vicinity of vegetation (Lowe et al., 1981). The processes of formaldehyde formation and degradation are discussed in section 4.

Formaldehyde is one of the volatile compounds formed in the early stages of decomposition of plant residues in the soil (Berestetskii et al., 1981).

3.2. Man-Made Sources

The most important man-made source of formaldehyde is automotive exhaust from engines not fitted with catalytic converters (Berglund et al., 1984; Guicherit & Schulting, 1985).

3.2.1 Production levels and processes

Table 3. World production figures for formaldehyde

Year	Area	Quantity (million kg)
1978	USA, 16 companies	1073
1978	Canada, 4 companies	88
1979	USA, 16 companies	1003
1983	USA	905
1983	Germany, Federal Republic of, 11 companies	534
1983	Japan, 24 companies	403
1983	Major producing countries total	3200
1984	Major producing countries total	5780
1985	USA, 13 companies	941

3.2.1.1 World production figures

The total production figures for formaldehyde are calculated on a 100% formaldehyde basis, though a variety of concentrations and forms are produced. In 1984, the overall production capacity of major industrial countries was approximately 5780 million kg/year (European Economic Community 1700 kg/year, other Western European countries 530, USA 1440, Japan 640, other Asian countries and Australia 1240, Latin America 230). Formaldehyde is also produced in Africa and the USSR. No production figures for formaldehyde are available for eastern industrialized countries (Izmerov, 1982). Table 3 shows actual production figures for some western industrialized countries.

3.2.1.2 Manufacturing processes

Formaldehyde is produced by oxidizing methanol using two different procedures: (a) oxidation with silver crystals or silver nets at 600-720 °C; and (b) oxidation with iron molybdenum oxides at 270-380 °C. Formaldehyde can be produced as a by-product of hydrocarbon oxidation processes (Walker, 1975), but this method is not used commercially.

Formaldehyde is an inexpensive starting material for a number of chemical reactions, and a large number of products are made using formaldehyde as a base. Thus, it is important in the chemical industry.

3.2.2 Uses

Products manufactured using formaldehyde as an intermediate product are listed in Table 4.

In animal nutrition, formaldehyde is used to protect dietary protein in ruminants (section 7.3). In the USA, formaldehyde is used as a food additive to improve the handling characteristics of animal fat and oilseed cattle food mixtures by producing a dry free-flowing product (US FDA, 1980). Urea formaldehyde fertilizer is used in farming as a source of nitrogen to improve the biological activity of the soil (section 7.1).

3.2.2.1 Aminoplastics (urea formaldehyde resins and melamine formaldehyde resins)

Reaction of formaldehyde with urea or melamine yields urea formaldehyde (UF) or melamine formaldehyde (MF) (condensation process). These synthetic resins are then delivered in solution or powder form at various concentrations for further processing.

In the Federal Republic of Germany, about 70% of the total amount of aminoplastics produced, i.e., 170 000 tonnes of formaldehyde per annum, is used as glue in the manufacture of particle boards. These boards are mostly manufactured from urea formaldehyde resins, the water resistance of which is less than that of other resins, but is

Table 4. Products produced with formaldehyde as a compound[a]

Intermediate product	Product
urea formaldehyde resins	particleboard, fibreboard, plywood, paper treatment, textile treatment, moulding compounds, surface coatings, foam
phenolic resins	plywood adhesives, insulation, foundry binders
melamine resins	surface coatings, moulding compounds, laminates, wood adhesives
hexamethylenetetramine	phenolic thermosetting, resin curing agents, explosives
trimethylolpropane	urethanes, lubricants, alkyd resins, multifunctional acrylates
1,4-butanediol	tetrahydrofuran, butyrolactone, polybutylene terephthalate
polyacetal resins	auto applications, plumbing components
pentaerythritol	alkyd resins, synthetic lubricants, tall oil esters, foundry resins, explosives
urea formaldehyde concentrates	controlled release fertilizers

[a] From: Archibald (1982).

sufficient for use in enclosed areas. About 10% of the aminoplastic glues used are melamine-urea-formaldehyde resins, i.e., products where melamine and urea are co-condensed with formaldehyde. Melamine resins are more damp-proof than urea resins, but they are also more expensive.

Formaldehyde can be released from such wood products over a long period, even years, at a continuously declining rate. This occurs especially if the particle board material has become wet due to careless handling, e.g., in construction work. The emission is composed of the excess of formaldehyde used during actual production of the wood products and that produced by hydrolytic cleavage of unreacted methylol groups in the resins. Melamine formaldehyde resins are generally more stable and the amounts of formaldehyde emitted from them are much lower (Deppe, 1982).

Aminoplastics are also used as glue for plywood and in the manufacture of furniture. Paper saturated with aminoplastics and with a high melamine-formaldehyde-resin content is used to coat surfaces of particle boards. Aminoplastics are used to increase the wet strength of certain products in the paper industry.

Urea formaldehyde resins are used as urea formaldehyde foam insulation (UFFI), or as reinforcing foams in the insulation of buildings and in mining, where hollow areas are filled with foam. UFFI is produced by the aeration of a mixture of urea formaldehyde resin and an aqueous surfactant solution containing a phosphoric acid curing catalyst (Meek et al., 1985). This type of foam can emit formaldehyde, even after completion of work, depending on factors such as process and installation, age of building materials, temperature, and humidity.

Condensed aminoplastics of very low relative molecular mass serve as textile treatments to make cotton and fabrics containing synthetic fibres creaseproof and permanently pressed. In the USA, it is estimated (CPSC, 1979) that approximately 85% of all fabrics used in the clothing industry have been treated in this way. Extremely stable aminoplastics are used in order to ensure that they will not degrade during the lifetime of the articles. Formaldehyde concentrations ranging from 1 to 3000 mg/kg were found in such fabrics in the early years of this type of use (Schorr et al., 1974). However, residues of free formaldehyde from the manufacturing process can largely be removed by heat treatment with washing during the textile finishing process. In the last 10 years, the processing of finishing agents in the textile industry has improved and textiles treated with formaldehyde-containing finishing agents contain very little free formaldehyde and cannot cause allergic contact dermatitis (Bille, 1981).

Compounds similar to those used in finishing textiles are used in the tanning of leather. Another field of application is for aminoplastics mixed with rock or wood dust, fibres, or synthetic pulp in hard materials manufactured by hot moulding. They are used in electrical engineering, e.g., in light switches, sockets, and in parts of electrical motors; in mechanical engineering; in the motor-vehicle industry; and for household articles, e.g., camping dishes, parts of electrical household appliances, lamps, and plumbing components.

Aminoplastics are used in the paint industry as carriers in binders for special types of lacquer and paint, e.g., for cars. In agriculture, they are used as preservatives. They are also used in carpet-cleaning agents in the form of foam resin.

The fields of application of aminoplastics in the Federal Republic of Germany are given in Tables 5 and 6.

3.2.2.2 Phenolic plastics (phenol formaldehyde resins)

Phenolic plastics are synthetic resins in which formaldehyde is condensed with phenols. Phenol, resorcinol, and cresols are among the phenolic components. Owing to the stable binding of phenol and formaldehyde, formaldehyde should not be emitted from the final products made of phenolic plastics, as long as there is no free formaldehyde present.

As in the case of aminoplastics, the wood-working industry is a major consumer.

Table 5. Uses of melamine formaldehyde resins in the Federal Republic of Germany during 1981-82[a]

Area of use	Proportion as % of resin consumption	Consumption of formaldehyde (tonnes)
Adhesive resins for timber products, especially particle boards (adhesives)	30	12 000
Resin varnishes	36	14 500
Hardenable moulding material for plastic products	10	4 000
Raw materials for paints	8	3 000
Paper and textile finishing	5	2 000
Other	11	4 500

[a] From: BASF (1984).

Other major areas of application are the production of hard materials, similar to those produced from aminoplastics, as a moulding material, and as a binder in enamel, paints, and lacquers.

Phenolic plastics are used as binders in the production of insulating materials from rock wool or glass fibres, in brake linings, abrasive materials, and moulded laminated plastics. They also serve as binding agents for moulding sand in foundries. Fields of application of phenolic plastics in the Federal Republic of Germany are listed in Table 7.

Emissions of formaldehyde are produced when processing phenolic plastics at high temperatures. Phenol and formaldehyde emissions during moulding led to complaints in previous decades about annoying smells. Now, resins have been improved to meet work-place environment standards and emissions should not cause annoyance.

3.2.2.3 Polyoxymethylene (polyacetal plastics)

Polyoxymethylenes (POM) are another type of plastics produced by polymerizing formaldehyde. Like the final products from phenolic plastics, articles made of polyoxymethylene are not expected to emit formaldehyde.

Polyoxymethylenes are harder, tougher, and longer-lasting than other plastics and are used in many areas of application in which metallic materials were previously used. They are used in producing motor-vehicle and machine parts that are subjected to mechanical or thermal stress, parts for precision and communication engineering, parts for household appliances, and plumbing fixtures.

Table 6. Uses of urea formaldehyde resins in the Federal Republic of Germany during 1981-82[a]

Area of use	Proportion as % of resin consumption	Consumption of formaldehyde (tonnes)
Adhesive resins for timber products, especially particle boards (adhesives)	80	160 000
Paper finishing	4	8 000
Hardenable moulding material for plastic products	4	8 000
Textile finishing	3	6 000
Resin varnishes for impregnating, e.g., moulded, laminated plastics	2	4 000
Foam resins	2	4 000
for: building insulation	0.2	
mining	1.0	
amelioration	0.4	
carpet-cleaning products	0.3	
other purposes	0.1	
Raw materials for paints	2	4 000
Binding agents for fibre mats, etc.	1	2 000
Foundry resins	1	2 000
Other	1	2 000

[a] From: BASF (1984).

3.2.2.4 Processing formaldehyde to other compounds

Formaldehyde is an important raw material in the industrial synthesis of a number of organic compounds.

In the Federal Republic of Germany during 1981-82, the chemical industry processed 34% of all formaldehyde products to the following derivative substances (BASF, 1984):

- 1,4 butane diol 10%
- pentaerythritol 6%
- methylenediphenyldiisocyanate 5%
- trimethylolpropane and neopentylglycol 4%
- hexamethylenetetramine 2%
- chelating agents (NTA, EDTA) 2%
- miscellaneous (e.g., dyes, dispersion, pesticides, perfumes, vitamins) 5%

Table 7. Uses of phenolic plastic resins in the Federal Republic of Germany during 1981-82[a]

Area of use	Proportion as % of resin consumption	Consumption of formaldehyde (tonnes)
Hardenable moulding material for plastic products	23	9000
Adhesive resins for timber products, especially particle boards (adhesives)	20	8000
Binding agents for rock wool, glass wool, etc.	17	7000
Raw materials for paints	14	5500
Foundry resins	7	3000
Resin varnishes for impregnating, e.g., moulded, laminated plastics	4	1500
Abradant binders, e.g., for sandpaper	3	1000
Binding agents for friction surfaces, e.g., brake linings	3	1000
Rubber chemicals	2	1000
Other	7	3000

[a] From: BASF (1984).

3.2.2.5 *Medical and other uses*

The use of formaldehyde in medical and other fields is relatively small (1.5% of the total production) compared with its use in the manufacture of synthetic resins and chemical compounds. However, its use in these areas is of great significance for human beings, since it occurs either as free formaldehyde and can therefore be easily liberated and affect people (e.g., when used as a disinfectant) or it may reach many people via various consumer goods, such as preservatives and cosmetics. The use of formaldehyde for the preservation of organic material is of historical importance.

Examples of fields of application are listed in Table 8.

Table 8. Use of products containing formaldehyde in medicinal and other technical areas[a]

Area	Use
Detergents and cleaning agents industry	Preservative in soaps, detergents, cleaning agents
Cosmetics industry	Preservative in soaps, deodorants, shampoos, etc; additive in nail hardeners and products for oral hygiene
Sugar industry	Infection inhibitor in producing juices
Medicine	Disinfection, sterilization, preservation of preparations
Petroleum industry	Biocide in oil well-drilling fluids; auxiliary agent in refining
Agriculture	Preservation of grain, seed dressing, soil disinfection, rot protection of feed, nitrogen fertilizer in soils, protection of dietary protein in ruminants (animal nutrition)
Rubber industry	Biocide for latex; adhesive additive; anti-oxidizer additive also for synthetic rubber
Metal industry	Anti-corrosive agent; vehicle in vapour depositing and electroplating processes
Leather industry	Additive to tanning agents
Food industry	Preservation of dried foods; disinfection of containers; preservation of fish and certain oils and fats; modifying starch for cold swelling
Wood industry	Preservative
Photographic industry	Developing accelerator; hardener for gelatin layers

[a] Modified from: BASF (1984).

(a) Disinfectants and sterilizing agents

At present, formaldehyde is the disinfectant with the broadest efficiency; its virucidal property makes it indispensable for disinfection in the clinical field. It is an important active substance in disinfectants that kill and inactivate microorganisms and are used in the prevention and control of communicable diseases and hospital infections (BGA, 1982). Agents containing formaldehyde are marketed as concentrated solutions and must be diluted appropriately by the user. These

concentrates usually contain 6-10% formaldehyde, occasionally up to 30%. The formaldehyde contents of the diluted mixtures lie between 0.3 and 0.5% and, in exceptional cases, 0.9%. Application of the solutions is supposed to kill pathogenic organisms on the surfaces of objects. The ensuing effect is proportional to the concentration of formaldehyde, length of application, and temperature (Spicher & Peters, 1981). The objects to be disinfected are either placed in the formaldehyde solution (e.g., disinfecting linen in washing machines) or wiped and/or sprayed with the solutions. When disinfecting a room, a formaldehyde solution is either vaporized or atomized. Disinfecting in a formaldehyde chamber and gas sterilization both work on a similar principle, that is a mixture of formaldehyde and water vapour is pumped into a special air-tight chamber in which the objects to be disinfected or sterilized have been placed. This method is also used to disinfect incubators for premature babies and haemodialysis equipment.

(b) Medicines

Pharmaceutical products containing formaldehyde are rarely used for disinfecting the skin and mucous membranes, but formaldehyde is added to pharmaceutical products as a preservative.

Root canal filling sealants containing paraformaldehyde are used in dental surgery.

(c) Cosmetics

Formaldehyde is used as a preservative in cosmetics and in nail-hardening agents. Traces can be found in cosmetics resulting from the disinfecting of apparatus used in their manufacture. Furthermore, products containing formaldehyde are used for other purposes, e.g., anti-perspirants and skin-hardening agents. The formaldehyde content of some cosmetics has been reported to be up to 0.6% and is as high as 4.5% in nail hardeners (Marzulli & Maibach, 1973; Consensus Workshop on Formaldehyde, 1984). Concentrations in dry-skin lotion, creme rinse, and bubble bath oil are in the range of 0.4-0.6%. Present regulatory values are given in section 11.

Formaldehyde is considered technically superior to a number of other preservatives, especially in products with a high water content, e.g., shampoos. As a preservative, formaldehyde also assures that the product is germ-free, prevents microbial contamination during production and packaging, multiplication of residual organisms during storage, and re-contamination during use.

(d) Consumer goods and other products

The use of formaldehyde in consumer goods is intended to protect the products from spoilage by microbial contamination.

It is used as a preservative in household cleaning agents, dish-washing liquids, fabric softeners, shoe-care agents, car shampoos and

waxes, carpet cleaning agents, etc. As a rule, the formaldehyde concentration is less than 1%. Disinfecting cleaning agents contain higher concentrations (up to 7.5%) and are diluted before use.

Flooring adhesives contain formaldehyde. It is added to paper, leather, dyes, wood preservatives, sealing agents for parquet floors, as a preservative with fungicidal and bactericidal properties (see also Table 4).

Formaldehyde is a component of reactive resins (urea formaldehyde resins, melamine formaldehyde resins, phenol formaldehyde resins, benzoguanomine formaldehyde, and polymers on a methyloacylamide and/or methylomethacrylamide basis), which control the hardening properties of lacquers and varnishes and are essential for the surface properties of the treated products. The resins used for these purposes contain free formaldehyde at concentrations of up to 3%, this means up to 0.3% in ready-to-use varnishes (BASF, 1983). This free formaldehyde is emitted during application. Thermal degradation of resins during the baking of paints may cause additional emissions of formaldehyde.

3.2.3 Sources of indoor environmental exposure

The major man-made sources affecting human beings are in the indoor environment. Primary sources include cigarette smoke, particle board and plywood, furniture and fabrics, gases given off by heating systems, and cooking.

Thus, the indoor levels of formaldehyde differ clearly from the concentrations in the outdoor air. Indoor concentrations are influenced by temperature, humidity, ventilation rate, age of the building, product usage, presence of combustion sources, and the smoking habits of occupants. When considering the indoor presence of formaldehyde, it is necessary to differentiate between:

- Hospitals or other scientific facilities, where formaldehyde has to be used as a disinfectant or preservative; and
- All other indoor areas, especially living spaces, schools, kindergartens, and mobile homes where there may be uncontrolled emissions of formaldehyde from sources such as smoking, building materials, and furniture. This sector presents the specific problems in indoor areas.

Possible sources of indoor formaldehyde emissions are:

- cigarettes and other tobacco products;
- particle boards;
- furniture; urea formaldehyde foam insulation (UFFI);
- gas cookers;
- open fireplaces;
- other building materials made with adhesives containing formaldehyde, such as plastic surfaces and certain parquet varnishes;

- carpeting, drapes, and curtains;
- paints, coatings, and wood preservatives; and
- disinfectants and sterilizing agents.

Other products containing formaldehyde do not noticeably contribute to indoor exposure because of their stable formaldehyde binding, e.g., plastic articles made by moulding, or because of their low rate of emission, e.g., cosmetics. Data are summarized in Tables 15 and 16 (section 5.2).

4. ENVIRONMENTAL TRANSPORT, DISTRIBUTION, AND TRANSFORMATION

4.1 Transport and Distribution

The degradation of methane is a major source of the natural background concentration of formaldehyde in the atmosphere. Since methane is widely distributed naturally and has a half-life of several years, formaldehyde is formed on a global scale.

Fig. 1 provides a survey of processes that may contribute to formaldehyde concentrations in ambient air.

Formaldehyde is a highly reactive compound with a half-life in the atmosphere of about 1-3 h in the sunlit troposphere at 30° N at mid-day (Bufalini et al., 1972; Lowe & Schmidt, 1983). Therefore, transportation of formaldehyde over distances is probably not of great importance.

The organic compounds from which formaldehyde is derived are usually much more stable. Thus, emissions of organic air pollutants can contribute to the formation of formaldehyde over considerable distances.

Various photochemical models have also been used to predict formaldehyde distribution in the troposphere, but the computed values are difficult to compare, because of the different assumptions used to generate the models.

Lowe et al. (1981) estimated a chemical life-time for formaldehyde using the following reactions for formaldehyde formation (Levy, 1971):

$$CH_4 + OH \rightarrow CH_3 + H_2O \quad (1)$$
$$CH_3 + O_2 + M \rightarrow CH_3O_2 + M \quad (2)$$
$$CH_3O_2 + NO \rightarrow NO_2 + CH_3O \quad (3)$$
$$CH_3O + O_2 \rightarrow HCHO + HO_2 \quad (4)$$

Wofsy et al. (1972) considered that reaction (3) was unlikely and suggested that methyl hydroperoxide (CH_3OOH) could be an intermediate in the reaction series producing formaldehyde.

$$CH_3O_2 + HO_2 \rightarrow CH_3OOH + O_2 \quad (5)$$
$$CH_3OOH + h\nu \rightarrow CH_3O + OH \quad (6)$$
$$CH_3O + O_2 \rightarrow HCHO + HO_2 \quad (7)$$

For the purposes of estimating a chemical life-time for formaldehyde in the troposphere, reactions (1)-(4) are assumed, with reaction (1) as the rate-limiting step. Hence, the rate of formaldehyde production (P) from methane can be written as:

$$P = K_1 [OH] \cdot [CH_4] \quad (8)$$

Using $K_1 = 2.4 \times 10^{-12} e^{-1710/T}$ (Lowe et al., 1981), OH profiles for latitude 45 °N (Logan, 1980), and a mean tropospheric methane

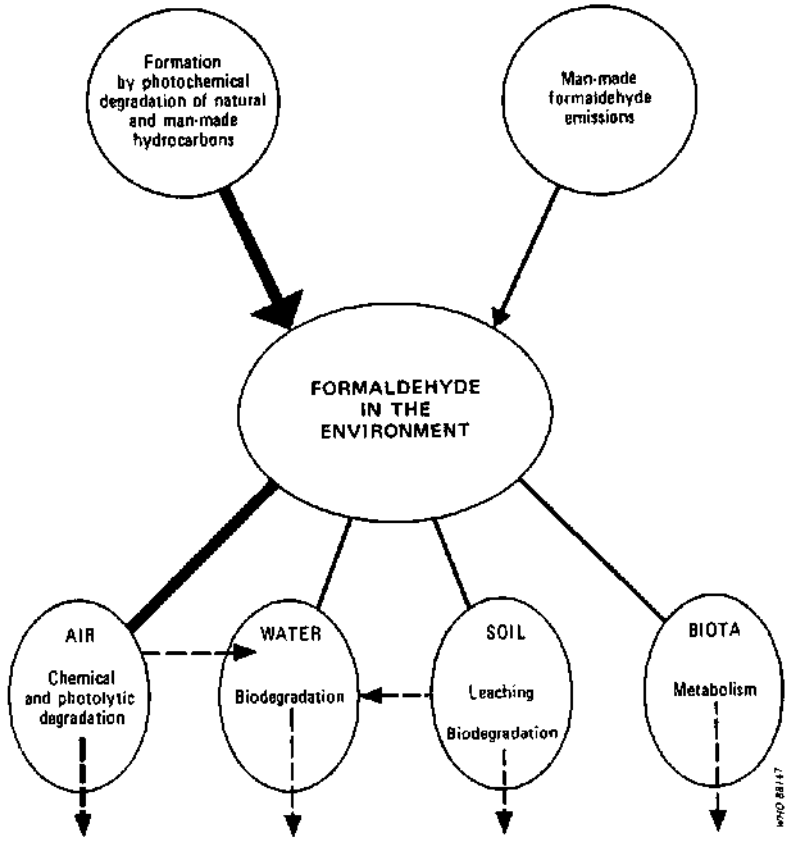

Fig. 1. Factors influencing formaldehyde concentration in the environment.

mixing ratio of 1.18 mg/m^3, equation (5) can be numerically integrated over a 10-km high troposphere to yield an average column formaldehyde production rate, due to methane oxidation, of 9 x 10^{-5} g/cm^2 per year.

Similar results are obtained using a mean tropospheric OH concentration of 6.5 x 10^5 molecules/cm^3 (Volz et al., 1981) with a mean methane mixing ratio of 1.18 mg/m^3 giving a column formaldehyde production in a 10-km high troposphere of 8 x 10^{-5}g/cm^2 per year. This is equivalent to an average world production rate of formaldehyde from methane of 4 x 10^{11} kg/year, which greatly exceeds the total industrial formaldehyde production rate (6 x 10^9 kg/year).

Various processes contribute to the removal of formaldehyde from tropospheric air. The action of solar ultraviolet radiation on formaldehyde results in its photolysis via two channels (Moortgat et al., 1978; Calvert, 1980).

$$HCHO + h\nu \rightarrow H_2 + CO \quad (9)$$
$$\rightarrow H + HCO \quad (10)$$

Formaldehyde is also removed from the troposphere by reaction with the OH radical (Stief et al., 1980).

$$HCHO + OH \rightarrow HCO + H_2O \quad (11)$$
$$HCO + O_2 \rightarrow HO_2 + CO \quad (12)$$

Through the reaction series (1)-(4) and reactions (9)-(12), CO and H_2 are produced in the atmosphere via formaldehyde as an intermediate product. The destruction of one methane molecule leads to the production of approximately one formaldehyde molecule and ultimately to the production of a CO molecule. The series of reactions also results in a net production of HO_2 radicals, resulting in an overall increase in the chemical reactivity of the atmosphere.

From equations (9), (10), and (11), it follows that the chemical destruction of formaldehyde (D) is given by:

$$D = [\bar{HCHO}][\bar{K}_{11}[\bar{OH}] + \bar{J}_9 + \bar{J}_{10}] = \frac{[HCHO]}{\tau} \quad (13)$$

where K_{11} is the rate constant of equation (11), J_9 and J_{10} are the photodissociation coefficients for equations (9) and (10) and τ $[s]^{-1}$ is the chemical life-time of formaldehyde in the lower troposphere.

Substituting $J_9 + J_{10} = 4.5 \times 10^{-5}$ s^{-1} (mean estimated from Calvert, 1980), $K_{11} = 1.05 \times 10^{-11}$ (Stief et al., 1979), and $[OH] = 5 \times 10^6$ molecules/cm^3 (Logan et al., 1981) into equation (13) yields an average chemical life-time for formaldehyde in the lower troposphere during daylight, of 3 h. Under atmospheric conditions in the presence of nitrogen dioxide (NO_2), the half-life of formaldehyde was found to be 35 min (Bufalini et al., 1972).

At ground level in the atmosphere, reaction with the OH radical is the dominant removal process for formaldehyde. However, in the first few kilometres of the troposphere, the importance of the OH radical as a removal process decreases with altitude and the photodissociation coefficients J_9 and J_{10} increase in importance.

Formaldehyde is also removed from the troposphere by rainout (gaseous constituents of the atmosphere are absorbed during the formation of cloud droplets), washout (falling raindrops scavenge gases, particles, and aerosols from the atmosphere), and by deposition at the surface. However, these processes are only of minor importance in the free troposphere. For example, from formaldehyde measurements made in rainwater collected at an equatorial site in the Pacific, Zafiriou et

al. (1980) estimated that rainout was responsible for removing only 1% of the formaldehyde produced in the atmosphere by the oxidation of methane. In addition, Warneck et al. (1978) showed that washout, as a removal process for gaseous formaldehyde in the troposphere, is important only in polluted regions and may be ignored in unpolluted air.

Dry deposition at the surface is usually defined by a deposition velocity, (v_o (cm/second)), and the flux (f_o) to the surface may be estimated by:

$$f_o = v_o \times [HCHO]_o \qquad (14)$$

where $[HCHO]_o$ is the mean formaldehyde concentration above the surface.

The deposition velocity depends on the surface. For example, from measurements made at an equatorial Pacific atoll, Zafiriou et al. (1980), deduced a value for v_o of 0.4 cm/second at the ocean surface.

The mean formaldehyde mixing ratio, $[HCHO]_o$, measured during an oceanographic expedition in the north and south Atlantic, was 0.29×10^{-3} mg/m^3, corresponding to a concentration of 5.9×10^9 molecules/cm^3 (Lowe et al., 1981). With a deposition velocity of 0.4 cm/second, equation (14) suggests a loss due to deposition at the ocean surface of 2.4×10^9 molecules/cm^2 per second or about 4% of the column formaldehyde production from methane oxidation calculated above. Although v_o for formaldehyde is expected to vary with wind velocity, it is unlikely to exceed 1 cm/second. Hence, loss of formaldehyde from the troposphere due to deposition will only be important near the surface itself.

More recently, consideration has been given to the possibility of how much formaldehyde indirectly contributes to the overacidification of precipitation (Richards et al., 1983). Formaldehyde reacts with sulfur dioxide (SO_2) and gives off relatively concentrated hydroxymethanesulfonic acid, whereby SO_2 may contribute to the acid content of precipitation without preceding oxidation to sulfuric acid, which is a relatively slow process. More in-depth investigations have to be carried out, in order to ascertain to what extent this process is important for acid formation.

4.2 Transformation

4.2.1 Special products of degradation under specific conditions

Highly carcinogenic bis(chloromethyl)ether can be produced by a condensation reaction between formaldehyde and hydrogen chloride (Thiess et al., 1973; Nelson, 1977; Albert et al., 1982; Sellakumar et al., 1985). The maximum equilibrium concentration of bis(chloromethyl)ether generated from atmospheric formaldehyde and hydrogen chloride was estimated to reach 4×10^{-16} ppb; it was concluded that this represented little impact on human health (NRC, 1981). According to Keefer & Roller (1973), formaldehyde is able to catalyze nitro-

sation of a series of secondary amines to carcinogenic nitrosamines or *N*-nitroso-compounds.

4.2.2 Microbial degradation

Formaldehyde released into the aquatic environment appears to undergo relatively rapid biodegradation. Kamata (1966) examined the biodegradation of formaldehyde in natural water obtained from a stagnant lake in Japan. Under aerobic conditions, known quantities of added formaldehyde were decomposed in ≈ 30 h at 20 °C, anaerobic decomposition required ≈ 48 h. No decomposition was noted in sterilized water.

Various activated sludges and microorganisms isolated from activated sludges have been shown to be very efficient in degrading formaldehyde in aqueous effluents, providing the formaldehyde concentration does not exceed 100 mg/litre (Verschueren, 1983). Essentially complete degradation is achieved in 48-72 h, if the proper temperature and nutrient conditions are maintained (Kitchens et al., 1976). Grabinska-Loniewska (1974) isolated 44 bacteria strains from an industrial activated sludge and found that formaldehyde was used as a sole carbon source by various *Pseudomonas* strains but not by strains of *Achromobacter, Flavobacterium, Mycobacterium,* or *Xanthomonas.* Several studies have revealed significant degradation of formaldehyde by mixed cultures obtained from sludges and settled sewage (Heukelekian & Rand, 1955; Hatfield, 1957; Sakagami & Yokoyama, 1980; Speece, 1983; Behrens & Hannes, 1984), while in other studies, little or no degradation has been found (Placak & Ruchhoft, 1947; Gerhold & Malaney, 1966; Belly & Goodhue, 1976; Kalmykova & Rogovskaya, 1978; Chou et al., 1979).

A number of pure culture studies have shown that formaldehyde is biologically degradable. Cell extracts of *Pseudomonas methanica* and *Methylosinus trichosporium* (Patel et al., 1979) and cell-free extracts of yeast strains of the *Candida* sp. are able to oxidize formaldehyde (Fujii & Tonomura, 1972, 1974, 1975; Sahm, 1975; Pilat & Prokop, 1976). Cell extracts of *Pseudomonas oleovorans* (Sokolov & Trotsenko, 1977), *Pseudomonas putida* Cl (Hohnloser et al., 1980), *Hansenula polymorpha* (Van Dijken et al., 1975), *Methylococcus capsulatus* (Patel & Hoare, 1971), *Methanobacterium thermoautotrophicum, M. voltae* and *M. jannaschii* (Escalante-Semerena & Wolfe, 1984) and *Alcaligenes faecalis* (Marion & Malaney, 1963) can also oxidize formaldehyde.

Yamamoto et al. (1978) isolated 65 strains of methanol-utilizing bacteria from seawater, sand, mud, and weeds of marine origin and found that all were able to use formaldehyde as a sole carbon source for growth. In contrast, Kimura et al. (1977) found that 336 strains of bacteria, isolated from coastal seawater and mud, could not use formaldehyde as a sole carbon source for growth.

5. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

5.1 Environmental Levels

5.1.1 Air

Measurements in maritime air yielded average formaldehyde concentrations of < 1-14 $\mu g/m^3$ (Table 9).

Table 9. Measurements of aldehyde mixing ratios in the air near the ground[a]

Location	RCHO	HCHO	Number of measurements	Reference
	($\mu g/m^3$)			
Baltic sea coast	-	0.7-2.7	5	Hadamczik (1947)
Panama	1.2-4.8	-	?	Lodge & Pate (1966)
Antarctica	<0.6-12	-	?	Breeding et al. (1973)
Panama	<0.3-3.7	-	?	Breeding et al. (1973)
Amazon Basin	1.2-7.4	-	?	Breeding et al. (1973)
Irish west coast	-	0.1-0.5	5	Platt et al. (1979)
Eastern Indian Ocean	-	< 1-14	63	Fushimi & Miyake (1980)
Central Pacific	-	0.1-0.8	7	Zafiriou et al. (1980)
South Africa	-	0.3-1.0	5	Neitzert & Seiler (1981)
Irish west coast	-	0.1-0.6	36	Lowe et al. (1981)
Bürserberg, Austria	-	0.05-2.3	55	Seiler (1982)

[a] Modified from: Lowe et al. (1981).

Higher values were generally obtained in the equatorial zone and the Pacific (Fushimi & Miyake, 1980; Guderian, 1981; Seiler, 1982). Measurements of the Nuclear Research Centre (Jülich, Federal Republic of Germany), carried out with different measurement procedures in the North and South Atlantic, yielded values of 0.1 $\mu g/m^3$ and less (Lowe et al., 1981). In the vicinity of the Pacific islands, values of up to 14 $\mu g/m^3$ were reported (Fushimi & Miyake, 1980). However, it should be borne in mind that considerable technical difficulties are involved in measuring such low concentrations, with ensuing uncertainties.

The values measured in continental air are higher (0-16 $\mu g/m^3$). Measurements in Bürserberg, Austria, at 1250 m above sea level (Seiler, 1982), showed a mean value of 0.6 $\mu g/m^3$ with a variation range of 0.05-2.3 $\mu g/m^3$.

Measurements made by the Federal Environmental Agency at Deuselbach, Hunsrück, Federal Republic of Germany, have proved to be representative for the air in the rural areas of Central Europe (Seiler, 1982). The mean value was about 1.5 $\mu g/m^3$, ranging from 0.1 to 4.5 $\mu g/m^3$ (Seiler, 1982). The lowest values were measured when there was a rapid inflow of maritime air over extended periods. The elevated values were probably due to man-made organic compounds that had been transported long distances. Values of 6 $\mu g/m^3$ generally appear together with increased concentrations of carbon monoxide and sulfur dioxide, indicating man-made air pollution. Man-made emissions dominate in the highly industrialized areas of Central Europe (Ehhalt, 1974).

Pronounced diurnal concentrations of formaldehyde are recognizable. A typical example is given in Fig. 2. The resulting values are higher in summer than in winter. They vary from season to season because of the variation in intensity of the ultraviolet radiation.

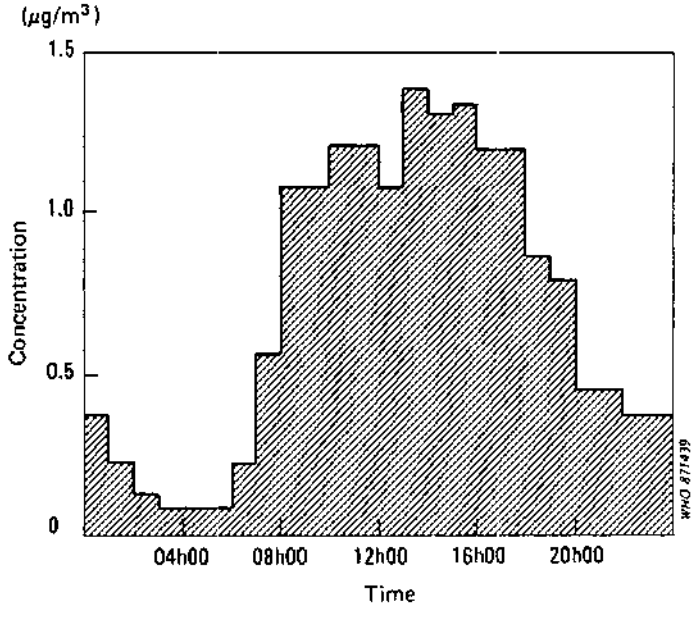

Fig. 2. Diurnal formaldehyde concentrations in Bürserberg/Tschengla, Austria in the month of July - clean air area. From: Seiler (1982).

5.1.1.1 Air in the vicinity of industrial sources and in urban communities

Estimated formaldehyde concentrations in emissions from various sources are summarized in Table 10.

Table 10. Estimated formaldehyde concentrations in emissions from various sources[a]

Emission source	Formaldehyde level
Natural gas combustion	
Home appliances and industrial equipment	2400-58 800 $\mu g/m^3$
Power plants	15 000 $\mu g/m^3$
Industrial plants	30 000 $\mu g/m^3$
Fuel-oil combustion	0-1.2 kg/barrel oil
Coal combustion	
Bituminous	< 0.005-1 g/kg coal
Anthracite	0.5 g/kg coal
Power plant, industrial and commercial combustion	
Incinerators	
Municipal	0.3-0.4 g/kg refuse
Small domestic	0.03-64 g/kg refuse
Backyard	11.6 g/kg (max) refuse
Oil refineries	
Catalytic cracking units	4.27 kg/barrel oil
Thermofor units	2.7 kg/barrel oil
Mobile sources	
Automobiles	0.2-1.6 g/litre fuel
Diesel engines	0.6-1.3 g/litre fuel
Aircraft	approximately 0.3-0.5 g/litre fuel

[a] From: Kitchens et al. (1976).

Motor vehicle exhaust from automobiles not equipped with catalyzers is the major source of formaldehyde in ambient outdoor air (Kitchens et al., 1976).

Only a few highly industrialized areas, which are also areas with heavy traffic, have been covered completely by measurements of the formaldehyde burden. In one such area in the Federal Republic of Germany

(Ludwigshafen-Frankenthal), annual mean values of 7-12 μg formaldehyde/m³ were measured during 1979-84. The annual mean value was the arithmetic average of all half-hour values measured within a year (long-term value). Peak concentrations in certain subareas, one square km in size, ranged from 16 to 69 mg/m³. These were based on the 95-percentile, i.e., 5% of the measured values were allowed to be in excess of the prescribed parameters for concentrations in ambient air (MSGU RP, 1984). The majority of subareas showed 95-percentile values of about 25 μg/m³.

A mean value of 7 μg/m³ was determined in 1971-73 for the 43 measurement points in the Lower Main District, Federal Republic of Germany, which is a radial measuring network with downtown Frankfurt/Main (Federal Republic of Germany) as its centre. This was based on 1-h measurements (n = 862). The 95% value of the cumulative frequency distribution was 18 μg/m³, and the 4 highest single values were 69, 65, 59, and 52 μg/m³ (Lahmann, 1977).

In another area at Mainz-Budenheim (Federal Republic of Germany), continuous exposure to 8-20 μg/m³ was measured, with short-term values of 23-99 μg/m³. Analysis of the causes of these high levels showed that they were not only caused by industrial emissions. Individual measurements showed a correlation with carbon monoxide levels and were not season-dependent. Hence, it can be assumed that motor vehicles not equipped with catalyzers are responsible, to a considerable extent, for the concentrations in ambient air (section 5.1.1.2). Usually, concentrations in ambient air are below 1 μg/m³. Data on concentrations of formaldehyde in ambient air are presented in Table 11.

Formaldehyde concentrations in ambient air in areas with a high level of air pollution, away from the vicinity of industrial plants, are presented in Table 12.

Ambient air concentrations of formaldehyde, measured in Los Angeles, California, during the autumn in 1961 and 1966, were 0.006-0.197 mg/m³ (Kitchens et al., 1976) and a daily average of 0.06-0.148 mg/m³ (Patterson et al., 1976), respectively. Concentrations of formaldehyde in the Los Angeles area ranged from 0.003 to 0.167 mg/m³ in 1969 (Kitchens et al., 1976). More recent air measurements taken during 1979 in Los Angeles indicated levels of less than 18.5 μg formaldehyde/m³ (Versar Inc., 1980).

The results of continuous analyses of formaldehyde concentrations in ambient air at the National Autoexhaust Monitoring Station at Kasumigaseki in Tokyo were studied by Matsumura et al. (1979). The hourly, daily, monthly, and yearly average concentrations were 1-88, 1-34, 3.7-23, and 5.5-12.6 μg/m³ (1-73, 1-28.4, 3.1-19.1, and 4.6-10.5 ppb), respectively, with a 9-year average value of 8.5 μg/m³ (7.1 ppb). Daily average concentrations showed logarithmic normal distribution. Ratios of the daily to hourly average concentrations were about 1 to 2. The daily maximum value was observed at around noon and the yearly maximum was found during June and August.

Richards et al. (1983) collected cloud water samples in the Los Angeles Basin during 5 aircraft flights (altitude not reported) and

Table 11. Levels of formaldehyde in ambient air[a]

Country	Sampling area	% of samples	Analytical method	Source	HCHO[b] ($\mu g/m^3$)	Comment	Reference
Federal Republic of Germany	Eifel Region (51°N, 6°E)	·	2,4 dinitrophenylhydrazine	easterly winds from industrial area; westerly maritime winds	5.0-6.1 0.37 0.12	Within boundary layer above boundary layer 5-7 km altitude	Schmidt & Lowe (1981)
Federal Republic of Germany	Mainz-outskirts of city; Deuselbach-rural	8 54	glass fibre filters	automobiles some automobile industry	0.063 0.037-0.39	formaldehyde aerosol only	Klippel & Warneck (1978)
France	Paris roadside		2,4-dinitrophenylhydrazine	automobiles	41-120	total aldehydes	Favart et al. (1984)
Ireland	Mace Head and Loop Head located on shoreline	28	glass fibre filters	maritime air	0.049-0.082	formaldehyde aerosol only	Klippel & Warneck (1978)
Italy	Northern - near Swiss border	15	2,4-dinitrophenylhydrazine		7.06		De Bortoli et al. (1985)
Netherlands	Terschelling Island-small population; Delft - small city; Rotterdam - heavily industrialized	350 at each site	chromatropic acid method		7.4		Guicherit & Schulting (1985)

Table 11 (contd).

Country	Sampling area	% of samples	Analytical method	Source	HCHO[b] ($\mu g/m^3$)	Comment	Reference
USA	Rural Illinois and Missouri; 3 samples 1 m above ground, 1 sample 20-15 m above tree tops	30	3-methyl-2-benzothiazolone hydrazone	-	< 1.2-5.0	total aldehydes	Breeding et al. (1973)
USA	Los Angeles-down town	31	30 or 60 litres of air at 1 litre per min through 20 ml of 0.1% chromotropic acid in conc. H_2SO_4	-	49.1 55.3	July-November, 1960 Sept-Nov. 1961	Altshuller & McPherson, (1963)
USA	Riverside, California	32	Fournier-transform infrared system		< 5-12		Tuazon et al. (1978)
USA	Lennox, Calif., roof top Azusa, Calif., roof top	36 36	Microimpinger method with 2,4-dinitrophenylhydrazine	industrial emissions photochemical pollutants	0.6-48.6 0.9-43	levels between 07h30 and 20h00 during air pollution episode	Grosjean & Swanson, (1983)
	Los Angeles Area	20			4.5-70.1	between 9h30 and 16h20 during air pollution episode	
USA	Bayonne, Camden, Elizabeth and Newark, New Jersey	hourly samples between May 1 and Sept. 30, 1974	dichlorosulfitomercurate complex and acid bleached pararosaniline hydrochloride	automobiles	17.2-20.0 4.7-8.1	range of max. levels from 4 sites range of average levels from 4 sites	Cleveland et al. (1977)

[a] Modified from: Meek et al. (1985).
[b] Unless other specified, mean or ranges.

Table 12. Measurements of formaldehyde in ambient air in areas remote from industrial emission sources[a]

Location	Period	Mean value or range ($\mu g/m^3$)	Maximum value ($\mu g/m^3$)	Remarks	Reference
Federal Republic of Germany					
Berlin	1973-74	0.6	18	118-h mean	Lahmann &
		2.1	32	119-h mean	Prescher
Berlin - Airport		2.2	29	72-h mean	(1979)
Berlin - Steglitz	1966-67		39	243-h mean	Lahmann & Prescher
Berlin - Tempelhof	1973-74	0.5	12	71-h mean	(1979)
Frankfurt - Airport	1983	9-11	23	half-hour mean	BGA (1985)
Frankfurt - City	1983	7-13	9-25		BGA (1985)
Köln - Neumarkt	December 1975	2.3	8.5	95-percentile	Deimel (1978)
	June 1978	8.2	18.3	95-percentile	Deimel (1978)
	June 1978		23.1	rush-hour traffic	Deimel (1978)
Mainz - University	1979	4.4	7.5	65 measurements	Seiler (1982)
Mainz - Finthen	1979-80	1.6	3.8	33 measurements	Seiler (1982)
Switzerland					
Street air	1976	11.4-12.3	-		Wanner et al. (1977)
USA					
California	1960-80	8-70	160		Versar Inc.(1986)
Los Angeles, California	1961-66	6-197	-		Kitchens et al. (1976)
Northeastern coastal site	1982-83	1-48	-		Tanner & Meng (1984)

[a] From: BGA (1985).

found a median of 2 mg formaldehyde/litre (68 μmol/litre) (range, 11-142 μmol/litre).

Measurements taken in 4 cities in New Jersey showed median daily concentrations in the range of 4.67-8.12 $\mu g/m^3$ (Cleveland et al., 1977).

A study in Switzerland showed formaldehyde concentrations of 11.4-12.3 $\mu g/m^3$ in street air (Wanner et al., 1977). Maritime air in the northern part of the Federal Republic of Germany has been reported to contain formaldehyde at levels of 0.12-8 $\mu g/m^3$ (Platt et al., 1979).

Tanner & Meng (1984) observed strong seasonal variations in the levels of formaldehyde, maximum levels being observed in the summer. The formaldehyde samples were collected at an unidentified northeast coastal site in the USA, using an impinger containing acetonitrile and DNPH; they were analysed using high-pressure liquid chromatography. The concentrations ranged from 1 to 58 $\mu g/m^3$ (0.9 to 48 ppbv) with an overall mean of 9 $\mu g/m^3$ (7.5 ppbv). The monthly average ambient levels were:

			equivalent to:
July/August:	1982:	15.8 ppbv, 16 samples	16 $\mu g/m^3$
October/November:	1982:	4.4 ppbv, 24 samples	4 $\mu g/m^3$
March:	1983:	3.8 ppbv, 59 samples	4 $\mu g/m^3$
April:	1983:	11.2 ppbv, 11 samples; and	11 $\mu g/m^3$
May:	1983:	12.2 ppbv, 25 samples	12 $\mu g/m^3$

5.1.1.2 Emissions from industrial plants

(a) Chemical industry

The following emission factors per metric tonne of formaldehyde produced by formaldehyde-manufacturing plants in the Federal Republic of Germany are given on a 100% basis (section 3.2.1.1).

Silver catalyst process with afterburning of flue gas in power plant and gas displacement devices: 0.003-0.008 kg/metric tonne formaldehyde produced; silver catalyst process with flaring of off-gas, without gas displacement devices: 0.05-0.2 kg/metric tonne produced; metal-oxide catalyst process without afterburning: approximately 0.5 kg/metric tonne produced; metal-oxide catalyst process with afterburning but without gas displacement devices: 0.08-0.2 kg/metric tonne produced.

(b) Wood-processing industry

Several studies are available that deal with formaldehyde emissions at particle board factories in the Federal Republic of Germany (WKI, 1978; Marutzky et al., 1980; Schaaf, 1982).

In 1980, the emissions in the exhaust air of several plants reached a mean value of 40 mg formaldehyde/m^3 off-gases. No measures had been

taken at any of the plants to clean the off-gases. Pilot studies at a particle board factory showed that a concentration (pure gas) of less than 20 mg/m^3 could be obtained using bioabsorption equipment. Meanwhile, the emittable formaldehyde content of the resins used was further reduced, resulting in even lower formaldehyde concentrations in the off-gases (BGA, 1985).

5.1.1.3 Emissions from furnaces

Incomplete combustion in furnaces is also a cause of formaldehyde emission (Schmidt & Götz, 1977). Various types of furnaces differ considerably in their emission of formaldehyde, depending on the rate of combustion.

Investigations on a small solid-fuel boiler running on wood (Schriever et al., 1983) showed that there was a formaldehyde concentration of more than 1000 mg/m^3 in the gaseous emission during the first phase of combustion, i.e., that of degasification. During the subsequent burning-out phase, the emissions of formaldehyde were about 50-100 mg/m^3.

Lipari et al. (1984) measured formaldehyde emissions in the exhaust gases of a free-standing wood-burning fireplace in the laboratory. When burning green ash (quartered logs), values of 708 mg/kg wood were found; the formaldehyde content of the exhaust gases, when burning red oak, ranged from 89 mg/kg (quartered logs) to 326 mg/kg (split wood). It is likely that wood burning in the home is a major source of primary aldehydes during the winter.

In the Federal Republic of Germany, it is estimated that about 2.8 million tonnes of firewood off-gas are consumed in small heating systems for heating buildings. On the basis of an average formaldehyde concentration of 100 mg/m^3 firewood, an overall annual emission of approximately 1000 tonnes of formaldehyde has been calculated.

5.1.1.4 Emissions from motor vehicles

Formaldehyde is also emitted as a product of incomplete combustion by internal combustion engines. The amounts emitted depend greatly on the operating conditions. Very high values are reached in emissions from a cold engine. Kitchens et al. (1976) reported a formaldehyde emission of 700 mg/litre gasoline or diesel fuel. Given an assumed average value for gasoline consumption of 23 million tonnes and for diesel fuel consumption of 13 million tonnes in the Federal Republic of Germany, the total formaldehyde emission would be 35 000 tonnes per year. Hence, motor vehicles are by far the most important source of formaldehyde emission. The use of exhaust catalytic converters reduces the emissions to less than one-tenth. Emission factors of between 1.8 and 2.4 mg/km have been reported for the USA (VDA, 1983).

Four-stroke engines, running on alcohol, emit more aldehydes than similar engines fuelled with petrol. The formaldehyde concentration in the exhaust fumes can be reduced by a factor of 10 by installing exhaust catalytic converters in vehicles powered with methanol, but the

concentration is still higher than that of vehicles with petrol-burning engines. Emission factors of about 250-300 mg/km have been given for vehicles with methanol-burning engines without an exhaust catalyser (Menrad & König, 1982). The odour of such amounts of formaldehyde is perceptible near the vehicle. Diesel engines also emit formaldehyde; diesel oil produces 1-2 g aldehydes/litre of which 50-70% is formaldehyde (Guicherit & Schulting, 1985).

5.1.2 Water

In the atmosphere, formaldehyde is absorbed during the formation of cloud droplets ("rainout") or scavenged by falling raindrops ("washout"). Some concentrations in rainwater and aerosols are given in Table 13. When the rainfall continued for a long period, remaining concentrations in the air of 0.05 $\mu g/m^3$ (detection limit: 0.03 $\mu g/m^3$) were found by Seiler (1982). Concentrations in rainwater at a remote site in the central equatorial Pacific averaged 8 ± 2 µg/kg (Zafiriou et al., 1980). Kitchens et al. (1976) reported concentrations of 0.31-1.38 mg/litre.

Table 13. Formaldehyde concentrations in rainwater and aerosol[a]

Location (year)	Rainwater concentration (mg/litre)	Aerosol concentration (ng/m^3)
Mainz, Federal Republic of Germany (1974-77)	0.174 ± 0.085	-
Deuselbach, Federal Republic of (1974-76)	0.141 ± 0.048	40.9 ± 26.0
Ireland (1975, 1977)	0.142 ± 0.059	5.36 ± 2.4
Ireland[b] (1977)	0.111 ± 0.059	-

[a] From: Klippel & Warneck (1978).
[b] Very clean air.

Fish-culture activities are also a source of formaldehyde in the aquatic environment. Formalin is one of the most widely and frequently used chemicals for treating fish with fungal or ectoparasitic infections. After use, formaldehyde solutions are often discharged into the hatchery effluent (NRC, 1981).

5.1.3 Soil

Formaldehyde is formed in the early stages of plant residue decomposition in soil (Berestetskii et al., 1981). It is degraded by certain bacteria in the soil, and therefore bioaccumulation does not

occur. Completely polymerized urea-formaldehyde resins persist in the environment and do not emit formaldehyde. Partially polymerized condensation products of low relative molecular mass degrade gradually, thus releasing formaldehyde vapour that can be broken down by soil microflora (Kitchens et al., 1976; Hsiao & Villaume, 1978).

5.1.4 Food

There is some natural formaldehyde in raw food. Formaldehyde concentrations in various food are given in Table 14.

Table 14. Formaldehyde content of foodstuffs

Food	Formaldehyde content (mg/kg)	Reference
Fruits and vegetables		
pear	60[a] (38.7)[b]	Möhler & Denbsky (1970)
apple	17.3 (22.3)	Tsuchiya et al. (1975)
cabbage	4.7 (5.3)	Tsuchiya et al. (1975)
carrot	6.7 (10)	Tsuchiya et al. (1975)
green onion	13.3 (26.3)	Tsuchiya et al. (1975)
spinach	3.3 (7.3)	Tsuchiya et al. (1975)
tomato	5.7 (7.3)	Tsuchiya et al. (1975)
white radish	3.7 (4.4)	Tsuchiya et al. (1975)
Meat		
pig	20	Florence & Milner (1981)
sheep	8	Mills et al. (1972)
poultry	5.7	Möhler & Denbsky (1970)
Milk and milk products		
goat's milk	1	Mills et al. (1972)
cow's milk	up to 3.3	Möhler & Denbsky (1970)
cheese	up to 3.3	Möhler & Denbsky (1970)
Fish		
freshwater (fumigated)	8.8	Möhler & Denbsky (1970)
sea (fumigated)	20	Möhler & Denbsky (1970)
cod (frozen)	20	Rehbein (1986)
shrimp (live)	1	Radford & Dalsis (1982)
crustacea (Mediterannean)	1-60	Cantoni et al. (1977)
crustacea (ocean)	3-98	Cantoni et al. (1977)

[a] Analysis by chromotropic acid.
[b] Analysis using Schiff's reagent.

Accidental contamination can occur through fumigation (e.g., in grain) or by using formaldehyde-containing food additives.

Hexamethylenetetramine has been reported to decompose gradually to formaldehyde under acidic conditions or in the presence of proteins (Hutschenreuter, 1956; WHO, 1974a). Its use is not recommended when there is a possibility that nitrate might also be present in food, because of the risk of nitrosamine formation (WHO, 1974b).

Formaldehyde can be introduced into food through cooking and especially through smoking of food, from utensils, and as a combustion product; it can be eluted from formaldehyde-resin plastic dishes with water, acetic acid, and ethanol in amounts directly proportional to the temperature (Table 15, 16).

Release of formaldehyde may increase with the repeated use of melamine resin tableware (Table 16). The molar concentration ratio of formaldehyde to melamine (y), in 4% acetic acid maintained at 95 °C for 30 min in melamine cups, decreases biexponentially between the first and fifth treatments according to the following formula: $\ln y = -1.0755 \ln x + 2.2462$, where x = the number of times that the heat treatment is repeated. After the sixth treatment, the value of y is reported to remain constant (Inoue et al., 1987).

Daily intake of formaldehyde through food is difficult to evaluate, but a rough estimate from 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.

5.2 Indoor Air Levels

Indoor air levels of formaldehyde in various countries were presented during the International Conference on Indoor Air Quality in Stockholm (Berglund et al., 1984).

A survey of indoor air quality under warm weather conditions, in a variety of residences in Houston, Texas, USA, not selected in response to occupant complaints, revealed a distribution of indoor formaldehyde concentrations ranging from < 0.01 to 0.35 mg/m^3, with an arithmetic mean of 0.08 mg/m^3 (Stock & Mendez, 1985). Levels in approximately 15% of the monitored residences exceeded 0.12 mg/m^3. Formaldehyde levels depended on the age and structural type of the dwelling. These factors were not independent and reflected the influence of more fundamental variables, i.e., the rate of exchange of indoor and outdoor air and the overall emission potential of indoor materials. The results of this survey suggested that considerable population exposure to excess (>0.12 mg/m^3) formaldehyde concentrations might have occurred in the residential environment, indicating the need for improved control strategies.

Hawthorne et al. (1984) measured formaldehyde levels in 40 East-Tennessee homes. Levels in older houses averaged 0.048 mg/m^3 while those in houses less than 5 years old averaged 0.096 mg/m^3.

The effects of foliage plants on the removal of formaldehyde from indoor air in energy-efficient homes is discussed in section 7.3.

Measurements made in living areas, schools, hospitals, and other buildings are listed in Table 17 to 19.

Table 15. Migration of formaldehyde from melamine and urea-resin tableware (mg/litre) into different solvents. Detection limit 0.4 mg/litre[a].

Resin	Temperature	Water		4% Acetic acid		15% Ethanol		35% Ethanol	
		30 min[b]	30 min[c]	30 min[b]	30 min[c]	30 min[b]	30 min[c]	30 min[b]	30 min[c]
Melamine resin	25 °C	n.d.[d]	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
	60 °C	n.d.	n.d.	0.5	n.d.	0.4	n.d.	n.d.	n.d.
	70 °C	n.d.	n.d.						
	80 °C	0.5	1.4	0.6	3.0	0.5	1.6	0.5	1.4
	90 °C	2.2	2.6						
	100 °C	2.6	5.2	0.8	8.9	0.5	4.6	0.5	4.8
Urea resin	25 °C	0.4	0.4	0.4	0.5	0.5	0.5	0.4	0.5
	60 °C	2.9	4.3	3.1	8.3	3.1	3.8	2.9	4.1
	70 °C	5.0	13.0						
	80 °C	9.1	23.4	9.6	126.0	7.4	30.0	8.6	28.2
	90 °C	13.0	39.2						
	100 °C	18.0	48.2	27.6	648.0	19.0	54.0	18.5	50.4

[a] From: Homma (1980).
[b] Standing at room temperature.
[c] Maintained at a definite temperature.
[d] Not detected.

Table 16. Migration from melamine cups with 4% acetic acid concentration in the migration solution[a]

Conditions	Melamine mg/litre	Formaldehyde mg/litre
60 °C, 30 min	0.5 ± 0.6	nd[b]
Microwave oven 1.5 min (90 °C) and stood at room temperature for 30 min (60 °C)	1.7 ± 1.2	(1.1 ± 0.4)
95 °C, 30 min		
repetition 1	9.5 ± 3.1	(4.1 ± 0.8)
2	28.1 ± 6.0	(12.0 ± 2.6)
3	37.7 ± 10.3	(17.3 ± 3.4)
5	46.4 ± 13.9	(19.4 ± 2.8)
7	50.4 ± 3.6	(22.2 ± 2.2)

[a] From: Ishiwata et al. (1986).
[b] Not detected.

Tobacco smoke contains an average of 48 mg formaldehyde/m^3 and is an important source of formaldehyde in indoor air. Two cigarettes smoked in a 30 m^3 room increased the formaldehyde level to more than 0.1 mg/m^3 (Jermini et al., 1976). Formaldehyde from tobacco smoke is absorbed by furniture, carpets, and curtains, and only slowly desorbed if the formaldehyde concentration in the indoor air decreases. Particle boards and, to a lesser extent, urea-formaldehyde-foam insulation (UFFI) were also listed as causes of increased indoor exposure. Disinfectant products may cause high exposure. These sources of emission are described in Table 17, 18, and 19.

Formaldehyde concentrations in 49 Dutch houses and 3 old peoples' homes where no UF-foam or particle board had been used were analysed by Cornet (1982). The houses were of different construction types and periods, in which it could be established that no particle board as construction material nor UF-foam had been used. However, several of these houses had particle board furniture. Overall, construction types and conditions of use were typical for Dutch circumstances. Average formaldehyde concentrations were 65 µg/m^3, ranging mainly from 30 to 100 µg/m^3. Ventilation rates ranged usually from 0.3-1.5 air changes per hour in living rooms and 0.2-1.2 in bedrooms. During the measurements no smoking took place.

No clear correlations could be established between the amount of particle board present in furnishings, ventilation rates, and formaldehyde concentrations.

5.2.1 Indoor exposure from particle boards

Nuisance from bad smells led to complaints by students and teachers in several new schools in Köln, Federal Republic of Germany, in 1975

Table 17. Formaldehyde levels in homes[a]

Country (Year)	No. of homes	Average age of homes	Room volume (m^3)	Air temp. (°C)	Humidity (% relative humidity or gH_2O/kg air)	HCHO (mg/m^3)[b]	Comments	Reference
Canada (1981)	378	-	-			0.042 (2.6% > 0.123)	homes without UFFI	UFFI (1981)
	1897	-	-			0.066 (10.4% > 1.23)	homes with UFFI	UFFI (1981)
Canada (1981)	6	67 (8-100) years		21.5 (21-23)	61% (59-65)	0.014 (<0.012-0.027)	homes without UFFI	Georghiou & Snow (1982)
	43	52 (3-140) years		20.4 (15-25)	62% (54-71)	0.066 (<0.012-0.246)	homes with UFFI	Georghiou & Snow (1982)
Canada (1983)	46	-	-	-	23-48% 39%	0.11 (0.04-0.30) > 0.123	low leakage homes	Dumont (1984)
Denmark (1973)	25[c]	15.3 months	23[d]	22.8	7.1	0.62		Andersen et al. (1975)
	25[g]	15.3 months	23[d]	23	7	0.64	corrected for standard conditions[e]	Andersen et al. (1979)
Denmark (1976)	7[f]	-	-	26	9.7	0.64		
	7[g]	-	-	23	7	0.30	corrected for standard conditions	Andersen et al. (1979)
Finland	432	-		-	-	0.20 0.11 0.33	average 25th percentile 75th percentile	Niemala (1985)

Table 17 (contd).

Country (Year)	No. of homes	Average age of homes	Room volume (m^3)	Air temp. (°C)	Humidity (% relative humidity or gH_2O/kg air)	HCHO (mg/m^3)[b]	Comments	Reference
Germany, Federal Republic of (1974)	1					0.069	middle of living and bedroom	Schulze (1975)
	1					0.10	room near cupboards	Schulze (1975)
	1	furniture 1 1.5 years old	60			0.039	middle of sickroom near cupboards	Schulze (1975)
	1		60			0.050	near cupboards	Schulze (1975)
	1	new house	11			0.16	kitchen, fitted cupboards	Schulze (1975)
	1	new house	54			0.10	living room	Schulze (1975)
	1	new house				0.084	kitchen	Schulze (1975)
	1	new house				0.075	living room	Schulze (1975)
	1	old house	35			0.242	living room (7 m^3 of cupboard space)	Schulze (1975)
Germany, Federal Republic of	984				57.3% 22.3% 22.3% 11.4% 3% 6%	< 0.05 < 0.05 0.05-0.07 0.071-0.096 0.097-0.12 > 0.12		Prescher & Jander (1987)
Italy (1983-84)	15					0.029 (0.008-0.052)	apartments and housing	De Bortoli et al.(1985)

Table 17 (contd).

Japan					up to 0.041 0.113	living room pre-fabricated house	Matsumura et al. (1983)
Switzerland (1981-82)	8	< 6 months to 1 year			0.33 0.14	just after occupancy	Wanner & Kuhn (1984)
The Netherlands (1980)	15				0.27	before corrective measures taken	Dept. Nat. Housing & Phys. Planning (1981)
	8				0.29 0.10	before treatment 6 weeks after treatment	
The Netherlands (1977-1980[b])	5		21	56%	0.17	living rooms, before treatment	Van der wal (1982)
			21	60%	0.09	after treatment	
	5		20	54%	0.32	bedrooms before treatment	
			21	60%	0.20	after treatment	
	36				0.34	average of highest measurements	
USA (1982)	40 18 11 11	0-30 years 0-5 years 5-15 years >15 years			0.076 ± 0.095 0.103 ± 0.112 0.052 ± 0.052 0.039 ± 0.052	5903 measurements	Hawthorne et al. (1983)
	18	0-5 years			0.107 ± 0.114 0.136 ± 0.125 0.058 ± 0.068	spring summer autumn	

Table 17 (contd).

Country (Year)	No. of homes	Average age of homes	Room volume (m^3)	Air temp. (°C)	Humidity (% relative humidity or gH_2O/kg air)	HCHO (mg/m^3)[b]	Comments	Reference
USA (1982) contd.								
	11	5-15 years				0.053 ± 0.049	spring	Hawthorne et al. (1983)
						0.060 ± 0.059	summer	
						0.042 ± 0.043	autumn	
	11	>15 years				0.044 ± 0.063	spring	
						0.036 ± 0.046	summer	
						0.032 ± 0.028	autumn	
USA (1981)	41					0.04 (0.012-0.098)	homes without UFFI	Ulsamer et al. (1982)
	636					0.15 (0.012-4.2)	homes with UFFI	
USA	244						UFFI homes	Breysse (1984)
						>1.23	2.8% of samples	
						0.61-1.22	1.9% of samples	
						0.12-0.60	24.1% of samples	
						<0.12	71.2% of samples	
							non-UFFI homes and apartments	
	59					>1.23	1.8% of samples	
						0.61-1.22	1.8% of samples	
						0.12-0.60	36.3% of samples	
						<0.12	60.1% of samples	
USA (1978-79)	13	building material 3-92 months (5.2 months median)				0.12 (median)		Dally et al. (1981)

Table 17 (contd).

USA (1979)	1		0.098 (0.04-0.15)	energy efficient house (0.01 mg HCHO/m^3 outdoors)	Berk et al. (1980)
	1		0.081 ±0.007	unoccupied without furniture	
			0.225 ±0.016	unoccupied with furniture	
			0.263 ± 0.026	occupied[h], daytime	
			0.141 ± 0.044	occupied[h], nighttime	
USA (1980/81)	9	2 years 445 (total)	0.044 ± 0.022	airtight construction (half had gas appliances)	Offermann et al. (1982)
			0.033 ± 0.020	mechanical ventilation	
	1	6 years 441 (total)	0.017	"loose" construction	
USA (1983)	20	<6 years	0.076	energy-efficient new homes	Grimsrud et al. (1983)
	16		0.037	low ventilation modernized homes	

[a] Modified from: Meek et al. (1985). Where blanks appear, relevant information not provided by authors.
[b] Means, ranges or standard deviations, unless otherwise specified.
[c] Ventilation = 0.8 air changes/h.
[d] Loading (ratio of unit area of formaldehyde source to room volume) = 1.2 m^2/m^3.
[e] Standard conditions were: 23 °C, 7 g H_2O/kg air, 1 air change/h.
[f] Ventilation = 0.32 air change/h.
[g] Ventilation = 1 air change/h.
[h] House had a gas stove and 3 occupants, no cigarette smokers.

Table 18. Formaldehyde levels in mobile homes[a]

Country	No. of mobile homes studied	Age of homes	HCHO (mg/m^3)	Comments	Reference
Germany, Federal Republic of		1 year	5.26	trailer	Schulze (1975)
		1 year	1.06	trailer opened up for 1 h	
		3 years	0.06	trailer shut for 1 day	
	3	1 year	0.11	trailer	
	3	2 years	0.05	trailer	
USA	110	< 2 years	0.95	complaint homes, Washington	Stone et al. (1981)
	38	< 2 years	0.89	complaint homes, Wisconsin	
	66	< 2 years	1.04	complaint homes, Minnesota	
		< 2 years	0.66	random sample, Wisconsin	
	77	2-10 years	0.58	complaint homes, Washington	
	9	2-7 years	0.56	complaint homes, Wisconsin	
	43	2-10 years	0.34	complaint homes, Minnesota	
USA	65	0.2-12 years median 1.3 years	0.59 (median)	complaint homes, Wisconsin	Dally et al. (1981)
USA	430		> 1.23	4 % of sample	Breysse (1984)
			0.61-1.22	18% of sample	
			0.12-0.60	64% of sample	
			< 0.12	14% of sample	
USA	431		0.47 (0.012-3.60)		Ulsamer et al. (1982)
USA	65		0.20 (median)	65 out of 208; random sample of mobile homes in Wisconsin	Hanrahan et al. (1984)

[a] From: Meek et al. (1985).

Table 19. Formaldehyde levels in public buildings[a]

Country	No. of buildings	Average age of buildings	Loading (m^2/m^3)[b]	Air temp. (°C)	Ventilation (air changes/h)	HCHO (mg/m^3)[c]	Comments	Reference
Denmark	7	6 months	-	-	0.5	0.45	mobile day care centre	Olsen (1982)
Germany, Federal Republic of	3	-	-	-	-	0.469	schools containing some UF building material	Burdach & Wechselberg (1980)
	441						dwellings, offices, hospitals, joiner's workshops, complaints	Prescher (1984)
	-	-	-	-	-	0.014-0.31 mean 0.06	dwellings with gas cooking	
	-	-	-	-	-	0.064-0.2 mean 0.06	dwellings without gas cooking	
	-	-	-	-	-	0.01-0.13 mean 0.05	offices, smokers	
	-	-	-	-	-	0.02-0.1 mean 0.05	offices, non-smokers	
	-	-	-	-	-	0.026-0.22 mean 0.12	joiner's workshops	
	-	-	-	-	-	0.012-0.1 mean 0.05	hospital rooms	

Table 19 (contd).

Country	No. of buildings	Average age of buildings	Loading (m^2/m^3)[b]	Air temp. (°C)	Ventilation (air changes/h)	HCHO (mg/m^3)[c]	Comments	Reference
Japan	-	-	-	-	-	0.048	department store	Matsumura et al. (1983)
						up to 0.046	grocer's shop	
						0.035	offices	
						0.003	cinema	
Switzerland	11	< 6 months	-	-		0.410	office: measurement taken after recent occupancy and after ageing, school: measurement taken after recent occupancy and after ageing	Wanner & Kuhn (1984)
	16	1 year	-	-	-	0.160		
		< 6 months				0.60		
		1 year				0.23		
The Netherlands	10	-	-	-	-	0.758	average of highest measurements in schools	Van Der Waal (1982)
	13	-	-	-	-	0.245	average of highest measurements in commercial establishments	
	1	-	-	-	-	2.30	highest value in UFFI building	
Yugoslavia	24	-	-	26	-	1.083	offices	Kuljak (1983)
	2	-	-	30	-	2.60	stores	
	3	-	-	18	-	0.15	furniture stores	

Table 19 (contd).

Yugoslavia	6	1-3 years	-	-	-	0.143	offices	Kalinic et al. (1985)
	6	11-43 years				0.087	offices	
	7	1-10 years				0.141	kindergarten	
	3	11-50 years				0.109	kindergarten	
	8	4-23 years				0.043	schools	
	2	90-100 years				0.023	schools	
USA	1	4 years	-	-	-	0.025-0.037	office recently renovated with UF material	Konopinski (1983)
	2	4 years	-	-	-	0.36-1.22	office recently renovated with particle board	
	1	-	-	-	-	0.14-0.45	particle board shelving	
	1	-	-	-	-	0.11-0.14	particle board furniture and plywood floors	

[a] Modified from: Meek et al. (1985). Where blanks appear, relevant information not provided by authors.
[b] Ratio of unit area of formaldehyde source to room volume.
[c] Means or ranges, unless otherwise specified.

and 1976. Formaldehyde concentrations of up to 1.2 mg/m^3 were measured with the windows closed (Deimel, 1978). A combination of ceilings and furniture made of particle boards and insufficient ventilation was the cause of these high indoor concentrations (Anderson et al., 1975). There have been complaints from schools, kindergartens, private homes, and, especially in the USA, mobile homes. Formaldehyde concentrations of more than 0.12 mg/m^3 and sometimes more than 1.2 mg/m^3 were measured.

During the 1970s, increased use of UF-bonded particle board as a construction material in The Netherlands resulted in many consumer complaints, attributed to formaldehyde. In 1978, a level of 120 μg/m^3 was officially recommended as an acceptable upper limit. In the years 1978-81, measurements of indoor formaldehyde concentrations were carried out, guided by consumer complaints. In 1981, a summary of 950 measurements was presented to the Dutch Parliament (Dutch State Secretary of Health and Environment, 1981). In 435 cases, formaldehyde concentrations exceeded 120 μg/m^3, whereas in 515 cases, notwithstanding complaints, levels were below 120 μg/m^3. Since 1981, many hundreds of measurements of formaldehyde levels in houses, schools, hospitals etc. have been carried out, guided also by consumer complaints. But the overall picture has remained the same, except for extremes; values exceeding 200–250 μg/m^3 have seldom been reported since the introduction of the new standard. However, occasionally, higher concentrations of up to 400 μg/m^3 have arisen as a result of the use of particle board or trimmings of bad quality in furniture.

5.2.2 Indoor air pollution from urea-formaldehyde foam insulation (UFFI)

Foam made from specific aminoplastic resins is used for the thermal insulation of spaces in walls or other elements of construction. In this process, an acidic surfactant solution is foamed by compressed air and continuously mixed with aqueous UF resin. Formaldehyde is emitted during and after completion of the hardening process. The resulting indoor exposure depends, among other factors, on the age of the building, type of resin, the application and the care taken, the amount of excess formaldehyde, the amount and rate of emission, the prevailing temperature, humidity, and rates of ventilation.

Most of the studies performed on UFFI and mobile homes have been carried out in Canada and the USA (Table 18), but they are currently of less importance.

Studies by Everett (1983) showed that there is some increase in formaldehyde levels in dwellings, directly after foaming, but that this decays over a period of a few weeks. Everett (1983) noted that, though there were isolated high values up to 1.2 mg/m^3, 70% of the results after foaming were below 0.1 mg/m^3.

Girman et al. (1983), conducting the 40-home East Tennessee study, obtained formaldehyde measurements that led to the following major conclusions:

The average formaldehyde levels exceeded 0.12 mg/m³ (0.1 ppm) in 25% of the homes;

Formaldehyde levels were positively related to temperature levels in homes. In houses with UFFI, a temperature-dependent relationship with measured formaldehyde levels frequently existed;

Formaldehyde levels generally decreased with increasing age of the house. This is consistent with decreased emission from materials due to aging;

Formaldehyde levels were found to fluctuate significantly both during the day and seasonally.

5.2.3 *Indoor air pollution from phenol-formaldehyde plastics*

Popivanova & Beraha (1984) carried out a study on phenol-formaldehyde penoplast in order to establish the amount and dynamics of formaldehyde migration into the indoor air in relation to three major factors, i.e., age of the material, air temperature, and air exchange rate. Age of the material was found to be the most important factor influencing formaldehyde migration, followed by temperature elevation. The rate of air exchange was inversely related to formaldehyde migration level. A mathematical model of these processes has been developed and a regression equation proposed. A review of factors influencing formaldehyde migration from formaldehyde resins was published by Popivanova (1985).

5.2.4 *Exposure to indoor air containing cigarette smoke*

As with all other incomplete combustion processes, formaldehyde is emitted in the smoke from cigarettes. About 1.5 mg of formaldehyde was found in the total smoke from one cigarette, which was distributed between the main and side stream in the ratio of 1:50, i.e., 30 μg in the main stream (= inhaled smoke) and 1526 μg in the side stream (Jermini et al., 1976; Klus & Kuhn, 1982). Other investigators measured up to 73 μg of formaldehyde per cigarette in the main stream (Newsome et al., 1965; Mansfield et al., 1977). Concentrations of 60-130 mg/m³ were measured in mainstream smoke. For an individual smoking 20 cigarettes per day, this would lead to an exposure of 1 mg/day (Weber-Tschopp et al., 1977). Exposure to sidestream smoke (or environmental tobacco smoke) can be estimated from chamber measurements. Thus, in a 50-m³ chamber with one air exchange per hour, 6 cigarettes smoked in 15 min yield over 0.12 mg/m³ (WKI, 1982). Weber-Tschopp et al. (1976) measured the yield of 5-10 cigarettes in a 30-m³ chamber with 0.2-0.3 air exchanges per hour as 0.21-0.35 mg/m³, which would be about 0.05-0.07 mg/m³ at one air exchange per hour. This concentration is in the same range as that likely to be found in the rooms of most conventional buildings where there is no smoking (section 5.2). Levels of formaldehyde emitted from combustion sources other than cigarette smoke are presented in Table 20.

Table 20. Formaldehyde levels from combustion[a]

Source	Comments	Emission rate (g fuel/min)	Air change per h	HCHO (mg/m^3)	Reference
Gas stove in test kitchen, 27 m^3	ventilation conditions:				
	no stove vent or hood		0.25	0.40	Hollowell et al. (1979)
	hood vent (without fan) above stove		1.0	0.26	
	hood vent, fan at low speed (1.4 m^3/min)		2.5	0.14	
	hood vent, fan at high speed (4 m^3/min)		7.0	0.035	
	outdoor concentration during test			0.010	
Undiluted exhaust gases:				10	Schmidt & Götz (1977)
Household natural gas appliances				6	Altshuller et al. (1961)
Cooking range (oven)				4	
Floor furnace				1.5	
Kerosine heaters:	27 m^3 environmental chamber, temp. < 26 °C		0.4		
radiant (new)	fired in chamber	3.13	5.1	5.1[b]	Traynor et al. (1983)
	10-min warm-up outside chamber	3.16	4.0		
radiant (1 year old)	10-min warm-up outside	2.54	0.67		
convection (new)	fired in chamber	3.03	0.36		
	10-min warm-up outside chamber	3.0	1.3		
convection (5 years old)	fired in chamber	2.1	6.7		
	10-min warm-up outside chamber	2.2	5.6		

Table 20 (contd).

Radiant heater	21 m^3 room, closed door,	3.6	0.5	0.025	Caceres et al.
Radiant heater		3.6		1.0[b]	(1983)
Convection heater		2.7		0.9[b]	
				0.4[b]	
Cigarette smoke	30 m^3 climate chamber,		0.3		
	1 cigarette (1 min)			0.06	Weber-Tschopp
	3 cigarettes (2 min)			0.16	et al. (1976)
	5 cigarettes (3 1/2 min)			0.29	
	10 cigarettes (7 min)			0.55	
	15 cigarettes (10 1/2 min)			0.76	
Cigarette smoke	45.8 m^3 room, 5 subjects,				Sundin (1978)
	20 cigarettes smoked over 30 min:				
	original background level			0.01	
	level after 30 min			0.33	
Cigarette smoke	undiluted smoke			40-140	Auerbach et al. (1977)

[a] From: Dept National Health Welfare Canada (1985).
[b] mg/h.

5.3 General Population Exposure

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

5.3.1 Air

The daily inhalation exposure for an average adult can be estimated by assuming a respiratory volume of 20 m^3/day, given the exposures mentioned above, and making different assumptions about the duration of exposure periods (Table 21). 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 it is assumed that normal work exposures are similar to home exposures, the daily exposure resulting from breathing is about 1 mg/day, with a few exposures of > 2 mg/day, and a maximum of 5 mg/day; this compares favourably with the estimated range of 0.3-2.1 mg/day, based on the work of Kalinic et al. (1984), with estimated weighted average exposures of 0.02-0.14 mg/m^3.

Matsumura et al. (1985) determined the levels of exposure to formaldehyde of housewives by using personal air sampling apparatus (Sampler: silica gel impregnated with triethanolamine, Hydrazine-method). The highest exposure level was 0.311 mg/m^3 (0.259 ppm) (3.73 mg/day), while the lowest was 0.011 mg/m^3 (0.009 ppm) (0.13 mg/day). The usual exposure range was 0.018-0.030 mg/m^3 (0.015-0.025 ppm) (0.22-0.36 mg/m^3). The highest exposure level was that of a housewife living in a newly constructed house, where irritation of the eyes and throat, lachrymation, and cough were observed in the family.

Chemical toilet fluids, used in caravans, on camping sites, in aeroplanes, and in boats often include formaldehyde. In an experiment, a 10% formaldehyde solution (normally found on the market) was applied in a 2 m^3 toilet room (Reus, 1981a). The toilet bowl was filled with 1 1/2 litres of water and 110 ml of the disinfectant, giving a solution of 0.75% formaldehyde. The ventilation rate was not determined, but estimated to be 3-5 air changes per hour, temperature 20-22 °C. Air concentrations of formaldehyde, which rose to 150-350 μg/m^3 during the filling of the toilet, gradually decreased within 1 h to 60-90 μg/m^3 and then remained constant. Closing the lid caused a further decrease to < 20 μg/m^3.

5.3.1.1 Smoking

Concentrations of 60-130 mg/m^3, measured in mainstream smoke, would lead to an average daily intake of 1 mg formaldehyde per day (daily consumption: 20 cigarettes; WHO, 1987).

Formaldehyde produced by cigarettes can also mean considerable exposure for the non-smoker through passive smoking, the more so since it has been reported that the effects of gaseous formaldehyde are potentiated by smoke particles and aerosols (Rylander, 1974; Weber-Tschopp et al., 1977; WHO, 1987).

Table 21. Contribution of various atmospheric environments to average exposure[a]

Source	Average exposure (mg/day)
Air	
Ambient air (10% of the time)	0.02
Indoor air	
Home (65% of the time)	
- Conventional	0.5-2
- Prefabricated (particle board)	1-10
Work-place air (25% of the time)	
- Without occupational exposure[b]	0.2-0.8
- Exposed occupationally to 1 mg/m^3	5
- Environmental tobacco smoke	0.1-1.0
Smoking	
20 cigarettes/day	1.0

[a] From: WHO (1987).
[b] Assuming the normal formaldehyde concentration in conventional buildings.

5.3.2 *Drinking-water*

Concentrations in drinking-water are normally less than 0.1 mg/litre, which means that, except for accidental ingestion of formaldehyde-contaminated water, intake is negligible (below 0.2 mg/day; WHO, 1987).

5.3.3 *Food*

The daily formaldehyde intake depends on the composition of the meal and may range between 1.5 and 14 mg for an average adult (see Table 14, section 5.1.4).

In a residue study of the Food Inspection Service in The Netherlands, it was found that 53% of 162 samples of soft drinks, alcoholic beverages, sugar-containing foodstuffs, such as marmalade, and meat and meat products contained formaldehyde at levels exceeding 1 mg/kg. Up to 20% of samples contained levels exceeding 2 mg/kg; levels in 15 samples of meat and meat products even exceeded 10 mg/kg, with some reaching about 20 mg/kg. The source of the formaldehyde could not be established for any of the cases (Nijboer, 1984). In an additional study, the formaldehyde contents of meat and meat products were analysed (Nijboer, 1985) and, in 62 out of 86 samples, were found to exceed a level of 1 mg formaldehyde/kg. Levels in 50% of samples

were between 1 and 2 mg/kg and 22% exceeded 2 mg/kg with some levels as high as 14-20 mg/kg. Again, no source for the formaldehyde residue could be established.

5.3.4 Other routes of exposure

Dermal exposure and absorption occur through contact with cosmetics, household products, disinfectants, textiles (especially of artificial origin) and orthopaedic casts. Most of these exposures are likely to remain localized (though gaseous formaldehyde will be available for inhalation). The estimates of the systemic absorption of formaldehyde through the entire epidermal layer and across the circulatory layer, are negligible (Jeffcoat, 1984; Robbins et al., 1984; Bartnik et al., 1985). Contact with liquid barriers, as in the eyes does not appear to lead to absorption. There have been case reports of newborn infants being exposed to formaldehyde-containing disinfectants in incubators.

In certain rare events, formaldehyde in aqueous solution enters the blood stream directly. These events are most likely to occur during dialysis or in circulation-assisted surgery in which the dialysis machine and tubes that have been disinfected with formaldehyde, still contain the compound because of adsorption or back wash, and it is then introduced into the patient's bloodstream (Beall, 1985).

5.4 Occupational Exposure

In the work-place, exposure may be caused by either producing or handling formaldehyde or products containing formaldehyde. Concentrations of formaldehyde in occupational settings in the USA were reported by the Consensus Workshop on Formaldehyde (1984) (Table 22, see also section 9.2).

Airborne formaldehyde concentrations in 7 funeral homes in 1980 in the USA ranged from 0.12 to 0.42 mg/m^3 during the embalming of non-autopsied bodies and from 0.6 to 1.4 mg/m^3 during the embalming of autopsied bodies (Williams et al., 1984). In a study on formaldehyde exposure in an embalming room, levels of up to 4.8 mg/m^3 were found when the exhaust ventilation system was not functioning (Anon., 1980a,b).

Formaldehyde concentrations were determined in Dutch pathological laboratories, under practical conditions, where a 4-6% solution of formaldehyde in water was used. No detailed information on ventilation is available, but a special ventilation system was applied at the dissection table, where concentrations amounted to 75 μg/m^3. A concentration of 195 μg/m^3 was found in the cleaning section of the laboratory (Reus, 1981).

Table 22. Formaldehyde monitoring data in occupational settings[a]

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observations	Method[b]	Reference
Formaldehyde production	production operator	-	1.68 (1.4)	-	personal	-	CT, IC	NIOSH (1980a)
	laboratory technician	-	1.57 (1.31)	-	personal	-	CT, IC	NIOSH (1980a)
Resin and plastic materials production	production operator	-	1.67 (1.39)	-	personal	-	CT, IC	NIOSH (1980a)
	resin plant	0.06-0.44 (0.05-0.37)	0.29 (0.24)	-	area	8	BI, CT, GC	NIOSH (1976a)
	resin plant	0.11-0.20 (0.09-0.17)	0.16 (0.13)	-	area	2	BI, CO	NIOSH (1978a)
	UF resin production (2 plants)	0.14-0.66 (0.12-0.55)	-	-	area	-	SS, IC	Herrick et al. (1983)
		0.22-6.48 (0.18-5.4)	-	-	area	-	SS, IC	Herrick et al. (1983)
		0.24-0.89 (0.2-0.74)	-	-	area	-	SS, IC	Herrick et al. (1983)
		0.72-0.41 (0.6-0.34)	-	-	area	-	SS, IC	Herrick et al. (1983)
	UF resin production	0.14-6.48 (0.12-5.4)	1.08 (0.90)	-	personal	18	BI, GA	NIOSH (1980b)
		0.24-0.89 (0.20-0.74)	0.47 (0.39)	-	personal	5	BI, GA	NIOSH (1980b)
		0.72-0.41 (0.06-0.34)	0.23 (0.19)	-	personal	5	BI, GA	NIOSH (1980b)

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observations	Method[b]	Reference
Textile finishing	textile warehouse	0.05-0.88 (0.04-0.73)	0.37 (0.31)	-	area, personal	11	CT, SP	NIOSH (1979a)
		0.10-0.61 (0.08-0.51)	0.30 (0.25)	-	area, personal	11	BI, SP	NIOSH (1979a)
	textile facilities	< 0.12-1.56 (< 0.1-1.3)	-	0.96 (0.8)	area, personal	28	-	NIOSH (1979b)
		< 0.12-1.68 (< 0.1-1.4)	-	0.84 (0.7)	area, personal	15	-	NIOSH (1979b)
	textile manufacture	0.13-1.60 (0.11-1.33)	0.83 (0.69)	0.77 (0.64)	personal	6	-	NIOSH (1981)
		0.18-1.44 (0.15-1.2)	0.64 (0.53)	0.54 (0.54)	area	13		NIOSH (1981)
Clothing production	permanent press	0.18-0.46 (0.15-0.38)	0.37 (0.31)	-	area	9	BI, I	US DHEW (1966)
		0-3.24 (0-2.7)	0.89 (0.74)	-	area	32	BI, I	US DHEW (1968)
	warehouse	0.13-0.68 (0.11-0.57)	0.47 (0.39)	0.44 (0.37)	personal	13	-	NIOSH (1979a)
		0.05-0.23 (0.04-0.19)	0.14 (0.12)	0.18 (0.15)	area	9	-	NIOSH (1979a)
	sewing machine operators	0.61-1.09 (0.51-0.91)	0.86 (0.72)	0.85 (0.71)	personal	16	-	NIOSH (1979a)
		0.36-2.16 (0.3-1.8)	1.44 (1.2)	1.44 (1.2)	personal	41	-	NIOSH (1979a)
	clothing pressers	0.006-1.14 (0.005-0.95)	0.08 (0.07)	0.065 (0.054)	personal	40	-	NIOSH (1976a)

Table 22 (contd).

Plywood particle-board production	all workers	-	1.2-3.0 (1.2.5)	-	area	-	-	NIOSH (1979b)
Wood furniture manufacture	particle board veneering	0.01-0.3 (0.008-0.25)	0.14 (0.12)	-	area	11	BI, CA	Herrick et al. (1983)
		1.08-7.68 (0.9-6.4)	3.30 (2.75)	-	area	-	BI, CA	Herrick et al. (1983)
		0.24-0.66 (0.2-0.55)	0.48 (0.40)	-	area	9	BI, CA	Herrick et al. (1983)
		0.24-3.0 (0.2-2.5)	0.84 (0.70)	-	area	13	BI, CA	Herrick et al. (1983)
Plastic moulding	injection mold	0.01-0.12 (0.01-0.1)	0.044 (0.037)	-	personal	9	CA	NIOSH (1973a)
	area samples	0.01-0.64 (0.01-0.53)	0.24 (0.20)	-	area	8	CA	NIOSH (1973a)
	operators	< 2.4 (< 2)	< 2.4 (< 2)	< 2.4 (< 2)	personal	28	DT	NIOSH (1973a)
	near grinder hopper	2.4-4.8 (2-4)	3.6 (3)	3.6 (3)	area	3	DT	NIOSH (1973a)
	sand mould production	0.12-0.84 (0.1-0.7)	0.37 (0.31)	0.24 (0.2)	personal	28	-	NIOSH (1976a)
		ND-1.32 (ND-1.1)	0.20 (0.17)	0.12 (0.1)	area	29	-	NIOSH (1976a)
Paper and paper-board manufacture	paper treatment (resin impregnated)	0.05-0.19 (0.04-0.16)	0.10 (0.08)	-	personal	15	BI, CT CA	NIOSH (1976b)
		0.04-0.08 (0.03-0.07)	0.07 (0.06)	-	area	7	BI, CT, CA	NIOSH (1976b)
		0.01-0.28 (0.01-0.23)	0.06 (0.05)	-	personal	30	BI, CT, CA	NIOSH (1976b)

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observations	Method[b]	Reference
Paper and paperboard manufacture (contd).		0.02-0.34 (0.02-0.28)	0.06 (0.05)	-	personal	10	BI, GT, CA	NIOSH (1976b)
	treated paper products	0.17-1.19 (0.14-0.99)	-	0.70 (0.59)	area	64	-	NIOSH (1979b)
		0.17-1.08 (0.14-0.90)	-	0.41 (0.34)	personal	37	-	NIOSH (1979b)
	coating preparation	< 0.01-3.6 (< 0.01-3)	1.2 (1.0)	0.01 (0.01)	area	7	-	NIOSH (1980a)
		0.96-0.50 (0.8-0.42)	0.61 (0.51)	0.50 (0.42)	area	4	-	NIOSH (1980a)
Foundries (steel, iron, and non-ferrous)	bronze foundry, core machine operators	0.29-0.96 (0.24-0.80)	0.64 (0.53)	0.66 (0.55)	personal	4	BI, CA	NIOSH (1976c)
		0.14-0.83 (0.12-0.69)	0.47 (0.39)	0.47 (0.39)	area	11	BI, CA	NIOSH (1976c)
	iron foundry, core machine operators	< 0.02-22.0 (0.02-18.3)	-	0.52 (0.43)	personal	14	-	NIOSH (1979b)
		0.08-0.40 (0.07-0.33)	0.19 (0.16)	-	personal	3	BI, CA	NIOSH (1973b)
	moulding	0.04-0.16 (0.03-0.13)	0.11 (0.09)	-	personal	6	BI, CO	NIOSH (1977a)
		0.08-0.94 (0.07-0.78)	0.25 (0.21)	-	area	6	BI, CO	NIOSH (1977a)
Rubber hose production	-	ND-0.05 (ND-0.04)	0.05 (0.04)	-	personal	10	BI, CO	NIOSH (1977b)

Table 22 (contd).

Asphalt shingle production	producers	0.04-0.08 (0.03-0.07)	0.06 (0.05)	0.06 (0.05)	area	2	BI, CO	NIOSH (1978b)
Fibreglass insulation	installers	0.008-0.04 (0.007-0.033)	0.028 (0.023) (TWA)[c]	0.023 (0.019)	personal	13	-	NIOSH (1980a)
Urea-formaldehyde foam insulation dealing and installation	suburban shopping centre insulated with UF foam	0.08-2.4 (0.07-2)	-	-	-	-	IC	Herrick et al. (1983)
		0.96-1.92 (0.8-1.6)	1.26 (1.05)	-	area	36	BI, CA	NIOSH (1979b)
		0.36-3.72 (0.3-3.1)	1.73 (1.44)	-	area	30	CT, IC	NIOSH (1979b)
		< 0-6.36 (< 0.5-3)	1.87 (1.56)	-	area	16	DT	NIOSH (1979b)
Fertilizer manufacturing	-	0.24-2.28 (0.2-1.9)	1.08 (0.9)	-	personal, area	11	-	NIOSH (1979b)
Mushroom farming	-	< 0.61-12+ (0.51-10+)	3.22 (2.68)	-	area	12	DT	NIOSH (1980b)
		ND-3.24 (ND-2.7)			personal	3	CT, IC	NIOSH (1980b)
		ND-5.92 (ND-4.93)	-	-	area	3	CT, IC	NIOSH (1980b)
Funeral homes	embalmers	0.1-6.3 (0.09-5.26)	0.89 (0.74)	-	area	187	CA	Kerfoot & Mooney (1975)
		0.24-4.79 (0.20-3.99)	1.32 (1.1)	0.65 (0.54)	area personal	8	CT	NIOSH (1980c)
		1.56-4.72 (1.30-3.99)	3.24 (2.7)	2.99 (2.49)	area personal	5	CT	NIOSH (1980c)
Pathology	autopsy room	0.07-9.5 (0.06-7.9)	5.76 (4.8)	-	area	10	BI, CA	Covino (1979)
		2.64-9.5 (2.20-7.9)	5.22 (4.35)	-	area	6	-	NIOSH (1979b)

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observa- tions	Method[b]	Reference
Biology teaching	laboratory	3.30-17.76 (2.75-14.8)	9.96 (8.3)	-	area	8	BI, CA	US EPA (1981)
Hospital	laboratory	2.64-2.76 (2.2-2.3)	2.70 (2.25)		personal	2	BI	Blade (1983)
		2.28 (1.9)			personal	1	CT	Blade (1983)
		2.64 (2.2)	2.4 (2)		area	2	CT	Blade (1983)
Government	laboratory	2.88 (2.4)	-		personal	1	CT	Blade (1983)
		0.96 (0.8)	-		area	1	CT	Blade (1983)
Hospital	dialysis unit	ND-1.08 (ND-0.90)	0.50 (0.42)		area	9	CT	Blade (1983)
		0.32-0.76 (0.27-0.63)	0.49 (0.41)		personal	5	CT	Blade (1983)
		0.05-0.60 (0.04-0.50)	0.61 (0.51)		area		CEA	Blade (1983)
Animal dissection	laboratory	< 0.46-1.25 (< 0.38-1.04)	-		personal	15	CA	Blade (1983)
		0.06-0.48 (0.05-0.40)	0.18 (0.15)		area	6	BI	Blade (1983)
		0.13-0.22 (0.11-0.29)	0.22 (0.18)		area	3	CEA	Blade (1983)
Garment manufac- turing (3 plants)	-	< 0.17-0.76 (< 0.14-0.63)	0.28-0.40 (0.23-0.33)		personal	40	CT	Blade (1983)
		< 0.04-0.48 (< 0.03-0.40)	0.23-0.31 (0.19-0.26)		area	43	CT	Blade (1983)
		0.04-0.48 (0.03-0.40)	0.25 (0.21)		area	43	BI	Blade (1983)

Table 22 (contd).

Garment manufacturing (contd)							
		0.06-1.34 (0.05-1.2)	0.55 (0.46)	area	42	CEA	Blade (1983)
Chemical manufacturing	-	0.05-1.92 (0.04-1.6)	0.66 (0.55)	- personal	3	BI	Blade (1983)
		0.04-0.52 (0.03-0.43)	0.20 (0.17)	- area	5	BI	Blade (1983)
Glass manufacturing	-	0.50 (0.42)	0.50 (0.42)	- personal	1	CT	Blade (1983)
		0.54-0.80 (0.45-0.64)	0.65 (0.54)	- area	2	CT	Blade (1983)
Hospital work	-	0.44-0.88 (0.37-0.73)	0.66 (0.56)	- area	2	BI	Blade (1983)
Paraformaldehyde packaging	-	< 0.30-1.02 (< 0.25-0.85)	0.66 (0.55)	- personal	10	CA	Blade (1983)
		0.34-4.08 (0.28-3.4)	1.40 (1.17)	- area	8	CEA	Blade (1983)
Office work (3 locations)	-	0.02-0.14 (0.02-0.12)	0.07 (0.06)	- area	39	BI	Blade (1983)
		< 0.05 (< 0.04)	< 0.05 (< 0.04)	- area	9	CT	Blade (1983)

Table 22 (contd).

Industry	Job or work area	Exposure levels mg/m^3 (ppm) range	mean	median	Area or personal monitor-	Number of observa-tions	Method[b]	Reference
Autopsy rooms	resident	-	1.90[d] (1.58)		personal	10	CA	Makar et al. (1975)
	pathologist	-	1.50[d] (1.24)		personal	9	CA	
	technician	-	0.68[d] (0.57)		personal	2	CA	Makar et al. (1975)
	assistants	0.16-16.28 (0.13-13.57)	0.86 (0.72)		area	23	CA	

[a] From: Consensus Workshop on Formaldehyde (1984).
[b] *Abbreviations for analytical procedures:*

AA = acetylacetone.
BI = bisulfite impingers.
CA = chromotropic acid procedure.
CL = chemiluminescence procedure.
CO = colorimetric analysis.
CT = charcoal tubes.
SS = solid sorbents.
DT = Draeger tubes.
FS = Fourier transform spectrometer.
GC = gas chromatography.
IC = ion chromatography.
MB = MBTH procedure.
SP = spectrophotometric procedure.
CEA = CEA instruments Model 555.

[c] TWA = time-weighted average.
[d] Average.

6. KINETICS AND METABOLISM

6.1 Absorption

6.1.1 Inhalation

6.1.1.1 Animal data

Eight male F-344 rats were exposed to 17.3 mg formaldehyde/m^3 (14.4 ppm) by nose only inhalation for 2 h, and the blood was collected immediately after exposure. Formaldehyde concentrations in the blood were determined by gas chromatography/mass spectrometry. The blood of 8 unexposed rats was collected and analysed in the same manner. Measured formaldehyde concentrations (mg/kg blood) were: exposed, 2.25 ± 0.07; controls, 2.24 ± 0.07 (mean ± SE) (Heck et al., 1985).

Under normal conditions, absorption is expected to occur in the upper respiratory tract (nasal passages in obligate nose-breathers; trachea, bronchi in oral breathers) where first contact occurs (Heck et al., 1983).

Absorption through the upper respiratory tract was estimated to be 100% at all respiratory rates tested. Detailed studies on the distribution of ^{14}C-formaldehyde in the rat nasal cavity have confirmed that it is absorbed primarily in the upper respiratory system. Following a 6-h exposure by inhalation, the amount of ^{14}C-formaldehyde absorbed appeared to be approximately proportional to the airborne concentration. The amount retained did not appear to vary following pre-exposure (Heck et al., 1982).

Chang et al. (1983) reported studies on the effects of inhaled formaldehyde vapour on respiratory minute volumes in mice and rats. The results showed that both rats and mice responded to formaldehyde inhalation by a reduction in their respiratory rates and minute volumes. However, mice responded to lower formaldehyde concentrations than rats. For example, respiratory rates were reduced by 50% at 7.2 mg/m^3 (6 ppm) in mice and 18 mg/m^3 (15 ppm) in rats. Rats developed some tolerance to formaldehyde during exposure. Both rats and mice pretreated with 18 mg formaldehyde/m^3 (15 ppm) were slightly more sensitive to respiratory-rate depression, but pretreated rats compensated for the decrease in respiratory rate by an increase in tidal volume. Thus, following pretreatment, the difference in sensitivity between the two species became more marked. As a result, mice were able to minimize the inhalation of formaldehyde more efficiently than rats, so that, at 18 mg/m^3 (15 ppm), the nasal mucosa in mice was exposed to approximately one-half of the dose of formaldehyde to which the rats were exposed. This species difference contributes to the differences in respiratory tract toxicity from inhaled formaldehyde.

The respiratory retention of inhaled formaldehyde (0.15-0.35 μg/ml) was studied in 4 sedated dogs by enforced ventilation (Egle, 1972). The percentage uptake was calculated by determining the amount inhaled

by means of a respirometer and the amount recovered after exhaling into a collection bag (Method: MBTH, Hauser & Cummins, 1964). Absorption was determined to be near 100%, even when the ventilation rate of the dogs was increased to 20 litre/min.

6.1.1.2 Human Data

In human volunteers exposed to 2.3 mg formaldehyde/m^3 (1.9 ppm) for 40 min, there was no significant difference between pre- and post-exposure formaldehyde levels in the blood (2.77 ± 0.28 μg and 2.61 ± 0.14 μg/100 ml, respectively). Individual human subjects differed in terms of their blood-formaldehyde levels and, in some subjects, there were significant differences between formaldehyde concentrations in the blood before and after exposure suggesting that blood-formaldehyde concentrations may vary with time (Heck et al., 1985).

In an earlier study, Einbrodt et al. (1976) measured the formate levels in blood and urine following formaldehyde inhalation. They concluded that the determination of formic acid is appropriate for estimating previous formaldehyde exposure. This could not be confirmed using modern analytical methods (Triebig et al., 1980, 1986; Bernstein et al., 1984). It has been demonstrated that biological monitoring of formaldehyde exposure is not a feasible technique for exposure levels of less than 0.6 mg/m^3 (0.5 ppm) (Gottschling et al., 1984).

6.1.2 Dermal

In *in vitro* experiments, Usdin & Arnold (1979) studied the transfer of ^{14}C-formaldehyde into guinea-pig skin. Aqueous ^{14}C-formaldehyde (0.20 μg) was applied in diffusion cells (area, 2 cm^2), and some were occluded to avoid uncontrolled evaporation of formaldehyde.

Under both occluded and non-occluded conditions, ^{14}C was found on and in the dehaired skin (up to 0.8% of the initial dose), and small amounts (0.4% of the initial dose) were excreted in the urine. However, the labelled material found was not identified, and it is not known whether or not it was formaldehyde.

In another *in vitro* experiment, the permeability of human skin to formaldehyde was examined using excised skin in a flow-through diffusion cell. The rate of resorption was determined by measuring the amount of substance found in the receptor fluid beneath the skin at steady-state. The rates of resorption were: formaldehyde from a concentrated solution of formalin, 319 μg/cm^2 per h, formaldehyde from a solution of 10% formalin in phosphate buffer, 16.7 μg/cm^2 per h (Loden, 1986).

An ointment containing 0.1% of ^{14}C-formaldehyde was applied to the shaved backs of rats by Bartnik et al. (1985). Three to 5% of the ^{14}C-formaldehyde was found to have been absorbed within 48 h.

^{14}C-formaldehyde or dimethyloldihydroxyethyleneurea (DMDHEU) were incorporated into cotton. Patches were applied to the shaved backs of rabbits for a period of 48 h; 0.09-2.61% of the total ^{14}C contained

in the patches was found in the skin. Other tissues and organs showed only low levels of radioactivity (0.001–0.005% of the total ^{14}C (Robbins et al., 1984).

Twenty-four hours after dermal application of 0.4–0.9 μg ^{14}C-formaldehyde/cm² in 5 male monkeys, most of the dose had been lost, mainly by evaporation from the skin (52%) or was bound (34%) to the surface layers of the skin at the application site. Percutaneous penetration was very low, calculated to be, at the most, 0.5% of the applied dose. The total body burden of a necropsied monkey, 24 h after dermal dosing, was 0.2% of the dose, confirming that aqueous formaldehyde does not penetrate the skin to any appreciable degree, even when applied directly to it (Jeffcoat, 1984).

6.1.3 Oral

Following oral exposure (gavage) of 5 anaesthetized dogs to formaldehyde (70 mg/kg), formate levels in the blood increased rapidly. However, fifteen minutes after treatment, all the dogs vomited making quantitative determinations impossible (Malorny et al., 1965).

6.2 Distribution

The normal values of blood-formaldehyde have been determined in both rats and human beings. In rats, the analyses were performed by gas chromatography/mass spectrometry using a stable isotope dilution technique (Heck et al., 1982); values of 2.24 ± 0.07 mg/kg (mean ± SE) were found.

The mean formaldehyde concentration in the blood of 6 human volunteers (4 males, 2 females) was 2.61 ± 0.14 mg/kg (mean ± SE) (Heck & Casanova-Schmitz, 1984) (see section 6.1.1.2).

Malorny et al. (1965) intravenously infused 0.2 mol formaldehyde into dogs and cats; McMartin et al. (1977) performed similar infusions in cynomolgus monkeys. There was no accumulation of formaldehyde in the blood, because of its rapid conversion to formate.

The disposition of radioactive formaldehyde was studied in A/J mice to determine its elimination and to assess its accumulation in tissues. Mice were dosed ip with $^{14}CH_2O$ at 6 mg/kg or 100 mg/kg body weight. Most of the dose (70–75%) was excreted as $^{14}CO_2$ within 4 h, but an additional 10% of the dose was eliminated as $^{14}CO_2$ in 24 h. The rate of $^{14}CO_2$ excretion in mice given $^{14}CH_2O$ was slower than the rate of $^{14}CO_2$ excretion in mice given an equivalent dose (100 mg/kg) of formate (HCOOH), the obligatory intermediate in the oxidation of formaldehyde to carbon dioxide. These results suggest that formaldehyde might accumulate in tissues. To assess this possibility, whole-body levels of $^{14}CH_2O$ were determined by the dimedone precipitation method following a dose of 100 mg/kg. The elimination half-time of formaldehyde was calculated to be 100 min, with a rate constant of 0.42/h. However, several rate constants were observed, 80% of the dose being recovered as formate at 30 min. At 2 h, the level of $^{14}CH_2O$ in

the plasma was 1.07 ± 0.25 mg/litre, and the liver level was 1.7 ± 0.87 mg/kg. Levels of $^{14}CH_2O$ in other tissues were similar to that in the liver. This level of $^{14}CH_2O$ is at least 50% lower than the endogenous level of formaldehyde that has been reported. These results suggest that there is more than a single formaldehyde pool in mice but that, nevertheless, it does not accumulate in tissues at levels that are significant relative to the endogenous tissue level (Billings et al., 1984).

Whole-body autoradiography of mice, sacrificed 5 min after an iv injection of ^{14}C-formaldehyde, showed localization of radioactivity, primarily in the liver and, to a lesser extent, in the kidneys. Following a survival time of 30 min or more, radioactivity appeared in the tissues with a high cell turnover (blood-forming organs, lymphoid system, gastrointestinal mucosa) and in those with a high rate of protein synthesis (exocrine pancreas, salivary glands) (Johansson & Tjalve, 1978).

Following a 6-h inhalation exposure of rats to up to 18 mg/m^3 (15 ppm) ^{14}C-formaldehyde, radioactivity was extensively distributed in other tissues, the highest concentrations occurring in the oesophagus, followed by the kidney, liver, intestine, and lung, indicating that absorbed ^{14}C-formaldehyde and its metabolites were rapidly removed by the mucosal blood supply. Studies on distribution and kinetics indicated that inhaled formaldehyde is extensively metabolized and incorporated (Heck et al., 1982).

DNA, RNA, protein, and lipid fractions of liver and spleen tissues of rats showed significantly elevated levels of ^{14}C incorporation after a single ip injection of 72 mg ^{14}C-formaldehyde (14.7 μCi/kg) (Upreti et al., 1987).

The retention of formaldehyde gas in the nasal passages of anaesthetized male F-344 rats exposed in a nose-only system to ^{14}C-formaldehyde at 2.4-60 mg/m^3 for 30 min was studied by Patterson et al. (1986). More than 93% was retained, regardless of airborne concentrations.

In order to localize absorption and distribution within the nasal cavity, rats and mice, not previously exposed or pretreated, were exposed to 18.0 mg ^{14}C-formaldehyde/m^3 (15 ppm) for 6 h and prepared for whole-body autoradiography. Formaldehyde-associated ^{14}C was heavily deposited in the anterior nasal cavity in both rats and mice. The amount of radioactivity was well correlated with the distribution of lesions in exposed animals. However, the radioactivity may represent metabolically incorporated material rather than covalently bound formaldehyde. No differences in the distribution of formaldehyde were observed between rats and mice (Swenberg et al., 1983).

6.3 Metabolic Transformation

The overall metabolism of formaldehyde is summarized in Fig. 3.

The oxidation into formic acid and carbon dioxide, the reaction with glutathione, and the covalent linkage with proteins and nucleic

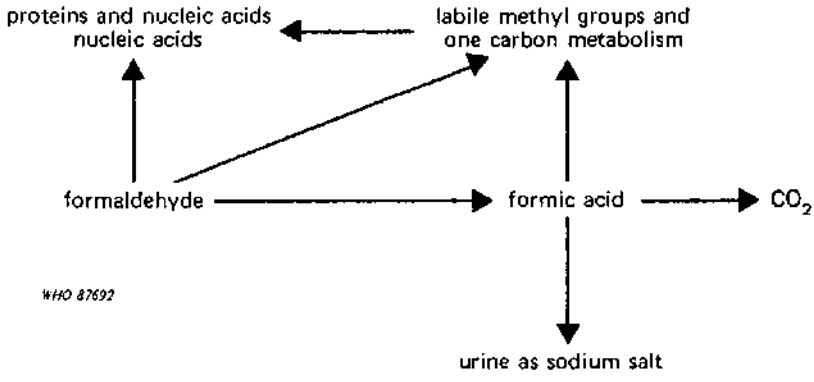

Fig. 3. Overall metabolism of formaldehyde. From: Kitchens et al. (1976).

acids, which are partly reversible, are of importance. The covalent linkage to formaldehyde cannot be directly determined, since radioactive formaldehyde is also incorporated into the DNA via the one-carbon metabolism.

In studies on several species, including human beings, formaldehyde underwent rapid biotransformation, immediately after resorption, and, therefore, could not be traced in tissue (Simon, 1914; Malorny et al., 1965; Rietbrock, 1965; Einbrodt et al., 1976; Delbrück et al., 1982). Heck & Casanova-Schmitz (1984) showed that blood-formaldehyde concentrations did not rise in human volunteers even immediately after inhalation exposure.

Kitchens et al. (1976) summarized the chemical reactions in biological systems as: (a) hydration in the presence of water; (b) reactions with the active hydrogen of ammonia, amines, or amides, resulting in the formation of stable methylene bridges; such reactions are important, because of the ubiquity of nitrogen compounds; and (c) reactions with active hydrogen (thiols, nitroalkanes, hydrogen cyanide, phenol).

Formaldehyde may be formed endogenously (Hutson, 1970) after contact with xenobiotics; 18 chemicals have been shown to be metabolized by the nasal microsomes of rats to produce formaldehyde (Dahl & Hadley, 1983). Formaldehyde is a normal metabolite in mammalian systems. It is rapidly metabolized to formate (Malorny et al., 1965), which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidized to carbon dioxide. Formaldehyde also reacts with proteins (French & Edsall, 1945) and nucleic acids (Haselkorn & Doty, 1961; Lewin, 1966; Collins & Guild, 1968; Feldman, 1973; Chaw et al., 1980); it reacts with single-strand DNA, but not with double-stranded DNA. This link is reversible. Only

formaldehyde cross-links of DNA and protein are stable (Brutlag et al., 1969) (section 8.5). The biological reactions and metabolism of formaldehyde are shown in Fig. 4.

The oxidation of absorbed formaldehyde to formic acid is catalyzed by several enzymes (Strittmatter & Ball, 1955). The most important enzyme is the NAD-dependent formaldehyde dehydrogenase, which requires reduced glutathione (GSH) as a cofactor. Thus, exogenous formaldehyde becomes a source for the so-called one-carbon pool in intermediary metabolism. Sources of formate are presented in Fig. 5.

There are at least 7 enzymes that catalyze the oxidation of formaldehyde in animal tissues, namely aldehyde dehydrogenase, xanthinoxidase, catalase, peroxidase, glycerinaldehyde-3-phosphate dehydrogenase, aldehyde oxidase, and a specific DPN-dependent formaldehyde dehydrogenase (Cooper & Kini, 1962).

6.4 Elimination and Excretion

As discussed in section 6.3, absorbed formaldehyde is metabolized rapidly to formate or enters the one-carbon pool to be incorporated into other molecules. Besides this, there are two pathways of final elimination via exhalation or renal elimination (Fig. 3). Du Vigneaud et al. (1950) administered ^{14}C-formaldehyde subcutaneously to rats and found 81% of the radioactivity as carbon dioxide; a small amount was found in choline. Neely (1964) administered formaldehyde intraperitoneally to rats; 82% of the radiolabel was recovered as carbon dioxide and 13-14% as urinary methionine, serine, and a cysteine adduct.

Even after high formaldehyde uptake, the elimination of formate via the kidneys of rats is virtually negligible (Delbrück et al., 1982). Robbins et al. (1984) injected ^{14}C-formaldehyde (100 μCi in a volume of 1 ml) in rabbits. Four hours after administration, 28.5% of the total dose of radioactivity was expired and 37%, after 48 h. By 48 h, 4.1% of the radioactivity had been excreted in the urine; significant levels or radioactivity were detected in the liver (2.4%), kidney (0.6%), and blood (2.2%).

6.5 Retention and Turnover

Elimination of formate is slower than its formation from absorbed formaldehyde and depends on the species. Stratemann et al. (1968) found a relationship between folate level shown in two biological test systems and the half-life of formic acid in the plasma of some mammals (Table 23).

Malorny et al. (1965) infused 0.2 mol formaldehyde intravenously into dogs; the plasma half-life for formate ranged between 80 and 90 min, and formaldehyde could not be detected. In similar studies on cynomolgus monkeys, by McMartin et al. (1979), infusing intravenously 1 mmol/kg over a 3-4 min period the blood half-life of formaldehyde was estimated to be 1.5 min. Rietbrock (1969) administered 1.17 mmol formaldehyde/kg iv to rats, guinea-pigs, rabbits, and cats, and found

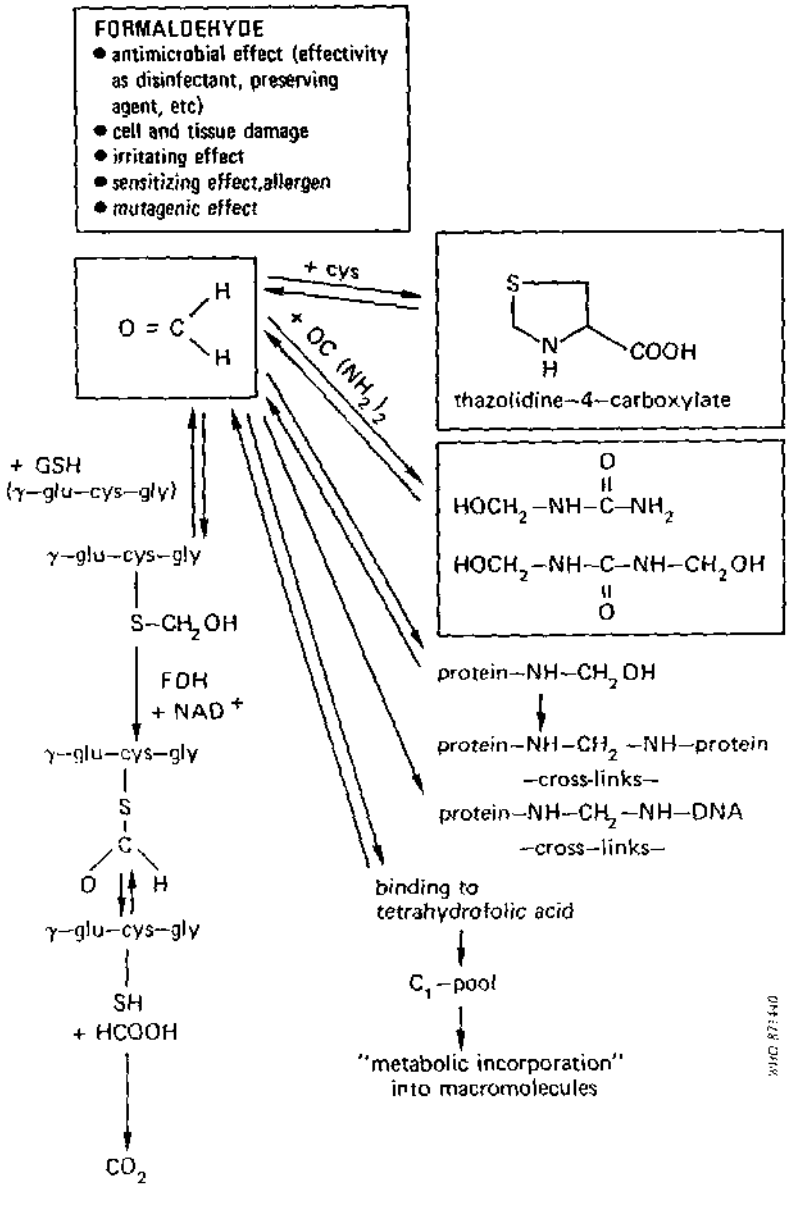

Fig. 4. Biological reactions and metabolism of formaldehyde. From: Bolt (1987).

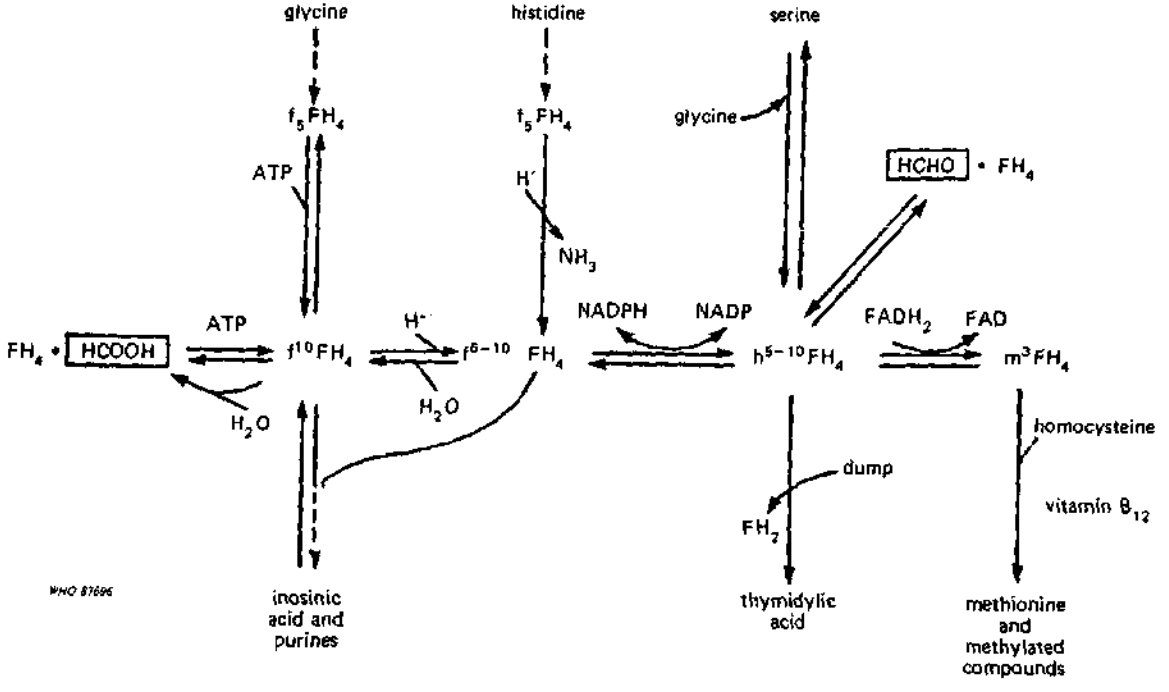

Fig. 5. Sources of formate. From: FPF (1982). FH_4 = tetrahydrofolic acid; $f^{10}FH_4$ = N^{10} formyltetrahydrofolic acid; f^5FH_4 = N^5 formyltetrahydrofolic acid; $f^{6-10}FH_4$ = N^5 - N^{10} methylnyltetrahydrofolic acid; fi^5FH_4 = N^5 formininotetrahydrofolic acid; $h^{5-10}FH_4$ = N^{10} methylenetetrahydrofolic acid.

Table 23. Relationship between folate level and the half-life of formic acid in plasma[a]

Species	Number of analyses	Folate activity (ng/ml)		Formate half-life (min)
		L. casei	*Strept. faec.*	
Man	11	15.5 ± 2.2	6.6 ± 0.7	55
Dog	37	15.5 ± 1.7	6.1 ± 0.9	77
Rabbit	17	49.2 ± 6.9	15.2 ± 1.4	32
Rat	21	126 ± 16.6	37.8 ± 8.9	12

[a] From: Stratemann et al. (1968).

the plasma half-life to be 1 min. The half-life of formate in human beings given 50-60 mg Na-formate/kg, body weight orally, was 45 min (Malorny 1969).

7. EFFECTS ON ORGANISMS IN THE ENVIRONMENT

7.1 Microorganisms

Formaldehyde is used as a disinfectant to kill viruses, bacteria, fungi, and parasites and has found wide use as a fumigant (section 3.2.2).

It produces mutagenic effects in prokaryotic and lower eukaryotic test systems (Table 31, and section 8.6).

In a population of *Aerobacter aerogenes*, treatment with 50 µg formaldehyde/ml of medium produced a reversible change in the base ratio of non-ribosomal RNA and induced enzymes capable of metabolizing formaldehyde at an increased rate (Neely, 1966).

Approximately 20-40% of the total nitrogen in most surface soils is in the form of amino acids. Because of the importance of amino acids as a nitrogen source for plant and microbial growth, Frankenberger & Johanson (1982) studied the enzyme (EC 4.3.1.3) that catalyzes the deamination of L-histidine in soils; treatment with formaldehyde markedly inhibited its activity. Negative effects on the biological properties of the soil owing to increased doses of urea-formaldehyde fertilizers have been reported by Rakhmatulina et al. (1984).

Berestetskii et al. (1981) found that formaldehyde was one of the volatile compounds formed in the early stages of plant residue decomposition in the soil. Kanamura et al. (1982) isolated a microorganism (genus *Hyphomicrobium)* from the soil that can use formaldehyde as the only source of carbon. Furthermore, formaldehyde has a significant role in the complex batch growth behaviour of a methanol-utilizing bacterium *(Methylomonas)* (Agrawal & Lim, 1984).

The bacterial content of the soil near industrial enterprises polluted with formaldehyde was 28-40 million bacteria/kg polluted soil; the level in control areas was 900 million bacteria/kg soil. There is no information on other pollutants or concentrations (Zhuravliova, 1969). Species of *Pseudomonas* were able to assimilate formaldehyde and formate (Grabinska-Loniewska, 1974). Hingst et al. (1985) studied the microorganism contents of sewage samples; species of *Pseudomonas* survived a 30-min exposure to formaldehyde at 5 g/kg (admixture to sewage samples).

Exposure to 2.4 mg formaldehyde/m^3 for 24 h killed all spores from pure cultures of various species of *Aspergillus*, *Scopulariopsis*, and *Penicillium crustosum* (Dennis & Gaunt, 1974).

The phytopathogenic fungi *Fusarium oxysporum*, *lycopersici*, and *Rhizoctonia solani* were completely eradicated after exposure for 30 min to an aqueous solution of formaldehyde at 4-5 g/litre. When tested in tuff (a granular plant growth medium of volcanic rock origin), the effectiveness of formaldehyde was lower compared with the corresponding amounts in aqueous solutions (Sneh et al., 1983).

7.2 Aquatic Organisms

The acute toxicity of formaldehyde for various species of aquatic organisms is shown in Table 24.

Many early studies conducted to determine the toxicity of formaldehyde and safe levels for therapeutic treatment against fungal infections and ectoparasites have been reported. This type of study is difficult to evaluate with respect to environmental hazard because of very short exposure periods and the way the data are presented.

From the data shown in Table 24, it appears that formaldehyde has a relatively low toxicity for fish, 96-h LC_{50} values being higher than 10 mg/litre in all cases.

The toxic effects of formaldehyde on fresh-water trout and salmon included changes in gill function, hypochloraemia, depressed plasma-calcium and carbon dioxide, reduced blood pH, and decreased oxygen consumption (Wedemeyer, 1971). Effects in rainbow trout occurred rapidly after a 1 h exposure at 200 mg/litre, and ≈24 h was required for recovery (Wedemeyer & Yasutake, 1974). In rainbow trout and Atlantic salmon, formalin treatment caused increased blood-haemoglobin, packed cell volume, blood-glucose levels, and plasma-protein concentrations (Nieminen et al., 1983). The toxicity of formaldehyde for rainbow trout was increased by high water temperature, soft water, and high pH levels (Bills et al., 1977).

Algae and some invertebrates seem to be more susceptible to formaldehyde. Acute toxicity occurs in green algae at formaldehyde concentrations of 0.3-0.5 mg/litre *(Scenedesmus sp.)*, in several species of protozoa, at 4.5-22 mg/litre, in *Daphnia*, at 2-20 mg/litre (EC_{50}) and in *Cyprinodopris* species at 0.42 mg/litre (96-h EC_{50}). Other invertebrates differ widely in their responses to formalin (Table 25).

For amphibia, the 24-, 48-, and 72-h LC_{50} values for larva of the frog, *Rana pipiens*, were 8.4, 8.0, and 8.0 mg formaldehyde/litre, with a 72-h LC_{100} at 11.4 mg/litre. Tadpoles of the bullfrog, *Rana catesbeiana*, were more resistant, having 24-, 48-, and 72-h LC_{50} values of 20.1, 17.9, and 17.9 mg/litre, respectively, with a 72-h LC_{100} of 30.4 mg formaldehyde/litre. In toad larvae *(Bufo* sp.) the 72-h LC_{50} and LC_{100} values were 17.1 and 19.0 mg/litre, respectively (Helms, 1964). Carmichael (1983) exposed tadpoles of *Rana berlandieri* to formalin for 24 h and found that no mortality occurred at concentrations $\leq$ 6.0 mg formaldehyde/litre, but at 9.2, 13.6, 20.4, and 30.5 mg formaldehyde/litre, mortality was 13, 35, 78, and 100%, respectively.

7.3 Terrestrial Organisms

Persson (1973) studied the influence of formalin on the eggs and larvae of the cattle parasites *Ostertagia ostertagia* and *Cooperia oncophora* in liquid cattle manure. A 1% solution destroyed the eggs and a 5% solution affected the larvae. It also had a negative effect on the germination and growth of crops fertilized with the manure.

Table 24. Acute toxicity of formaldehyde for some aquatic organisms (static bioassay)

Organism/species	Temperature (°C)	pH	Hardness degree	Duration of exposure (h)	(LC_{50}) (mg/litre)	Reference
Algae						
Scenedesmus quadricauda	-	7.5	12	-	0.3	Bringmann & Kühn (1960)
Scenedesmus	27	7.5-7.8	12	24	0.4	Bringmann & Kühn (1980a)
Bacteria						
Escherichia coli	25	7.5-7.8	-	-	1	Bringmann & Kühn (1960)
Pseudomonas fluorescens	25	7.5-7.8	-	-	2	Bringmann & Kühn (1960)
Protozoa						
Chilomonas paramaecum	-	6.9	-	48	4.5	Bringmann et al. (1980)
Mikroregma	27	7.5-7.8	12	24	5	Bringmann & Kühn (1980b)
Uronema parduczi	-	6.9	-	20	6.5	Bringmann & Kühn (1980b)
Entosiphon sulcatum	25	6.9	-	72	22	Bringmann (1978)
Water fleas						
Daphnia magna	27	7.5-7.8	12	24	2	Corstjens & Monnikendam (1973)
Daphnia magna	23	7.5	12	48	2	Corstjens & Monnikendam (1973)

Table 24 (contd).

Water fleas (contd).						
Daphnia magna (IRCHA)	-	8	16	24	42	Bringmann & Kühn (1982)
Daphnia magna	20-22	7.6-7.7	16	24	52	Bringmann & Kühn (1977)
Daphnia magna	-	-	-	24	100-1000	Dowden & Bennett (1965)
Fish						
Black bullhead - fingerling -	12	6.5-9.5	8	96	62.1[a]	Bills et al. (1977)
Channel catfish - fingerling -	12	6.5	8	96	65.8[a]	Bills et al. (1977)
Bluegill - fingerling -	12	6.5	8	96	100[a]	Bills et al. (1977)
Lake trout - fingerling -	12	6.5	8	96	100[a]	Bills et al. (1977)
Smallmouth bass (*M. dolomieuri*) - fingerling -	12	6.5	8	96	136[a]	Bills et al. (1977)
Largemouth bass (*M. salmoides*) - fingerling -	12	6.5	8	96	143[a]	Bills et al. (1977)
Atlantic salmon	12	6.5	-	96	173	McKim et al. (1976)

Table 24 (contd).

Organism/species	Temperature (°C)	pH	Hardness degree	Duration of exposure (h)	(LC_{50}) (mg/litre)	Reference
Fish (contd).						
Atlantic salmon (fingerling)	12	6.5	8	3	564[a]	Bills et al. (1977)
	12	6.5	8	6	336[a]	Bills et al. (1977)
	12	6.5	8	24	156[a]	Bills et al. (1977)
	12	6.5	8	96	69.2	Bills et al. (1977)
Green sunfish	12	-	-	96	173	McKim et al. (1976)
Green sunfish (fingerling)	12	6.5	8	24	129[a]	Bills et al. (1977)
	12	6.5	8	96	69.2[a]	Bills et al. (1977)
	-	-	-	72	> 34.2	Helms (1967)
Rainbow trout (green egg)	12	6.5-9.5	46-48	96	565-1020	McKim et al. (1976)
Rainbow trout (eyed egg)	12	6.5-9.5	-	96	198-435	McKim et al. (1976)
Rainbow trout (sac larvae)	12	6.5-9.5	-	96	89.5-112	Brungs et al. (1978)
Rainbow trout (fingerling)	12	6.5-9.5	-	96	61.9-106	Brungs et al. (1978)
Rainbow trout (fingerling)	12	6.5	8	3	492[a]	Bills et al. (1977)
	12	6.5	8	6	262[a]	Bills et al. (1977)
	12	6.5	8	24	120[a]	Bills et al. (1977)
	12	6.5	8	96	47.2[a]	Bills et al. (1977)
Rainbow trout	12	-	20	96	118	Brungs et al. (1978)

Table 24 (contd).

Fish (contd).						
Rainbow trout	12	7.5	40-48	24	214-7200	McKim et al. (1976)
Rainbow trout	12	7.5-8.2	30-245	96	440-618	McKim et al. (1976)
Rainbow trout	-	-	-	48	59.2	Schneider (1979)
	-	-	-	24	76.6	Willford (1966)
	-	-	-	48	62.2	Willford (1966)
Brown trout	-	-	-	24	120.3	Willford (1966)
	-	-	-	48	68.5	Willford (1966)
Brook trout	-	-	-	24	72.5	Willford (1966)
	-	-	-	48	58.1	Willford (1966)
Lake trout	-	-	-	24	81.4	Willford (1966)
(fingerling)	-	-	-	48	61.8	Willford (1966)
	12	6.5	8	6	241[a]	Bills et al. (1977)
	12	6.5	8	24	56.4[a]	Bills et al. (1977)
	12	6.5	8	96	40.0[a]	Bills et al. (1977)
Bluegill sunfish	-	-	-	24	68.5	Willford (1966)
(fingerling)	-	-	-	48	51.8	Willford (1966)
	-	-	-	72	30.4	Helms (1967)
	12	6.5	8	3	916[a]	Bills et al. (1977)
	12	6.5	8	6	640[a]	Bills et al. (1977)
	12	6.5	8	24	84.4[a]	Bills et al. (1977)
	12	6.5	8	96	40.0[a]	Bills et al. (1977)
	-	-	-	24	53.7	Schneider (1979)
	-	-	-	48	34.0	Schneider (1979)
	-	-	-	96	25.2	Schneider (1979)
Largemouth bass	-	-	-	72	38	Helms (1967)
(fingerling)	12	6.5	8	6	412[a]	Bills et al. (1977)
	12	6.5	8	24	113[a]	Bills et al. (1977)
	12	6.5	8	96	57.2[a]	Bills et al. (1977)

Table 24 (contd).

Organism/species	Temperature (°C)	pH	Hardness degree	Duration of exposure (h)	(LC_{50}) (mg/litre)	Reference
Fish (contd).						
Smallmouth bass	12	6.5	8	24	88.8[a]	Bills et al. (1977)
(fingerling)	12	6.5	8	96	54.4[a]	Bills et al. (1977)
Striped bass	-	-	-	24	31.8	Wellborn (1969)
	-	-	-	48	11.8	Wellborn (1969)
	-	-	-	96	6.7	Wellborn (1966)
Channel catfish	-	-	-	24	50.7	Willford (1966)
	-	-	-	48	35.5	Willford (1966)
	-	-	-	96	25.5[b]	Clemens & Sneed (1958, 1959)
(fingerling)	12	6.5	8	3	198[a]	Bills et al. (1977)
	12	6.5	8	6	92.8[a]	Bills et al. (1977)
	12	6.5	8	24	48.8[a]	Bills et al. (1977)
	12	6.5	8	96	26.3[a]	Bills et al. (1977)
Black bullhead	-	-	-	72	17.1	Helms (1967)
(fingerling)	12	6.5	8	24	69.2[a]	Bills et al. (1977)
	12	6.5	8	96	24.8[a]	Bills et al. (1977)
Golden shiner				72	23.6	Helms (1967)
American eel					31.1	Hinton & Eversole
glass stage	-	-	-	96		(1978, 1979, 1980)
black stage	-	-	-	96	83.1	Hinton & Eversole (1978, 1979, 1980)
yellow stage	-	-	-	96	122.1	Hinton & Eversole (1978, 1979, 1980)

Table 24 (contd).

Fish (contd).						
Carp	-	-	-	72	> 26.6	Helms (1967)
	-	-	-	2	74[a]	Suzuki & Kimura (1977)
Zebrafish	-	-	-	96	41	Wellens (1982)
Golden orfe	-	-	-	48	22	Wellens (1982)
	-	-	-	48	32.4[b]	Juhnke & Luedemann (1978)
	-	-	-	48	15.0[b]	Juhnke & Luedemann (1978)
Harlequin fish	-	-	-	24	76	Alabaster (1969)
	-	-	-	48	50	Alabaster (1969)
Tilapia	-	-	-	72	> 38.0	Helms (1967)

[a] Flow through bioassay.
[b] Method not stated.

Table 25. Toxicity of formalin (37% formaldehyde) for selected aquatic invertebrates in soft water at 16 °C[a]

Species	LC_{50} and 95% confidence interval (µlitre/litre) at				
	1 h	3 h	6 h	24 h	96 h
Seed shrimp (ostracods)[b] *Cypridopsis sp.*	9.00 6.83-11.9	6.40 4.91-8.34	1.20 0.664-2.17	1.15 0.690-1.97	1.05 0.590-1.87
Freshwater prawn[b] *Palaemonetes kadiakensis*	- -	2150 1948-2373	1900 1588-2273	1105 896-1362	465 368-588
Bivalves[c] *Corbicula sp.*	-	-	-	800 638-1003	126 80.9-196
Snail[d] *Helisoma sp.*	3525 3201-3881	1340 953-1883	780 629-967	710 544-925	93.0 69.5-124
Backswimmer[d] *Notonecta sp.*	-	-	-	4500 3006-6735	835 652-1069

[a] From: Bills et al. (1977).
[b] Toxicity based on immobility.
[c] Toxicity based on ability to resist attempts to open valves and respond to tactile stimulus.
[d] Toxicity based on ability to respond to tactile stimulus.

Nematodes in peat were killed by application of 370 g formaldehyde/litre solution at 179 ml/m^3 (Lockhart, 1972).

Changes in populations of the cereal cyst nematode *Heterodera avenae* and in crop growth in a sandy loam soil were studied in 1974-78 (Kerry et al. 1982). Fungal parasites attack *H. avenae* females and eggs resulting in poor multiplication of the nematode. The number of cysts containing nematode eggs, after harvest, was not affected by formalin (380 g formaldehyde/litre) applied as a drench at 3000 litre/ha in 1977. However, fecundity doubled in treated soil, and nematode multiplication increased 18.6 times compared with 3.8 times in untreated plots. When the plots were irrigated in 1978, the numbers of cysts and fecundity increased in formalin-treated soils, resulting in a 0.3- to 14.6-fold increase due to suppression of fungal parasites.

The yellow rice borer *(Tryporyza incertulas) (Lepidoptera)* is one of the most serious pests of rice. To obtain sterile males, it has to be mass-reared on an artificial diet containing formaldehyde (Wang et al., 1983); the same has been reported for the pink borer *(Sesamia inferens)* (Siddiqui et al., 1983).

In ruminants, deamination of dietary proteins by rumen microorganisms is of importance, because of loss of essential nitrogen from the rumen as ammonia. Formaldehyde protects dietary-protein from microbial proteolysis in the rumen by reacting with free amino groups in the protein, forming inter- and intramolecular methylene bridges (Siddons et al., 1982). Thus, there is an increase in the efficiency of utilization of amino acids for wool (10 g formaldehyde/kg protein) and body growth in sheep and other ruminants (Faichney, 1970; Ferguson, 1970; Hemsley et al., 1973). Differences in nitrogen retention were found, but no significant differences in wool growth or live-weight gain, when sheep were fed formaldehyde-treated linseed meal and meatmeal (2.5% formalin) (Rattray & Joyce, 1970). Mills et al. (1972) showed that ^{14}C-formaldehyde bound to a sodium caseinate-oil mixture was rapidly metabolized by sheep and goat tissues and eliminated via expired air, urine, and faeces, but was not accumulated in the milk or in the carcass. To study the digestion in the small intestine of young bulls of the protein of rapeseed meal, treated or not treated with formaldehyde, Kowalczyk et al. (1982) fitted each bull with cannulae in the rumen and abomasum. Formaldehyde-treated rapeseed meal was poorly digested. The nutritional value of soybean meal that had been treated with 3 g formaldehyde/kg was investigated by Crooker et al. (1983). Analysis of covariance revealed that the digestibility of dietary crude protein by cows fed formaldehyde-treated meal was lower than that in the controls (62.4% versus 65.4%) as was the milk-protein content. Erfle et al. (1986) fed lactating cows with formaldehyde-treated soybean meal and found that milk-protein levels were significantly decreased. After treatment with formaldehyde, lysine and tyrosine were lost from the soybean meal.

Grenet (1983) studied the utilization of grass-silage nitrogen in growing sheep and found that formic acid had a beneficial effect (decreased urinary-nitrogen loss). However, the addition of 1.5 litre

formalin/tonne of green forage did not improve nitrogen-retention; higher quantities of formaldehyde tended to have an unfavourable effect, particularly with lucerne silage.

7.4 Plants

A study was carried out by Sangines et al. (1984) to examine the protective effects of formaldehyde on ensilaged whole peanut plant protein. Formaldehyde (50, 100, 150, and 200 g/litre) was added at the rate of 5 litres/tonne. A control without any formaldehyde was included. There were no significant differences in pH among treatments (5.56-5.70). The ammonia concentration dropped significantly in all treatments, a finding that suggests a protective effect against protein-nitrogen degradation to non-protein nitrogen (NH_3). Lactic acid fermentation was observed, without any difference between treated and control silage. Nevertheless, there was a reduction in the propionic acid and ethanol concentrations in all the silages. It was concluded that there was an inhibition of the fermentation process in all the silages treated, and that the addition of formaldehyde at the 5% level is a satisfactory way of protecting this type of feed.

In agriculture, urea-formaldehyde fertilizers are used to improve crops. At concentrations of up to 0.3 g/kg soddy podsolic soil, formaldehyde did not change the nitrogen and carbohydrate metabolism in barley plants (Lebedeva et al., 1985). However, increased doses of the fertilizer caused negative effects on the biological properties of the soil (Rakhmatulina et al., 1984).

Doman et al. (1961) studied the conversion of gaseous formaldehyde absorbed by leaves of kidney beans and barley plants from the atmosphere, using ^{14}C tracing. The activity appeared first in phosphate ester fractions and later in the amino acids alanine, serine, aspartic acid and unidentified products, especially when the experiments were conducted in the dark. Zemlianukhin et al. (1972), also using ^{14}C tracing, studied the metabolism in 12-day-old maize seedlings, of formic acid, which was oxidized to carbon dioxide or metabolized to cellular constituents.

Pollen germination has been shown to be sensitive to various air pollutants. Masaru et al. (1976) sowed lily pollen grains *(Lilium longiflorum)* on culture medium. After being exposed to formaldehyde in a fumigation chamber, for 24 h, pollen tube length was measured. A 5-h exposure to formaldehyde at 0.44 mg/m^3 (0.37 ppm) resulted in a significant reduction in pollen-tube length, whereas a 1- or 2-h exposure was innocuous. When the formaldehyde concentration was increased to 2.88 mg/m^3 (2.4 ppm), a 1-h exposure caused a decrease in tube length. The investigators observed that, with respect to pollen, the activity of formaldehyde was comparable with that of nitrogen dioxide. To test combinations of pollutants, pollen grains were exposed to sulfur dioxide at 1.79 mg/m^3 (0.69 ppm) for 30 min or to nitrogen dioxide at 0.28 mg/m^3 (0.15 ppm) for 30 or 60 min. This treatment led to slight inhibition of tube elongation. A second exposure to formaldehyde at

0.3 mg/m^3 (0.26 ppm) led to significant inhibition of pollen tube length (about 30-40% of the length of control pollen-tubes).

A sealed Plexiglas® chamber with temperature and humidity control and illuminated externally with wide spectrum grow lights was used to evaluate the ability of golden pothos *(Scindapsus aureus)*, nephthytis *(Syngonium podophyllum)*, and the spider plant *(Chlorophytum elatum* var. *vittatum)* to remove formaldehyde from contaminated air at initial concentrations of 18-44 mg/m^3. Under the conditions of this study, the spider plant proved most efficient by sorbing and/or removing up to 2.27 μg formaldehyde/cm^2 leaf surface area in a 6-h exposure (Wolverton et al., 1984).

Various factors influence the response of a plant receptor to formaldehyde exposure. These include genetic factors, stage of plant development, age of tissue, climatic factors, such as temperature, relative humidity, light quality, light intensity, photoperiod, rate of air movement, and soil factors, such as moisture, aeration, and nutrients. Most studies dealing with the influence of formaldehyde exposure on plants suffer from lack of such information.

8. EFFECTS ON EXPERIMENTAL ANIMALS AND *IN VITRO* TEST SYSTEMS

Concern about the toxicological effects of formaldehyde is related to effects resulting from single or repeated exposures including irritation, cytotoxicity, cell proliferation, and sensitization, and effects resulting from long-term exposures, particularly cancer.

The most significant properties of formaldehyde are its potential to cause irritation and, at high concentrations after long-term exposure, nasal tumours in rats and statistically not significant nasal tumours in mice.

8.1 Skin and Eye Irritation, Sensitization

Formaldehyde is known to be a primary skin and eye irritant, the local tissue reaction increasing with increased dose. However, this is based on anecdotal evidence rather than animal studies. The only report is that of Carpenter & Smyth (1946) who found formaldehyde to be an eye irritant for rabbits.

The sensitizing potential of aqueous formaldehyde was evaluated with the guinea-pig maximization test (GPMT) in two laboratories (Copenhagen and Stockholm) using different guinea-pig strains (Andersen et al., 1985). Six intradermal (0.1-30 g/litre) and 6 topical (5-200 g/litre) concentrations were used for induction, and formaldehyde at 10 and 1 g/litre was used for challenge. The incidence of contact sensitivity depended on the intradermal, but not on the topical, induction dose. Statistical analyses showed a non-linear dose-response relationship. The estimated maximal sensitization rate in Copenhagen was 80% after intradermal induction with 0.65% formaldehyde; in Stockholm, it was 84% after induction with 0.34%. The data from the two laboratories gave parallel displaced dose-response curves, suggesting that the guinea-pig strain used in Stockholm was significantly more susceptible to formaldehyde than the strain used in Copenhagen. The EC_{50} (formaldehyde concentration at which 50% of the guinea-pigs were sensitized at 72 h) at a 10 g/litre challenge concentration was 0.6 g/litre in Copenhagen and 0.24 g/litre in Stockholm.

Other studies are summarized in Table 26. The results show that aqueous formaldehyde solution is a sensitizer for the skin.

Lee et al. (1984) exposed guinea-pigs to formaldehyde at 7.2 mg/m^3 or 12 mg/m^3, for 6 or 8 h/day, on 5 consecutive days. The animals were evaluated for skin sensitivity (production of anti-formaldehyde antibody) and respiratory sensitivity (both immediate and delayed-onset) to formaldehyde, which was shown to be a skin sensitizer without causing detectable pulmonary hypersensitivity.

8.2 Single Exposures

Acute toxicity has been studied in several animal species (Table 27).

Table 26. Contact allergy predictive tests in guinea-pigs

Induction dose (%)	Challenge dose (%)	Sensitization (number positive/ number tested)	Test	Reference
30	1	2/7	open epicutaneous	Maibach (1983)
10	1	5/8		
3	1	3/8		
1	1	2/6		
0.3	1	2/6		
0.1	1	0/6		
5	5	7/20	epicutaneous maximization	Guillot & Gonnet (1985)
10	5	3/10	cumulative contact enhancement test	Tsuchiya et al. (1985)
5	5	2/10		
1	5	0/10		
0.2	5	0/10		
10	1	4/10		Tsuchiya et al. (1985)
5	1	2/10		
1	1	0/10		
0.2	1	0/10		
10	0.2	1/10		Tsuchiya et al. (1985)
5	0.2	0/10		
1	0.2	0/0		
0.2	0.2	0/0		

Table 27. Acute toxic effects of formaldehyde on laboratory animals

Species	Route	Dose (duration)	Effect/response	Reference
Rat	oral	800 mg/kg body weight	LD_{50}	Smyth et al. (1941); Tsuchiya et al. (1975)
	subcutaneous	420 mg/kg body weight	LD_{50}	Skog (1950)
	intravenous	87 mg/kg body weight	LD_{50}	Langecker (1954)
	inhalation	984 mg/m^3 (30 min)	LC_{50}	Skog (1950)
	inhalation	578 mg/m^3 (4 h)	LC_{50}	Nagorny et al. (1979)
Mouse	subcutaneous	300 mg/kg body weight	LD_{50}	Skog (1950)
	inhalation	497 mg/m^3 (4 h)	LC_{50}	Nagorny et al. (1979)
Rabbit	dermal	270 mg/kg body weight	LD_{50}	Lewis & Tatken (1980)
	dermal	0.1-20%	skin irritation: mild to moderate	NRC (1981)
	eye	0.5 ml	eye irritation: grade 8 on a scale of 10	Carpenter & Smyth (1946)
Guinea-pig	oral	260 mg/kg body weight	LD_{50}	Smyth et al. (1941)
	dermal	0.1-20%	skin irritation: mild to moderate	Colburn (1980)
	dermal	1% (open application)	sensitization: positive	US CPSC (1978)
		3% (open application)	sensitization: positive	US CPSC (1978)
		1% (intradermal)	sensitization: positive	Colburn (1980)

The odour and irritant properties of formaldehyde serve as repellents. Kane & Alarie (1977) used the decrease in respiratory rate of mice as an index of irritation. At 0.6 mg formaldehyde/m^3 air, an irritant effect on the eyes, nose, and throat occurred, and tolerance to the irritant effects of formaldehyde did not develop.

Exposure to high concentrations of formaldehyde vapour (> 120 mg/m^3) caused hypersalivation, acute dyspnoea, vomiting, muscular spasms, and can finally lead to the death of test animals (Skog, 1950; Horton et al., 1963; Bitron & Aharonson, 1978).

8.3 Short-term Exposures

8.3.1 Inhalation studies

Inhalation studies are summarized in Table 28.

A range finding study was conducted in which rats and mice were exposed to atmospheres containing 4.8, 15, or 46 mg formaldehyde/m^3 (4, 12.7, or 40 ppm). Exposures were for approximately 6 h/day, 5 days/week, for 13 weeks, except for the high dose level, which was terminated after 2 weeks (Mitchell et al., 1979). Exposure of both mice and rats to concentrations of inhaled formaldehyde of 46 mg/m^3 (40 ppm) resulted in ulceration or necrosis of the nasal turbinate mucosa in a significant number of animals of each species. Both sexes of rats had a high incidence of tracheal mucosal ulceration and necrosis, whereas only a few male mice exhibited this lesion. Pulmonary congestion was prominent in both male and female rats and in male mice at the highest dose level. Female mice of both the control and high-dose group had a similar incidence of pulmonary congestion. Secondary lesions encountered in rats exposed to this dose of formaldehyde seemed to be related to bacterial septicaemia due to a damaged respiratory mucosa.

Groups of 10 male and 10 female B6C3F1 mice were exposed to 2.4, 4.8, 12, 24, or 48 mg formaldehyde vapour/m^3 (2, 4, 10, 20, or 40 ppm) for 6 h/day, 5 days/week, over 13 weeks (Maronpot et al., 1986). Clinical abnormalities (dyspnoea, listlessness, and hunched posture), significant mortality, and body weight loss were observed in the 48 mg/m^3 groups. Pathological changes were observed in the nose, larynx, trachea, and bronchi of treated males and females, and in the uterus and ovaries of treated females. Squamous metaplasia and inflammation were present in the nasal tissues of both male and female mice in the 12-48 mg/m^3 (10, 20, 40 ppm) groups and in the larynx of both males and females in the 24 and 48 mg/m^3 (20, 40 ppm) groups. In some mice, epithelial-lined, irregular connective tissue bands spanned the tracheal lumen. Metaplasia of the bronchial epithelium was confined to the groups exposed to 48 mg/m^3. The effects on the respiratory system were more prevalent in male than in female mice. Hypoplasia of the uterus and ovaries, probably secondary to body weight loss, was confined to the 48 mg/m^3 (40 ppm) exposure group.

Table 28. Short-term formaldehyde inhalation studies

Species	Exposure	Concentration mg/m^3 (ppm)	Effect	Reference
	Nose-only inhalation			
Rat	6 h/day, 5 days/week, for 4 weeks	3.6 (3)	no adverse findings	AIHA (1983)
	6 h/day, 5 days/week, for 4 weeks	19, 73, 120 (16, 61, 99)	antibody inhibition	AIHA (1983)
	Inhalation			
Rat	8 h/day (continuous), 5 days/week, for 4 weeks	6, 12 (5, 10) (equivalent to 40 ppm x h or 80 ppm x h)	slightly increased proliferation of nasal epithelium; slight hypermetaplasia of nasal epithelium	Wilmer et al. (1987)
	8.5 h/day (interrupted), 5 days/week, for 4 weeks	12, 24 (10, 20) (equivalent to 40 ppm x h or 80 ppm x h)	strongly increased proliferation of nasal epithelium; moderate hypermetaplasia of nasal epithelium	Wilmer et al. (1987)
Rat	22 h/day, for 90 days	1.9 (1.6)	no adverse findings	Dubreuil et al. (1976)
	22 h/day, for 45 days	5.4 (4.55)	decreased weight gain	Dubreuil et al. (1976)
	22 h/day, for 60 days	9.6 (8.07)	decreased liver weight; eye irritation	Dubreuil et al. (1976)
	6 h/day, 5 days/week, for 13 weeks	4.8 (4)	no adverse effect	Mitchell et al. (1979)

Table 28 (contd).

	Inhalation (contd).				
Rat	6 h/day, 5 days/week, for 13 weeks	15	(12.7)	nasal erosion	Mitchell et al. (1979)
	6 h/day, 5 days/week, for 2 weeks	48	(40)	nasal ulceration	Mitchell et al. (1979)
	8 h/day (continuous), 5 days/week, for 13 weeks	1.2 9.6	(equivalent to 8 ppm x h)	no adverse effects	Wilmer et al. (1986)
	8.5 h/day (intervals), 5 days/week, for 13 weeks	2.4 9.6	(equivalent to 8 ppm x h)	no adverse effects	Wilmer et al. (1986)
	8 h/day, 5 days/week, for 13 weeks	2.4 19.2	(equivalent to 16 ppm x h)	no adverse effects	Wilmer et al. (1986)
	8.5 h/day, 5 days/week, for 13 weeks	4.8 19.2	(equivalent to 16 ppm x h)	hyper- and metaplasia of nasal respiratory epithelium	Wilmer et al. (1986)
	6 h/day, 5 days/week, for 13 weeks	0.36	(0.3)	transient, slight increase in cell turnover rate of the nasal respiratory epithelium	Zwart et al. (1987)
	6 h/day, 5 days/week, for 13 weeks	1.2	(1)	transient, slight increase in cell turnover rate of the nasal respiratory epithelium	Zwart et al. (1987)
	6 h/day, 5 days/week, for 13 weeks	3.6	(3)	5- to 10-fold increase in cell turnover rate and squamous metaplasia of the nasal respiratory epithelium	Zwart et al. (1987)

Table 28 (contd).

Species	Exposure	Concentration mg/m^3	(ppm)	Effect	Reference
	Inhalation (contd).				
Rat	6 h/day, 5 days/week, for 13 weeks	1.2	(1)	questionable hypermetaplasia of the nasal respiratory epithelium	Woutersen et al. (1987)
	6 h/day, 5 days/week, for 13 weeks	12	(10)	squamous metaplasia of nasal respiratory epithelium	Woutersen et al. (1987)
	6 h/day, 5 days/week, for 13 weeks	24	(20)	transient excitation and uncoordinated locomotion; growth retardation; decreased level of plasma-protein; increased activity of several plasma enzymes; squamous metaplasia of the nasal respiratory and olfactory epithelium; squamous metaplasia of laryngeal epithelium	Woutersen et al. (1987)
	6 h/day, 5 days/week, for 13 weeks	2.4-48	(2-40)	12-48 mg/m^3: histological lesions in the upper respiratory system; 48 mg/m^3: death	Maronpot et al. (1986)
	22 h/day, 7 days/week, for 26 weeks	1.2	(1)	no adverse findings	Rusch et al. (1983)
	22 h/day, 7 days/week, for 26 weeks	3.6	(3)	squamous metaplasia; depression in body weight gain	Rusch et al. (1983)

Table 28 (contd).

	Inhalation (contd).				
Mouse	6 h/day, 5 days/week, for 13 weeks	4.8	(4)	no adverse findings	Mitchell et al. (1979)
	6 h/day, 5 days/week, for 13 weeks	15	(12.7)	no adverse findings	
	6 h/day, 5 days/week, for 2 weeks	48	(40)	nasal ulceration in males	
Hamster	22 h/day, 7 days/week, for 26 weeks	1.2 and 3.6	(1 and 3)	no adverse findings	Rusch et al. (1983)
Guinea-pig	6 h/day, 5 days/week, for 8 weeks	1.2	(1)	hyperkeratosis in the cavity (reversible after 30 days); mucus flow elevated; foci of squamous metaplasia of respiratory epithelium	Marshall (1983)
Monkey (cynomolgus)	22 h/day, 7 days/week, for 26 weeks	1.2	(1)	metaplasia in nasal turbinates in 1/6 exposed	Rusch et al. (1983)
	22 h/day, 7 days/week, for 26 weeks	3.6	(3)	metaplasia in nasal turbinates in 6/6 exposed	Rusch et al. (1983)
Monkey (rhesus)	6 h/day, 5 days/week, for 1 or 6 weeks	7.2	(6)	mild degeneration and early squamous metaplasia of nasal passages, trachea and bronchi in 6/6 exposed. Percentage of nasal surface area affected was greater in 6-week exposure group	Monticello et al. (1989)

Groups of 6 male cynomolgus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Syrian golden hamsters were exposed to 0, 0.24, 1.2, or 3.7 mg/m^3 (0, 0.2, 1, or 3 ppm) formaldehyde vapour (98.8% pure) for 22 h/day, 7 days/week, over 26 weeks. Squamous metaplasia of the nasal turbinates was evident in 6/6 monkeys exposed to 3.7 mg/m^3 (3 ppm) and in 1/6 exposed to 1.2 mg/m^3 (1 ppm). Squamous metaplasia and basal cell hyperplasia of the respiratory epithelium of the nasal cavity were significantly increased in rats exposed to 3.7 mg/m^3 (3 ppm). The same group exhibited marked depressions in body weight gain. No exposure-related effects were demonstrated in hamsters (Rusch et al., 1983).

Two groups of 3 adult (aged 4-5 years) male rhesus monkeys were exposed to 7.2 mg/m^3 (6 ppm) formaldehyde in inhalation chambers. One group was exposed 6 h/day for 5 days; the other group was exposed for 6 h/day, 5 days/week for 6 weeks. A control group of 3 monkeys was sham exposed to filtered room air for 6 h/day, 5 days/week for 6 weeks. Both exposed groups showed mild degeneration and early squamous metaplasia in parts of the transitional and respiratory epithelium of the nasal passages and respiratory epithelium of the trachea and major bronchi. The nasal surface area involved was significantly increased in the 6 week exposure group. Cell proliferation rates were significantly increased and remained elevated 6 weeks after the termination of exposure (Monticello et al., 1989).

Fifteen-week-old male Hartley guinea-pigs were exposed for 6 h/day, 5 days/week, for 8 weeks, to 0.12, 1.2, or 12 mg formaldehyde/m^3 (Marshall et al., 1983). Animals were sacrificed at 1 and 30 days after the end of exposure, and tissue samples were taken to study the histology and lung biochemistry. Body weight, nasal mucous clearance velocity, and airway sensitivity to inhaled histamine were measured after 2, 4, and 8 weeks of exposure and 2 and 4 weeks after completion of exposure. Nasal mucous clearance velocity increased by 25% after 4 weeks of exposure to 12 mg/m^3, but returned to control values 2 weeks after the end of exposure. Dose-related histological findings included hyperkeratosis and squamous metaplasia of the respiratory epithelium occurring in foci in the anterior half of the nasal cavities. Thirty days after exposure, squamous metaplasia had resolved; however, slight hyperkeratosis of respiratory epithelium was still present in guinea-pigs exposed to 12 mg formaldehyde/m^3. Altered airway sensitization to inhaled histamine was not noted in exposed guinea-pigs. No differences were observed in body weights and lung biochemical end-points between control and exposed guinea-pigs.

The acute effects of inhaled formaldehyde on the nasal mucociliary apparatus of male F-344 rats were studied by Morgan et al. (1986) using whole-body exposures. Formaldehyde exposures ranged from a single 6-h period up to repeated 6-h exposures daily for 3 weeks, with exposure concentrations of 18, 7.2, 2.4, or 0.6 mg/m^3. Within 1 h of the last exposure, the rats were killed and the nasal passages examined for effects on nasal mucociliary function. Exposure to 18 mg formaldehyde/m^3 induced inhibition of mucociliary function in

specific regions of the nose, and mucostasis was generally more extensive than ciliastasis. These effects, which were initially confined to the anterior regions of the nose, became progressively more extensive for up to 2 weeks of exposure with only very slight progression during the third week. Inhibition of mucociliary function was much less severe with exposure to 7.2 mg/m^3, minimal at 2.4 mg/m^3, and not detected in rats following exposure to 0.6 mg/m^3.

Woutersen et al. (1987) exposed male and female rats to 0, 1.2, 12, or 24 mg formaldehyde/m^3 for 6 h/day, 5 days/week, over 13 weeks; definite adverse effects were observed at 12 and 24 mg/m^3, but the study was inconclusive with respect to whether 1.2 mg/m^3 was a cytotoxic effect level for the nasal epithelium.

The possibility of the hepatotoxicity of formaldehyde for rats was investigated by Woutersen et al. (1987). It was concluded that formaldehyde was not hepatotoxic at concentrations as high as 12 mg/m^3 (10 ppm). At 24 mg/m^3 (20 ppm), there was a slight increase in the levels of certain plasma-enzymes suggesting a hepatotoxic effect, however, histopathological examinations did not reveal any liver damage, and there were no changes in liver weight or liver-glutathione concentrations. The slight increase in plasma-enzyme levels may have been caused by growth retardation (Woutersen et al., 1987).

Zwart et al. (1987) exposed rats (50 per sex and group) to 0, 0.36, 1.2, or 3.6 mg formaldehyde/m^3 for 6 h/day, 5 days/week, over 13 weeks. Definite adverse effects on the nasal epithelium were observed at 3.6 mg/m^3. The authors concluded there was some indication that formaldehyde at levels of 0.36 and 1.2 mg/m^3 challenged the nasal mucociliary and regenerative defence systems at the beginning, but not at the end, of the study.

In a 13-week inhalation study, male rats were exposed for 5 days per week to 0, 1.2, or 2.4 mg formaldehyde/m^3, continuously (8 h per day), or to 2.4 or 4.8 mg formaldehyde/m^3 intermittently (8 successive 1-h periods a day, each consisting of 30 min of exposure and 30 min of non-exposure) (Wilmer et al., 1986). The only adverse effect (hypermetaplasia of the nasal respiratory epithelium) was found in animals exposed to 4.8 mg/m^3. This study showed that the concentration is more important than the total dose for the cytotoxic effects of formaldehyde on the nose.

A 4-week inhalation study on male rats was carried out by Wilmer et al. (1987) in which the animals were exposed for 5 days/week to 0, 6, or 12 mg formaldehyde/m^3, continuously for 8 h/day, or 12 or 24 mg formaldehyde/m^3 intermittently (8 successive 1-h periods per day, each consisting of 30 min of exposure and 30 min of non-exposure). This study also showed that the concentration rather than the total dose of formaldehyde determined the severity of the cytotoxic effects on the nasal epithelium.

Fifteen male rats were exposed to vapourizing 10% formalin solution (3.7% formaldehyde) by inhalation for 2-22 weeks; their tracheas were removed and examined microscopically after various periods of exposure; a wide spectrum of morphological changes in the epithelium and under-

lying connective tissues was observed. In addition to chronic inflammation, metaplastic changes, including squamous metaplasia and dysplasia of the epithelium, were induced by formaldehyde (Al-Abbas et al., 1986).

The immunotoxicity of formaldehyde was studied in mice by Dean et al. (1984). Female B6C3F1 mice underwent inhalation exposure to 18 mg/m^3 for 6 h/day, 5 days/week, over 3 weeks. Most immune functions involving T and B lymphocytes and macrophages were not impaired and there was an enhanced resistance to *Listeria monocytogenes*. In a later study by the same group (Adams et al., 1987), exposure of mice to 18 mg formaldehyde/m^3 (15 ppm) for 6 h daily over 3 weeks caused an increased (approximately two-fold) competence for release of hydrogen peroxide (H_2O_2) from the peritoneal macrophages. Enhanced function of the macrophages may be responsible for the enhanced lost resistance reported by Dean et al. (1984).

8.3.2 Oral studies

In a 4-week, drinking-water study on rats, using formaldehyde levels of 0, 5, 25, or 125 mg/kg body weight per day, adverse effects attributable to formaldehyde were encountered in the high-dose group only, and comprised decreased plasma-protein levels and hyperkeratosis and gastritis in the fore- and glandular stomach, respectively (Til et al., 1987).

Administration of formaldehyde in the drinking-water to Sprague-Dawley rats at a dose of 150 mg/kg body weight per day and in the diet to beagle dogs at a dose of 100 mg/kg body weight per day for a period of 13 weeks was found to result in a slightly depressed growth rate; no effects on the stomach were observed (Johannsen et al., 1986).

During an 18-day study, rats were fed a diet of soybean meal treated with formaldehyde (Schmidt et al., 1973). The use of more than 2 ml formalin (40%)/100 g soybean protein reduced growth, and also nitrogen retention in nitrogen balance studies.

8.4 Long-Term Exposure and Carcinogenicity

8.4.1 Inhalation

Exposure of B6C3F1 mice and Fischer 344 rats to 2.4, 7.2, or 18 mg formaldehyde vapour/m^3 (2, 6, or 15 ppm) for up to 24 months resulted in chronic toxicity. The survival of mice did not appear to be related to the concentration of formaldehyde to which they were exposed; however, exposure to a level of 17.6 mg/m^3 resulted in reduced body weight. Several lesions were seen in the nasal cavities of mice exposed to concentrations of 7.2 or 18 mg/m^3 (6 or 15 ppm), including dysplasia and squamous metaplasia of the respiratory epithelium, purulent or seropurulent rhinitis, and atrophy of the olfactory epithelium. Three months after exposure was discontinued (27 months), the nasal lesions had regressed. In the rats, several

lesions occurred in the nasal cavities at the low concentration of 2.4 mg/m^3 (2 ppm); these increased in extent and severity with increasing concentrations. The lesions included dysplasia and squamous metaplasia of the respiratory epithelium, goblet-cell hyperplasia, and purulent or seropurulent rhinitis. Rats exposed to 18 mg/m^3 (15 ppm) also exhibited goblet-cell metaplasia of the olfactory epithelium, respiratory epithelial hyperplasia, squamous epithelial hyperplasia, squamous atypia, and papillary hyperplasia; dysplasia and squamous metaplasia of the tracheal epithelium were also detected. The incidence of squamous metaplasia in rats exposed to 2.4 or 6.7 mg/m^3 (2 or 5.6 ppm) regressed within 3 months of the termination of exposure (Swenberg et al. 1980; Kerns et al., 1983) (see Table 30). Male Syrian golden hamsters exposed to diethylnitrosamine by sc injection (0.5 mg, once per week, for 10 weeks) and to formaldehyde (36 mg/m^3 via inhalation, 48 h/week prior to each injection, and subsequently continued for the life-time of each animal) developed tracheal carcinomas (Dalbey, 1982). Male Syrian golden hamsters exposed to up to 12 mg formaldehyde/m^3 (10 ppm) for 5 h/day and 5 days per week for their life-time did not show any tumours but 5% showed hyperplastic and metaplastic areas on the nasal epithelium. The author concluded that formaldehyde may act as a cofactor in carcinogenesis in the trachea.

Following exposure of Sprague-Dawley rats to formaldehyde 17 mg/m^3 (14 ppm) alone, or in combination (pre-mixed or non-pre-mixed) with HCl 14 mg/m^3 (10 ppm), for 6 h/day, 5 days/week, for life (Table 29), rhinitis, hyperplasia, and squamous metaplasia in laryngeal-tracheal segments and nasal mucosa were observed (Albert et al., 1982; Sellakumar et al., 1985).

Albert et al. (1982) exposed rats to a mixture of gaseous formaldehyde (17.9 mg/m^3) and hydrogen chloride (16.9 mg/m^3) for 6 h/day, 5 days/week, for life. In the exposure chamber, a bis-chloromethyl-ether (BCME) concentration of 0.5-2 μg/m^3, due to the chemical reaction of formaldehyde and hydrogen chloride, was estimated. Sellakumar et al. (1985) calculated levels of BCME under similar conditions of 0.5-2.05 μg/m^3 (0.1-0.4 ppb). Nasal squamous cell carcinomas were found in 25/99 rats and papillomas in 3/99 rats; squamous metaplasia of the nasal epithelium was found in 64/99 of the exposed rats.

A subsequent report (Sellakumar et al., 1985) of studies on combined exposure to hydrogen chloride and formaldehyde showed that the carcinogenic response to formaldehyde does not result from the BCME formed by the mixture of the gases.

Tobe et al. (1985) exposed male F-344 rats for 6 h/day, 5 days/week, over 28 months, to 0.36, 2.4, or 17 mg formaldehyde/m^3. Rhinitis accompanied by desquamation was found in all groups. In all formaldehyde-exposed groups, nasal epithelial hyperplasia and squamous metaplasia with hyperplasia were seen. In the 17 mg/m^3 group, squamous cell carcinoma was recognized in 14 rats and papilloma in 5 of 32 rats exposed.

Table 29. Summary of carcinogenicity studies of formaldehyde on animals

Species/ Strain	Number of animals (sex)	Route of exposure	Dosage	Findings	Reference
Mouse	42-60	inhalation	0, 50, 100, or 200 mg/m^3; three 1-h periods/week, for 35 weeks	no pulmonary tumours at 0-100 mg/m^3	Horton et al. (1963)
Mouse	36	inhalation	50 mg/m^3 for 35 weeks + 150 mg/m^3 for 29 weeks; three 1-h periods/week in addition	no pulmonary tumours	Horton et al. (1963)
Mouse	26	inhalation	100 mg/m^3; three 1-h periods/week for 35 weeks followed by a coal-tar aerosol for 35 weeks	formaldehyde did not modify the pulmonary carcinogenesis of coal-tar	Horton et al. (1963)
Mouse: B6C3F1	119-121 (male) 119-121 (female)	inhalation	0, 2.4, 6.72, or 17.16 mg/m^3; 6 h/day, 5 days/week, for up to 24 months; 6-month follow-up	squamous cell carcinoma of the nasal cavity in 2 males (at high exposure only)	Kerns et al. (1983)
Mouse: CTM, SWR +C3Hf	29-99 (male) 27-100 (female)	ingestion	0 or 0.5 HMT in drinking-water for 60 weeks or 5% for 30 weeks (CTM only); follow-up for 110-130 weeks[a]	no increased tumour incidence	Della Porta et al. (1968)
Mouse: CTM	39 (male) 44 (female)	subcutaneous	5 g/kg on alternate days, for 110-130 weeks[a]	no increased tumour incidence	Della Porta et al. (1968)
Mouse	60	Injection (route not described)	µl "formol oil" 50 times to the cervix uteri (dose not defined)	no tumours[d]	Klenitzky (1940)

Table 29 (contd).

Mouse: SENCAR	30 (female)	topical, back skin	3.7% formaldehyde in acetone once a week, 48 weeks	formaldehyde is probably not a complete carcinogen or an initiator (preliminary findings only)	Spangler & Ward (1983)
Mouse: CD-1	30 (female)	subcutaneous	0.1-1.0 mg, 3 times a week for 180 days	no incidence of initiator/promotor activity (preliminary findings)	Krivanek et al. (1983a)
Mouse	16 (male) 16 (female)	topical, back skin	200 µg 1% or 10% sol., twice a week, 60 weeks	no tumours	Iversen (1986)
Rat: Sprague Dawley	100 (male)	inhalation	17 mg/m^3 (14.2 ppm); 382 exposures over a 588-day period; 6 h/day, 5 days/week	10 squamous cell carcinomas of the nasal cavity (significant with regard to controls (preliminary findings only)	Albert et al. (1982)
Rat: Sprague Dawley	99	inhalation	16.80 mg/m^3 (14.7 ppm) formaldehyde + 14.00 mg/m^3 (10.6 ppm) HCl (BCME estimated 1 µg/m^3), 6 h/day, 5 days/week, for life	25/99 squamous cell carcinomas of the nasal cavity and 3 papillomas	Albert et al. (1982)
Rat: Sprague Dawley	100 (male)	inhalation	17.16 mg/m^3 (14.3 ppm) formaldehyde + 14 mg/m^3 (10 ppm) HCl (pre-mixed); 378 exposures over 588 days; 6 h/day, 5 days/week	12 squamous cell carcinomas of the nasal cavity (significant with regard to controls) (preliminary results only)	Albert et al. (1982)
Rat: Sprague Dawley	100 (male)	inhalation	16.92 mg/m^3 (14.1 ppm) formaldehyde + 13.30 mg/m^3 (9.5 ppm) HCl (not pre-mixed); 378 exposures over 588 days; 6 h/day, 5 days/week	6 nasal (significant with regard to controls) (5 squamous cell carcinomas, 1 adenocarcinoma) (preliminary results only)	Albert et al. (1982)

Table 29 (contd).

Species/ Strain	Number of animals (sex)	Route of exposure	Dosage	Findings	Reference
Rat: F-344	119-121 (male) 119-121 (female)	inhalation	0, 2.4, 6.72, or 17.16 mg/m^3; for up to 24 months; 6 h/ day, 5 days/week; 6-month follow-up	non-significant polypoid adenoma at all doses; 2/235 (non-significant) and 103/232 (significant) squamous cell carcinomas of nasal cavity, at the medium and high doses, respectively (see also Table 30)	Kerns et al. (1983)
Rat: F-344	32	inhalation	0.36, 2.4, or 17 mg/m^3; 6 h/day, 5 days/week, for 28 months	rhinitis; epithelial cell hyperplasia; squamous metaplasia at 17 mg/m^3, 14/32 squamous cell carcinomas ($P < 0.01$) and 5/32 papillomas ($P < 0.05$)	Tobe et al. (1985)
Rat: Sprague Dawley	100 (male)	inhalation	18.24 mg/m^3 (15.2 ppm) formaldehyde + 13.86 mg/m^3 (9.9 ppm) HCl (pre-mixed) (BCME, 0.1-0.4 µg/m^3); 6 h/day, 5 days/week, for life	13 polyps/papillomas; 45 squamous cell carcinomas; 1 adenocarcinoma 1 fibrosarcoma; esthesic neuroepithelioma resp	Sellakumar et al. (1985)
Rat: Sprague Dawley	100 (male)	inhalation	17.88 mg/m^3 (14.9 ppm) formaldehyde + 13.58 mg/m^3 (9.7 ppm) HCl (not pre-mixed); 6 h/ day, 5 days/week for life	27 squamous cell carcinomas; 2 adenocarcinomas; 11 polyps/ papillomas	Sellakumar et al. (1985)
Rat: Sprague Dawley	100 (male)	inhalation	17.76 mg/m^3 (14.8 ppm) formaldehyde; 6 h/day, 5 days/ week, for life	38 squamous cell carcinomas; 1 fibrosarcoma; 1 mixed carcinoma	Sellakumar et al. (1985)
Rat	30	stomach tube	0.4 g/day[a], for 333 days	no treatment-related tumours	Brendel (1964)

Table 29 (contd).

Rat: Wistar	48 (male) 48 (female)	ingestion	1% HMT in drinking-water for 104 weeks, for 3 years[a]	no increased tumour incidence	Della Porta et al. (1968)
Rat: Wistar	280 (male) 280 (female)	ingestion	0, 1.2, 15, or 81 mg/kg bw (males); 0, 1.8, 21, or 109 mg/kg bw (females) (drinking-water, 2 years)	no tumours (except 1 skin mesenchymoma in high-dose male)	Til et al. (1988)
Rat: Wistar	80 (male) 80 (female)	ingestion	0, 10, 50, or 300 mg/kg bw; (drinking-water, 2 years)	no significant increase in tumours	Tobe et al. (1988)
Rabbit	6	oral tank	3% formalin, 90 min, 5 times/week for 10 months	2/6 leukoplakias[b]	Mueller et al. (1978)
Syrian golden hamsters	88	inhalation	12 mg/m^3, 5 h/day, 5 day/week, lifetime	no increase in tumour incidence	Dalbey (1982)
Syrian golden hamsters	50	inhalation	36 mg/m^3, 5 h/day, 5 day/week, lifetime (with diethylnitrosamine)	no increase in nasal tumour incidence	Dalbey (1982)
Rat	10	subcutaneous	1 ml/week for 15 months 0.4% solution	4/10 injection-site sarcomas	Watanabe et al. (1954)
Rat	20	subcutaneous	1-2 ml/week till tumour development 9-40%[d]	7/20 injection-site sarcomas; 1/20 injection-site adenoma	Watanabe & Sugimoto (1955)
Rat: Wistar	20 (male) 20 (female)	subcutaneous	5 g/kg on alternate days, for 2 years[d]	no increased tumour incidence	Della Porta et at. (1968)

[a] Hexamethylenetetramine (HMT) (from which formaldehyde is liberated *in vivo*).
[b] Showed "histological features of carcinoma *in situ*" (Mueller et al., 1978).
[c] Aspartame (sweetener) was administered to rats at a dosage level of 8 g/kg body weight, which has been assumed to biodegrade (10%) in the animals yielding 800 mg formaldehyde/kg.
[d] No tumours, even after treatment with dibenzpyrene and coal tar.

Table 30. Neoplastic changes in the nasal cavities of Fischer 344 rats[a]

Formaldehyde mg/m^3	(ppm)	Sex	Number of nasal cavities evaluated	Squamous cell carcinomas	Nasal carcinomas	Undifferentiated carcinomas/ sarcomas	Malignant sarcomas	Polypoid adenomas	Osteochondromas
0	(0)	male	118	0	0	0	0	1	1
		female	114	0	0	0	0	0	0
2.4	(2)	male	118	0	0	0	0	4	0
		female	118	0	0	0	0	4	0
6.7	(5.6)	male	119	1	0	0	0	6	0
		female	116	1	0	0	0	0	0
17.2	(14.3)	male	117	51[c]	1[b]	2[b]	1	4	0
		female	115	52[d]	1	0	0	1	0

[a] From: Kerns et al. (1983) and BCA (1985).
[b] One animal also exhibited a squamous cell carcinoma.
[c] 36 of these animals were among the 57 that died prematurely.
[d] 15 of these animals were among the 67 that died prematurely.

Male rats were exposed to 0, 12, or 24 mg formaldehyde/m^3 for 4, 8, or 13 weeks (6 h/day, 5 days/week) and were then observed for periods of up to 126 weeks (Feron et al., 1987a). Non-neoplastic histopathological changes in the nasal respiratory epithelium (hyper- and metaplasia) and olfactory epithelium (disarrangement, thinning, and simple cuboidal or squamous metaplasia) occurred at 24 mg/m^3, similar, but less pronounced, changes of the nasal respiratory epithelium were seen at 12 mg/m^3 and a limited and not statistically significant number of nasal tumours occurred at 24 mg/m^3, mainly in rats that had been exposed for 13 weeks (6/132: 3 squamous cell carcinomas, 1 carcinoma *in situ* and 2 polypoid adenomas).

Feron et al. (1987b) carried out an inhalation study on male rats with a severely damaged (by electrocoagulation) or undamaged nasal mucosa. They were exposed to 0, 0.12, 1.2, or 12 mg formaldehyde/m^3 6 h/day, 5 days/week, over periods of either 28 months or 3 months, followed by an observation period of 25 months. A significant number of nasal squamous cell carcinomas (17/60) occurred only in rats with a damaged nose that had been exposed to 12 mg/m^3 for a period of 28 months.

Basal-cell hyperplasia and/or squamous metaplasia were observed in the tracheo-bronchial epithelium of C3H mice exposed to 50, 100, or 200 mg formaldehyde/m^3, for 4 h/day, 3 days/week, over 35 weeks; atrophic metaplasia was also observed in the highest dose group (Horton et al., 1963).

Neoplastic lesions found in the nasal cavities of Fischer 344 rats exposed to formaldehyde gas are summarized in Table 30 (Kerns et al., 1983). Several studies were performed to examine whether formaldehyde acts as a complete carcinogen, a promoter, or an initiator of tumours. Horton et al. (1963) exposed mice to coal-tar aerosol and to formaldehyde (48 or 120 mg/m^3, 1 h/day, 3 days/week, over 35 weeks). Coal-tar aerosol exposure resulted in lung tumour formation, but there was no evidence of any co-carcinogenic effect of formaldehyde.

8.4.2 Dermal studies

Studies were carried out on mice (Krivanek et al., 1983a; Spangler & Ward, 1982; Iversen, 1986) to test whether formaldehyde solution applied to the skin induced papilloma or malignant tumours as an initiator, or promoter of cancer, or as a complete carcinogen. Formaldehyde proved to be neither a complete carcinogen, nor an initiator (with phorbolmyristateacetate as a promoter). With respect to promoting activity (with benzo(a)pyrene or dimethylbenyanthracene as an initiator) the results were either negative or inconclusive. Details can be found in Table 29.

8.4.3 Oral studies

Some studies were performed using HMT instead of formaldehyde. It is used as an urinary tract antiseptic and antimicrobial food additive

(Della Porta et al., 1968) and owes its activity to its degradation to formaldehyde and ammonia in an acid medium (digestive tract) with conversion of 20% of the theoretical amount of formaldehyde at pH 5 (Goodman & Gilman, 1975).

Slightly reduced growth rate and survival were observed in CTM mice given 5% hexamethylenetetramine (HMT) in the drinking-water for 30 weeks; a slightly reduced growth rate was also observed in SWR mice exposed to 1% HMT in the drinking-water for 60 weeks (Della Porta et al., 1968) (Table 29).

Formaldehyde, and other compounds were tested for tumour-promoting activity in a 2-stage stomach carcinogenesis study (Takahashi et al., 1986). Male Wistar rats were given *N*-methyl- *N'*-nitro-*N*-nitroso-guanidine (MNNG) in the drinking-water (100 mg/litre) and a diet supplemented with 10% sodium chloride for 8 weeks. Thereafter, they were maintained on drinking-water containing 0.5% Formalin for 32 weeks. Formaldehyde increased the incidence of adenocarcinoma in the glandular stomach, after initiation with MNNG and sodium chloride. The incidence of squamous cell papilloma in the forestomach was significantly increased in the groups given formaldehyde, irrespective of prior initiation. The results indicate that formaldehyde induces forestomach papilloma and exerts tumour-promoting activity.

Groups of 70 male and 70 female SPF Wistar rats, 31 days old, were administered formaldehyde at 1.2, 15, or 81 and 1.8, 21, or 109 mg/kg body weight per day, respectively, as a 5% (w/w) solution in the drinking-water for up to two years. A group of 70 males and 70 females served as controls. Groups of 10 rats per sex per group were killed at weeks 53 and 79 and the remaining animals at week 105. Mortality was elevated among mid-dose males by the end of the study but there was no difference among other groups. Mean body weights were lower in high-dose animals; this was accompanied by a decrease in food and liquid intake. The limiting ridge of the forestomach was raised and thickened in most animals of the high-dose group at each interim killing and at the end of the study; a similar effect was observed in some other treated groups and occasionally in controls. Papillary epithelial hyperplasia, hyperkeratosis, and focal ulceration in the forestomach were observed in high-dose animals as were chronic atrophic gastritis, ulceration, and hyperplasia in the glandular stomach. In addition, a higher incidence and degree of renal papillary necrosis was seen in high-dose animals at the end of the study compared to other treated groups and controls. One mesenchymoma of the skin was observed in a high-dose male killed at 52 weeks and two gastric papillomas were observed, one in a low-dose male and one in a female control, at the end of the study. No other gastric tumours were reported and no treatment-related tumours were found (Til et al., 1988).

A similar study was carried out on Wistar rats administered formaldehyde in the drinking-water (Tobe et al., 1989). Groups of 20 male and 20 female Wistar rats, four weeks old, were administered 10, 50, or 300 mg formaldehyde/kg body weight per day as 0.02, 0.1, or 0.5% solutions, respectively, in the drinking-water for up to 2 years. A

group of 20 males and 20 females served as controls. Groups of 6 rats per sex per group were killed at 12 and 18 months and the remaining surviving animals were killed at 24 months. Mortality was elevated in the high-dose group and reached 45% and 55% in males and females, respectively, at 12 months; all animals in this group had died by 21 months (females) and 24 months (males). Body weight gain and food and liquid intake were significantly reduced in high-dose animals. Erosions, ulcers, squamous cell hyperplasia, hyperkeratosis, and basal cell hyperplasia with submucosal cell infiltration were observed in the forestomach in animals of both sexes in the high-dose group at 12 months. Erosions, ulcers, and submucosal cell infiltration also occurred in the glandular stomach among this group at 12 months and glandular hyperplasia was observed along the limiting ridge of the fundic mucosa. In the mid-dose group, hyperkeratosis occurred in the forestomach in one male and one female among animals killed at 18 and 24 months. No such lesion was found in animals in the low-dose group at any time. There was no significant increase in the incidence of any neoplastic lesion in any treated group compared with controls. The types of tumours observed were similar to those that occur spontaneously in this strain of rats.

8.5 Mutagenicity and Related End-Points

The mutagenic properties of formaldehyde have been studied in different test systems (Tables 31 and 32). Extensive data have resulted from the treatment of *Drosophila* with formaldehyde-treated food (Auerbach et al., 1977).

In general, the available data show that formaldehyde is mutagenic in different test systems, especially when high concentrations act directly on cells (gene and chromosome mutations). Addition of metabolizing systems to the assay system tends to reduce the activity of formaldehyde. The mutagenic effects of formaldehyde in *Drosophila* depend on the route of administration. Inconsistent responses were obtained in *in vitro* mammalian mutagenicity assays, increases in mutation frequency being obtained in the mouse lymphoma assays, but not with Chinese hamster ovary cells.

Positive cell transformation assays have been reported *in vitro*. After inhalation of the compound, local DNA adducts were observed in rats without simultaneous systemic genetic effects (Casanova-Schmitz et al., 1984b).

DNA-protein cross-links have been studied in cultures of mammalian cells. Some DNA strand breakage was reported, but DNA-DNA cross-links were not observed. Formaldehyde has been shown to induce chromosome aberrations and sister chromatid exchanges in a number of cell lines. The results of studies on the induction of sister chromatid exchanges in human lymphocyte cultures (Kreiger & Garry, 1983) demonstrated that there was no significant sister chromatid exchange response below an apparent "threshold" of 5 ml culture medium.

Table 31. The genetic toxicology of formaldehyde: *in vitro* studies

Assay	Strain/type	Metabolic activation	Result	Comments	Reference
Procaryotes					
Escherichia coli	WP2 Hcr+ WP2 Hcr-	none	- +		Nishioka (1973)
Escherichia coli	WP2 WP67 CM871 spot test	± Aroclor induced rat liver S-9	+ + + +	strain was not specified for spot test, nor was metabolic activation used	De Flora et al. (1984)
Escherichia coli	WP2 uvrA	none	-		Hemminki et al. (1980)
Salmonella typhimurium	TM677	± Aroclor induced rat liver S-9	+	toxicity and mutagenicity reduced with S-9	Temcharoen & Thilly (1983)
Salmonella typhimurium	no strain data		-		Gocke et al. (1981)
Salmonella typhimurium	Ames; no strain data	± hepatic activation	-	paraformaldehyde	Bruisick et al. (1980)
Salmonella typhimurium	TA1535, TA1538, TA1537, TA97 TA98 TA100	none	- - - - - -		De Flora et al. (1984)

Table 31 (contd).

Salmonella typhimurium	TA97 TA98 TA100	± Aroclor induced rat and hamster liver S-9	- - -	effects of S-9 not given; assumed from abstract all strains negative	Hughes et al. (1984)
Salmonella typhimurium	TM677 TA97 TA98 TA100	± Aroclor induced rat liver S-9	+ + + +		Donovan et al. (1983)
Salmonella typhimurium	TM677 TA100	none	+ +		Sarrit et al. (1983)
Salmonella typhimurium	TA98 TA100 UTH8414 UTH8413	± Aroclor induced rat liver S-9	+ + - -	formaldehyde as formalin (10-15% methanol)	Connor et al. (1983)
Salmonella typhiorium	TA1535 TA1537 TA1538 TA98 TA100	none	- - - - -	formalin tested	De Flora (1981)
Salmonella typhimurium	TA98 TA100	± KC500 induced rat liver S-9	- +	negative with S-9	Sasaki & Endo (1978)
Salmonella typhimurium	TA98 TA100	± rat liver microsomes	+ +	activity of formaldehyde was reduced in the presence of rat liver microsomes	Oerstavik & Hongslo (1985)
Salmonella typhimurium	TA1535 + plasmids 5310002/psk1002	none	+		Yoshimitsu et al. (1985)

Table 31 (contd).

Assay	Strain/type	Metabolic activation	Result	Comments	Reference
Salmonella typhimurium	TA97 TA102	± Aroclor induced rat liver S-9	- +	weak response	De Flora et al. (1984)
Salmonella typhimurium	TA100 TA102	± Aroclor induced rat liver S-9	+	pre-incubation procedure	Simmons et al. (1986)
Salmonella typhimurium	no strain data	± hepatic activation	-		Brusick (1983)
Salmonella typhimurium	TA100	± clophen A50 induced rat liver S-9	+ (weak)		Schmid et al. (1986)
Salmonella typhimurium	TA102 TA2638	none	-		Levin et al. (1982)
Salmonella typhimurium	TA98 TA100 TA1537	± PCB, KC-100 induced rat liver S-9	- -	formalin; positive in strain TA100 without S-9	Ishidate et al. (1981)
Salmonella typhimurium	TA98 TA100 TA1535 TA1537	± Aroclor induced rat and hamster liver S-9	- - - -		Haworth et al. (1983)
Eucaryotes					
Nematode	*Caenorhapolitis elalgans*	-		Point mutation in unc-22 gene for "twitching" on exposure to nicotine	Moerman & Baillie (1981)

Table 31 (contd).

Neurospora crassa	H-59 (repair deficient)	-	+		Brockman et al. (1981)
	H-12		+		
Neurospora crassa	Ade		+		Jensen et al. (1951)
Drosophila			+	FA generated ADH mutants	Benyajati et al. (1983)
Drosophila	-	-	-	not susceptible to mutagenicity when fed formaldehyde in the food; mutations on injection into the larvae	Auerbach et al. (1977)
Tradescantia (micronucleus)		-	-	strain absorption	Ma et al. (1985)
			+	fumigation	
Saccharomyces cerevisiae (recombination)	D4	-	+		Chanet et al. (1975)
	D3		+		
Saccharomyces cerevisiae (recombination)	N123		+	mitotic recombination	Chanet & Von Borstel (1979)
Mammalian cell mutation					
Mouse lymphoma	L5178Y	± hepatic activation	+	paraformaldehyde	Brusick (1980)
Mouse lymphoma	L5178Y TK±	± S-9	+	negative on the addition of cofactors FDH and NAD+	Dooley (1985)

Table 31 (contd).

Assay	Strain/type	Metabolic activation	Result	Comments	Reference
Mammalian cell mutation (contd).					
CHO cells	HGPRT locus	none	-		Hsie et al. (1978)
CHO cells	HGPRT locus	± Aroclor induced rat liver S-9	equivocal (without S-9) + (with S-9 very weak)		Stankowski et al. (1986)
CHO cells	AS52 locus		+		
Human lymphoblasts	TK6	none	+		Goldmacher & Thilly (1983)
Cell transformation					
	C3H10T 1/2	none	-		Ragan & Boreiko (1981)
	hamster embryo	none	+		Sonner & Riverdal (1983)
	rat kidney cell	none	±	formaldehyde transformed cells when incubated with TPA	Sonner & Riverdal (1983)
	Balb/C3T3 1/2	none	+		Brusick (1983)
	BKH-21/C1.13	± Aroclor induced rat liver S-9	+		Plesner & Henson (1983)

Table 31 (contd).

DNA repair					
	hamster embryo cells (SA7 virus) (enhanced viral transformation)	none	+		Hatch et al. (1983)
	human diploid fibroblasts		+ -	nick translation did not inhibit repair	Snyder & Van Houten (1986)
DNA cross-linking	CHO-KI	none	+		Marinari et al. (1984)
DNA assay					
DNA-cell binding		none	?		Kubinski et al. (1981)
Unscheduled DNA synthesis	Hela		+		Martin et al. (1978)
DNA damage	L1210 mouse leukaemia cells		+	DNA-protein cross-links	Ross et al. (1981)
Unscheduled DNA synthesis	rat tracheal epithelial cells	none	-		Doolittle & Butterworth (1984)
	bronchial epithelial and fibroblast cells	none	+	DNA-protein cross-links; single-strand breaks in DNA and inhibited resealing inhibition of DNA repair (UDS)	Grafstrom et al. (1983)
	human fibroblasts		+		Levy et al. (1983)

Table 31 (contd).

Assay	Strain/type	Metabolic activation	Result	Comments	Reference
DNA-protein cross-linking	rat nasal epithelium	none	+		Bermudez & Delahanty (1986)
Unscheduled DNA synthesis	rat nasal epithelium	none	-		Bermudez & Delahanty (1986)
Scheduled DNA synthesis	rat nasal epithelium	none	+		Bermudez & Delahanty (1986)
RNA synthesis	rat nasal epithelium	none	-		Bermudez & Delahanty (1986)
Cytogenetic assays					
Sister chromatid exchange	CHO	hepatic activation	+	paraformaldehyde	Brusick et al. (1980)
Chromosome aberration	CHO	hepatic activation	+		
Sister chromatid exchange	V79	± Aroclor induced rat liver S-9 ± hepatocytes	+	FA induced sister chromatid exchanges; frequency decreased with S-9 to almost that of control values; this was shown to be due to metabolism, not binding to macromolecules	Basler et al. (1985)
Sister chromatid exchange	human lymphocyte		+		Garry & Kreiger (1981)
Sister chromatid exchange	human lymphocyte		+		Kreiger & Garry (1983)

Table 31 (contd).

	human lymphoblast TK6		+ +	TK locus DNA-protein cross-links	Craft et al. (1987)
Chromosome aberration	CHO	± metabolic activation	+		Natarajan et al. (1983)
Sister chromatid exchange	human lymphocytes	none	+		Bassendowstakarska & Zawadzkakos (1983)
Sister chromatid exchange	CHO human lymphocytes	none none	+ +		Obe & Beek (1979)
Chromosome aberration	embryonic kidney culture	none	-	formalin	Kalmykova (1979)
Sister chromatid exchange	CHO	± hepatic activation	+	metabolic activation decreased the dose at which sister chromatid exchange activity was detected	Brusick (1983)
Chromosome aberration	CHO		-		
Chromosome aberration Sister chromatid exchange	human lymphocyte human lymphocyte	± clophen A50 induced rat liver S-9	+ +		Schmid et al. (1986)
Chromosome aberration	CHO cells	± PCB KC-400 induced rat liver S-9	+ (in absence of S-9)		Ishidate et al. (1981)
Chromosome aberration Sister chromatid exchange	CHO CHO	± Aroclor induced rat liver S-9	+ +		Galloway et al. (1985)

Table 32. The genetic toxicology of formaldehyde: *in vivo* studies

Assay	Strain/type	Result	Comments	Reference
Cytogenetic assays				
Sister chromatid exchange	mouse	+ in female mice at mid- and higher dose levels	formaldehyde concentrations were greater that the target concentrations of 14.4 and 30 mg/litre	Brusick et al. (1983)
Chromosome aberration	mouse	?	formalin (correct CAS number not given); 24-h and 25-month exposures caused insignificant increase in cells with chromosomal aberrations; symmetrical translocations in the germ cells found in the spermatocyte stage and increased post-implantation embryonic mortality	Kalmykova (1979)
Chromosome aberration	CBA mouse	-	bone marrow + spleen; 0.4 ml ip at doses of 6.25, 12.5, and 25 mg/kg	Natarajan et al. (1983)
Micronucleus	CBA mouse	-		
Micronucleus	NMRI mouse	-	bone marrow; single ip injection of 10, 20, or 30 mg/kg; sampled at 3 and 6 years; 2 males and 2 females per group	Gocke et al. (1981)
Sister chromatid exchanges/chromosome aberration	Fischer rat	-	0.6, 7.2, or 18 mg/m^3 (0.5, 6, or 15 ppm); 6 h/day, for 5 days	Kligerman et al. (1984)

Table 32 (contd).

Chromosome aberration	rat	- at week 1 and 32 months bone marrow; + at high dose in lung macrophage at 1 week and 2 months	0, 0.6, 3.6, or 18 mg/m^3 (0, 0.5, 3, or 15 ppm) paraformaldehyde); 6 h/day, 5 days/week, for 6 months; at 4 and 6 months the mitotic index in the lung cells of all animals, including controls had dropped, and the number of cells available for scoring was inadequate	Scott et al. (1985)
Unscheduled DNA synthesis				
	rat (tracheal epithelial cells)	-	0.47, 2, 5.9, or 14.8 mg/litre for 1, 3, or 5 days	Doolittle & Butterworth (1984)
Dominant lethal				
	mouse	- (spermatogonial chromosome)	mixture of formaldehyde and hydrogen peroxide (30 mg/kg, 90 mg/kg)	Fontignie-Houbrechts et al. (1982)
		weak dominant lethal effects weeks 1 and 6	number of pregnancies not reduced; no increase in post-implantation lethality; number of live embryos never decreased below 7.4/female; pre-implantation loss significantly increased during the whole study, except for the 5th and 7th weeks	
	ICR-Ha Swiss mouse (8- to 10-week-old males)	-	32, 40, 16, or 20 mg/kg ip; mated for 3 or 8 weeks (females replaced weekly)	Epstein et al. (1972)

Table 32 (contd).

Assay	Strain/type	Result	Comments	Reference
Dominant lethal (contd).				
	Q-strain mouse	- (spermatogonial chromosome	50 mg/kg ip	Fontignie-Houbrechts (1981)
		weak dominant lethal effect	no effect was observed on the number of pregnant females; an increase in embryonic mortality observed in the first week after treatment is attributable to an increase in the number of pre- and post-implantation deaths; only in the 3rd week was the number of pre-implantation deaths significantly increased	
Spot test				
Somatic cell mutation	C57Bl/6J"Ha" mouse (T-stock)	-	6 - 6.1 and 17.8 - 18.1 mg/m^3, 6 h/day, for 3 days	Jensen & Cohr (1983)

Craft et al. (1987) exposed human lymphoblasts *in vitro* to various concentrations of formaldehyde (0-150 µmol/litre x 2 h). Both the induction of mutations and the formation of DNA-protein cross-links by formaldehyde are non-linear functions occurring at overlapping concentration ranges. Holding the culture for 24 h resulted in complete removal of the cross-links.

Definite evidence that formaldehyde may induce mutations *in vivo* has not been found. Tests for the induction of sister chromatid exchanges in mouse bone marrow cells gave equivocal results. Dominant lethal tests in ICR-Ha Swiss mice were reported to be negative at doses up to 40 mg/kg; more recent studies on Q-strain mice showed effects, except during the first and third week, after treatment of males with 50 mg formaldehyde/kg. Micronucleus and chromosomal assays failed to reveal any formaldehyde-induced lesions in both exposed rats and mice. The results of a mouse somatic cell mutation assay (spot test) were also negative for formaldehyde.

Formaldehyde damage induced in DNA in different human cell culture systems comprised DNA-protein cross-links and DNA single-strand breaks; these lesions undergo efficient repair by complex mechanisms (Grafstrom et al., 1984). An earlier finding that formaldehyde may inhibit DNA repair (Grafstrom et al., 1983) has not been confirmed (Snyder & van Houten, 1986).

8.6 Reproduction, Embryotoxicity, and Teratogenicity

This topic has been studied in inhalation, feeding, drinking-water, gavage, and dermal studies. The results are summarized in Table 33.

In a dominant-lethal study, formaldehyde did not appear to affect spermatogenesis or fertility in mice at single dose levels up to 40 mg/kg body weight (ip) or produce any increases in fetal death or pre-implantation losses (Epstein et al., 1972).

Yasamura et al. (1983) gave mice doses of 0, 30, 40, or 50 mg formaldehyde/kg per day by intraperitoneal injection on days 7-14 of pregnancy. The mean body weight of treated fetuses was lower than that in the controls, and the incidence of prenatal death was slightly increased in treated mice. There was a significant increase in the frequency of abnormal fetuses from treated dams, the major malformations being cleft palate and malformations of the extremities. Strain differences were observed.

A teratology study on the rat was undertaken by the Formaldehyde Council of Canada (Martin, 1985). Twenty-five mated Sprague-Dawley rats were exposed through inhalation (whole-body exposure) for 6 h/day to formaldehyde doses of 2.4, 6, or 12 mg/m^3, from day 0 to day 15 of gestation, inclusive. Two control groups were included in the study. The females used for the study were 13 weeks of age and weighed between 221 and 277 g. Proven males of the same strain and source were used for mating. The pregnancy rate in all groups was at least 80%. Uterine parameters, including numbers of corpora lutea, implantation sites, live fetuses, dead fetuses, and resorptions, fetal weight, sex ratio,

Table 33. Reproduction and teratology studies

Species	Route of exposure	Number of animals Female	Male	Dosage	Time of treatment	Effects on offspring/ reproduction	Remarks	Reference
Rat	inhalation	12	3	0.012 mg/m^3	10-15 days before gestation (females)	14-15% increase in duration of gestation; increase in body, heart, and kidney weight; decrease in weight of liver and lungs	no data concerning ratio of pregnancy, litter size; insufficient number of dose levels	Gofmekler et al. (1968)
		12	3	1 mg/m^3				
Rat	inhalation	12	3	0.012 mg/m^3	10-20 days before gestation (females)	decrease in ascorbic acid in the whole embryo; lower DNA content in fetal liver; increase in liver ascorbic acid[a]	no data concerning ratio of pregnancy, litter size; insufficient number of dose levels	Gofmekler et al. (1968); Pushkina et al. (1968)
		12	3	1 mg/m^3				
Rat	inhalation	12	3	0.012 mg/m^3	10-20 days before gestation (females)	changes in kidney and liver; decrease in myocardial glycogen; disintegration of lymphocytes[a]; involution of thymic lymphoid tissue[a]	no gross fetal malformations	Gofmekler & Bonashevskaya (1969)
		12	3	1 mg/m^3				
Rat	inhalation	15	-	0.0005 mg/litre	4 h/day, on days 1-19 of gestation	sacrifice on day 20; increase in number of preimplantation deaths; no external malformations; offspring of 6 dams delivered on day 22; at one-month postpartum, females, but not males, were shorter; decrease in mobility of females	none	Sheveleva (1971)
		15	-	0.005 mg/litre				

Table 33 (contd).

Rat	combined inhalation and ingestion	6 -	3[b] -	0.005 mg/litre and 0.12 mg/m^3; 0.01 mg/litre and 0.25 mg/m^3; 0.1 mg/litre and 0.5 mg/m^3	6 months; water; 4 h, 5 times/week	no adverse effects on reproduction; decrease in the amount of nucleic acid in the testes	no information concerning macroscopic examination of offspring	Guseva (1972)
Rat	inhalation	334 in 12 groups		0.4 mg/m^3 6 mg/m^3	4 h/day for 20 days	decrease in susceptibility to adverse effects on pregnant rats (compared with non-pregnant rats); altered renal and hepatic function[a], decrease in blood haemoglobin[a]	female rats; other chemicals also tested beside formaldehyde	Sanotskii et al. (1976)
Dog	ingestion	9-11	-	125 mg/kg (125 ppm) 375 mg/kg (375 ppm)	4 days after mating to day 56	no adverse findings	dams delivered naturally	Hurni & Ohder (1973)
Rat	ingestion	16	16	0.16% HMT	parents: from 2 to 5 months of age; offspring: from birth to 123 days of age	no adverse findings	dams delivered naturally	Natvig et al. (1971)
Rat	ingestion	12	6	1% HMT in drinking-water	start: at 8 weeks of age during pregnancy and nursing F1 treated until 20 weeks	no adverse findings	body weight of treated animals was less than controls	Della Porta et al. (1970)

Table 33 (contd).

Species	Route of exposure	Number of animals Female	Male	Dosage	Time of treatment	Effects on offspring/ reproduction	Remarks	Reference
Rat	ingestion	2	1	1% HMT[c]	F1, F2, and F3; 2.5 years	no adverse findings	small number of animals; only one dose level	Della Porta et al. (1970)
Rat	ingestion	5		2% HMT[c]	P and F1; 2.5 years	no adverse findings	no control	Della Porta et al. (1970)
Mouse	stomach tube	34	-	74 mg/kg per day; 148 mg/kg per day; 185 mg/kg per day	days 6-15 of gestation	no malformations; toxic for 22/34[a]		Marks et al. (1980)
Mouse	stomach tube	-	7	100 mg/kg	5 days	no effects on sperm	a total of 500 sperm per rat were evaluated	Ward et al. (1984)
Hamster	dermal	22		0.5 ml of 37% formaldehyde solution (but no information on amount absorbed)	day 8, 9, 10, or 11 of gestation	increased resorptions, but no effects on fetal weight or length and no malformations	total of 259 fetuses in 22 litters	Overman (1985)

[a] Only after exposure to the high dose.
[b] Female untreated, male treated.
[c] Hexamethylenetetramine (HMT) (from which formaldehyde is liberated in vivo).

and pre- and post-implantation losses, were unaffected by treatment. The overall incidence of litters and fetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies was not affected by treatment with formaldehyde.

Pregnant hamsters were treated with dermal applications of formaldehyde solution on day 8, 9, 10, or 11 of gestation (Overman, 1985). Fetuses were removed on day 15 and were weighed, measured, and examined for teratogenic effects. The resorption rate increased in the formaldehyde-treated groups, but treatment did not significantly affect weight or length, and no malformations that could be related to treatment appeared. It was concluded that fetal risk due to topical exposure to formaldehyde was minimal in this model system. However, there is no information in this study on the amount of formaldehyde actually absorbed.

The results in Table 33 do not show any evidence of the embryo being unusually sensitive to formaldehyde, and there is no information to show that formaldehyde is teratogenic in rodents when administered orally or applied dermally in non-toxic amounts to the dams. Furthermore, the data do not provide any evidence indicating that formaldehyde causes terata at exposure concentrations that are not toxic for the adult.

8.7 Mechanisms of Carcinogenicity

8.7.1 Reactions with macromolecules

Formaldehyde reacts readily with a variety of cellular nucleophiles, including glutathione, forming adducts of varying stability (Feldman, 1973; Uotila & Koivusalo, 1974; McGhee & von Hippel, 1975). The glutathione adduct of formaldehyde is the true substrate of formaldehyde dehydrogenase, which catalyzes the oxidation of the adduct to *S*-formyl-glutathione (Uotila & Koivusalo, 1974). Reaction products with DNA, which have been demonstrated *in vitro*, include adducts (McGhee & von Hippel, 1975a,b) and DNA protein cross-links (Brutlag et al., 1969; Doenecke, 1978; Ohba et al., 1979).

Investigations in rats exposed to formaldehyde through inhalation have shown that formaldehyde induces the formation of DNA protein cross-links in the nasal respiratory mucosa *in vivo* (Casanova-Schmitz & Heck, 1983; Casanova-Schmitz et al., 1984). The concentration-response curve for DNA protein cross-linking was sublinear below 7.2 mg/m^3 (6 ppm) but apparently linear at higher concentrations (Casanova-Schmitz et al., 1984). In rats depleted of glutathione, either by simultaneous exposure to acrolain (Lam et al., 1985) or by ip injection with phorone (2,6-dimethyl-2,5-heptadien-4-one) (Casanova & Heck, 1987) a significant increase in the yield of formaldehyde-induced DNA protein cross-links was observed, suggesting that the formaldehyde dehydrogenase-catalyzed oxidation of formaldehyde is an important defence mechanism against the covalent binding of formaldehyde with nucleic acids in the nasal respiratory mucosa.

DNA protein cross-links could not be detected in the bone marrow of rats exposed to formaldehyde through inhalation (Casanova-Schmitz et al., 1984; Casanova & Heck, 1987), suggesting that these are formed only at the site of entry. Minini (1985) found DNA protein cross-links in the stomach and beginning of the small intestine of rats that had been administered formaldehyde by gavage. These cross-links were detected only after the administration of a very high dose of formaldehyde (750 mg/kg, i.e., about 3/4 of the LD_{50}) (McGhee & von Hippel, 1975a,b).

8.7.2 Cytotoxicity and cell proliferation

Increased cell replication occurs as a result of the cytotoxic effects of formaldehyde on the nasal mucosa.

Morphological changes (acute degeneration, swelling, formation of "dense bodies", and vacuoles in epithelial cells) were described in the respiratory epithelium of rats after a single 6-h exposure to 18 mg formaldehyde/m^3 (Chang et al., 1983; Swenberg et al., 1983). When such exposure was repeated 3-5 times, ulceration was observed in the respiratory epithelium in most experimental animals. After a 9-day exposure, reparative hyperplasia and metaplasia were found. At 7.2 mg/m^3, hyperplasia and slight degenerative changes were still detected. In contrast, morphological changes could not be proved at 0.6 and 2.4 mg formaldehyde/m^3 (Starr & Gibson, 1985).

Further research clarified the dependence of cytotoxic effects on the concentration of formaldehyde and on the length of exposure. After exposing rats to 7.2 or 18 mg formaldehyde/m^3 (6 or 15 ppm) for 6 h per day over 3 days, the rate of incorporation of ^{3}H-thymidine into the DNA of the respiratory epithelium, 2 h after the end of the exposure, was increased by a factor of 20 or 10, respectively, indicating increased cell proliferation. On the other hand, no statistically significant increase in thymidine incorporation compared with that in the controls was found in rats after exposure to 0.6 or 2.4 mg/m^3 (0.5 or 2 ppm) and in mice after exposure to 0.6, 2.4, or 7.2 mg/m^3 (0.5, 2, or 6 ppm) for 6 h/day over 3 days. Exposure to formaldehyde at 18 mg/m^3 (15 ppm) led to thymidine incorporation being increased by a factor of 8, in mice (Swenberg et al., 1983).

Despite nearly equal doses (concentration x time), significantly increased effects were observed with exposure to 18 mg/m^3, (15 ppm) for 6 h/day, 5 days/week (= 448 mg/m^3 (540 ppm) x h/week) (Kerns et al., 1983) compared with exposure to 3.6 mg/m^3, for 22 h/day, 7 days/week (= 460 mg/m^3 (554 ppm) x h/week) (Rusch et al., 1983). This indicates that formaldehyde concentration is more important than the accumulated dose (Swenberg et al., 1985).

A slight increase in cell proliferation (^{3}H-thymidine labelling, 18 h after the end of exposure) was observed after a single 6-h inhalation exposure of rats to 0.6 or 2.4 mg formaldehyde/m^3 (0.5 or 2 ppm), but not after 3 or 9 such exposures carried out on consecutive days (Swenberg et al., 1985). In contrast, exposure to 7.2 mg/m^3 (6 ppm)

6 h/day for 1 or 3 days caused a marked increase in cell turnover, which did not normalize as it did after exposure to 0.6 or 2.4 mg/m^3 (0.5 or 2 ppm).

The results of recent inhalation studies have confirmed that the concentration rather than the dose determines the severity of the cytotoxic effects. In a 4-week study, Wilmer et al. (1987) showed that there were no appreciable differences in the type, degree, and incidence of nasal lesions between rats continuously exposed to 12 mg (10 ppm) formaldehyde/m^3 (66 mg/m^3 (80 ppm)/h per day) and those exposed intermittently to 12 mg/m^3 (10 ppm) (33 mg/m^3 (40 ppm)/h per day). Moreover, intermittent exposure of rats to 12 mg/m^3 (10 ppm) (33 mg/m^3 (40 ppm)/h per day) induced more severe nasal changes than continuous exposure to 6 mg/m^3 (also 48 mg/m^3 (40 ppm)/h per day). From a subsequent 13-week study (Wilmer et al., 1986), it appeared that hyperplasia and metaplasia of the nasal respiratory epithelium occurred in rats intermittently exposed to 4.8 mg/m^3 (13 mg/m^3 (16 ppm)/h per day) but did not occur in rats continuously exposed to 2.4 mg/m^3 (2 ppm) (also 13 mg/m^3 (16 ppm)/h per day). In a 28-month inhalation study, male rats with severely damaged (by electrocoagulation) or undamaged nasal mucosa were exposed to formaldehyde concentrations of up to 12 mg/m^3 (10 ppm); exposure to 12 mg/m^3 (10 ppm) resulted in a much higher incidence of nasal tumours in rats with a damaged mucosa (17/60) than in rats with an undamaged nose (1/29) (Feron et al., 1987).

Small ultrastructural changes were reported in the cell membrane of nasal ciliated epithelial cells of rats exposed to formaldehyde through inhalation (Monteiro-Riviere & Popp, 1986). Similar changes were also found in the controls, but the significance is unclear.

9. EFFECTS ON MAN

9.1 Sources of Exposure

The general population may be exposed to formaldehyde in tobacco smoke, automobile emissions, from materials used in buildings and home furnishings, in consumer and medicinal products, and in nature (section 3).

9.2 General Population Exposure

A large number of occupations are associated with formaldehyde exposure (Tables 4 and 34).

Table 34. Potential occupational exposure to formaldehyde[a]

Anatomists	Glass etchers
Agricultural workers	Glue and adhesive makers
Bakers	Hexamethylenetetramine makers
Beauticians	Hide preservers[b]
Biologists	Histology technicians (assumed to including necropsy and autopsy technicians)
Bookbinders	
Botanists	
Carpenters	Ink makers
Crease-resistant textile finishers	Lacquerers and lacquer makers
	Medical personnel (assumed to include pathologists)
Deodorant manufacturers	
Disinfectant manufacturers	Mirror makers
Disinfectors	Oil-well workers
Dress shop personnel	Paper makers[b]
Dressmakers	Particle board makers[b]
Drugmakers	Pentaerythritol makers
Dyemakers	Photographic film makers
Electrical insulation makers	Plastic workers
Embalmers	Resin makers
Embalming fluid makers	Rubber makers[c]
Ethylene glycol makers	Soil sterilizers and greenhouse workers
Fertilizer makers	
Fire-proofers	Surgeons
Formaldehyde resin makers	Tannery workers[b]
Formaldehyde employees	Taxidermists
Foundry employees	Textile mordanters and printers
Fumigators	Textile waterproofers
Fungicide workers	Varnish workers[b]
Furniture workers	Wood-based material workers
Fur processors[b]	Zoologists

[a] From: NIOSH (1976a).
[b] See IARC (1981).
[c] See IARC (1981).

The most predominant effects of formaldehyde exposure usually reported in human beings are various kinds of physical symptoms

emanating from the irritation of the mucosa in the eyes and upper airways as well as the sensitivity of the skin. Sensory reactions are apparently the most typical effects in the non-industrial indoor environment. Most human beings are exposed to low concentrations of formaldehyde (less than 0.06 mg/m^3) in the environment and sensory effects (odour and irritation) are by far the most common response; symptoms of hyperactivity in the lower respiratory tract may also be produced.

It should be realized that extrapolation from animal studies to estimate human response is dubious in most cases and, for some effects, impossible. Although some effects, e.g., skin reactions may be comparable between animals and human beings, other effects, such as pulmonary function reactions, are more questionable and others, such as sensory irritation, cannot be compared.

9.2.1 Sensory effects

The odour of formaldehyde is detected and/or recognized by most human beings at concentrations below 1.2 mg/m^3 (1 ppm) (Leonardos et al., 1969; Gemert & Nettenbreijer, 1977; Fazzalari, 1978; Brabec, 1981). The absolute odour threshold is defined as the concentration at which a group of observers can detect the odour in 50% of the presentations (from a series of concentrations) (WHO, 1987) and, for formaldehyde, it has been shown to be between 0.06 and 0.22 mg/m^3 (Feldman & Bonashkevskaya, 1971; Berglund et al., 1985, 1987; Ahlström et al., 1986). However, the individual odour detection thresholds cover a wide concentration range, over two powers of ten, and the distribution is extremely positively skewed. Berglund et al. (1987) showed that over a period of one year, the odour detection and odour strength reports for formaldehyde were consistent for a group of 10 observers. For a group of 50 observers, they also showed that the 50-percentile detection threshold for formaldehyde odour (ED_{50}, method of constant stimuli including blanks) was 180 µg/m^3 (145 ppb), the 10-percentile (ED_{10}) threshold was 25 µg/m^3 (20 ppb), and the 90-percentile (ED_{90}) threshold was 600 µg/m^3 (500 ppb).

If formaldehyde is mixed with contaminated indoor air from a "sick" building, an increase in the odour intensity of the stimulus mixture is found at formaldehyde concentrations of less than 0.25 mg/m^3 while, at higher concentrations, the odour strength remains largely unchanged (Ahlström et al., 1986). At high concentrations, formaldehyde has a distinct and pungent odour.

The difference between odour and irritation concentration may be noticeable, but there is no evidence that there is a threshold at which odour is superceded by irritation. However, for most inhaled odorous compounds, the trigeminal nerve has a higher threshold than the olfactory nerve (Moncrieff, 1955). When the formaldehyde concentration is increased and affects both the eyes and the nostrils, sensory irritation is first experienced in the eyes, then the odour is perceived, and finally nasal irritation occurs (Moncrieff, 1955).

In recent studies with short-term exposures, eye irritation was reported for formaldehyde from a level of 0.06 mg/m^3 and irritation of the respiratory tract, from 0.12 mg/m^3 (Niemelä & Vainio, 1981; NRC, 1981). Clinical and epidemiological data show substantial variations in individual irritant responses to formaldehyde. The sensory effects of formaldehyde determined for odour and sensory irritation are listed in Table 35. The table only lists the reports that have included information on reasonable experimental control. In evaluating the different studies, it should be noted that many of the reported elevated lower limit values for sensory irritation emanate from studies in which the observers were not exposed to very low concentrations of formaldehyde or clean air was not included as the control condition.

Anderson (1979) showed that eye, nose, and throat irritation were reported by 3 of 16 observers exposed for 5 h daily to 0.288 mg formaldehyde/m^3 and by 15 of 16 observers exposed to 0.96 mg/m^3 in an environment chamber. A direct relationship between concentration and sensory irritation was observed only above 0.96 mg/m^3 and only at the highest concentration, 1.92 mg/m^3, was slight discomfort experienced (18 on a scale of 100). Bender et al. (1983) evaluated eye irritation according to the time of detection of the first trace of irritation as well as according to subjective ranking of severity. Both time and severity appeared to be functions of formaldehyde concentration; severity of response was above "slight" only with the highest test concentration of 1.2 mg/m^3 (28 observers).

In a study by Cain et al. (1986), a group of 33 observers judged the perceived irritation and odour of formaldehyde during 29-min chamber exposures to concentrations ranging from 0.3 to 2.4 mg/m^3. The sensory irritation increased with time for the lower concentrations and decreased with time for the highest. This effect was true for irritation of eyes, nose, and throat and the sensitivity proved to be roughly equal for all three sites. The sensory irritant effect of formaldehyde at 1.2 mg/m^3 was shown to decrease when the chemical pyridine was injected into the chamber; such sensory interactions occur in environmentally realistic situations (see Ahlström et al., 1986). Apart from Cain et al. (1986), Weber-Tschopp et al. (1977) and Bender et al. (1983) have shown sensory adaptation to occur with longer exposure durations.

Weber-Tschopp et al. (1977) exposed healthy volunteers (24 men, 9 women) to formaldehyde concentrations ranging between 0.036 and 4.8 mg/m^3 air (33 volunteers for 35 min, 48 volunteers for 1.5 min). Eye blinking rates as well as subjective irritation effects were determined. The irritation threshold was found to range between 1.2 and 2.4 mg formaldehyde/m^3. A similar threshold (1 mg/m^3) was found in other studies (BGA, 1985). Triebig et al. (1980) noted that 9 out of 53 medical student volunteers exposed to formaldehyde concentrations of between 0.39 and 0.60 mg/m^3 for 8 h/week, over 8 weeks, complained of headaches, a burning sensation in the eyes, sore throat, and annoyance because of the smell.

Table 35. Sensory effects of formaldehyde on man

Type of exposure	Exp. control	Method	Site	Conc. range mg/m^3 (ppm)	(No. stimuli) conc. in air mg/m^3 (ppm)	Length of stimulus	No. volunteers (sex)	Irritant and odour detection (d) thresholds mg/m^3 (ppm)	Effect	Reference
30-m^3 chamber	-	Constant stimuli	Eye	0.04-4.8 (0.03-4)	(4) 0.04; 1.2; 2.4; 3.6; 4.8 (0.03; 1; 2; 3; 4)	1 1/2 min (short exposure)	35 (M) 13 (F)	1.2-2.4 (1-2 ppm)	Eye irritation	Weber-Tschopp et al. (1977)
30-m^3 chamber	-	Constant stimuli	Eye	0.04-4.8 (0.03-4)	(4) 0.04; 1.2; 2.4; 3.6; 4.8 (0.03; 1; 2; 3; 4)	37 min (long continuous exposure)	24 (M) 9 (F)	1.2-2.4 (1-2 ppm)	Eye irritation	Weber-Tschopp et al. (1977)
17-m^3 aluminium smog chamber equipped with 7 sets of eye ports	-	Constant stimuli	Eye	0.01-1.2 (0.01-1)	(5) 0; 0.4; 0.7; 0.8; 1.1; 1.2 (0; 0.35; 0.56; 0.7; 0.9; 1.0)	6 min	5-28	0.46-1.1 (0.38-0.9 ppm) 1.2 (1.0 ppm)	Slight eye irritation Severe eye irritation	Bender et al. (1983)
Chamber	23 ± 0.5 °C 50 ± 5% RH	Constant stimuli	Eye throat nose	0.3-2.0	(4) 0.3; 0.5; 1.0; 2.0	5 min	11 (M) 5 (F)	1.0	Eye, nose and throat irritation	Andersen & Mølhave (1983)
Exposure hood	22 ± 1 °C Pyridine as master stimulus	Limit with forced choice responses	nose	0.06-1.15	(7) 0.06; 0.10; 0.17; 0.28; 0.46; 0.77; 1.15	6 second	8 (M) 14 (F)	0.06 (50% d) 0.20 (100% d)	-	Ahlström et al. (1986)

Formaldehyde has been identified as one of the chemical components of photochemical smog. However, photochemical smog is a complex mixture of chemicals in which not all the components have been identified. Schuck et al. (1966) showed that eye irritation appeared at 0.012 mg formaldehyde/m^3, but the formaldehyde had been generated by irradiating ethylene or propylene-nitrogen dioxide mixtures. The authors noted that irritating components other than formaldehyde, such as peroyzlacyl nitrate, which is also a potent sensory irritant present in photochemical smog, may have been generated during irradiation. Since formaldehyde usually appears in complex mixtures in the human environment (automobile exhaust, photochemical smog, tobacco smoke, contaminated indoor air), it is evident that the mixture may cause sensory irritation at much lower formaldehyde concentrations than when formaldehyde is present alone. For example, Weber-Tschopp et al. (1976) showed that, during 29-min chamber exposures, formaldehyde concentrations of 0.3 mg/m^3 in a tobacco smoke environment resulted in moderate, strong, or very strong eye irritation.

It has been shown that sensory irritation is the earliest human reaction to formaldehyde, both in exposure studies and from complaints about indoor environments. An expert committee at the US National Academy of Sciences (NRC, 1980) calculated that less than 20% of an exposed human population would react to concentrations of less than 0.3 mg/m^3 with slight sensory irritation of the eyes, nose, and throat, and possibly also with a slight decrease in mucosal secretion/flow in the nose (Newell, 1983). Since differences in individual reactions to formaldehyde are large in both the normal population and in hyperreactive and sensitized persons, it is difficult to estimate a concentration guaranteed not to produce negative reactions in the general population.

9.2.2 Toxic effects

The clinical features of toxicity are weakness, headache, abdominal pain, vertigo, anaesthesia, anxiety, burning sensation in the nose and throat, thirst, clammy skin, central nervous system depression, coma, convulsions, cyanosis, diarrhoea, dizziness, dysphagia, irritation and necrosis of mucous membranes and gastrointestinal tract, vomiting, hoarseness, nausea, pallor, shock, and stupor. Respiratory system effects caused by high formaldehyde concentrations are pneumonia, dyspnoea, wheezing, laryngeal and pulmonary oedema, bronchospasm, coughing of frothy fluid, respiratory depression, obstructive tracheobronchitis, laryngeal spasm, and sensation of substernal pressure. Coagulation necrosis of the skin, dermatitis and hypersensitivity, lachrymation and corrosion of the eyes, double vision, and conjunctivitis can occur. Acute ingestion may cause renal injury, dysuria, anuria, pyuria, and haematuria, and lead to an increase in formate levels in the urine. Death is due to pulmonary oedema, respiratory failure, or circulatory collapse (Hallenbeck & Cunningham-Burns, 1985).

Kline (1925) reported 12 cases where ingestion of formaldehyde (a few drops to 89 ml of concentrated solution) led to death. The largest amount ingested from which a patient has recovered is 120 ml. A 60-year-old man swallowed 60-90 ml of a 40% formaldehyde solution. Thirty hours after death, the mucosa of the lower part of the oesophagus, stomach, and first portion of duodenum were dark chocolate brown in colour and of the consistency of leather. All organs and tissues in contact with the stomach were "hardened" to a depth of about 8 mm (Levison, 1904).

Allen et al. (1970) reported corrosive injuries of the stomach due to formaldehyde ingestion.

9.2.3 Respiratory effects

No cases of death from formaldehyde inhalation have been published. There are numerous reports that exposure to formaldehyde vapour causes direct irritation of the respiratory tract. However, precise thresholds have not been established for the irritant effects of inhaled formaldehyde but, within the range of 0.1-3.1 mg/m^3, most people experience irritation of the throat (Table 35).

The effects of formaldehyde on ciliary movement and mucociliary clearance were studied by Andersen & Mölhave (1983). They measured nasal mucociliary flow by external detection of the motion of a radiolabelled resin particle placed on the surface of the inferior turbinate. The nasal mucous flow rate in the nose decreased during exposure to formaldehyde, but the response did not increase at concentrations ranging from 0.5 mg/m^3 to 2 mg/m^3 or on prolongation of the exposure period from 3 h to 5 h.

The potential of formaldehyde to produce chronic respiratory tract disease was studied by Yefremov (1970). At a wood-processing plant, the incidence of chronic upper respiratory disease was higher in 278 workers exposed to formaldehyde than in 200 controls. However, formaldehyde concentrations were not measured, and possible confounders were not evaluated.

Forty-seven subjects exposed to formaldehyde (mean air concentration 0.45 mg/m^3) and 20 unexposed subjects, all of whom were employed at a carpentry shop, were studied by Alexandersson et al. (1982) with regard to symptoms and pulmonary function. Symptoms involving the eyes and throat as well as chest oppression were significantly more common in the exposed subjects than in the unexposed controls. Spirometry and simple breath nitrogen washout were normal on the Monday morning, before exposure to formaldehyde. A reduction in forced expiratory volume in 1 second by an average of 0.2 litres (P = 0.002), percent forced expiratory volume by 2% (P = 0.04), maximum mid-expiratory flow by 0.3 litre/second (P = 0.04) and an increase in closing volume in percentage of vital capacity by 3.4% (P = 0.002) were seen after a day of work and exposure to formaldehyde, suggesting bronchoconstriction. Smokers and nonsmokers displayed similar changes in spirometry and nitrogen washout.

Schoenberg & Mitchell (1975) performed standardized respiratory questionnaire and pulmonary function tests (FVD, FEV_1, MEF 50%) on 63 employees in an acrylic-wool filter department (40 production line workers, 8 former production line workers, and 15 employees who had never been on the production line). Formaldehyde levels in the work environment were between 0.5 and 1 mg/m^3, and phenol levels, between 7 and 10 mg/m^3; particles and fibres were not well suppressed. In spite of the high proportion (85%) of subjects reporting acute respiratory symptoms, only small and insignificant changes in pulmonary function were found.

Andersen & Mølhave (1983), in a study of 16 healthy volunteers in a chamber, could not find any increase in airway resistance or any effects on vital capacity and maximum expiratory flow volume from exposure to formaldehyde levels of up to 2.0 mg/m^3 in a 5-h study.

To study pulmonary function during and after exposure to formaldehyde, Schachter et al. (1986) exposed 15 non-smoking healthy volunteers (mean age, 25.4 years) in a double-blind random manner to 0 or 2.4 mg formaldehyde/m^3, for 40 min on one day and again on a second day but with the subjects performing moderate exercise (450 kpm/min) for 10 min. No significant bronchoconstriction was noted (FEV_1 test), and subjective complaints following such exposure were confined to irritative phenomena of the upper airways. Post-exposure symptoms (up to 24 h following exposure) were infrequent and confined to headache. Another study by the same group (Witek et al., 1986, 1987) on 15 healthy and 15 asthmatic volunteers resulted in similar findings.

Main & Hogan (1983) examined 21 subjects exposed to formaldehyde (0.14-1.9 mg/m^3) in a mobile home trailer. Eighteen unexposed controls were included. No differences in lung function were found between the 2 groups. However, there were significantly more complaints of eye and throat irritation, headache, and fatigue among the exposed.

In controlled studies, Day et al. (1984) exposed 18 volunteers to a formaldehyde concentration of 1.2 mg/m^3. Nine subjects had previously complained of various non-respiratory adverse effects from the urea formaldehyde foam insulation (UFFI) in their homes. Pulmonary function was assessed before and after exposure in a laboratory. Each subject was exposed, on separate occasions, to formaldehyde at 1.2 mg/m^3 in a environmental chamber for 90 min and to UFFI off-gas yielding a formaldehyde concentration of 1.4 mg/m^3 in a fume hood for 30 min. None of the measures of pulmonary function used showed any clinically or statistically significant responses to the exposure either immediately or 8 h after, commencement of exposure. There were no statistically significant differences between the responses of the group that had previously complained of adverse effects and of the groups that had not. There was no evidence that either formaldehyde or UFFI off-gas behaved as a lower airway allergen or important bronchospastic irritant in this heterogeneous population but, because of the small number of persons under study, it cannot be excluded.

Fifteen non-smoking volunteers (mean age, 25.1 years) who suffered from substantial bronchial hyperreactivity, were studied by Harving et

al. (1986). The mean provocation concentration of histamine producing a 20% decrease (PC_{20}) in peak expiratory flow rate was 0.37 g/litre (standard deviation (SD) = 0.36). All except one patient regularly required bronchodilator treatment. None used methylxanthines or corticosteroids. They were exposed to formaldehyde once a week for 3 consecutive weeks. The studies were carried out in a double-blind random fashion, under controlled conditions, in a climate chamber with particle-free air. All underwent the same 3 treatments, being exposed to mean formaldehyde concentrations of 0.85 mg/m^3 (SD = 0.07), 0.12 mg/m^3 (SD = 0.07), and zero. The mean exposure time at a steady-state concentration was 89.4 min (SD = 9.5). Bronchodilator drugs were withheld for 4 h before the studies. During the exposure, each participant rated his symptoms of asthma every 15 min on a visual analogue scale, and forced expiratory volume in one second was measured on a spirometer every 30 min.

Before and after exposure to formaldehyde, functional residual capacity and airways resistance were determined in a body plethysmograph, and flow-volume curves were measured. Immediately after exposure, a histamine challenge test was performed.

No significant changes in forced expiratory volume in one second, airways resistance, functional residual capacity flow-volume curves, or subjective ratings of symptoms of asthma were found in the group as a whole, or among the 9 participants with high histamine reactivity (PC_{20} < 0.50 mg/ml). Histamine challenge tests were highly reproducible and were unaffected by exposure to formaldehyde. No appreciable symptoms were reported after exposure.

Asthma-like symptoms have been elicited by irritant concentrations of formaldehyde. Precise thresholds have not been established for the irritant effects of inhaled formaldehyde. However, lower airway and pulmonary effects are likely to occur between 6 and 36 mg/m^3, independent of confirmed sensitization.

Several studies have addressed the problem of the mobile home situation, especially in Canada and the USA, without measurements of other confounders (section 9.2.8).

9.2.4. Dermal, respiratory tract, and systemic sensitization

Formaldehyde is a known sensitizer for the skin (DFG, 1987), but no thresholds for induction of dermal, respiratory tract, or systemic sensitization have been reliably determined.

9.2.4.1 Mucosal effects

Wilhelmsson & Holmström (1987) investigated possible mechanisms underlying nasal symptoms in 30 formaldehyde-exposed workers in a factory producing formaldehyde. The mean concentration of airborne formaldehyde was somewhat below 1 mg/m^3, but there were higher peak values. About 40% of the workers had rhinitis with nasal obstruction and discharge associated with the work place. The sera of the subjects

were analysed for IgE antibodies by RAST and 2 workers were found to be positive with a high level of IgE.

There is no evidence in the literature of allergic reactivity of the mucous membranes of the eyes being caused by airborne formaldehyde or by formaldehyde solutions. There are only a few case reports about asthmatic symptoms caused by formaldehyde.

9.2.4.2 Skin effects

Allergic sensitization is caused by formaldehyde in solution only, not by gaseous formaldehyde. Prolonged and repeated contact with liquid solutions can cause skin irritation or allergic contact dermatitis, including sensitization. It is not known whether dermal reactions occur in human beings from airborne exposure to formaldehyde.

Formaldehyde allergy may be associated with the use of disinfectants, formaldehyde-based plastics, and contact with textiles impregnated with formaldehyde-based resins. Patch-test studies with different concentrations of formaldehyde have shown that concentrations below 0.05% rarely elicit an allergic reaction, even in sensitive individuals (Schulz, 1983). Marzulli & Maibach (1973) reported that one of 5 sensitized volunteers reacted, under controlled conditions, to a challenge concentration of 0.01% formaldehyde.

Formaldehyde solution is a primary skin-sensitizing agent inducing allergic contact dermatitis (Type IV, T-cell mediated delayed hypersensitivity reaction); it may induce immunological contact urticaria (Type I, perhaps IgE mediated, immediate hypersensitivity reaction).

Patch tests performed with formaldehyde challenge concentrations of 1% or less resulted in positive reactions in about 2% of all patients tested throughout the world; higher formaldehyde challenge concentrations may be irritant (Anon., 1987).

There are geographical and demographical differences in the incidence of contact sensitivity to allergens. The Japanese Contact Dermatitis Research Group (1982) published a study dealing with the results of patch tests performed at 17 Japanese hospitals in 1981. A total of more than 900 patients and healthy volunteer subjects were patch-tested with 2% formaldehyde solution (10 mg formaldehyde/cm^2). This caused irritation in 2.78% and a delayed reaction in 2.62% of the patients.

An allergic contact dermatitis reaction was provoked by a dose of formaldehyde of 0.25 μg/cm^2 skin (challenge dose: 50 μg/cm^2 with 0.5% percutaneous penetration).

In the past, formaldehyde dermatitis provoked by clothing textiles was a problem in certain countries. Modern textile finishing agents contain *N*-methylol compounds with only low amounts of free formaldehyde, so that formaldehyde allergies due to textiles are no longer expected to occur (Bille, 1981; Edman & Möller, 1982).

Contact eczema caused by formaldehyde may clear within 1-3 weeks, even without treatment, when the cause has been recognized and contact is strictly avoided.

Allergic reactions to cosmetics containing formaldehyde as a preservative, especially shampoos, are unusual (Eckardt, 1966) and appear mostly among those who have been sensitized by occupational exposure.

In a haemodialysis unit where formalin was used as a sterilant, 6 out of 13 staff members developed dermatitis within 3 weeks (Sneddon, 1968); 4 of the 6 were positive in patch tests with 3% formalin.

9.2.4.3 Respiratory tract sensitization

Well-controlled scientific studies on allergic airway responses to formaldehyde are few.

Nordman et al. (1985) gave a total of 230 patients, who suffered from "asthma like" respiratory symptoms, a bronchial provocation test with formaldehyde. On the basis of the medical and occupational histories of the patients, the specific bronchial provocation test and other tests results, 12 cases were considered to be caused by specific sensitization to formaldehyde.

Burge et al. (1985) reported tests on 15 formaldehyde-exposed workers with symptoms suggesting occupation-related asthma. Bronchial provocation tests with a mean formaldehyde concentration of 4.8 mg/m^3 (range not given) showed 3 subjects with delayed bronchiospasm and 6 with an immediate reduction in forced expiratory volume in one second (FEV_1).

In a similar study on 13 patients with asthma suspected of being related to formaldehyde exposure, no significant drop in FEV was seen when bronchial provocation tests with formaldehyde concentrations of up to 3.6 mg/m^3 were carried out. Five of the subjects were on bronchodilator treatment at the time (Frigas et al., 1984).

Eight cases of occupational asthma (3 smokers, 5 non-smokers) were reported among 28 members of the nursing staff at a haemodialysis unit where formalin was used to sterilize the artificial kidney machine (Hendrick & Lane, 1977). In 2 out of 5 subjects with histories of recurrent attacks of wheezing, inhalation provocation tests led to asthmatic attacks similar to those at work.

Hendrick et al. (1982) reinvestigated the nurses of the haemodialysis unit. One nurse had not worked with formaldehyde since 1976 and had had no further symptoms. Her 1981 test (15-min exposure to 7.2 mg formaldehyde/m^3) did not provoke any asthmatic response. The other nurse had continued to work with formaldehyde, though under much improved conditions, and had continued to suffer mild intermittent attacks of asthma. Her test (5-min exposure to 3.6 mg formaldehyde/m^3) provoked a late asthmatic reaction similar to the one observed in 1975.

9.2.4.4 Systemic sensitization

A case report has been described involving an anaphylactic shock reaction after accidental iv application of formaldehyde during haemodialysis treatment due to formaldehyde remaining in the equipment after disinfection. No measurements of the residual formaldehyde in

the reconditioned dialyser were given. There was no personal or family history of atopy. Prick tests and radioallergosorbent tests (RAST) with common food and inhalant allergens were negative. Prick tests performed with 0.1 and 1% formaldehyde were positive in the patient, whereas they were negative in control subjects. The RAST with formaldehyde was performed using discs specially prepared and coated with serum-albumin. RAST was strongly positive. RAST to ethylene oxide was negative. A patch test with formaldehyde (concentration 1%) was performed and induced an anaphylactic shock, 26 h after the skin application of formaldehyde. The patient did not present any anaphylactic symptoms with the use of non-reconditioned dialysers. An immediate-type allergy to formaldehyde mediated by IgE may have occurred in this patient (Maurice et al., 1986). Because, after 26 h, the patch test resulted in an anaphylactic, but not delayed allergic contact dermatitis, reaction, the findings seem to be contradictory.

Wilhelmsson & Holmström (1987) investigated possible mechanisms underlying nasal symptoms in 30 formaldehyde workers exposed through inhalation in a formaldehyde-producing factory. Two cases showed a positive RAST with formaldehyde with high total IgE values (177 and 360 kU/litre). One of them suffered from severe rhinitis, the other from nasal and skin symptoms associated with the work place. A skin test with formaldehyde was negative at 15 min but positive at 72 h.

Systemic sensitization arising from the release of formaldehyde into the circulation in chronic haemodialysis patients showed evidence of formaldehyde-dependent immunization. The production of auto-anti-nuclear-like antibodies was dependent on the length (years) of the haemodialysis treatment (Lynen et al., 1983) and on the formaldehyde concentration released from the dialysers (Lewis, 1981).

Auto-anti-nuclear-like antibodies were found in 5 out of 18 patients after 1 year of dialysis; 10 out of 12 patients after 3-5 years, and in all 9 patients exposed to formaldehyde through dialysis for more than 5 years (Lynen et al., 1983).

Auto-anti-nuclear-like antibodies were observed in 30% of the patients when the formaldehyde concentration in the rinse of the dialysers was 8 mg/litre (8 ppm); however, the incidence was zero at a concentration of 0.6-1.2 mg/litre (Lewis et al., 1981).

The presence of auto-anti-nuclear-like antibodies and autoimmune haemolytic anaemia are evidence of Type II autoallergy. Some severe asthmatic reactions suggest Type I allergy in dialysis patients.

Pross et al. (1987), using a wide range of immunological tests, studied the effects of controlled short exposures to formaldehyde. They found a minimal increase in the percent eosinophils, basophils, and T8 positive cells and a reduction in the response of natural killer cells to low-dose human α-Interferon. According to the authors, the meaning of these minimal, but statistically significant, changes remains unclear.

The antigenicity of formaldehyde-treated proteins were reported 70 years ago by Landsteiner & Lample (1917). A study by Patterson et al. (1986) demonstrated that sera of human beings exposed to

intravenous formaldehyde during dialysis, contained antibodies of various immunoglobulin classes against formaldehyde-serum-albumin, as did sera of two dialysis nurses with histories of formaldehyde-induced asthma.

9.2.4.4.1 Allergic reaction following the dental use of paraformaldehyde

Adverse reactions have been reported following the use of root canal filling materials containing paraformaldehyde. The extrusion of a root canal sealant containing paraformaldehyde beyond the apex may be followed by an allergic reaction in sensitive individuals. The number of cases is very small in relation to the extensive use of such materials. However, 3 cases of allergic angiooedema in response to periapical paraformaldehyde have recently been reported (UK-CSM, 1987).

9.2.5 Skin Irritation

Primary toxic or irritative skin reactions occur through direct contact with formaldehyde solutions.

The concentration of aqueous formaldehyde solution causing irritant contact reactions after application on human skin has not been confirmed. For human skin, a single application of 1% formalin in water with occlusion will produce an irritant response in approximately 5% of the population (Maibach, 1983).

Cosmetics containing a formaldehyde concentration of 0.2% as a preservative and nail hardeners containing at least 5% formaldehyde did not provoke toxic or irritative contact reactions on normal skin.

Other reactions may occur in cases of previously damaged skin surfaces and/or atopic individuals.

There are observations but no published experimental or clinical findings confirming the induction of irritant contact dermatitis by gaseous formaldehyde (Axelson, 1987, Personal Communication).

9.2.6 Genotoxic effects

Studies on pathology staff, occupationally exposed to formaldehyde, failed to demonstrate any increase in the incidence of chromosomal aberrations or the frequency of sister chromatid exchanges (Thomson et al., 1984). Similarly, there were no increases in the incidence of chromosomal aberrations in workers exposed to formaldehyde during its manufacture and processing (Fleig et al., 1982), or in the incidence of sister chromatid exchanges in workers exposed to formaldehyde in a paper factory (Bauchinger & Schmid, 1985).

Yager et al. (1986) reported an increased incidence of sister chromatid exchanges in anatomy students, but the values reported fell within the normal range. Furthermore, the authors reported that the subjects were in a "stress situation" at the time of the study and

were also exposed to other agents, including phenol. Bauchinger & Schmid (1985) reported an increased incidence of chromosomal aberrations in a study of workers in a paper factory who were exposed to formaldehyde; the statistical methods used and the relevance of the types of aberrations found have been questioned (Engelhardt et al., 1987).

No increase was found in the mutagenicity of urine of autopsy workers exposed to formaldehyde (Corren et al., 1985). Ward et al. (1984) did not observe any effects on sperm morphology or sperm count attributable to formaldehyde.

Goh & Cestero (1979) studied chromosomal patterns of direct bone marrow preparations from 40 patients undergoing maintenance haemodialysis. Aneuploidies, chromosomal structure abnormalities, and chromosomal breaks were seen in the metaphase. During the period of this study, each patient could have received up to 126 ± 50 mg of formaldehyde during each dialysis.

9.2.7 Effects on reproduction

Shumilina (1975) reported an increased incidence of menstrual disorders, mainly dysmenorrhoea, and problems with pregnancy in 446 women workers using urea-formaldehyde resins (130 exposed to work-place formaldehyde concentrations of 1.4-4.3 mg/m^3 and 316 exposed to concentrations of 0.005-0.67 mg/m^3). There were no differences in fertility between the exposed and control group, but anaemia, toxaemia, and low birth weight of offspring were more frequent in the exposed group. However, possible confounding factors were not evaluated in this study. There is a lack of information on the workers' environment and the socioeconomic conditions of the study and control groups.

Hemminki et al. (1982, 1983) studied spontaneous abortions among hospital staff engaged in sterilizing instruments with chemical agents. They reported that there was no increase in spontaneous abortions associated with the use of formaldehyde.

In a population of hospital autopsy service workers, 11 exposed individuals and 11 matched controls were evaluated for sperm count, abnormal sperm morphology, and 2F-body frequency (Ward et al., 1984). Subjects were matched for age, and use of alcohol, tobacco, and marijuana. Additional information was collected on health, medication, and other exposures to toxic substances. Ten subjects were employed for 4.3 months (range: 1-11 months) prior to the first sample, and one was employed for several years. Formaldehyde exposures were episodic, but with a time-weighted average of between 0.73 and 1.58 mg/m^3 (weekly exposure range, 3.6-48 mg/m^3 per h). Samples were taken from exposed and control subjects 3 times at 2- to 3-month intervals. No statistically significant differences in the variables were observed between the exposed and control groups. Reduced sperm count was correlated with increased abnormal morphology and 2F-body frequency in the exposed group but not in the control group. Evaluation of the impact of incidental exposures suggests a reduced count with marijuana use and

increased abnormal morphology with medications used by controls. No effects on sperm due to formaldehyde or its metabolites were observed in this occupationally-exposed population. However, it was considered that the lack of an effect in this study might be due to a lack of statistical power to detect effects at this exposure level.

9.2.8 Other observations in exposed populations

Dally et al. (1981) measured formaldehyde in the air of 100 homes, containing particle board or urea-formaldehyde foam insulation, in which residents reported symptoms of eye, nose, and throat irritation. They found levels ranging from < 0.12 to 4.42 mg/m^3 (< 0.1 ppm to 3.68 ppm) and concluded that indoor environmental exposure to formaldehyde may exceed occupational exposure levels. Sardinas et al. (1979) studied individuals from 68 households in which 167 complaints related to urea-formaldehyde insulation were being investigated. Twice as many individuals reported eye irritation in homes in which formaldehyde was detected by Draeger tubes (0.5–10 µg/litre) compared with the number in homes in which there was no detectable formaldehyde.

In a study by Woodbury & Zenz (1983), 20 symptomatic infants were followed up, whose mobile home environment was suspected to be related to their illness. The authors noted a relationship between the occurrence of symptoms and the time spent at home. However, no statistically significant association was found between symptoms and air levels of formaldehyde.

All three studies suffer from possible selection bias, the absence of appropriate controls, and no mention of whether other chemical exposures and smoking habits were considered.

In a pilot study, Schenker et al. (1982) studied the health of 24 full-time residents from 6 homes containing urea-formaldehyde foam insulation. The results of standardized allergy skin tests and spirometry tests were normal in all subjects. Memory difficulty was a frequently reported symptom. Memory storage deficits could not be demonstrated, but the results of tests of attention span were abnormal in 11/14 subjects; furthermore, 8 out of the 11 subjects suffered from elevated depression scores. The sample size in this pilot study was small (adults: 9 males, 9 females; children: 2 males, 4 females) and may have been biased by self-referrals; there was no control group.

The Consensus Workshop on Formaldehyde (1984) reviewed several reports linking long-term formaldehyde exposure to a range of psychological or behavioural problems (depression, irritability, memory loss, decreased attentional capacity, sleep disturbances). Most of the studies used subjective self-report symptom inventories. Control data, describing the incidence of such symptoms from unexposed persons are often inadequate or completely absent. Olson & Dossing (1982) administered a standardized questionnaire based on the linear analogue self-assessment method to 70 employees (66 responded) at 7 mobile day-care centres, in which urea-formaldehyde glued particle boards had been used, and to 34 (26 responded) employees at 3 control institutions,

selected at random, which did not contain any particle boards. Mean concentrations of formaldehyde were 0.43 and 0.08 mg/m^3, respectively. Among the staff at the mobile day-care centres, there was a significantly greater prevalence and intensity of symptoms of mucous membrane irritation, headache, abnormal tiredness, menstrual irregularities, and use of analgesics, but there were no differences in terms of memory disturbance and concentration (50% of the cohort were smokers).

Two groups of male workers exposed to formaldehyde (group 1 employed in the phenol-formaldehyde-plastic foam matrix embedding of fibreglass (batt making); group 2, in the fixation of tissues for histology) were studied by Kilburn et al. (1985) for work-related neurobehavioural, respiratory, and dermatological symptoms, and for pulmonary function impairment. Forty-five male fibreglass batt makers were studied during the initial work shift after a holiday, with regard to combined neurobehavioural (impact on sleep, memory, equilibrium, and mood), respiratory, and dermatological symptoms. Average frequencies of 17.8 (for the hot areas of the process) and 14.6 (for the cold areas) were found. Their symptom counts were significantly higher than those for 18 male histology technicians (average 7.3), and those for 26 unexposed male hospital workers (average 4.8).

The fibreglass batt makers were also exposed to numerous other products, such as phenol, surfactants, particulate smoke, glass fibre, etc. The formaldehyde work-place concentrations were not measured. No consideration was given to potential respondent bias in symptoms or exposures or to the socioeconomic differences between the workers and the technicians.

9.2.9 Carcinogenic effects

The evaluation of the risks for human health from occupational or environmental agents relies heavily on the evidence gleaned from epidemiological studies. It is, therefore, important to emphasize the procedures that should be adopted, in order to assess the value of such epidemiological investigations, particularly with reference to the shortcomings inherent in the epidemiological method.

For practical purpose, three types of study are in common use: The cohort, the case-control, and the correlation (surveillance) study. Cohort and case-control studies relate individual exposure to the agent under study with the occurrence of a health effect (in this case, cancer) in individuals, and provide an estimate of relative risk as the main measure of association. Cohort studies, which follow populations prospectively, are inherently less subject to bias than the more commonly used retrospective (historical) cohort studies as the data on health outcome are not acquired from past records. However, because retrospective cohort studies cannot be based on a well defined population, it is possible to use proportionate mortality (or morbidity) studies which give, by definition, less precise estimates of risk. Case-control studies always rely on retrospective exposure assessments

and although such studies are usually easier to execute than cohort studies, they are sensitive to various types of bias that are difficult to eliminate. Correlation (surveillance) studies use whole populations according to geographical area or time period as the initial data base and health outcome (cause-specific deaths or cancer incidence) is related to a summary measure of the population exposure. Individual exposure is not documented, thus causal relationships are difficult to infer from the results.

All epidemiological studies are subject to some extent to factors that can affect their quality with, as a general rule, cohort studies being superior to case-control studies. Four factors are particularly important: bias, confounding, chance, and qualitative measures of exposure and outcome. Bias means the operation of factors in the design or execution of the study that can lead to erroneous associations between the exposure and the health outcome, because of a failure to estimate these factors independently. Confounding refers to a situation in which the relationship between the exposure and the health outcome is altered by one or more factors that separately and independently influence the outcome. The likelihood that the results of the study could have occurred by chance is estimated by using appropriate statistical analyses. Finally, the accuracy and completeness of the information gathered on exposure and health outcome needs to be reviewed. Cancer is a relatively easy outcome to document but epidemiological studies are often seriously deficient in their assessments of exposure to the agent of interest, i.e., the degree, the duration, and even the misclassification of exposure of individual members of the study population.

Thus, epidemiological studies need to be evaluated, not only for their results, but also for the way in which the investigators have addressed the methodological problem outlined above. Sufficient information should be available in the study reports to make these value judgements.

Thereafter, the reviewer is frequently confronted with a series of studies from which to make an evaluation. Causality, that is the contention that the agent in question causes the disease in question, depends on a number of considerations. The most important are: the size of the relative risk estimate (coupled with a relatively narrow confidence interval), the observation of a putative relationship between agent and disease in a number of studies using similar or different designs in different populations; evidence that the agent acts on specific organ systems which are biologically plausible; and, finally, that the effect of the agent has been assessed in studies covering an observation period long enough to allow for the latent period and the period of induction of disease. In cancer studies, this may require an observation period of several decades for each study member.

In short, the evaluation of epidemiological studies initially requires value judgements regarding the quality of the design and execution of the study. Thereafter an assessment is needed of groups of studies to estimate the likelihood or otherwise that the relation-

ship between the exposure and the disease is causal. Such evaluation procedures have been adopted here for formaldehyde and human cancer.

Observed and expected deaths for professional and industrial workers exposed to formaldehyde are summarized in Table 36. The occupations studied consisted of professionals who use formaldehyde in the preservation of biological tissues (embalmers, anatomists, pathologists, and zoologists), and industrial workers involved in the production and use of formaldehyde. The pattern and intensity of exposure to formaldehyde differed for both groups.

Table 36. Observed and expected deaths for professional and industrial workers exposed to formaldehyde (with 95% confidence limits)[a]

Cause	*Professional*		*Industrial*	
	Observed/ expected	Confidence limits	Observed/ expected	Confidence limits
Cancer				
Nasal	0/1.7	0-2.17	0/1.3	0-2.84
Mouth	20/23.8	0.51-1.30	12/9.2	0.67-2.28
Brain	40/22.6	1.26-2.41	6/13.2	0.17-0.99
Lymphatic and haematopoietic	80/64.0	0.98-1.53	25/30.6	0.53-1.21
Leukaemia	40/27.2	1.05-2.00	9/11.4	0.36-1.50
Other lymphatic and haematopoietic	40/36.8	0.78-1.48	16/19.2	0.48-1.35
Lung	175/243.6	0.62-0.83	214/227.3	0.82-1.08
Prostate	61/51.6	0.90-1.52	2/0.6	0.40-12.04
Skin	12/11.4	0.54-1.84	0/0.4	0-9.22
Bladder	23/24.3	0.60-1.42	1/0.3	0.18-18.6
Kidney	21/18.6	0.70-1.73	1/0.4	0.06-13.93
Digestive system	211/245.2	0.74-0.98	8/10.4	0.33-1.52
Other causes				
Cirrhosis of liver	83/59.3	1.11-1.74	10/9	0.53-2.04
Non-neoplastic respiratory disease	109/163.7	0.55-0.80	243/241.1	0.88-1.14

[a] From: Consensus Workshop on Formaldehyde (1984).

A summary of epidemiological studies with formaldehyde is presented in Tables 37, 38, and 39. An excess of several forms of cancer, i.e., Hodgkin's disease, leukaemia, cancers of the buccal cavity and pharynx, lung, nose, prostate, bladder, brain, colon, skin and kidney, has been seen in more than one of the epidemiological studies relating to formaldehyde. Some of these excesses may be due to random variation and others may depend on factors other than formaldehyde exposure. Such explanations might be suggested, especially when only a few cases are involved or when the risk ratios are low. Some studies involve the same populations and therefore do not provide completely independent information (Marsh, 1983; Wong, 1983; Liebling et al., 1984).

In view of the solubility and rapid metabolism of formaldehyde (section 6.3), it seems that (upper) respiratory tract cancers would be more likely to be causally related to formaldehyde exposure than other forms of cancer. Besides various types of occupational exposure,

Table 37. Summary of epidemiological proportional mortality rate (PMR) studies with formaldehyde[a]

Author(s) (Year)	Study population	Study period	Site	Risk estimates (PMR)	Decedents	Control Tobacco
Marsh (1982)	chemical workers (USA)	1950-76			136	no
			respiratory system	80		
			digestive system	127		
			genital system	121		
			lymphatic system	86		
Walrath & Fraumeni (1983)	male embalmers (New York)	1925-80			1010	no
			buccal and pharyngeal	126		
			nasopharynx	-		
			respiratory	102		
			nasal	-		
			prostate	89		
			bladder	92		
			brain	157		
			leukaemia	132		
			colon	140		
			skin	253		
			Hodgkins	-		
			kidney	170		
			lymphatic and haemato-poietic	115		

Table 37 (contd).

Author(s) (Year)	Study population	Study period	Site	Risk estimates (PMR)	Decedents	Control Tobacco
Walrath & Fraumeni (1984)	embalmers (California)	1925-80			1007	no
			buccal	131		
			respiratory	94		
			nasal	-		
			prostate	175		
			brain & CNS	194		
			leukaemia	175		
			colon	187		
			skin	59		
			Hodgkins	-		
			bladder	138		
			kidney	100		
			rectum	102		
			gallbladder and liver	85		
			pancreas	135		
			stomach	79		
Stayner et al, (1985)	garment workers	1959-82			256	no
			buccal	229		
			nasal Pha.	-		
			digestive	126		
			gallbladder and liver	313		
			lung	95		
			skin	179		
			bladder and kidney	92		
			lymphatic	163		
			leukaemia	168		

[a] Exposure characteristics described.

Table 38. Summary of epidemiological case-control studies with formaldehyde

Author(s) (Year)	Study population	Study period	Type of exposure	Cases	Controls	Site	Risk	Comments
Jensen et al. (1982)	physicians	1943-76	speciality	84	252	lung	1.0	-
							Odds Ratio	
Fayerweather et al. (1983)[a,b]	chemical workers	1957-79	levels and duration	481	481	multiple		-
						buccal cavity	1.0	
						oesophagus	0.5	
						stomach	1.0	
						liver, gall-bladder,	0.9	
						lung	0.8	
Coggon et al. (1984)[c]	workers (United Kingdom)	1975-79	occupational	296	472	bronchus	1.5	r.r. 0.9 in higher exposure
		1975-79	occupational	132	268	bladder	1.0	r.r. 1.5 in higher exposure
Olsen et al. (1984)	workers (Denmark)	1970-82	exposure assessed	754	2465	nasal	2.8	o.r. 1.8 for exposure to wood dust men
						nasopharynx	0.7	
Partanen et al. (1985)[a]	wood workers	1957-80	levels and duration	57	171	respiratory	1.3	no exposure-response relationship
Bond et al. (1986)[a]	chemical workers	1940-80	ever exposed	308	588	lung	0.6	dose-response relationship
Hayes et al. (1986)[a]	wood workers (Netherlands)	1978-81	levels	91	195	nose and nasal sinuses	2.5	low wood-dust exposure
							1.9	high wood-dust exposure

Table 38 (contd).

Author(s) (Year)	Study population	Study period	Type of exposure	Cases	Controls	Site	Risk	Comments
Vaughan et al. (1986a)[a]	Tumour registry	1979-83	occupational	285	552	nasopharynx nasopharynx buccal cavity buccal cavity	1.4 2.1 0.6 1.3	for high exposure 20+ years for high exposure 20+ years
							Odds Ratio	
Vaughan et al. (1986b)[a]	Tumour registry	1979-83	residential	285	552	nasopharynx nasal cavity buccal cavity	5.5 0.6 0.8	10+ years mobile home
Brinton et al. (1984)[a]	industrial workers	1970-80	occupational	160	290	nasal cavity	0.4	-
Olsen & Asnaes (1986)	Tumour registry Denmark	1970-82	occupational	759	2465	nasal cavity nasopharynx	2.3 2.2	squamous cell carcinoma only; wood dust adencarcinoma looked for but not found
Roush et al. (1985)	Tumour registry	1940-81	occupational	371	605	nasopharynx nasal cavity	1.1 0.8	
Hardell et al. (1982)[a]	Tumour registry Sweden	1970-79	occupational	44	541	nasal	6.1	r.r. calculation based on 2 exposed out of 44 nasal cancers versus 4 out of 541 controls

[a] Study controlled for tobacco use.
[b] Selection criteria < 20 years after first exposure.
[c] Selection criteria male < 40 years.

Table 39. Summary of epidemiological cohort studies with formaldehyde[a]

Author(s) (Year)	Study population	Study period	Site	Risk estimates (SMR)	Study population	Type of exposure	Comments
Acheson et al. (1984)	chemical workers	1941-81			7680	levels and duration	a) lung cancer increased with level of exposure in one factory
			bucco-pharyngeal	109			
			nasopharynx	-			
			lung	95			
			nasal	-			b) lung cancer not increased with cumulative exposure
			digestive	101			
			larynx	88			
Harrington & Oakes (1984)	male pathologists	1974-80			2307	none	all brain cancers were gliomas
			digestive	20			
			lung	41			
			bladder	107			
			brain, CNS	331			
			lymphatics	54			
			leukaemia	90			
Levine et al. (1984)	embalmers, (Canada)	1950-77			1477	none	all brain cancers were gliomas
			bucco-pharyngeal	48			
			lung	94			
			prostate	88			
			urinary organs	54			
			brain, CNS	115			
			colorectal	85			
			leukaemia	160			
			lymphatic	124			
			digestive	75			

Table 39 (contd).

Author(s) (Year)	Study population	Study period	Site	Risk estimates (SMR)	Study population	Type of exposure	Comments
Stroup et al. (1986)	anatomists	1925-79			2317	duration special	brain cancers were gliomas and increased with duration of employment
			bucco-pharyngeal	15			
			nasopharynx	-			
			lung	28			
			nasal	-			
			prostate	100			
			bladder	68			
			brain, CNS	270			
			leukaemia	147			
			colon	108			
			lymphatic	123			
Blair et al. (1986)	industrial workers	1934-80			26 561	levels, duration, and peaks	exposure-response relationship for prostate and Hodgkin's disease
			buccal cavity	96			
			nasopharynx	300			
			lung, pleura	111			
			nasal cavity	91			
			prostate	115			
			bladder	96			
			kidney	123			
			brain	81			
			leukaemia	80			
			colon	87			
			skin	80			
			Hodgkin's	142			
Blair et al. (1987)	industrial workers	1930-80			26 561	none	dose-response relationship for those also exposed to particulates
			nasopharynx	384			
			oropharynx	167			

Table 39 (contd).

Bertazzi et al. (1986)	resin workers	1959-80			1332	
			bucco-pharyngeal	-		
			digestive	156		
			oesophagus	-		
			stomach	148		
			lung	236		
			lymphatic	201		
Edling et al. (1987)	abrasive manufacturers	1958-83			521	no correlation with exposure
			bucco-pharyngeal	-		
			nasopharynx	-		
			stomach	80		
			colon	100		
			pancreas	180		
			lung	57		
			prostate	85		
			lymphatic	200		
Stayner et al. (1988)	textile workers	1953-77			11 030	
			buccal cavity	343		
			digestive system	58		
			lung	114		
			bladder	112		
			kidney	55		
			brain	71		
			lymphatic system	91		
			leukaemia	114		

[a] There are no cohort studies with control of tobacco use.

smoking and other use of tobacco would have to be considered with regard to potential confounding factors, especially when exerting strong effects, such as those of tobacco smoking in relation to lung cancer. Furthermore, because of the formaldehyde contents of mainstream and side-stream smoke, there would be a potential increase in any reference population, and this would mask the effects of formaldehyde with regard to cancers that might be related to occupational or other specified exposure to formaldehyde. Finally, it should be noted, within this general epidemiological context, that there is experimental evidence providing a relatively clear suggestion of a possible cancer risk for human beings from exposure to formaldehyde.

Excess of nasal or nasopharyngeal cancer in relation to formaldehyde exposure was reported in 6 of the case-control studies reviewed (Table 38) (Hardell, 1982; Olsen et al., 1984; Roush et al., 1985; Hayes et al., 1986; Vaughan et al., 1986a,b). In 2 other case-control studies (Fayerweather et al., 1983; Brinton et al., 1984), the question of a relationship with formaldehyde was addressed either by primary design or by reporting formaldehyde exposure for either cases or controls, but no excess risk was demonstrated. None of the cohort or PMR studies listed in Tables 37 and 39 had adequate power to detect even a considerably increased risk though, in aggregate, the studies might have had the power to reveal, at least, a higher risk for nasal cancer. It should also be noted that with regard to nasal and nasopharyngeal cancer, smoking is not likely to exert any particularly strong confounding effect, since the relation of these cancer types to smoking is only moderately strong, i.e., up to a risk ratio of about five (Axelson & Sundell, 1978; IARC 1986) and has been lower in many studies.

Cancers of the buccal cavity and pharynx have either not been included in studies or in some case-control studies the risk has appeared about normal (Fayerweather et al., 1983; Vaughan et al., 1986a,b). There was no excess in the largest cohort (Blair et al., 1986), though an excess appeared in other studies involving small numbers (Stayner et al., 1985, 1988; Walrath & Fraumeni, 1983, 1984).

Some excess of respiratory cancer has appeared in 3 case-control studies in comparison with low exposures in general (Coggon et al., 1984) or comparable unexposed workers (Partanen et al., 1985) and between physicians in surgery and internal medicine, though these findings were based on small numbers (Jensen et al., 1982). Two other studies have come out as non-positive (Fayerweather et al., 1983; Bond et al., 1986). Of these cohort and PMR studies, which had adequate power and were designed to elucidate the risk of respiratory cancer from formaldehyde, 3 (Walrath, 1983; Bertazzi et al., 1986; Blair et al., 1986) showed an excess (significantly high in the study by Bertazzi et al., 1986). Blair et al. (1986) showed some excess in laryngeal cancer (Table 40). Seven studies with reasonable power were negative (Harrington & Oakes, 1984; Stroup et al., 1984, 1986) or non-positive with regard to respiratory cancer (Marsh, 1983; Acheson et al., 1984; Levine et al., 1984; Walrath & Fraumeni, 1984; Stayner et

Table 40. Mortality from subsites of cancer of the buccal cavity and pharynx through cumulative exposure to formaldehyde[a]

Cancer	Mortality after formaldehyde exposure at:											
	0 mg/m^3-years			< 0.6 mg/m^3-years			0.6 - 6.6 mg/m^3-years			> 6.6 mg/m^3-years		
	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR	Observed	Expected	SMR
Lip	0	0.1	-[b]	1	0.2	477	0	0.2	-[b]	1	0.1	764
Tongue	0	0.5	-[b]	0	1.8	-[b]	2	2.1	96	0	1.3	-[b]
Salivary glands	0	0.2	-[b]	0	0.5	-[b]	0	0.6	-[b]	0	0.3	-[b]
Gum, floor, other mouth sites	0	0.4	-[b]	1	1.5	66	0	1.8	-[b]	1	1.1	88
Nasopharynx	1	0.2	530	2	0.7	271	2	0.8	256	2	0.5	433
Oropharynx	0	0.3	-[b]	4	0.9	443[c]	1	1.0	95	0	0.7	-[b]
Hypopharynx	1	0.2	594	1	0.6	172	0	0.7	-[b]	0	0.4	-[b]
Other parts of pharynx	0	0.4	-[b]	1	1.4	73	0	1.6	-[b]	0	1.0	-[b]

[a] From: Blair et al. (1986).
[b] No deaths.
[c] $P < 0.05$.

al., 1985, 1988). The deviations in both directions from the expected in these studies are explainable by the lack of control for smoking and/or the so-called "healthy worker effect", which means that the study population is not comparable with the general population.

Leukaemia has come out somewhat high in all the studies involving reasonable numbers of cases (Stroup et al., 1984, 1986; Walrath & Fraumeni, 1983) and even significantly high in one study (Walrath & Fraumeni, 1984). Three of these studies involved either embalmers (Walrath & Fraumeni, 1983, 1984) or anatomists (Stroup et al., 1984, 1986), which might suggest some other alternative or contributing etiological factor operating. Similarly, for brain cancer, which was found in significant excess in some studies (Harrington & Oakes, 1984; Stroup et al., 1984, 1986; Walrath & Fraumeni, 1984), a confounding factor may be suspected regarding the relationship between brain cancer and social class (Table 41). An excess of colon cancer among embalmers (Walrath & Fraumeni, 1983, 1984; Stroup et al., 1984, 1986) may perhaps be explained by a recently observed association with sedentary work (Garabrant et al., 1984; Gerhardsson et al., 1986). Of the other cancer forms previously mentioned as appearing in excess in more than one study, cancers of the skin, bladder, kidney, and prostate, as well as Hodgkin's disease are represented by small numbers and/or small excesses, though prostatic cancer was significantly high in one study on embalmers, based on 23 cases (Walrath & Fraumeni, 1984) and skin, but not prostatic cancer was significantly high in the other study on embalmers (Walrath & Fraumeni, 1983).

Table 41. Mortality ratios of men according to social class[a]

Disease Place Race	Age (years)	*Population* Year	Ratio[b]	*Social class* High I	II	III	IV	Low V	Reference
Brain cancer									
United Kingdom									
all	15-64	1970-72	SMR	108	101	111, 105	100	92	Registrar General (1978)
all	65-74	1970-72	PMR	225	137	109, 99	85	56	Registrar General (1978)
all	20-64	1949-53	SMR	133	96	104	88	99	Registrar General (1978)
all	65	1949-53	PMR	136	112	105	90	71	Registrar General (1978)
all	35-65	1930-32	SMR	167	92	116	97	66	Registrar General (1978)
all	20-65	1921-23	CMFR	160	160	120	80	60	Registrar General (1978)
USA									
California									
all	20-64	1949-51	SMR	130	127	108	77	58	Buell et al. (1960)
Massachusetts									
white	20	1971-73	SMOR	164	97	114	62[c]		Dubrow & Wegman (1984)
USA									
all	20-64	1950	SMR	136	121	109	94	81	Curalnick (1963)
Leukaemia									
United Kingdom									
all	15-64	1970-72	SMR	113	100	107, 101	104	95	Registrar General (1978)
all	65-74	1970-72	PMR	138	124	108, 98	90	77	Registrar General (1978)
all	20-64	1949-53	SMR	123	98	104	93	89	Registrar General (1978)
all	65	1949-53	PMR	202	115	101	78	74	Registrar General (1978)
all	20-65	1930-32	SMR	152	126	97	95	86	Registrar General (1978)

Table 41 (contd).

Disease Place Race	Age (years)	*Population* Year	Ratio[b]	*Social class* High I	II	III	IV	Low V	Reference
USA California all	20-64	1949-51	SMR	104	116	101	86	104	Buell et al. (1960)
Massachusetts white	20	1971-73	SMOR	126	97	108	89[c]	-	Dubrow & Wegman (1984)
USA all	20-64	1950	SMR	117	100	105	89	98	Guralnick (1963)

a From: Levine (1985).
b SMR = standardized mortality ratio.
PMR = proportional mortality ratio.
SMOR = standardized mortality odds ratio.
CMFR = comparative mortality figure ratio.
c Including classes IV and V.

10. EVALUATION OF HUMAN HEALTH RISKS AND EFFECTS ON THE ENVIRONMENT

10.1 Evaluation of Human Health Risks

The absolute odour threshold for formaldehyde is between 0.06 and 0.22 mg/m^3 (a group of observers detected the odour in 50% of the presentations, 10% of an untrained population detected a level of 0.03 mg/m^3). There is a low probability that human beings will be able to detect formaldehyde in air at concentrations below 0.01 mg/m^3.

Since interaction and adaptation processes are characteristic of the sensory systems involved in the perception of odour and irritation, the duration of exposure and the other components of environmental air exposure influence the perception. Although sensory adaptation because of length of exposure may weaken the perceptual response, there is a high probability that exposure duration will enhance the perception, especially at low concentrations. In addition, formaldehyde often appears in complex gas mixtures that contain other low concentrations of odorous or irritating components. Examples are photochemical smog, automobile exhaust, environmental tobacco smoke, and contaminated indoor air, with building materials as the source.

There are no data on the absolute irritation threshold for formaldehyde, but sensory irritation has been reported for the eyes at 0.06 mg/m^3 and for the respiratory tract at 0.12 mg/m^3.

Formaldehyde vapour causes direct irritation of the human respiratory tract. However, precise thresholds have not been established for the irritant effects of inhaled formaldehyde. Some people experience throat irritation at 0.1 mg/m^3 and almost everybody will experience it before a level of 3.0 mg/m^3 is reached.

The effects on the nasal cavity, the site of impact for most of the inhaled formaldehyde, is impairment of mucociliary flow at or above a level of 0.5 mg/m^3. This effect may also lead to the secondary complication of respiratory disease. There is a higher incidence of chronic respiratory disease in occupationally-exposed subjects or children living in a formaldehyde-polluted environment. Long-term exposure to 0.45 mg/m^3, independent of tobacco-smoking habits, may cause bronchoconstriction.

Formaldehyde has been shown to cause pulmonary effects on healthy and on asthmatic subjects (not sensitized to formaldehyde) at a concentration that is already irritant. Precise thresholds have not been established for the pulmonary irritant effects of inhaled formaldehyde. However, lower airway and pulmonary effects are likely to occur at levels above 6 mg/m^3.

There are no data on the exact exposure level at which inhaled formaldehyde has a sensitizing effect, but once sensitization has developed, short-term exposure to concentrations that can be found in occupational or home environments is sufficient to produce an asthma-

like response. Asthmatic responsiveness may persist if intermittent exposure to low levels continues. Removal from exposure has a favourable effect on symptoms.

Although few proven formaldehyde-induced asthma patients have been reported, it appears likely that this condition is underreported.

There is a possibility of the induction of sensitisation via haemodialysis, where formaldehyde may enter the circulation through the disinfecting of the dialysis equipment. This can be influenced by the state of health and previous medication of the patient.

Skin sensitisation in human beings is induced by direct contact with formaldehyde solutions, only in concentrations higher than 2%. The lowest patch-test challenge concentration producing a reaction in sensitized persons was 0.05% formaldehyde in an aqueous solution. Patch tests performed with formaldehyde challenge concentrations of < 1% formaldehyde resulted in positive reactions in about 2% of all patch-tested patients throughout the world.

Positive patch tests results with formaldehyde challenge concentrations of 2% or more may be due to skin irritation.

Formaldehyde may induce contact urticarial reactions, but these are rarely observed and have not been confirmed as IgE-mediated Type I reactions.

Cell-mediated allergic dermatitis, arising from systemic exposure, and antibody (IgE)-mediated exanthematous phenomena have not been observed after ingestion of formaldehyde.

Irritant skin reactions occur through direct contact with formaldehyde solutions. A single application of 1% formalin in water with occlusion will produce an irritant response in approximately 5% of the test population.

Mental or behavioural problems at levels present in the home environment have been claimed to be due to long-term formaldehyde exposure, as adjudged by questionnaires, but there were no differences in terms of memory loss, sleep disturbance, and concentration. Possible impaired memory, equilibrium, and dexterity, in some cases has been suggested in relation to long-term, high-level occupational exposure.

Animal data do not indicate that formaldehyde is embryotoxic or teratogenic.

Formaldehyde reacts with macromolecules, including DNA. The genotoxic effects of formaldehyde have been reported in a wide range of mutagenicity tests *in vitro* in the absence of a metabolizing system.

In vivo, most mutagenicity tests are negative. However, DNA-protein cross-links are induced at the site of exposure, after inhaling formaldehyde. The importance of this local genotoxic effect with respect to the induction of cancer requires further evaluation.

The importance of positive mutagenicity findings with regard to germ-cell mutations is limited. In the light of known metabolic mechanisms, it should not be assumed that formaldehyde induces mutations in germ cells and it is unlikely that formaldehyde leads to a heritable genetic risk.

Formaldehyde is a nasal carcinogen in rats. A highly significant incidence of nasal cancer was induced in rats exposed to a level of

18 mg/m^3, but the concentration-response curve was extremely non-linear, and only a low, not statistically significant, incidence of nasal tumours occurred at 7.2 mg/m^3. The results of this and other studies consistently indicate that, at low concentrations, the risk of cancer is *disproportionately* low. It is likely that defence mechanisms in the respiratory tract, including the mucociliary clearance apparatus, metabolism by formaldehyde dehydrogenase and other enzymes, and DNA repair, are effective at low concentrations, but that, at high concentrations, these defence mechanisms can be overwhelmed and may even be inactivated, thus resulting in tissue damage.

On the basis of these data it can be concluded that the induction of nasal cancer in rats by formaldehyde requires repeated exposure to high concentrations, i.e., concentrations that are very irritating and cause considerable damage to the nasal mucosa followed by regenerative hyperplasia and metaplasia. The increased cell turnover, as well as subsequent cycles of DNA-damage provoked by continuous exposure to formaldehyde, may strongly increase the likelihood of relevant DNA damage, and subsequently may greatly enhance the progression of pre-neoplastic cells to cancer. Formaldehyde, in concentrations not leading to cell damage, probably cannot act as a complete carcinogen, causing initiation, promotion, and progression, and, as a result, is very unlikely to induce cancer by itself. From the above, it appears that the cytotoxic effects are likely to play a highly significant role in the formation of nasal tumours by formaldehyde.

Despite differences in the anatomy and physiology of the respiratory tract between rats and human beings, the respiratory tract defence mechanisms are similar. Therefore, it is reasonable to conclude that the response of the human respiratory tract mucosa to formaldehyde will be qualitatively similar to that of the rat respiratory tract mucosa.

Evidence from rat studies suggests that recurrent tissue damage occurs in conjunction with exposure to high, cytotoxic concentrations of formaldehyde, and that this is necessary for nasal tumours to be produced. If respiratory-tract tissue is not repeatedly damaged, exposure of human beings to low, non-cytotoxic concentrations of formaldehyde can be assumed to represent a negligible cancer risk. However, if exposure were to be accompanied by recurrent tissue damage at the initial site of contact, formaldehyde may be assumed to have carcinogenic potential for man.

Some excess has been shown for several types of cancer in more than one of the epidemiological studies relating to formaldehyde, i.e., Hodgkin's disease, leukaemia, and cancers of the buccal cavity and pharynx, lung, nose, prostate, bladder, brain, colon, skin and kidney. Some of these excesses may be due to random variation and others may depend on factors other than formaldehyde exerting confounding effects. Such explanations might be suggested, especially when only a few cases are involved or when the risk ratios are low.

In view of the solubility and rapid metabolism of formaldehyde, it seems that upper respiratory tract cancers would be more likely to be

causally related to formaldehyde exposure than other forms of cancer, especially as there is experimental evidence providing a relatively clear suggestion of a possible cancer risk for human beings from exposure to formaldehyde. Besides various types of occupational exposure, smoking and other use of tobacco would have to be considered as potentially confounding factors, especially when exerting strong effects, such as those of tobacco smoking in relation to lung cancer. Furthermore, because of the formaldehyde content of mainstream and environmental tobacco smoke, there is exposure of any reference population, and this would mask effects with regard to cancers that might be related to occupational or other specified exposure to formaldehyde.

Some excess of nasal or nasopharyngeal cancer was reported in relation to formaldehyde exposure in 6 of the case-control studies reviewed. In 2 other case-control studies, the question of a relationship with formaldehyde was addressed either by primary design or by reporting formaldehyde exposure, but no excess risk was demonstrated. None of the cohort or PMR studies reviewed had adequate power to detect even a considerable increased risk though, in aggregate, the studies might have had the power to reveal, at least, a higher risk for nasal cancer. It should be noted that, with regard to nasal and nasopharyngeal cancer, smoking is not likely to exert any particularly strong confounding effect, since the relationship between these types of cancer and smoking is only moderately strong, i.e., a risk ratio of up to about five, and considerably less in many studies.

Cancers of the buccal cavity and pharynx have either not been included in studies or else the risk has appeared approximately normal in some case-control studies. There was no excess in the largest cohort, though an excess had appeared in other studies involving small numbers.

Some excess respiratory cancer appeared in 3 case-control studies, but these studies were based on small numbers. Two other studies came out as non-positive. Four of the cohort and PMR studies that had adequate power and were designed to elucidate the risk of respiratory cancer from formaldehyde exposure showed an excess risk (significantly high in workers producing resins containing formaldehyde, Bertazzi et al., 1986). There was an excess of laryngeal cancer in one study. Seven studies with reasonable power were either negative or non-positive with regard to respiratory cancer. The deviations in both directions from the expected in these studies are explicable by lack of control for smoking and/or the so-called "healthy worker effect" due to lack of comparability of the study population with the general population.

The incidence of leukaemia was increased in all the studies with reasonable numbers and was significantly high in one study. Three of these studies involved either embalmers or anatomists, which might suggest the operation of some other alternative or contributing etiological factors. Similarly, a confounding effect from some other factors might be suspected with regard to the relation between brain cancer (which was found in significant excess in some studies) and

social class. An excess of colon cancer among embalmers must be considered against a recently observed association between this type of cancer and sedentary work. Of the other cancer forms previously mentioned as appearing in excess in more than one study, cancers of the skin, bladder, kidney, and prostate, as well as Hodgkin's disease, are represented by small numbers and/or small excesses. However, in one study based on 23 cases, prostate cancer was significantly high but not skin cancer, whereas in another study on embalmers, skin cancer was significantly high but not prostate cancer.

The available human evidence indicates that formaldehyde does not have a high carcinogenic potential. There are some studies which indicate an excess of nasal and/or nasopharyngeal tumours in exposed individuals or population though the relative risks are, in general, small.

Given the relative rarity of tumours in the biologically plausible area of the upper respiratory tract, and the widespread past occupational exposures to formaldehyde in various work situations, it can be concluded that formaldehyde is, at most, a weak human carcinogen.

Human exposure to formaldehyde should be minimized, not only for its probable carcinogenic effect, but also for its potential for tissue damage. One practical way of moving towards an effective preventive strategy would be to control the formaldehyde level in the work place below that likely to produce a significant irritant effect.

The epidemiological studies on carcinogenicity that contain some exposure assessments imply that, in the past, working populations showing an excess of nasal epithelial tumours had generally been exposed to formaldehyde levels in excess of the tissue-damage threshold. Such a threshold is probably about 1.0 mg/m^3 (range 0.5-3 mg/m^3).

With regard to atmospheric exposure limit values for odour and sensory irritation for the general population and the non-industrial indoor environment, formaldehyde concentrations should not exceed 0.1 mg/m^3. In the case of specially sensitive groups that show hypersensitivity reactions without immunological signs, formaldehyde concentrations should be kept to a minimum and should not exceed 0.01 mg/m^3.

To avoid strong sensory reactions in work-place environments where formaldehyde is being produced or used, peak concentrations above 1.0 mg/m^3 should not be allowed and mean concentrations should be kept below 0.3 mg/m^3.

10.2 Evaluation of Effects on the Environment

Formaldehyde is present in the environment as a result of natural processes and from man-made sources; the quantities produced by the former greatly exceed those from the latter. Nevertheless, the compound should be considered as an environmental contaminant, because it has been detected at levels higher than background concentrations in areas influenced by man-made sources. Air is the most relevant compartment in the formaldehyde cycle, as most of the formaldehyde produced

and/or emitted enters the atmosphere and this is also where most of the degradation processes occur. The half-life of formaldehyde in the air is short, due to photodegradation. Formaldehyde is also biodegraded in water and soil in a relatively short time and does not accumulate in organisms. Data available for ecotoxicological assessment refer almost exclusively to formaldehyde in water. It can be classified as toxic for aquatic biota, with a lowest acute effect level for several aquatic organisms of about 1 mg/litre. However, fish seem to be more tolerant. No long-term toxicity tests have been performed, but the possibility of elimination via biodegradation, the low bioaccumulation factor, and the ability of organisms to metabolize formaldehyde, suggest that its impact on the aquatic environment would be limited, except in the case of massive discharge. With regard to the terrestrial environment, the lack of ecotoxicological data gives rise to concern, because most of the formaldehyde is distributed in the air. However, it should be noted that photooxidation in air is the main degradation process and that the reaction is fast. Data on the effects on plant foliage of exposure to peak concentrations of formaldehyde could be of relevance for a complete evaluation, though the highest concentrations detected have not lasted for very long.

10.3 Conclusions

- Formaldehyde occurs naturally and is a widely produced industrial chemical.

- Formaldehyde is a product of normal metabolic pathways.

- Formaldehyde undergoes rapid decomposition and does not accumulate in the environment.

- Major sources of formaldehyde are:

  - automobile and aircraft exhaust emissions;
  - tobacco smoke;
  - natural gas;
  - fossil fuels;
  - waste incineration; and
  - oil refineries.

- Formaldehyde exposure varies widely because of local variations. Significant levels of formaldehyde have been reported in indoor air. Among the sources are tobacco smoke, building and furnishing materials, and disinfectants.

- In work places, exposure may occur during the production or handling of formaldehyde or products containing formaldehyde.

- The most prominent features of formaldehyde vapour are its pungent odour and its irritant effects on the mucosa of eyes and upper airways. Odour-detection thresholds are generally reported to be in the range of 0.1-0.3 mg/m^3.

- Eye and respiratory-tract irritation generally occurs at levels of about 1 mg/m^3, but discomfort has been reported at much lower levels.

- Direct contact with formaldehyde solutions (1-2%) may cause skin irritation in approximately 5% of patients attending dematological clinics.

- Long-term exposure can lead to allergic contact dermatitis; this has been demonstrated for formaldehyde solution only, not for gaseous formaldehyde.

- Reversible airways obstruction has been produced by irritant concentrations of formaldehyde.

- Long-term exposure to formaldehyde at a level as low as 0.5 mg/m^3 may cause a slight elevation in airway resistance.

- Formaldehyde-related asthma has rarely been reported despite the widespread population exposure to formaldehyde.

- To avoid adverse reactions in dental surgery practice, root canal sealers should not be extruded beyond the apex in short-term exposure situations.

- There is no convincing evidence that formaldehyde is a teratogen, in either animals or human beings.

- Formaldehyde has not produced any adverse effects on reproduction in test animals or in human beings.

- Formaldehyde is positive in a wide range of mutagenicity test systems *in vitro*; results of *in vivo* test systems are conflicting.

- Formaldehyde has been shown to form DNA-protein crosslinks *in vitro* and *in vivo*. *In vivo*, this has been shown to occur at an exposure concentration of 1.1 mg/m^3.

- Formaldehyde interferes with DNA repair in human cells *in vitro*.

- Following inhalation exposure at levels causing cell damage, a significant incidence of squamous cell carcinomas of the nasal cavity was induced in 2 strains of rats.

Nasal tumours in mice have also been reported, but the incidence was not statistically significant. There were no tumours at other sites.
A limited number of forestomach papillomas have been reported in rats following administration of formaldehyde in the drinking-water.
Formaldehyde-related tumours were not observed beyond the initial site of contact.

- Although an excess has been reported for a number of cancers, the evidence for a causal role of formaldehyde is likely only for nasal and nasopharyngeal cancer.

11. RECOMMENDATIONS

11.1 Recommendations for Future Research

The absolute detection and recognition thresholds for formaldehyde should be determined. Psychophysical function relating the perceived irritation to the concentration of formaldehyde should be determined. Special attention should be given to low-concentration effects on the skin of the face (cheeks, eyes) for both surface exposure and inhaled air mixtures. The possible potentiation of sensory irritation by formaldehyde at low concentrations should be further investigated in mixtures of irritants with different durations of exposure. Sensory effects, when human beings are exposed either to air containing formaldehyde or air without formaldehyde, should be compared.

- The link between the perception of irritation and hyperreactivity and allergic reactions to formaldehyde needs further study, in order to evaluate fully the health implications of sensory effects.

- General interaction effects of physical, environmental factors (humidity, radiant heat, temperature, etc.) and low-concentration formaldehyde exposure should be investigated with regard to odour and sensory irritation.

- The combined effects of skin exposure to formaldehyde vapour and inhalation exposure, on various symptoms, including sensory irritation, feeling of warmth on the skin surface, quality of tactile perception, itching, tickling, and smarting of the eyes, need investigation. Both air and contact exposure of various body skin sites to formaldehyde at low concentrations should be studied for sensory effects and irritant contact dermatitis. The interaction effects of various host factors, such as age, psychological stress, skin disease, skin sensitivity, genetic factors (e.g., atopic), and hormonal balance, should be studied.

- the possible production of antibodies (IgE or other) to formaldehyde should be investigated. The detection of IgE antibodies by RAST should be included.

- Workers, who have undergone long-term exposure to formaldehyde should be examined for immunological effects, including clinical and laboratory findings.

- Animal studies on the induction of antibodies and T-cells specifically reacting with formaldehyde should be undertaken.

- More knowledge is needed about the factors involved in the induction of an irritant contact dermatitis by formaldehyde, dependent on occupational and/or other factors. Research should be directed to the formaldehyde concentrations producing such effects as well as to the skin parameters conditioning the start of the irritative skin contact reaction.

- Mechanisms involved in the carcinogenicity of formaldehyde, such as the effectiveness of mucus as a barrier, the genotoxic consequences of DNA-protein cross-links, and the role of tissue damage, should be studied in more detail.

- More knowledge is needed on the interactions of formaldehyde with other air pollutants.

- Further epidemiological studies are needed including studies on groups of people believed to be susceptible to the effects of formaldehyde.

- There is a need for extensive follow-up studies on working populations already investigated (maybe in excess of 20 years), because a long minimum latent period may be a feature of the response of the human nasal epithelium to cancer-causing agents.

- Epidemiological studies should also be re-evaluated for mortality due to cancers of the buccal cavity and pharynx, (human beings are not obligate nose breathers).

11.2 Recommendations for Preventive Measures

To prevent unacceptable risks, exposure to cytotoxic concentrations of formaldehyde should be avoided.

It is recommended that consumer goods containing formaldehyde should be labelled, in order to protect persons with a formaldehyde allergy.

(a) Indoors:

The formaldehyde air concentration allowed in living, sleeping, and working rooms should not be higher than 0.12 mg/m^3, in order to minimize the risk of repeated or continuous low concentration exposure to formaldehyde.

(b) Occupational areas:

It is recommended that formaldehyde concentrations in the work place air should be reduced to non-toxic concentrations. A no-observed-adverse-effect level in monkeys was 1.2 mg/m^3 (1 ppm). For

protective reasons, the concentration at the work place should be below 1.2 mg/m³ (1 ppm).

The exposure may reach a maximum of 1.2 mg/m³ (1 ppm) for 5 min with not more than 8 peaks in one working period (up to 8 h).

(c) Cosmetics:

Formaldehyde concentrations in cosmetics (creams) that are higher than 0.05% should be labelled and levels should be limited to 0.1% in oral cosmetics.

The upper-level for the use of formaldehyde as a preservative in cosmetics should be 0.2%, except in nail hardeners, which may contain up to 5% formaldehyde.

(d) Hospitals:

1) Because of the sensitizing effect, skin contact with formaldehyde should be avoided by wearing impermeable gloves.

2) Thermal procedures are preferred for the disinfection or sterilization of appliances and instruments. Closed containers should be used in the disinfection of instruments using formaldehyde. Incubators, scopes, and tubes should not be treated with formaldehyde.

3) Thermal laundering procedures are preferred for the disinfection of clothing. Any "tub-disinfection" of clothing in formaldehyde solution should be exceptional. The tub must be closed with a lid. On handling clothing, gloves (and eventually respirators) should be worn.

4) Steam disinfecting is the method of choice for mattresses; spraying with disinfectants is obsolete. Mattresses covered with synthetic materials can be disinfected by wiping with formaldehyde solution, providing ventilation is sufficient.

5) Area disinfection: Wiping or scrubbing is recommended, while spraying with formaldehyde-containing solutions should be confined to non-accessible places. Direct contact with the disinfectant should be avoided by the use of gloves. Large-area disinfecting, - laboratories etc., should be scheduled for off-work times. Sufficient ventilation is mandatory.

6) Fixation of tissues in formalin baths should be performed in closed containers and/or using an exhaust hood. If possible, tissue slices should be washed with water, to remove superfluous formaldehyde, before viewing them under the microscope.

12. PREVIOUS EVALUATIONS BY INTERNATIONAL BODIES

In 1983, a WHO Study Group reviewed formaldehyde in order to recommend a health-based occupational exposure limit (WHO, 1984). The recommendations were as follows:

> "The Study Group recommends a short-term (15 minutes), health-based occupational exposure limit for formaldehyde in air of 1.0 mg of formaldehyde per m^3 of air.
>
> "A *tentative* health based exposure limit of 0.5 mg of formaldehyde per m^3 of air is recommended as an 8-hour time-weighted daily average during a 40-hour working week.
>
> "In view of the reported dose-dependent carcinogenic effect of formaldehyde in the rat, and the present inadequate epidemiological data on the cancer risk in man, it is advisable to reduce workplace exposure to formaldehyde to the lowest feasible level."

The carcinogenic risks for human beings were evaluated by an International Agency for Research on Cancer ad hoc expert group in 1981. The evaluation was updated in 1987 and it was concluded that there was limited evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals (IARC, 1987).

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