FORMALDEHYDE

This substance was considered by previous working groups, in October 1981 (IARC, 1982) and March 1987 (IARC, 1987a). Since that time, new data have become available, and these have been incorporated in the monograph and taken into consideration in the evaluation.

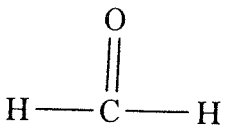
1. Exposure Data

1.1 Chemical and physical data

1.1.1 Nomenclature

Chem. Abstr. Serv. Reg. No.: 50-00-0
Deleted CAS Reg. Nos: 8005-38-7; 8006-07-3; 8013-13-6; 112068-71-0
Chem. Abstr. Name: Formaldehyde
IUPAC Systematic Name: Methanal
Synonyms: Formaldehyde, gas; formic aldehyde; methaldehyde; methyl aldehyde; methyl oxide; methylene oxide; oxomethane; oxymethylene

1.1.2 Structural and molecular formulae and relative molecular mass



CH_2O

Relative molecular mass: 30.03

1.1.3 Chemical and physical properties of the pure substance

From Lide (1993), unless otherwise noted

(*a*) *Description*: Colourless gas with a pungent odour (Reuss *et al.*, 1988)
(*b*) *Boiling-point*: –21 °C
(*c*) *Melting-point*: –92 °C
(*d*) *Density*: 0.815 at 20 °C/4 °C
(*e*) *Spectroscopy data*: Infrared [prism, 2538], ultraviolet [3.1] and mass spectral data have been reported (Weast & Astle, 1985; Sadtler Research Laboratories, 1991).
(*f*) *Solubility*: Very soluble in water, ethanol and diethyl ether
(*g*) *Stability*: Commercial formaldehyde–alcohol solutions are stable; the gas is stable in absence of water; incompatible with oxidizers, alkalis, acids, phenols and urea

(Gerberich *et al.*, 1980; IARC, 1982; Cosmetic Ingredient Review Expert Panel, 1984; Reuss *et al.*, 1988).

(*h*) *Reactivity*: Reacts explosively with peroxide, nitrogen oxide and performic acid; can react with hydrogen chloride or other inorganic chlorides to form bis(chloromethyl) ether (see IARC, 1987b) (Gerberich *et al.*, 1980; IARC, 1982; Cosmetic Ingredient Review Expert Panel, 1984; Reuss *et al.*, 1988).

(*i*) Octanol/water partition coefficient (P): log P = 0.35 (Sangster, 1989)

(*j*) Conversion factor: $mg/m^3 = 1.23 \times ppm$[a]

1.1.4 Technical products and impurities

Trade names: BFV; FA; Fannoform; Floguard 1015; FM 282; Formalin; Formalin 40; Formalith; Formol; Fyde; Hoch; Ivalon; Karsan; Lysoform; Morbicid; Paraform; Superlysoform

Formaldehyde is most commonly available commercially as a 30–50% (by weight) aqueous solution, commonly referred to as 'formalin'. In dilute aqueous solution, the predominant form of formaldehyde is its monomeric hydrate, methylene glycol. In more concentrated aqueous solutions, oligomers and polymers that are mainly polyoxymethylene glycol are formed and may predominate. Methanol and other substances (e.g. various amine derivatives) are usually added to the solutions as stabilizers, in order to reduce intrinsic polymerization. The concentration of methanol can be as high as 15%, while that of other stabilizers is of the order of several hundred milligrams per litre. Concentrated liquid formaldehyde–water systems containing up to 95% formaldehyde are also available, but the temperature necessary to maintain solution and to prevent separation of the polymer increases from room temperature to 120 °C, as the concentration in solution increases. Impurities include formic acid, iron and copper (Cosmetic Ingredient Review Expert Panel, 1984).

Formaldehyde is marketed in solid form as its cyclic trimer, trioxane $(CH_2O)_3$, and its polymer, paraformaldehyde, with 8–100 units of formaldehyde (Cosmetic Ingredient Review Expert Panel, 1984; Reuss *et al.*, 1988; WHO, 1991).

1.1.5 Analysis

The most widely used methods for the determination of formaldehyde are based on spectrophotometry, with which sensitivities of 0.01–0.03 mg/m^3 can be achieved. Other methods include colorimetry, fluorimetry, high-performance liquid chromatography, polarography, gas chromatography, infrared detection and gas detector tubes. High-performance liquid chromatography is the most sensitive method (limit of detection, 0.002 mg/m^3). In all of these methods, other organic and inorganic chemicals, such as sulfur dioxide, other aldehydes and amines, cause interference.

The method of sampling and the treatment of samples before analysis are important in the accuracy of the determination. Gas detector tubes (WHO, 1989) and infrared analysers are often

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[a]Calculated from: mg/m^3 = (relative molecular mass/24.45) × ppm, assuming normal temperature (25 °C) and pressure (103.5 kPa)

used for monitoring workplace atmospheres, with a sensitivity of about 0.4–0.5 mg/m^3 (Gollob & Wellons, 1980; Heck *et al.*, 1982; Kennedy *et al.*, 1985; Kennedy & Hull, 1986; Stewart *et al.*, 1987a; Bicking *et al.*, 1988; Greenblatt, 1988; WHO, 1989; United States Occupational Safety and Health Administration, 1991; WHO, 1991). Selected methods for the determination of formaldehyde in various matrices are presented in Table 1.

Four methods have been developed to measure formaldehyde emissions from wood products. The large-scale chamber test developed by the Wilhelm Klauditz Institute in Germany is the principal method used in Europe. A value of 0.1 mg/m^3 in this test, used for the German 'E-1' classification, is often applied for approval of the use of formaldehyde-emitting building products. The large-scale chamber formaldehyde test method 2 (FTM-2) is used to test wood panels in Canada and the United States (European Commission, 1989; American Society for Testing and Materials, 1990; Groah *et al.*, 1991; Jann, 1991). A 2-h desiccator test (FTM-1) is a small-scale method for determining formaldehyde emitted from wood products; formaldehyde, absorbed in distilled water, reacts specifically with a chromotropic acid–sulfuric acid solution (National Particleboard Association, 1983; Groah *et al.*, 1991).

In the perforator method for extracting formaldehyde, small samples are boiled in toluene, and the formaldehyde-laden toluene is distilled through distilled/deionized water, which absorbs the formaldehyde; a sample of the water is then analysed photometrically by the acetylacetone or pararosaniline method. In the iodometric method, formaldehyde in water is determined by adding sulfuric acid solution and an excess of iodine; the iodine oxidizes the formaldehyde, and the excess is back-titrated with sodium thiosulfate (British Standards Institution, 1989).

1.2 Production and use

1.2.1 Production

Since 1889 in Germany, formaldehyde has been produced commercially by the catalytic oxidation of methanol. Various methods were used in the past, but only two are widely used currently: the silver catalyst and metal oxide catalyst processes (Reuss *et al.*, 1988; Gerberich & Seaman, 1994).

The silver catalyst process is conducted in one of two ways: (i) partial oxidation and dehydrogenation with air in the presence of silver crystals, steam and excess methanol at 680–720 °C and atmospheric pressure (also called the BASF process; methanol conversion, 97–98%); and (ii) partial oxidation and dehydrogenation with air in the presence of crystalline silver or silver gauze, steam and excess methanol at 600–650 °C (primary conversion of methanol, 77–87%); the conversion is completed by distilling the product and recycling the unreacted methanol. Carbon monoxide, carbon dioxide, methyl formate and formic acid are by-products (Gerberich *et al.*, 1980; Reuss *et al.*, 1988; Gerberich & Seaman, 1994).

In the metal oxide (Formox) process, methanol is oxidized with excess air in the presence of a modified iron–molybdenum–vanadium oxide catalyst at 250–400 °C and atmospheric pressure (methanol conversion, 98–99%). By-products are carbon monoxide and dimethyl ether and small amounts of carbon dioxide and formic acid (Gerberich *et al.*, 1980; Reuss *et al.*, 1988; Gerberich & Seaman, 1994).

Table 1. Methods for the analysis of formaldehyde in air and food

Sample matrix	Sample preparation	Assay procedure	Limit of detection	Reference
Air	Draw air through impinger containing aqueous pararosaniline; treat with acidic pararosaniline and sodium sulfite	S	0.01 mg/m^3	Georghiou *et al.* (1993)
	Draw air through PTFE filter and impingers, each treated with sodium bisulfite solution; develop colour with chromotropic acid and sulfuric acid; read absorbance at 580 nm	S	0.03 mg/m^3	Eller (1989a) [Method 3500]
	Draw air through solid sorbent tube treated with 10% 2-(hydroxymethyl) piperidine on XAD-2; desorb with toluene	GC/FID	0.3 mg/m^3	Eller (1989b) [Method 2541]
		GC/NSD	0.02 mg/m^3	United States Occupational Safety and Health Administration (1990) [Method 52]
	Draw air through impinger containing hydrochloric acid/2,4-dinitrophenyl-hydrazine reagent and isooctane; extract with hexane/dichloromethane	HPLC/UV	0.002 mg/m^3	United States Environmental Protection Agency (1988a) [Method TO5]
	Draw air through silica gel coated with acidified 2,4-dinitrophenylhydrazine reagent	HPLC/UV	0.002 mg/m^3	United States Environmental Protection Agency (1988b) [Method TO11]
	Expose passive monitor (Du Pont Pro-Tek® Formaldehyde Badge) for at least 2 ppm-h. Analyse according to manufacturer's specifications	Chromotropic acid test	0.1 mg/m^3	Kennedy & Hull (1986); Stewart *et al.* (1987a)
Food	Distil sample; add 1,8-dihydroxy-naphthalene-3,6-disulfonic acid in H_2SO_4; purple colour indicates presence of formaldehyde	Chromotropic acid test	NR	Helrich (1990) [Method 931.08]
	Distil sample; add to cold H_2SO_4; add aldehyde-free milk; add bromine hydrate solution; purplish-pink colour indicates presence of formaldehyde	Hehner-Fulton test	NR	Helrich (1990) [Method 931.08]

S, spectrometry; PTFE, polytetrafluoroethylene; GC/FID, gas chromatography/flame ionization detection; GC/NSD, gas chromatography/nitrogen selective detection; HPLC/UV, high-performance liquid chromatography/-ultraviolet detection; NR, not reported

Paraformaldehyde, a solid polymer of formaldehyde, consists of a mixture of poly(oxymethylene) glycols [HO–$(CH_2O)_n$–H; n = 8–100]. The formaldehyde content is 90–99%, depending on the degree of polymerization, n and product specifications; the remainder is bound or free water. Paraformaldehyde, a convenient source of formaldehyde for certain applications, is prepared commercially by concentrating aqueous formaldehyde solutions under vacuum in the presence of small amounts of formic acid and metal formates. An alternative solid source of formaldehyde, 1,3,5-trioxane, is the cyclic trimer of formaldehyde and is prepared commercially by strong-acid-catalysed condensation of formaldehyde in a continuous process (Reuss *et al.*, 1988; Gerberich & Seaman, 1994).

Formaldehyde is reported to be produced by 11 companies in Japan, eight companies each in China and the United States, seven companies in Italy, six companies each in Brazil, Mexico, Spain and the United Kingdom, five companies in Germany, four companies in India, three companies each in Austria and Canada, two companies each in Argentina, Australia, Finland, France, Israel, the Republic of Korea, Sweden, Turkey and the former Yugoslavia and one company each in Bulgaria, Colombia, the former Czechoslovakia, Ecuador, Greece, Hungary, New Zealand, Norway, Pakistan, Peru, Philippines, Poland, Portugal, South Africa, Switzerland, the Russian Federation and Thailand. Paraformaldehyde is reported to be produced by three companies in Japan and China, two companies in Spain and one company each in Argentina, Brazil, France, Germany, Israel, Mexico, the United Kingdom and the United States. 1,3,5-Trioxane is produced by three companies Germany (Chemical Information Services Ltd, 1991).

Worldwide production of formaldehyde in 1992 was approximately 12 million tonnes (Smith, 1993). Production of formaldehyde in selected years and countries is shown in Table 2. In 1986, most of the worldwide production capacity was based on silver catalyst processes (Reuss *et al.*, 1988).

1.2.2 Use

The widest use of formaldehyde is in the production of resins with urea, phenol and melamine and, to a small extent, their derivatives. Formaldehyde-based resins are used as adhesives and impregnating resins in the manufacture of particle-board, plywood, furniture and other wood products. They are also used for the production of curable moulding materials (appliances, electric controls, telephones, wiring services) and as raw materials for surface coatings and controlled-release nitrogen fertilizers. They are used in the textile, leather, rubber and cement industries. Further uses are as binders for foundry sand, stonewool and glasswool mats in insulating materials, abrasive paper and brake linings. Smaller amounts of urea–formaldehyde resins are used in the manufacture of foamed resins for mining and for building insulation (Reuss *et al.*, 1988; WHO, 1989; Gerberich & Seaman, 1994).

Another major use of formaldehyde is as an intermediate for synthesizing other industrial chemical compounds, such as 1,4-butanediol, trimethylolpropane and neopentyl glycol, which are used in the manufacture of polyurethane and polyester plastics, synthetic resin coatings, synthetic lubricating oils and plasticizers. Other compounds produced from formaldehyde

Table 2. Production of formaldehyde in selected countries (thousand tonnes)

Country or region	1982	1986	1990
Brazil	152	226	NA
Canada	70	117	106
China	286	426	467
Former Czechoslovakia	254	274	NA
Denmark	NA	3	0.3
Finland	NA	5	48
France	79	80	100
Germany	630	714	680
Hungary	13	11	NA
Italy	125	135	114
Japan	NA	1188	1460
Mexico	83	93	NA
Poland	219	154	NA
Portugal	NA	70	NA
Republic of Korea	NA	122	NA
Spain	NA	91	136
Sweden	NA	223	244
Taiwan	NA	204	215
Turkey	NA	21	NA
United Kingdom	107	103	80
United States[a]	2185	2517	3048
Former Yugoslavia	108	99	88

From Anon. (1985, 1989); Japan Chemical Week (1991); Anon. (1993); China National Chemical Information Centre (1993); Anon. (1994); Data-Star/Dialog (1994)
NA, not available
[a] 37% by weight

include pentaerythritol, used primarily in raw materials for surface coatings and explosives, and hexamethylenetetramine, used as a cross-linking agent for phenol–formaldehyde resins and explosives. The complexing agents nitrilotriacetic acid (see IARC, 1990a) and ethylenediaminetetraacetic acid are derived from formaldehyde and are components of some detergents. There is a steadily increasing demand for formaldehyde for the production of 4,4′-diphenylmethane diisocyanate (see IARC, 1979), which is a constituent of polyurethanes used in the production of soft and rigid foams and, more recently, as an adhesive and for bonding particle-board (Reuss *et al.*, 1988; WHO, 1989; Gerberich & Seaman, 1994).

Polyacetal plastics produced by polymerization of formaldehyde are incorporated into automobiles to reduce weight and fuel consumption, and are used to make functional components of audio and video electronics equipment. Formaldehyde is also the basis for products used to manufacture dyes, tanning agents, dispersion and plastics precursors, extraction

agents, crop protection agents, animal feeds, perfumes, vitamins, flavourings and drugs (Reuss *et al.*, 1988; WHO, 1989).

Formaldehyde itself is used for preservation and disinfection, for example, in human and veterinary drugs and biological materials (viral vaccines contain 0.05% formalin as an inactivating agent), for disinfecting hospital wards and preserving and embalming biological specimens. It is used as an antimicrobial agent in many cosmetics products, including soaps, shampoos, hair preparations, deodorants, lotions, make-up, mouthwashes and nail products (Cosmetic Ingredient Review Expert Panel, 1984; Reuss *et al.*, 1988). Formaldehyde is also used directly to inhibit corrosion, in mirror finishing and electroplating, in the electrodeposition of printed circuits and in photographic film development (Reuss *et al.*, 1988).

Paraformaldehyde is used in place of aqueous formaldehyde solutions, especially when the presence of water interferes, e.g. in the plastics industry for the preparation of phenol, urea and melamine resins, varnish resins, thermosets and foundry resins. Other uses include the synthesis of chemical and pharmaceutical products (e.g. Prins reaction, chloromethylation, Mannich reaction), the production of textile products (e.g. for crease-resistant finishes), preparation of disinfectants and deodorants (Reuss *et al.*, 1988) and in selected pesticide applications (United States Environmental Protection Agency, 1993).

The pattern of use of formaldehyde in the United States in 1992 (3 million tonnes) was: urea–formaldehyde resins, 24%; phenolic resins, 21%; acetylenic chemicals (precursors to diol monomers), 11%; polyacetal resins, 9%; pentaerythritol, 6%; urea–formaldehyde concentrates, 5%; diphenylmethane diisocyanate, 5%; hexamethylenetetramine, 4%; melamine, 4%; other (including chelating agents, trimethylolpropane, pyridine chemicals), 10% (Anon., 1992). The pattern of use in Japan in 1992 (1.4 million tonnes) was: urea–melamine adhesive, 25.4%; polyacetal resins, 22.7%; pentaerythritol, 7.4%; phenolic resins, 7.3%; paraformaldehyde, 6.0%; diphenylmethane diisocyanate, 4.4%; urea–melamine resin, excluding adhesives, 3.3%; hexamethylenetetramine, 3.1%; other uses, 20.1% (Japan Chemical Week, 1993).

1.3 Occurrence

The natural and man-made sources of formaldehyde in the environment and environmental levels in indoor and outdoor air, water, soil and food have been reviewed (WHO, 1989; see also IARC, 1982). Information on sources and emissions of formaldehyde in the United States has been compiled by the Environmental Protection Agency (Vaught, 1991).

1.3.1 Natural occurrence

Formaldehyde is ubiquitous in the environment; it is an important endogenous chemical that occurs in most life forms, including humans. It is formed naturally in the troposphere during the oxidation of hydrocarbons, which react with hydroxyl radicals and ozone to form formaldehyde and other aldehydes, as intermediates in a series of reactions that ultimately lead to the formation of carbon monoxide and dioxide, hydrogen and water. Of the hydrocarbons found in the troposphere, methane is the single most important source of formaldehyde. Terpenes and isoprene, emitted by foliage, react with hydroxyl radicals, forming formaldehyde

as an intermediate product. Because of their short half-life, these potentially important sources of formaldehyde are important only in the vicinity of vegetation. Formaldehyde is one of the volatile compounds formed in the early stages of decomposition of plant residues in the soil (WHO, 1989), and it occurs naturally in fruits and other foods (WHO, 1991).

1.3.2 Occupational exposure

(a) Extent of exposure

As nonoccupational exposure to formaldehyde is ubiquitous, all work, e.g. in offices, contributes to total human exposure. About 1 500 000 workers in the United States in 1981–83 were estimated in the National Occupational Exposure Survey to be exposed to formaldehyde all or part of the time, representing about 0.6% of the population of the country. Industries in which more than 50 000 workers were exposed included health services, business services, printing and publishing, manufacture of chemicals and allied products, apparel and allied products, paper and allied products, personal services, machinery except electrical, transport equipment and furniture and fixtures. The minimal exposure to formaldehyde was not specified in this survey (United States National Institute for Occupational Safety and Health, 1990). In Finland, 9000–10 000 workers, representing about 0.2% of the Finnish population, were estimated to have been exposed to an 8-h time-weighted concentration of at least 0.3 mg/m^3 during at least one day per year. If the minimal level considered is decreased to 0.15 mg/m^3 (0.12 ppm), the number of people exposed increases by many thousands (Heikkilä *et al.*, 1991). It is impossible to estimate accurately the number of people occupationally exposed to formaldehyde worldwide, but it is likely to be several millions in industrialized countries alone.

Formaldehyde occurs in occupational environments mainly as gas. Inhalation of formaldehyde-containing particulates may occur when paraformaldehyde or powdered resins are being used. For example, production of solid resins may include dust-forming operations, such as drying, crushing grinding and screening (Stewart *et al.*, 1987b). Formaldehyde-based resins may also occur in air attached to carrier agents, such as wood dust from sawing of plywood (Kauppinen, 1986). Dermal exposure to formaldehyde is possible when formalin solutions or liquid resins come into contact with the skin.

(b) Manufacture of formaldehyde, formaldehyde-based resins and other chemical products

The concentrations of formaldehyde measured in the 1980s during the manufacture of formaldehyde and formaldehyde-based resins are summarized in Table 3. The mean levels during manufacture were below 1 ppm (1.2 mg/m^3). The values are sometimes reported as geometric means, which give less weight to occasional heavy exposures than arithmetic means. The workers may also be exposed to methanol (raw material), carbon monoxide, carbon dioxide and hydrogen (process gases) (Stewart *et al.*, 1987b).

The reported mean concentrations in the air of factories producing formaldehyde-based resins vary from < 1 to > 10 ppm (< 1.23–> 12.3 mg/m^3) . There are obvious differences between the factories but no consistent seasonal variation. The earliest measurements are from 1979. The chemicals other than formaldehyde to which exposure may occur depend on the types

of resins manufactured: Urea, phenol, melamine and furfural alcohol are the chemicals most commonly reacted with liquid formaldehyde (formalin) or hexamethylenetetramine. Some processes require addition of ammonia. Alcohols are used as solvents in the production of liquid resins (Stewart *et al.*, 1987b).

Some potential occupational exposures to formaldehyde

Agricultural workers
Anatomists
Beauticians
Biologists
Bookbinders
Botanists
Chemical production workers
Cosmetic formulators
Crease-resistant textile finishers
Disinfectant makers
Disinfectors
Dress-goods shop personnel
Electrical insulation makers
Embalmers
Embalming-fluid makers
Fireproofers
Formaldehyde production workers
Formaldehyde resin makers
Foundry employees (see IARC, 1984)
Fumigators (see IARC, 1991)
Fur processors (see IARC, 1981)
Furniture makers (see IARC, 1981)
Glue and adhesive makers
Hide preservers (see IARC, 1981)
Histology technicians (including necropsy and autopsy technicians)
Ink makers
Lacquerers and lacquer makers
Medical personnel (including pathologists)
Mirror manufacturers
Paper makers (see IARC, 1981)
Particle-board makers (see IARC, 1981)
Photographic film makers
Plastics workers
Plywood makers
Rubber makers (see IARC, 1982)
Taxidermists
Textile mordanters and printers
Textile waterproofers
Varnish workers (see IARC, 1981)
Wood preservers (see IARC, 1981)

From United States National Institute for Occupational Safety and Health (1976)

No measurements were available to the Working Group of exposure to formaldehyde in other chemical plants where it is used, e.g. in the production of pentaerythritol, hexamethylenetetramine or ethylene glycol.

(c) Manufacture of wood products and paper

Table 4 is a summary of the formaldehyde concentrations in wood and pulp and paper industries. Formaldehyde-based glues have been used in the assembly of plywood for over 30 years. The highest mean concentrations are usually measured in glueing departments, where the glue mixture is prepared, veneers are glued to form plywood and the plywood is cured in hot presses; the mean levels were usually > 1 ppm (1.2 mg/m^3) before the mid-1970s but have been below that level more recently. This decrease in levels is consistent in each operation and is due

Table 3. Concentrations of formaldehyde (in ppm [mg/m^3]) in the workroom air in formaldehyde and resin manufacturing plants

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Chemical factory producing formaldehyde and formaldehyde resins (Sweden)	62	0.2 [0.3]	0.04–0.4 [0.05–0.5]	1979–85	Holmström *et al.* (1989a)
Production of formaldehyde (Sweden)	9	0.3 [0.34]		1980s	Rosén *et al.* (1984)
Formaldehyde manufacture (USA)				1983	Stewart *et al.* (1987b)
Plant no. 2, summer	15	0.6[b] [0.7]	0.03–1.9 [0.04–2.3]		
Plant no. 10, summer	9	0.7[b] [0.9]	0.6–0.8 [0.7–1.0]		
Resin plant (Finland)					Heikkilä *et al.* (1991)
Furan resin production	3	2.3 [2.9]	1.0–3.4 [1.3–4.2]	1982	
Maintenance	4	2.9 [3.6]	1.4–5.5 [1.8–6.9]	1981	
Urea–formaldehyde resin production	7	0.7 [0.87]	0.6–0.8 [0.7–1.1]	1981	
Resin manufacture (Sweden)	22	0.5 [0.6]		1980s	Rosén *et al.* (1984)
Resin manufacture (USA)				1983–84	Stewart *et al.* (1987b)
Plant no. 1, summer	24	3.4[b] [4.2]	0.2–13.2 [0.3–16.2]		
Plant no. 6, summer	6	0.2[b,c] [0.3]	0.1–0.2 [0.1–0.3]		
Plant no. 7, summer	9	0.2[b] [0.3]	0.1–0.3 [0.1–0.4]		
Plant no. 7, winter	9	0.6[b] [0.7]	0.4–0.9 [0.5–1.1]		
Plant no. 8, summer	13	0.4[b–d] [0.7]	0.2–0.8 [0.3–1.0]		
Plant no. 8, winter	9	0.1[b–d] [0.1]	0.1–0.2 [0.1–0.3]		
Plant no. 9, summer	8	14.2[b–d] [17.5]	4.1–30.5 [5.0–37.5]		
Plant no. 9, winter	9	1.7[b] [2.1]	1.1–2.5 [1.4–3.1]		
Plant no. 10, summer	23	0.7[b,d] [0.9]	0.3–1.2 [0.4–1.5]		
Special chemical manufacturing plant (USA)	8		< 0.03–1.6 [0.04–2.0]		Blade (1983)

[a] Arithmetic mean unless otherwise specified

[b] Mean and range of geometric means

Some of the results were affected by the simultaneous occurrence in the samples (Stewart *et al.*, 1987b) of:

[c] phenol (leading to low values)

[d] particulates containing nascent formaldehyde (leading to high values).

Table 4. Concentrations of formaldehyde (in ppm [mg/m^3]) in the workroom air of plywood mills, particle-board mills, furniture factories, other wood product plants and paper mills

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Plywood mills					
Plywood factory (Italy)				NR	Ballarin *et al.* (1992)
Warehouse	3	O.3 [0.4]	0.1–0.5 [0.2–0.6]		
Shearing press	8	0.08 [0.1]	0.06–0.11 [0.08–0.14]		
Plywood mills (Finland)					Kauppinen (1986)
Glue preparation, short-term	15	2.2 [2.7]	0.6–5.0 [0.7–6.2]	1965–74	
Glue preparation, short-term	19	0.7 [0.9]	0.1–2.3 [0.1–2.8]	1975–84	
Assembling	32	1.5 [1.9]	<0.1–4.4 [< 0.1–5.4]	1965–74	
Assembling	55	0.6 [0.7]	0.02–6.8 [0.03–8.3]	1975–84	
Hot pressing	41	2.0 [2.5]	<0.1–7.7 [< 0.1–9.5]	1965–74	
Hot pressing	43	0.5 [0.6]	0.06–2.1 [0.07–2.6]	1975–84	
Sawing of plywood	5	0.5 [0.6]	0.3–0.8 [0.4–1.0]	1965–74	
Sawing of plywood	12	0.1 [0.1]	0.02–0.2 [0.03–0.3]	1975–84	
Coating of plywood	7	1.0 [1.2]	0.5–1.8 [0.6–2.2]	1965–74	
Coating of plywood	28	0.3 [0.4]	0.02–0.6 [0.03–0.7]	1975–84	
Plywood mill (Indonesia)	40	0.6 [0.8]	0.2–2.3 [0.3–2.8]	NR	Malaka & Kodama (1990)
Plywood production (Sweden)	47	0.3 [0.36]		1980s	Rosén *et al.* (1984
Plywood panelling manufacture (USA)				1983–84	Stewart *et al.* (1987b)
Plant no 3, winter	27	0.2[b] [0.3]	0.08–0.4 [1.0–0.5]		
Plant no 3, summer	26	0.1[b] [0.1]	0.01–0.5 [0.01–0.6]		
Particle-board mills					
Particle-board mills (Finland)					Kauppinen & Niemelä (1985)
Glue preparation	10	2.2 [2.7]	0.3–4.9 [0.4–6.0]	1975–84	
Blending	10	1.0 [1.2]	0.1–2.0 [0.1–2.5]	1965–74	
Blending	8	0.7 [0.9]	<0.1–1.4 [< 0.1–1.7]	1975–84	
Forming	26	1.7 [2.1]	<0.5–4.6 [< 0.6–5.7]	1965–74	

Table 4 (contd)

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Particle-board mills (contd)					
Particle-board mills (Finland) (contd)					
Forming	32	1.4 [1.7]	0.1–4.8 [0.1–5.9]	1975–84	
Hot pressing	35	3.4 [4.2]	1.1–9.5 [1.4–11.7]	1965–74	
Hot pressing	61	1.7 [2.1]	0.2–4.6 [0.25–5.7]	1975–84	
Sawing	17	4.8 [5.9]	0.7–9.2 [0.9–11.3]	1965–74	
Sawing	36	1.0 [1.2]	< 0.1–3.3 [< 0.1–4.1]	1975–84	
Coating	7	1.0 [1.2]	0.5–1.8 [0.6–2.2]	1965–74	
Coating	12	0.4 [0.5]	0.1–1.2 [0.1–1.5]	1975–84	
Particle-board mill (Indonesia)	9	2.4 [3.0]	1.2–3.5 [1.5–4.3]	NR	Malaka & Kodama (1990)
Particle-board production (Sweden)	21	0.3 [0.4]		1980s	Rosén *et al.* (1984)
Chip-board production (Germany)	24	1.5 [1.9]	< 0.01–8.4 [< 0.01–10]	1980–88	Triebig *et al.* (1989)
Block-board mill (Indonesia)	6	0.5 [0.6]	0.4–0.6 [0.5–0.7]	NR	Malaka & Kodama (1990)
Medium-density fibre-board production (Sweden)	19	0.2 [0.3]		1980s	Rosén *et al.* (1984)
Furniture factories					
Furniture factories, surface finishing with acid curing paints (Sweden)				NR	Alexandersson & Hedenstierna (1988)
Paint mixer/supervisor	6	0.2 [0.3]	0.1–0.4 [0.2–0.5]		
Mixed duties on the line	5	0.4 [0.5]	0.3–0.5 [0.3–0.6]		
Assistant painters	3	0.5 [0.6]	0.2–0.7 [0.2–0.9]		
Spray painters	10	0.4 [0.5]	0.1–1.1 [0.2–1.3]		
Feeder/receiver	13	0.2 [0.3]	0.1–0.8 [0.1–0.9]		
Furniture factories (Finland)				1981–86	Heikkilä *et al.* (1991)
Glueing	73	0.3 [0.4]	0.07–1.0 [0.09–1.2]		
Machining in finishing department	9	0.3 [0.5]	0.1–0.9 [0.1–1.1]		
Varnishing	150	1.1 [1.4]	0.1–6.3 [0.1–7.9]		

Table 4 (contd)

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Furniture factories (contd)					
Furniture factories (Finland) (contd)				1975–84	Priha *et al.* (1986)
Feeding painting machine	14	1.1 [1.4]	0.3–2.7 [0.4–3.3]		
Spray painting	60	1.0 [1.2]	0.2–4.0 [0.3–5.0]		
Spray painting assistance	10	1.0 [1.2]	0.2–1.6 [0.3–2.0]		
Curtain painting	18	1.1 [1.4]	0.2–6.1 [0.3–7.5]		
Before drying of varnished furniture	34	1.5 [1.8]	0.1–4.2 [0.1–5.2]		
After drying of varnished furniture	14	1.4 [1.7]	0.2–5.4 [0.3–6.6]		
Furniture factories (Sweden)				1980s	Rosén *et al.* (1984)
Varnishing with acid-cured varnishes	32	0.7 [0.9]			
Manufacture of furniture (Denmark)				NR	Vinzents & Laursen (1993)
Painting	43	0.2 [0.3]	0.15–0.2 [0.2–0.24]		
Glueing	68	0.1 [0.2]	0.1–0.14 [0.1–0.2]		
Cabinet-making (Canada)	48		<0.1 [< 0.1]	NR	Sass-Kortsak *et al.* (1986)
Other wood product plants					
Match mill, impregnation of matchbox parts, short-term (Finland)	2	2.0 [2.5]	1.9–2.1 [2.3–2.6]	1963	FIOH (1994)
Wooden container mill, glueing and sawing (Finland)	6	0.3 [0.4]	0.2–0.4 [0.3–0.5]	1961	FIOH (1994)
Manufacture of wooden bars (Finland)				1983	Heikkilä *et al.* (1991)
Glueing	33	0.6 [0.7]	0.16–1.9 [0.2–2.4]		
Machining	7	1.2 [1.5]	0.2–2.2 [0.3–2.7]		
Parquet plant (Finland)				1981	Heikkilä *et al.* (1991)
Machining	3	0.3 [0.4]	0.16–0.5 [0.2–0.6]		
Varnishing	5	0.8 [1.0]	0.2–1.4 [0.3–1.7]		
Production of wooden structures (Finland)				1981–86	Heikkilä *et al.* (1991)
Glueing	36	0.7 [0.8]	0.07–1.8 [0.1–2.2]		
Machining	19	0.4 [0.44]	0.1–0.8 [0.1–0.9]		
Glueing in wood industry (Sweden)	65	0.2 [0.26]		1980s	Rosén *et al.* (1984)

Table 4 (contd)

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Paper mills					
Paper mill (Finland)					Finnish Institute of Occupational Health (1994)
Glueing, hardening, lamination and rolling of special paper	12	0.9 [1.1]	0.3–2.5 [0.4–3.1]	1971–73	
Impregnation of paper with phenol resin, partly short-term	38	7.4 [9.1]	< 1.0–33.0 [< 1.1–40.6]	1968–69	
Paper storage, diesel truck traffic	5	0.3 [0.4]	0.2–0.4 [0.25–0.5]	1969	
Paper mill (Finland)				1975–84	Heikkilä *et al.* (1991)
Coating of paper	30	0.7 [0.9]	0.4–31 [0.5–39]		
Gum paper production	4	0.4 [0.5]	0.3–0.6 [0.3–0.8]		
Impregnation of paper with amino resin	6	3.1 [3.9]	0.5–13 [0.6–16]		
Impregnation of paper with phenol resin	20	0.1 [0.1]	0.05–0.3 [0.06–0.4]		
Laminated paper production (Sweden)	23	0.3 [0.39]		1980s	Rosén *et al.* (1984)
Manufacture of offset paper (Sweden)	8	0.2 [0.21]		1980s	Rosén *et al.* (1984)
Lamination and impregnation of paper with melamine and phenol resins (USA)				1983	Stewart *et al.* (1987b)
Plant no 6, summer	53	0.7[b–d] [0.9]	< 0.01–7.4 [< 0.01–9.1]		
Plant no 6, winter	39	0.3[b,d] [0.4]	0.05–0.7 [0.06–0.9]		

NR, not reported

[a] Arithmetic mean unless otherwise specified

[b] Mean and range of geometric means

Some of the results were affected by the simultaneous occurrence in the samples (Stewart *et al.*, 1987) of:

[c] phenol (leading to low values)

[d] particulates containing nascent formaldehyde (leading to high values).

mainly to the introduction of glues that release less formaldehyde (Kauppinen, 1986). Other exposures in plywood mills include wood dust (see monograph, p. 74), phenol (see IARC, 1989a), pesticides (see IARC, 1991), heating products from coniferous veneers, solvents from coating materials and engine exhaust from forklift trucks (see IARC, 1989b). These exposures are described in more detail in the monograph on wood dust.

Particle-board mills, which started operating in many countries in the 1950s, use urea–formaldehyde resins, which are mixed with wood particles to form particle-board and then cured in hot presses. Phenol–, melamine– and resorcinol–formaldehyde resins are less commonly used in particle-board mills than in plywood mills, mainly for economic reasons. The levels of formaldehyde measured in particle-board mills before the mid-1970s were high—often well over 2 ppm (2.5 mg/m^3)—but the development of glues with a lower formaldehyde content and ventilation systems have decreased the levels to about 1 ppm (1.2 mg/m^3) or below (Kauppinen & Niemelä, 1985). Other exposures in particle-board and other reconstituted-board mills are usually similar to those in plywood mills. Exposure to wood dust is described in detail in the monograph on wood dust.

Furniture varnishes may contain urea–formaldehyde (carbamide) resins dissolved in organic solvents. Finnish workers varnishing, lacquering or painting wooden furniture in 1975–84 were continuously exposed to an average level of about 1 ppm (1.2 mg/m^3) formaldehyde (Priha *et al.*, 1986), but the levels decreased slightly during this period. The levels in Sweden in the 1980s were somewhat lower (Rosén *et al.*, 1984; Alexandersson & Hedenstierna, 1988). Formaldehyde-based glues are also used occasionally in veneering wood-based boards, but the levels associated with glueing are generally lower, 0.1–0.3 ppm [0.12–0.37 mg/m^3] (Heikkilä *et al.*, 1991; Vinzents & Laursen, 1993). Other exposures in furniture factories are to wood dust, organic solvents and pigments, described in detail in the monograph on wood dust.

Some paper mills produce special products coated with formaldehyde-based phenol or amino (urea or melamine) resins. Coating agents and other chemicals used in paper mills may also contain formaldehyde as a bactericide. The average levels related to lamination and impregnation of paper in a mill in the United States in the 1980s were below 1 ppm (Stewart *et al.*, 1987b). In Sweden and Finland, the levels of formaldehyde are also usually below 1 ppm, but there is considerable variation, depending on the resin used and the product manufactured. The earliest measurements, from the late 1960s, suggest that much higher exposure may occur in some circumstances (Table 4). Other exposures in paper-coating mills include phenol, urea, melamine, paper dust, solvents and engine exhaust from factory trucks.

(d) Manufacture of textiles and garments

The use of formaldehyde-based resins to produce crease-resistant fabrics started in the 1950s. The early resins contained substantial amounts of extractable formaldehyde: over 0.4% by weight of fabric. Introduction of dimethyloldihydroxyethyleneurea resins in 1970 reduced the levels of free formaldehyde in fabrics to 0.15–0.2%. Since then, methylation of dimethyloldihydroxyethyleneurea and other modifications of the resin have decreased the level of formaldehyde gradually to 0.01–0.02% (Elliott *et al.*, 1987). Some flame-retardants, such as Pyrovatex CP, however, contain agents that release formaldehyde (Heikkilä *et al.*, 1991).

Measurements of formaldehyde in the air of textile mills in the late 1970s and 1980s show average levels of 0.2–2 ppm (0.25–2.5 mg/m^3) (Table 5). Levels were probably higher in the 1950s and 1960s because the content of free formaldehyde in resins was higher (Elliott *et al.*, 1987). Finishing workers in textile mills may also be exposed to textile dyes, flame retardants, carrier agents, textile finishing agents and solvents. The exposures of textile workers are described in an earlier monograph (IARC, 1990b).

Measurements from the 1980s indicated that the formaldehyde levels in the garment industry were relatively low, usually averaging 0.1–0.2 ppm (0.12–0.25 mg/m^3) (Table 5). Exposures in the past were probably higher owing to the higher content of formaldehyde in fabrics. For example, the mean formaldehyde concentration in air increased from 0.1 to 1.0 ppm (0.12–1.23 mg/m^3) in a study in the United States when the formaldehyde content of the fabric increased from 0.015 to 0.04% (Luker & Van Houten, 1990). The concentration of formaldehyde was reported to have been 0.9–2.7 ppm (1.1–3.3 mg/m^3) in a post-cure garment manufacturing plant and 0.3–2.7 ppm (0.4–3.3 mg/m^3) in eight other garment plants in the United States in 1966. Few chemicals other than formaldehyde are used in garment factories. Cutting and sewing of fabrics release low levels of textile dust, and small amounts of chlorinated organic solvents are used in cleaning spots. Pattern copying machines may emit ammonia and dimethylthiourea in some plants (Elliott *et al.*, 1987).

(e) Manufacture of metal products, mineral wool and other products

Formaldehyde-based resins are commonly used as core binders in foundries. Urea–formaldehyde resin is usually blended with oleoresin or phenol–formaldehyde resin and mixed with sand to form a core, which is then cured by baking in an oven or by heating from inside the core box (hot box method). The original hot box binder was a mixture of urea–formaldehyde resin and furfuryl alcohol, commonly referred to as furan resin. The furan resins were then modified with phenol to produce urea–formaldehyde/furfuryl alcohol, phenol–formaldehyde/-furfuryl alcohol and phenol–formaldehyde/urea–formaldehyde resins. The mean levels of formaldehyde measured in core-making and operations following core-making in the 1980s in Sweden and Finland were usually below 1 ppm (Table 6); however, measurements made before 1975 suggest that past exposures may have been considerably higher (Heikkilä *et al.*, 1991). Many other chemicals occur in foundries, e.g. silica (IARC, 1987c) and other mineral dusts, polynuclear aromatic hydrocarbons (IARC, 1983), asbestos (IARC, 1987d), metal fumes and dusts, carbon monoxide, isocyanates (IARC, 1986a), phenols (IARC, 1989a), organic solvents and amines. These have been described in a previous monograph (IARC, 1984).

Phenol–formaldehyde resins are commonly used to bind man-made mineral fibre products. Measurements in glass-wool and stone-wool plants in the 1980s showed mean concentrations of 0.1–0.2 ppm (0.12–0.25 mg/m^3) formaldehyde (Table 6). Highest levels were measured occasionally in Finnish factories close to cupola ovens and hardening chambers (Heikkilä *et al.*, 1991). Other exposures in man-made mineral fibre production were described in a previous monograph (IARC, 1988).

Formaldehyde-based plastics are used in the production of electrical parts, dishware and various other plastic products. The concentrations of formaldehyde measured in such industries

Table 5. Concentrations of formaldehyde (in ppm [mg/m^3]) in the workroom air of textile mills and garment factories

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Textile mills					
Textile plants (Finland)				1975–78	Nousiainen & Lindqvist (1979)
Finishing department, mixing	8	0.8 [1.1]	< 0.2–>5 [< 0.2–> 6]		
Crease-resistant treatment	52	0.4 [0.5]	< 0.2–>3 [< 0.2–> 4]		
Finishing department (excluding crease-resistant and flame-retardant treatment)	17	0.3 [0.4]	< 1.3 [< 1.5]		
Flame-retardant treatment	67	1.9 [2.5]	< 0.2–>10 [< 0.2–> 11]		
Fabric store	6	0.8 [1.1]	0.1–1.3 [0.1–1.6]		
Textile mills (Sweden)				1980s	Rosén *et al.* (1984)
Crease-resistant treatment	29	0.2 [0.23]			
Flame-retardant treatment	2	1.2 [1.5]			
Garment factories					
Manufacture from crease-resistant cloth (USA)	181		< 0.1–0.9 [< 0.1–1.1]		Blade (1983)
Manufacture of shirts from fabric treated with formaldehyde-based resins (USA)	326	~0.2 [~0.25]	< 0.1–0.4 [< 0.1–0.5]	1980s	Elliott *et al.* (1987)
Garment industry (Finland)				1981–86	Heikkilä *et al.* (1991)
Handling of leather	3	0.1 [0.1]	0.02–0.1 [0.03–0.13]		
Pressing	32	0.2 [0.3]	0.02–0.7 [0.03–0.86]		
Sewing	15	0.1 [0.1]	0.02–0.3 [0.05–0.34]		
Sewing plant (USA)				NR	Luker & Van Houten (1990)
Processing of 0.04% formaldehyde fabric	9	1.0 [1.2]	0.5–1.1 [0.6–1.4]		
Processing of 0.016% formaldehyde fabric	9	0.1 [0.1]	< 0.1–0.2 [< 0.1–0.25]		

NR, not reported

Table 6. Concentrations of formaldehyde (in ppm [mg/m^3]) in the workroom air of foundries and other industrial facilities

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Foundries					
Foundries (Finland)					Heikkilä *et al.* (1991)
Coremaking	43	2.8 [3.4]	< 0.1–> 10 [< 0.1–> 11]	Before 1975	
Coremaking	17	0.3 [0.4]	0.02–1.4 [0.03–1.8]	1981–86	
Casting	10	0.15 [0.19]	0.02–0.2 [0.03–0.8]	1981–86	
Moulding	25	0.3 [0.39]	0.04–2.0 [0.05–2.5]	1981–86	
Foundries (Sweden)					Åhman *et al.* (1991)
Moulders and coremaker handling furan resin sand (8-h TWA)	36	0.1 [0.1]	0.02–0.2 [0.02–0.27]	NR	
Foundry (Sweden)				1980s	Rosén *et al.* (1984)
Hotbox method	5	1.5 [1.9]			
Moulding	17	0.1 [0.12]			
Man-made mineral fibre plants					
(Finland)				1981–86	Heikkilä *et al.* (1991)
Production	36	0.2 [0.25]	0.02–1.5 [0.03–1.7]		
Form pressing	24	0.1 [0.11]	0.01–0.3 [0.01–0.44]		
(Sweden)				1980s	Rosén *et al.* (1984)
Production	16	0.15 [0.19]			
Form pressing	4	0.16 [0.20]			
Plastics production					
Plastics production (Finland)				1981–86	Heikkilä *et al.* (1991)
Casting of polyacetal resin	10	0.3 [0.36]	0.06–0.7 [0.08–0.82]		
Casting of urea–formaldehyde resin	4	0.4 [0.46]	0.2–0.5 [0.27–0.59]		
Casting of other plastics	29	< 0.1	< 0.1–0.2 [< 0.1–0.3]		

Table 6 (contd)

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Plastics production (contd)					
Production of moulded plastic products (USA)				1983–84	Stewart *et al.* (1987b)
Plant no. 8, phenol resin, summer	10	0.5[b] [0.6]	0.1–0.9 [0.1–1.1]		
Plant no. 9, melamine resin, summer	13	9.2[b] [11.3]	< 0.01–26.5 [< 0.01–32.6]		
Moulding compound manufacture (USA)				1983–84	Stewart *et al.* (1987b)
Plant no. 9, winter	9	2.8[b] [3.4]	0.04–6.7 [0.05–8.2]		
Plant no. 9, summer	18	38.2[b,c] [45]	9.5–60.8 [11.7–74.8]		
Plant no. 1, winter	12	1.5[b] [1.8]	0.9–2.0 [1.1–2.1]		
Plant no. 1, summer	24	9.7[b] [11.9]	3.8–14.4 [4.7–17.7]		
Plant no. 8, winter	13	0.3[b] [0.4]	0.07–0.7 [0.09–0.9]		
Plant no. 7, summer	43	0.3[b] [0.4]	0.05–0.6 [0.06–0.8]		
Plant no. 2, summer	15	6.5[b] [8.0]	0.3–20.6 [0.4–25.3]		
Metalware plant, bake painting (Finland)	18	0.3 [0.4]	0.03–0.7 [0.04–0.9]	1981–86	Heikkilä *et al.* (1991)
Electrical machinery manufacture (Finland)				1977–79	Niemelä & Vainio (1981)
Soldering	47	< 0.1			
Lacquering and treatment of melamine plastics	8	0.35 [0.4]			
Painting with bake-drying paints (Sweden)	13	< 0.1		1980s	Rosén *et al.* (1984)
Miscellaneous					
Photographic film manufacture (USA)				1983–84	Stewart *et al.* (1987b)
Plants no. 4 and 5, summer	49	0.1[b]	< 0.01–0.4 [< 0.01–0.5]		
Plants no. 4 and 5, winter	29	0.3[b] [0.4]	0.02–0.9 [0.03–1.1]		
Print (Finland)				1981–86	Heikkilä *et al.* (1991)
Development of photographs	11	0.04 [0.05]	0.02–0.1 [0.03–0.13]		

Table 6 (contd)

Industry and operation	No. of measurements	Mean[a]	Range	Year	
Miscellaneous (contd)					
Photographic laboratories (Finland)	10	0.07 [0.09]	0.02–0.3 [0.03–0.40]	1981–86	Heikkilä *et al.* (1991)
Abrasive production (Sweden)	20	0.2 [0.3]		1980s	Rosén *et al.* (1984)
Coal coking plant (former Czechoslovakia)	NR	0.05[d] [0.06]	< 0.01–0.25 [< 0.01–0.3]	NR	Mašek (1972)
Pitch coking plant (former Czechoslovakia)	NR	0.4[d] [0.5]	0.05–1.6 [0.07–2.0]	NR	Mašek (1972)
Rubber processing (USA)	NR	NR	0.4–0.8 [0.5–0.98]	1975	IARC (1982)
Sugar mill (Sweden)				1980s	Rosén *et al.* (1984)
Preservation of sugar beets	26	0.4 [0.5]	NR		
Malt barley production (Finland)				1981	Heikkilä *et al.* (1991)
Preservation of malt barley	6	0.7 [0.9]	0.4–1.5 [0.5–1.8]		

[a]Arithmetic mean unless otherwise specified
[b]Mean of geometric mean
[c]Some of the results were affected by the simultaneous occurrence in the samples (Stewart *et al.*, 1987b) of particulates containing formaldehyde (leading to high values)
[d]Mean of arithmetic means

have usually been < 1 ppm, but much higher exposures may occur (Table 6). Plastic dust and fumes may be present in the atmospheres of moulded plastics product plants, and exposures in these facilities are usually considerably higher than those in facilities where the products are used. The mean concentration of formaldehyde was > 1 ppm in many plants in the United States where moulding compounds were used. Some workers may be exposed to pigments, lubricants and fillers (e.g. asbestos and wood flour) used as constituents of moulding compounds (Stewart *et al.*, 1987b).

Heating of bake-drying paints and soldering may release some formaldehyde in plants where metalware and electrical equipment are produced, but the measured levels are usually well below 1 ppm (Table 6).

The mean concentrations of formaldehyde measured during coating of photographic films and during development of photographs are usually well below 1 ppm (Table 6). Methanol, ethanol, acetone and ammonia are other volatile agents that may occur in film manufacturing facilities (Stewart *et al.*, 1987b). Skin contact with numerous photographic chemicals occurs occasionally in photographic laboratories.

Formaldehyde is also used or formed during many other industrial operations, such as preservation of fur, leather, barley and sugar beets, coal and pitch coking, rubber processing and abrasive production. Some of these activities may entail heavy exposure. For example, treatment of furs with formaldehyde resulted in the highest exposure to formaldehyde of all jobs and industries studied in a large Swedish survey in the early 1980s. The 8-h time-weighted average concentration of formaldehyde was assessed to be 0.8–1.6 ppm (1.0–2.0 mg/m^3), and high peak exposures occurred many times per day (Rosén *et al.*, 1984).

(f) Mortuaries, hospitals and laboratories

Formaldehyde is used as a tissue preservative and disinfectant in embalming fluids. Some parts of bodies to be embalmed are also cauterized and sealed with a hardening compound that contains paraformaldehyde powder. The concentration of formaldehyde in the air during embalming depends on the content of embalming fluid, type of the body, ventilation and work practices; the mean level is about 1 ppm (Table 7). Embalming of a normal intact body usually takes about 1 h. A survey in West Virginia (United States of America) in 1979 showed that undertakers prepare an average of 75 bodies per year, 15 of which have been autopsied; the 8-h time-weighted average exposure is therefore likely to be 0.1–0.4 ppm (0.1–0.5 mg/m^3). Disinfectant sprays are occasionally used which may release small amounts of solvents, such as isopropanol (Williams *et al.*, 1984). Methanol is used as a stabilizer in embalming fluids, and levels of 0.5–22 ppm (0.7–28.4 mg/m^3) have been measured during embalming. Low levels of phenol have also been detected in embalming rooms (Stewart *et al.*, 1992).

Formaldehyde is widely used in hospitals for disinfection. The mean concentrations, summarized in Table 7, range from 0.1 to 0.8 ppm (0.1–1.0 mg/m^3), but many of the measurements were made during disinfection, which usually takes a relatively short time. Low levels are found when detergents are used for cleaning; higher levels, which may occasionally exceed 1 ppm, occur when more concentrated formalin solutions are used, e.g. during the disinfection of operating theatres and dialysers (Salisbury, 1983).

Table 7. Concentrations of formaldehyde (in ppm [mg/m^3]) in the workroom air of mortuaries, hospitals and laboratories

Industry and operation (type of sample)	No. of measurements	Mean[a]	Range	Year	Reference
Embalming, six funeral homes (USA)	NR	0.7 [0.9]	0.09–5.3 [0.1–6.5]	NR	Kerfoot & Mooney (1975)
Embalming, 23 mortuaries (USA)	NR	1.1 [1.4]	0.03–3.15 [0.04–3.9]	NR	Lamont Moore & Ogrodnik (1986)
8-h TWA		0.16 [0.2]	0.01–0.49 [0.01–0.6]		
Embalming, seven funeral homes				1980	Williams *et al.* (1984)
Intact bodies (personal samples)	8	0.3 [0.4]	0.18–0.3 [0.2–0.4]		
Autopsied bodies (personal samples)	15	0.9 [1.1]	2.1 [0–2.6]		
Embalming (USA)				NR	Stewart *et al.* (1992)
Personal samples	25	2.58 [3.2]	0.31–8.72 [0.4–10.7]		
Area 1	25	2.03 [3.0]	0.23–7.52 [0.3–9.2]		
Area 2	25	2.16 [2.7]	0.28–8.15 [0.3–10.0]		
Embalming (Canada)				NR	Korczynski (1994)
Intact bodies (personal samples)	24	0.6 [0.8]	0.10–4.57 [0.12–5.64]		
Autopsied bodies (personal samples)	24	0.6 [0.8]	0.09–3.35 [0.11–4.13]		
Area samples	72	0.5 [0.6]	0.04–6.79 [0.05–8.37]		
Autopsy service (USA)[b]				NR	Coldiron *et al.* (1983)
Personal samples	27	1.3[c] [1.66]	0.4–3.28 [0.5–4.0]		
Area samples	23	4.2 [5]	0.1-13.6 [0.1-16.7]		
Autopsy (Finland)	5	0.7 [0.8]	< 0.1–1.4 [< 0.1–1.7]	1981–86	Heikkilä *et al.* (1991)
Anatomical theatre (Germany)	29	1.1[d] [1.4]	0.7–1.7 [0.9–2.2]	1980–88	Triebig *et al.* (1989)
Cleaning hospital floors with detergent containing formaldehyde (38–74 min) (Italy) (personal)	4	0.18 [0.22]	0.15–0.21 [0.18–0.26]		Bernardini *et al.* (1983)
Disinfecting operating theatres (Germany)[b]				NR	Binding & Witting (1990)
3% cleaning solution	43	0.8 [1.1]	0.01–5.1 [0.01–6.3]		
0.5 % cleaning solution	26	0.2 [0.22]	0.01–0.43 [0.01–0.53]		
Disinfecting operating theatres (Germany)	43	0.4[c] [0.5]	0.04–1.4 [0.05–1.7]	NR	Elias (1987)

Table 7 contd

Industry and operation (type of sample)	No. of measurements	Mean[a]	Range	Year	Reference
Disinfection of dialysis clinic (USA), personal samples (37–63 min)	7	0.6 [0.8]	0.09–1.8 [0.12–2.2]	1983	Salisbury (1983)
Disinfection in hospitals (Finland)	18	0.1 [0.14]	0.03–0.2 [0.04–0.3]	1981–86	Heikkilä *et al.* (1991)
Bedrooms in hospital (Germany)	14	0.05 [0.06]	< 0.01–0.7 [< 0.01–0.9]	1980–88	Triebig *et al.* (1989)
Pathology laboratory (Sweden)	13	0.5 [0.66]	NR	1980s	Rosén *et al.* (1984)
Pathology laboratories (Germany)	21	0.5[d] [0.6]	< 0.01–1.2 [< 0.01–1.6]	1980–88	Triebig *et al.* (1989)
Hospital laboratories (Finland)	80	0.5 [0.6]	0.01–7.3 [0.01–9.1]	1981–86	Heikkilä *et al.* (1991)

[a] Arithmetic means unless otherwise specified
[b] Mean is 8-h time-weighted average
[c] Mean of arithmetic means
[d] Median

Formalin solution is commonly used to preserve tissue samples in histopathology laboratories. The concentrations of formaldehyde are sometimes high, e.g. during tissue disposal, formalin preparation and changing of tissue processor solutions (Belanger & Kilburn, 1981). The mean level during exposure is usually about 0.5 ppm (0.6 mg/m^3) (Table 7). Other agents to which pathologists and histology technicians may be exposed include xylene (see IARC, 1989c), toluene (see IARC, 1989d), chloroform (see IARC, 1987e) and methyl methacrylate (see IARC, 1994). The 8-h time-weighted average concentrations were from nondetectable to 22 ppm (95.5 mg/m^3) for xylene, 9–13 ppm (34–49 mg/m^3) for toluene and 0.4–7 ppm (2.0–34.3 mg/m^3) for chloroform in a study of the exposure and symptoms of histology laboratory technicians in the United States (Belanger & Kilburn, 1981).

(g) Building, agriculture, forestry and other activities

Exposure to formaldehyde may also occur in the construction industry, agriculture, forestry and the service sector. Specialized construction workers who varnish wooden parquet floors may have relatively high exposure. The mean levels of formaldehyde in the air during varnishing with urea–formaldehyde varnishes were 2–5 ppm (2.5–6.2 mg/m^3) (Table 8). One coat of varnish takes only about 30 min to apply (Riala & Riihimäki, 1991), but the same worker may apply five or even 10 coats per day. Use of water-based polyurethane varnishes that do not release formaldehyde reduces exposure. Other chemical agents to which parquetry workers are usually exposed include wood dust from sanding (see the monograph on wood dust) and solvent vapours from varnishes, putties and adhesives. The concentrations of solvents measured during varnishing were 6.5 times the exposure limit of the solvent mixture during nitrocellulose varnishing and 3.4 times the exposure limit during urea–formaldehyde varnishing in a Finnish study. The main solvents released from nitrocellulose varnishes were acetone, ethyl alcohol, ethyl acetate, hexane and other aliphatic hydrocarbons. The solvents in the urea–formaldehyde varnishes were mainly ethanol, acetone, isobutyl alcohol, ethyl acetate and propylene glycol monomethyl ether (Riala & Riihimäki, 1991). Other operations that may result in exposure to formaldehyde in the building trades are insulation with urea–formaldehyde foam and machining of particle-board. Various levels of formaldehyde have been measured during insulation with urea–formaldehyde foam, but exposure during handling and sawing of particle-board seems to be consistently low (Table 8).

Formaldehyde is used in agriculture as a preservative for fodder and as a disinfectant. For example, fodder was preserved with a 2% formalin solution for several days per year from the late 1960s until the early 1980s on farms in Finland. As the concentration during preservation was < 0.5 ppm (0.6 mg/m^3), the annual mean exposure is probably very low. Formaldehyde gas is also used 5–10 times a year to disinfect eggs in brooding houses. The concentration of formaldehyde in front of the disinfection chamber immediately after disinfection was as high as 7–8 ppm (8.6–9.8 mg/m^3), but annual exposure from this source probably remains very low (Heikkilä *et al.*, 1991).

Engine exhausts contain a small amount of formaldehyde (see section 1.3.3). The average exposure of lumberjacks using chainsaws in Sweden and Finland was, however, < 0.1 ppm (Table 8).

Table 8. Concentrations of formaldehyde (in ppm [mg/m^3]) in the workroom air in building sites, agriculture, forestry and miscellaneous other activities

Industry and operation	No. of measurements	Mean[a]	Range	Year	Reference
Varnishing parquet with urea–formaldehyde varnish (Finland)	10	2.9 [3.6]	0.3–6.6 [0.4–8.1]	1976	Heikkilä *et al.* (1991)
Varnishing parquet with urea–formaldehyde varnish (Finland)	6	4.3 [5.3]	2.6–6.1 [3.2–7.5]	1987	Riala & Riihimäki (1991)
Insulating buildings with urea–formaldehyde foam (USA)	66	1.3[b] [1.6]	0.3–3.1 [0.4–3.8]	NR	WHO (1989)
Insulating buildings with urea–formaldehyde foam (Sweden)	6	0.1 [0.18]	NR	1980s	Rosén *et al.* (1984)
Sawing particle-board at construction site (Finland)	5	< 0.5 [< 0.6]	NR	1967	Finnish Institute of Occupational Health (1994)
Agriculture (Finland)				1982	Heikkilä *et al.* (1991)
Handling of fodder	NR	NR	0.02–0.4 [0.03–0.46]		
Disinfection of eggs	11	2.6 [3.2]	0.2–7.8 [0.3–9.6]	1981–86	
Chain-sawing (Sweden)	NR	0.05 [0.06]	0.02–0.1 [0.03–0.13]	NR	Hagberg *et al.* (1985)
Chain-sawing (Finland) (8-h TWA)	NR	< 0.1	< 0.1–0.5 [0.1–0.6]	NR	Heikkilä *et al.* (1991)
Retail dress shops (USA)	NR	NR	0.1–0.5 [0.15–0.6]	1959	Elliott *et al.* (1987)
Fabric shops (Finland)	3	0.16 [0.2]	0.1–0.2 [0.15–0.3]	1985–87	Priha *et al.* (1988)
Fire-fighting (USA)	30	0.1 [0.16]	0.04–0.3 [0.05–0.4]	1989	Materna *et al.* (1992)
Museum, taxidermy (Sweden)	8	0.2 [0.3]	NR	1980s	Rosén *et al.* (1984)

NR, not reported; TWA, time-weighted average
[a]Arithmetic mean unless otherwise specified
[b]Mean of arithmetic means

The use of formaldehyde-based resin in finishing textiles and some garments may also result in exposure in retail shops. Measurements in dress shops in the United States of America in the 1950s showed levels up to 0.5 ppm [0.62 mg/m^3]. The air in three Finnish fabric shops in the 1980s contained 0.1–0.2 ppm [0.12–0.25 mg/m^3] formaldehyde (Table 8).

Low concentrations of formaldehyde may occur also during firefighting and taxidermy (Table 8).

1.3.3 Ambient air

Although formaldehyde is a natural component of ambient air, anthropogenic sources usually contribute the most formaldehyde in populated regions, since the ambient levels are generally < 1 μg/m^3 in remote areas. For example, in the unpopulated Eniwetok Atoll in the Pacific Ocean, a mean of 0.5 μg/m^3 and a maximum of 1.0 μg/m^3 formaldehyde were measured in outdoor air (Preuss *et al.*, 1985). Other authors have reported similar levels in remote, unpopulated areas (Gammage & Travis, 1989; WHO, 1989).

Outdoor air concentrations in urban environments are more variable and depend on local conditions. They are usually 1–20 μg/m^3 (United States National Research Council, 1980, 1981; Preuss *et al.*, 1985; Gammage & Travis, 1989; WHO, 1989). A major source of formaldehyde in urban air is incomplete combustion of hydrocarbon fuels, especially from vehicle emissions (Sittig, 1985; WHO, 1989; Vaught, 1991). Urban air concentrations in heavy traffic or during severe inversions can range up to 100 μg/m^3 (United States National Research Council, 1980, 1981; Preuss *et al.*, 1985; WHO, 1989).

1.3.4 Residential indoor air

The levels of formaldehyde in indoor air are often higher than those outside (Gammage & Gupta, 1984). The concentrations in dwellings depend on the sources of formaldehyde that are present, the age of the source materials, ventilation, temperature and humidity. Major sources of formaldehyde in some dwellings have been reported to be off-gassing of urea–formaldehyde foam insulation and particle-board. In studies summarized by Preuss *et al.* (1985), the mean levels in conventional homes with no urea–formaldehyde foam insulation were 25–60 μg/m^3.

Many studies have been reported since the late 1970s of formaldehyde levels in 'mobile homes' (caravans) (see, for example, the review of Gammage & Travis, 1989). The levels appear to decrease as the mobile home (and its formaldehyde-based resins) age, with a half-life of four to five years (Preuss *et al.*, 1985). In the early 1980s, a mean levels of 0.4 ppm [0.49 mg/m^3] and individual measurements as high as several parts per million were measured in new mobile homes. As a result of new standards set in the mid-1980s for building materials used in mobile homes and voluntary reductions by the manufacturers, formaldehyde levels in mobile homes are now typically around 0.1 ppm [0.12 mg/m^3] or less (Gammage & Travis, 1989; Sexton *et al.*, 1989; Gylseth & Digernes, 1992; Lehmann & Roffael, 1992).

1.3.5 Other exposures

Several studies have been conducted to determine exposures of students in laboratories. Skisak (1983) measured formaldehyde in the breathing zone at dissecting tables and in the ambient air in a medical school in the United States for 12 weeks. Concentrations > 1.2 mg/m^3 were found in 44% of the breathing zone samples and 11 ambient air samples; 50% of the breathing zone samples contained 0.7–1.2 mg/m^3, with a range of 0.4–3.2 mg/m^3. Korky *et al.* (1987) studied the dissecting facilities at a university in the United States during the 1982–83 academic year. The airborne concentration of formaldehyde was 7–16.5 ppm (8.6–20.3 mg/m^3) in the laboratory, 1.97–2.62 ppm (2.4–3.2 mg/m^3) in the stockroom and < 1 ppm (< 1.2 mg/m^3) in the public hallway. In another study, of 253 samples of air taken during laboratory dissection classes at a university in the United States, 97 contained concentrations above the detection limit of 0.01 mg/m^3; all but four samples had levels < 1.2 mg/m^3. The average concentration detected was 0.5 mg/m^3 (Poslusny *et al.*, 1992).

Cigarette smoke has been reported to contain levels of a few micrograms to several milligrams of formaldehyde per cigarette. A 'pack-a-day' smoker may inhale as much as 0.4–2.0 mg formaldehyde (IARC, 1986b; WHO, 1989; American Conference of Governmental Industrial Hygienists, 1991).

Cosmetic products containing formaldehyde, formalin and/or paraformaldehyde may come into contact with hair (e.g. shampoos and hair preparations), skin (deodorants, bath products, skin preparations and lotions), eyes (mascara and eye make-up), oral mucosa (mouthwashes and breath fresheners), vaginal mucosa (vaginal deodorants) and nails (cuticle softeners and nail creams and lotions). Aerosol products (e.g. shaving creams) result in potential inhalation of formaldehyde (Cosmetic Ingredient Review Expert Panel, 1984).

Formaldehyde occurs naturally in foods, and foods may be contaminated as a result of fumigation (of e.g. grain), cooking (as a combustion product) and release from formaldehyde resin-based tableware (WHO, 1989). It has been used as a bacteriostatic agent in some foods, such as cheese (Restani *et al.*, 1992). Fruits and vegetables typically contain 3–60 mg/kg, milk and milk products about 1 mg/kg, meat and fish 6–20 mg/kg and shellfish 1–100 mg/kg. Drinking-water normally contains < 0.1 mg/L (WHO, 1989).

Other exposures to formaldehyde are reviewed by IARC (1982) and WHO (1989).

1.4 Regulations and guidelines

Occupational exposure limits and guidelines for formaldehyde are presented in Table 9. International regulations and guidelines related to emissions of and exposures to formaldehyde in occupational settings, indoor air and building materials have been reviewed (Scheuplein, 1985; Sundin, 1985; Coutrot, 1986; Meyer, 1986; McCredie, 1988; Gylseth & Digernes, 1992; Halligan, 1992; Lehmann & Roffael, 1992; McCredie, 1992).

Table 9. Occupational exposure limits and guidelines for formaldehyde

Country or region	Year	Concentration (mg/m^3)	Interpretation
Australia	1991	1.5	TWA; probable human carcinogen, sensitizer
		3	STEL
Austria	1982	1.2	TWA
Brazil	1978	2.3	TWA
Belgium	1991	1.2	TWA; probable human carcinogen
		2.5	STEL
Bulgaria	1984	1	TWA
Chile	1983	2.4	Ceiling
China	1982	3	TWA
Czech Republic	1991	0.5	TWA
		1	STEL
Denmark	1991	0.4	STEL; suspected carcinoegn
Egypt	1959	6.2	TWA
Finland	1993	1.3	STEL, 15 min; significant absorption through skin
France	1991	3	STEL
Germany	1993	0.6	TWA; suspected carcinogenic potential; local irritant; sensitizer
Hungary	1991	0.6	Ceiling; probable human carcinogen; irritant; sensitizer
India	1983	3	Ceiling
Indonesia	1978	6	Ceiling
Italy	1978	1.2	TWA
Japan	1991	0.61	TWA; suspected carcinogenic potential
Mexico	1983	3	TWA
Netherlands	1986	1.5	TWA
		3	Ceiling, 15 min
Norway	1990	0.6	TWA; allergen; suspected carcinogen
		1.2	Ceiling
Poland	1991	2	TWA
Romania	1975	4	MAX
Russian Federation	1991	0.5	STEL; significant absorption through skin; allergen
Sweden	1991	0.6	TWA; sensitizer
		1.2	Ceiling
Switzerland	1991	0.6	TWA; sensitizer
		1.2	STEL
Taiwan	1981	6	TWA; significant absorption through skin
United Kingdom	1992	2.5	TWA; maximum exposure limit
		2.5	STEL, 10 min
USA			
ACGIH	1993	0.37	Ceiling; suspected human carcinogen
NIOSH	1992	0.02	TWA; potential human carcinogen
		0.12	Ceiling, 15 min
OSHA	1993	0.9	TWA
		2.5	STEL

Table 9 (contd)

Country or region	Year	Concentration (mg/m^3)	Interpretation
Venezuela	1978	3	TWA, ceiling
Former Yugoslavia	1971	1	TWA

From Arbeidsinspectie (1986); Cook (1987); Direktoratet for Arbeidstilsynet (1990); International Labour Office (1991); United Kingdom Health and Safety Executive (1992); United States National Institute for Occupational Safety and Health (NIOSH) (1992); American Conference of Governmental Industrial Hygienists (ACGIH) (1993); Deutsche Forschungsgemeinschaft (1993); Työministeriö (1993); United States Occupational Safety and Health Administration (OSHA) (1993)

TWA, time-weighted average; STEL, short-term exposure limit; MAX, maximum

The European Union has adopted a Directive that imposes concentration limits for formaldehyde and paraformaldehyde in cosmetics. These substances are permitted at a maximal concentration of 0.2% (expressed as free formaldehyde) in all cosmetic formulations except nail hardeners, oral hygiene products and aerosol dispensers. Nail hardeners and oral hygiene products may contain maximal concentrations of 5 and 0.1%, respectively, whereas formaldehyde and paraformaldehyde are prohibited for use in aerosol dispensers (except for foams). Cosmetic product labels are required to list formaldehyde and paraformaldehyde as ingredients when the concentration of either exceeds 0.05% (Cosmetic Ingredient Review Expert Panel, 1984; European Commission, 1990).

Guidelines for ambient air levels of formaldehyde in living spaces have been set in several countries and range from 0.05–0.4 ppm (0.06–0.5 mg/m^3), with a preference for 0.1 ppm (0.12 mg/m^3) (Lehmann & Roffael, 1992).

In the United States, all plywood and particle-board materials bonded with a resin system or coated with a surface finish containing formaldehyde cannot exceed the following formaldehyde emission levels when installed in manufactured homes: plywood materials and particle-board flooring products (including urea–formaldehyde bonded particle-board) cannot emit more than 0.25 mg/m^3 formaldehyde, and particle-board materials and medium-density fibre-board cannot emit more than 0.37 mg/m^3 (National Particleboard Association, 1992, 1993; National Particleboard Association, 1994; United States Department of Housing and Urban Development, 1994). Several other countries have similar regulations (Lehmann & Roffael, 1992).

2. Studies of Cancer in Humans

2.1 Case reports

Halperin *et al.* (1983) and Brandwein *et al.* (1987) reported cases of squamous-cell carcinoma of the sinonasal cavities associated with exposure to formaldehyde at work or at home. Holmstrom and Lund (1991) drew attention to the possibility of a causal relationship with malignant melanoma of the nasal cavity on the basis of three cases seen after occupational exposure to formaldehyde.

2.2 Descriptive studies

Gallagher *et al.* (1989) calculated proportionate mortality ratios (PMRs) by occupation for 320 423 men who died in British Columbia, Canada, during 1950–84. One of the 79 funeral directors included in the study had died from sinonasal cancer (PMR, 16; 95% confidence interval [CI], 0.4–87).

A similar analysis was conducted by Petersen and Milham (1980) on about 200 000 white male residents of California, USA, for the period 1959–61. Funeral directors and embalmers accounted for 130 deaths, none of which were from cancer of the buccal cavity or pharynx (one expected) or from sinonasal cancer (< 0.1 expected).

Malker *et al.* (1990) used data from the Swedish Cancer–Environment Registry, which combines data from the 1960 census with those from the National Cancer Registry through 1979, to calculate standardized incidence ratios (SIRs) for nasopharyngeal cancer (471 cases) in various occupational and industrial groups in 1961–79. Significant excesses were seen for glassmakers (SIR, 6.2; 3 cases), bookbinders (6.1; 3 cases), shoemakers (3.8; 5 cases) and workers in shoe repair (4.0; 5 cases) and fibre-board manufacture (3.9; 4 cases). No significantly high risks for nasopharyngeal cancer were seen in other occupations in which exposure to formaldehyde probably occurs [expected numbers not given].

2.3 Cohort studies

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

cohort definition. Reviews are available which summarize the epidemiological data (Blair *et al.*, 1990a; Partanen, 1993; McLaughlin, 1995); in the first two, the technique of meta-analysis was used.

For each point estimate expressed as an SMR, PMR, PCMR or SIR, a 95% CI is given, even if the original authors did not report one. The 95% CI bears a relationship to the usual judgement of statistical significance, in that a CI that does not include the value of 1.0 occurs when the point estimate is significant at the traditional 5% level. The 95% CI provides more information, however, in that it shows the magnitude of the estimated random variation around the point estimate.

2.3.1 Professional groups

Pathologists, anatomists, embalmers and funeral directors were studied because they use formaldehyde as a tissue preservative. Investigations of these occupations have several methodological problems. Use of national statistics to generate expected numbers may bias estimates of relative risks toward the null for some cancers and away from the null for others because these groups have a higher socioeconomic level than the general population; only a few investigations included a special referent population designed to diminish potential socio-economic confounding. None of these studies had the data necessary to adjust for tobacco use. Since anatomists and pathologists in the United States generally smoke less than the general population (Sterling & Weinkam, 1976), estimates of relative risks for smoking-related cancers will be artificially low. Without adjustments, the biases introduced by socioeconomic factors and smoking may be strong enough to preclude any possibility of detecting excess occurrence of tobacco-related cancers. This may be less of a problem for embalmers, however, because their smoking habits may not differ from those of the general population (Sterling & Weinkam, 1976). In no study were risk estimates developed by level of exposure, and in only a few studies were risks evaluated by duration of exposure. When exposure estimates are not summarized in the following text, they were not provided in the original study. Non-differential error in exposure assessment, which occurs when the measures of exposure are about equally inaccurate for study subjects with and without the cancer of interest, diminishes the chances of uncovering an underlying association, as it biases estimates of the relative risk toward the null.

Harrington and Shannon (1975) evaluated the mortality of pathologists and medical laboratory technicians in the United Kingdom. Members of the Royal College of Pathologists and the Pathological Society who were alive in 1955 were enrolled and followed through 1973. Of the 2079 pathologists included, only 13 could not be traced successfully; 156 deaths were identified. The Council for Professions Supplementary to Medicine was used to identify 12 944 technicians; 154 subsequently died and 199 could not be traced. Ten of the pathologists who died and 20 of the medical technicians who died were women, but the number of women included in the cohort was not provided. Expected numbers of deaths were calculated from sex-, five-year calendar period- and five-year age group-specific rates for England and Wales or Scotland, as appropriate. The SMRs for all causes of deaths were 0.6 for pathologists and 0.7 for medical technicians; the numbers of deaths from all cancers and from ischaemic heart disease were also fewer than expected. The SMR for lymphatic and haematopoietic cancer was elevated

among pathologists ([2.0; 95% CI, 0.9–3.9]; 8 observed), but not among technicians ([0.6; 0.1–1.6]; 3 observed). The SMRs for cancers at other sites were below 1.0.

The study of British pathologists was extended and expanded by Harrington and Oakes (1984), who added new entrants and traced new and previously studied subjects from 1974 through 1980. The population now included 2307 men and 413 women. Vital status was confirmed for 99.9% of the men and 99.5% of the women. SMRs were calculated using expected rates based on age-, sex- and calendar time-specific data from England and Wales. The SMRs for all causes and for all cancers among men were both 0.6; among women, the SMR for all causes was 1.0 and that for all cancers, 1.4. Mortality from brain cancer was elevated among men (SMR, 3.3 [95% CI, 0.9–8.5]; 4 deaths). No nasal cancer and no cancer of the nasal sinuses was seen.

This cohort was further evaluated by Hall *et al.* (1991), who extended follow-up of mortality from 1980 through 1986 and added new members of the Pathological Society, resulting in 4512 individuals available for study (3478 men; 803 women; and 231 unaccounted subjects [who may have been women from Scotland, but it was not clear in the article]). Sex-specific SMRs were based on expected rates for England and Wales or Scotland, as appropriate, and were adjusted for age and calendar time. The SMRs for all causes of death were all considerably below 1.0: men from England and Wales, 0.4 (95% CI, 0.4–0.5); women from England and Wales, 0.7 (0.4–1.0); men from Scotland, 0.5 (0.3–0.7). The SMRs for cancers at all sites were 0.4 (0.3–0.6) and 0.6 (0.3–1.1) among men from England and Wales and Scotland, respectively, and 1.0 (0.5–1.9) among women from England and Wales. No significant excess was seen for cancer at any site. Nonsignificant excesses occurred for brain cancer (SMR, 2.4; 0.9–5.2) and lymphatic and haematopoietic cancer (1.4; 0.7–2.7) among men from England and Wales, breast cancer (1.6; 0.4–4.1) among women from England and Wales and prostatic cancer (3.3; 0.4–12) among men from Scotland.

Walrath and Fraumeni (1983) used licensure records from the New York State (United States) Department of Health, Bureau of Funeral Directing and Embalming to identify 1678 embalmers who had died between 1925 and 1980. Death certificates were obtained for 1263 (75%) decedents (1132 white men, 79 nonwhite men, 42 men of unknown race and 10 women), and PMRs and PCMRs were calculated for white men and nonwhite men on the basis of age-, race-, sex- and calendar time-specific proportions in the general population. Observed and expected numbers were generally not provided for nonwhite men, but the paper indicated that there was significant excess mortality from arteriosclerotic heart disease (PMR, 1.5 [95% CI, 1.1–2.2]; 33 observed) and from cancers of the larynx (2 observed) and lymphatic and haematopoietic system (3 observed). Among white men, the PMRs were 1.1 [1.0–1.3] for all cancer combined, 1.1 [1.0–1.3] for arteriosclerotic heart disease, 0.7 [0.3–1.2] for emphysema, and 1.3 [0.9–1.9] for cirrhosis of the liver. The PCMRs for other cancers were 1.0 [0.4–2.0] for buccal cavity and pharynx, 1.3 [0.9–1.9] for colon, 1.1 [0.9–1.4] for lung, 0.8 [0.4–1.4] for prostate, 1.4 [0.6–2.7] for brain, 1.2 [0.8–1.8] for lymphatic and haematopoietic system (PMR), 0.8 [0.3–1.9] for lymphoma and 1.2 [0.6–2.1] for leukaemia. No deaths occurred from cancer of the nasal sinuses or nasopharynx. There was little difference in PMR by time since first licensure. Although the subjects had been licensed as either embalmers or embalmers/funeral

directors, these two groups were analysed separately because the authors assumed that embalmers would have had more exposure to formaldehyde than embalmers/funeral directors. The PMR for brain cancer was increased among people licensed only as embalmers (2.3 [0.8–5.0]; 6 observed) but not among those also licensed as a funeral director (0.9 [0.2–2.7]; 3 observed). A difference was also observed for mortality from cancer of the buccal cavity and pharynx; the PMR for embalmers was 2.0 ([0.8–4.1] 7 observed), and that for embalmers/funeral directors was 0.3 ([0.0–1.5] 1 observed).

Walrath and Fraumeni (1984) used the records of the California (United States) Bureau of Funeral Directing and Embalming to examine mortality among embalmers first licensed in California between 1916 and 1978. They identified 1109 embalmers who died between 1925 and 1980, comprising 1007 white men, 39 nonwhite men, 58 white women and five nonwhite women. Only mortality of white men was analysed. The expected numbers of deaths were calculated on the basis of age-, race-, sex- and calendar year-specific proportions from the general population. The PMRs for major categories of death were 1.2 [95% CI, 1.0–1.4] for all cancers combined (205 observed), 1.2 [1.1–1.3] for ischaemic heart disease (355 observed), 0.4 [0.1–1.0] for emphysema (4 observed) and 1.8 [1.3–2.4] for suicide (44 observed). The PCMRs for specific cancers were 1.0 [0.4–2.0] for buccal cavity and pharynx (8 observed), 1.4 [0.9–2.0] for colon (30 observed), 0.9 [0.6–1.2] for lung (41 observed), 1.3 [0.8–2.0] for prostate (23 observed), 1.7 [0.8–3.2] for brain (9 observed), 1.2 (PMR) [0.7–1.9] for lymphatic and haematopoietic system (19 observed), [1.0 (PMR); 0.2–2.8] for lymphoma (3 observed) and 1.4 [0.7–2.4] for leukaemia (12 observed). There was no death from cancer of the nasal passages (0.6 expected). The PMRs by length of licensure (< 20 years and ≥ 20 years) were 2.0 and 1.9 for brain cancer and 1.2 and 2.2 for leukaemia.

Mortality among 1477 male embalmers licensed by the Ontario (Canada) Board of Funeral Services between 1928 and 1957 was evaluated by Levine *et al.* (1984a) by following-up the cohort through 1977: 359 deaths were identified; 54 (4%) could not be traced. The expected numbers were derived from the mortality rates for men in Ontario in 1950–77, adjusted for age and calendar year. Since mortality rates for Ontario were not available before 1950, person-years and deaths in the cohort before that time were excluded from the analysis, leaving 1413 men known to be alive in 1950. The SMRs for all causes and for all cancers were 1.0 [95% CI, 0.9–1.1] and 0.9 [0.7–1.1], respectively. Excesses were seen for chronic rheumatic heart disease (2.0 [0.9–3.9]; 8 observed) and cirrhosis of the liver (2.4 [1.4–3.7]; 18 observed). For specific cancers, the numbers of deaths and those expected were as follows: buccal cavity and pharynx (1/2.1), nose, middle ear, sinuses (0/0.2), lung (19/20.2), prostate (3/3.4), brain (3/2.6), lymphatic and haematopoietic system (SMR, 1.2; 8/6.5) and leukaemia (4/2.5).

Stroup *et al.* (1986) evaluated mortality among members of the American Association of Anatomists. A total of 2317 men had joined the Association between 1888 and 1969; because only 299 women had joined during this time period, they were not included. Follow-up of the cohort for vital status through 1979 resulted in 738 deaths; 39 individuals could not be traced. The expected numbers of deaths were calculated from age-, race-, sex- and calendar time-specific rates for the general population of the United States for the period 1925–79 or for male members of the American Psychiatric Association, a population that should be similar to

anatomists with regard to socioeconomic status, in 1900–69. Between 1925 and 1979, 738 anatomists died and only 2% were of unknown vital status at the close of the follow-up. In comparison with the general population, the cohort showed a very large 'healthy worker effect', with SMRs of 0.7 for all causes (738 observed), 0.6 (95% CI, 0.5–0.8) for cancer at all sites (118 observed) and 0.8 (0.7–0.9) for ischaemic heart disease (271 observed). The SMRs were less than 1.0 for individual cancers (e.g. lung cancer, SMR, 0.3; 0.1–0.5; 12 observed; oral and pharyngeal cancer, 0.2; 0.0–0.8; 1 observed), except for cancers of the brain (2.7; 1.3–5.0; 10 observed), lymphatic and haematopoietic system (2.0; 0.7–4.4; 6 observed) and leukaemia (1.5; 0.7–2.7; 10 observed). No death from nasal cancer occurred (0.5 expected). The risk for brain cancer increased with duration of membership, from 2.0 for < 20 years, to 2.8 for 20–39 years and to 7.0 for ≥ 40 years [trend cannot be calculated]; no such pattern was seen for lung cancer. Anatomists had deficits of lung cancer (0.5; 0.2–1.1) and leukaemia (0.8; 0.2–2.9) when compared with members of the American Psychiatric Association, but they still had an excess of brain cancer (6.0; 2.3–16).

Logue *et al.* (1986) evaluated mortality among 5585 members of the College of American Pathologists listed in the Radiation Registry of Physicians; 496 deaths were identified. The cohort was established by enrolling members between 1962 and 1972 and following them up through 1977. SMRs were calculated on the basis of the mortality rates for white men in the United States in 1970, but information on age and calendar-year categories was not provided. The SMRs were 0.7 [observed number of cases calculated from rates, 4] for cancer of the buccal cavity and pharynx, 0.2 [14] for cancer of the respiratory system ($p < 0.01$), 0.8 [36] for cancer of the digestive organs, 0.5 [5] for cancers of the lymphatic and haematopoietic system and 1.1 [7] for leukaemia. The age-adjusted mortality rates for these cancers were similar to those calculated for members of the American College of Radiology who were also listed in the Registry.

Hayes *et al.* (1990), in the United States, identified 6651 deceased embalmers/funeral directors from the records of licensing boards and state funeral directors' associations in 32 states and the District of Columbia and from the vital statistics offices of nine states and New York City between 1975 and 1985. Decedents included in studies in New York (Walrath & Fraumeni, 1983) and California (Walrath & Fraumeni, 1984) were excluded. Death certificates were received for 5265. Exclusion of 449 decedents included in previous studies of embalmers, 376 subjects who probably did not work in the funeral industry, eight subjects of unknown race or age and 386 women left 4046 decedents available for analysis (3649 whites and 397 nonwhites). PMRs and PCMRs were calculated on the basis of expected numbers from race- and sex-specific groups of the general population, adjusted for five-year age and calendar-time categories. The PMR for all cancers was 1.1 (95% CI, 1.0–1.2; 900 observed) for whites and 1.1 (0.9–1.3; 102 observed) for nonwhites. The PMR for ischaemic heart disease was elevated in both whites (1.1; 1.1–1.2; 1418 observed) and nonwhites (1.5; 1.2–1.7; 135 observed). That for emphysema was about as expected among whites (1.0; 0.8–1.4; 48 observed), but only one death from this cause occurred among nonwhites (0.5; 0.1–2.6; 1 observed). The PMRs for specific cancers were: buccal cavity and pharynx (whites: 1.2; 0.8–1.7; 26 observed; nonwhites: 1.3; 0.3–3.2; 4 observed), nasopharynx (whites: 1.9; 0.4–5.5; 3 observed; nonwhites: 4.0; 0.1–22;

1 observed), colon (whites: 1.2; 1.0–1.4; 95 observed; nonwhites: 2.3; 1.3–3.8; 16 observed), nasal sinuses (whites and nonwhites: 0 observed, 1.7 expected), lung (whites: 1.0; 0.9–1.1; 285 observed; nonwhites: 0.8; 0.5–1.1; 23 observed), prostate (whites: 1.1; 0.8–1.3; 79 observed; nonwhites: 1.4; 0.8–2.1; 19 observed), brain (whites: 1.2; 0.8–1.8; 24 observed; nonwhites: 0 observed, 0.8 expected) and lymphatic and haematopoietic system (whites: 1.3; 1.1–1.6; 100 observed; nonwhites: 2.4; 1.4–4.0; 15 observed). The risks for cancers of the lymphatic and haematopoietic system and brain did not vary substantially by licensing category (embalmer versus funeral director), by geographic region, by age at death or by source of data on mortality. Among the lymphatic and haematopoietic cancers, the PMRs were significantly elevated for myeloid leukaemia (1.6; 1.0–2.3; 24 observed) and other and unspecified leukaemia (2.3; 1.4–3.5; 20 observed); nonsignificant excesses were observed for several other histological types.

In a study of users of various medicinal drugs based on computer-stored hospitalization records of the out-patient pharmacy at the Kaiser–Permanente Medical Center in San Francisco (CA, United States), Friedman and Ury (1983) evaluated cancer incidence in a cohort of 143 574 pharmacy users from July 1969 through August 1973 and followed them up to the end of 1978. The number of cases among users of specific drugs was compared with the number expected on the basis of rates for all pharmacy users, adjusted for age and sex. Since many analyses were performed (56 cancers and 120 drugs, for 6720 combinations), chance findings would be expected. Five cancers were associated with use of formaldehyde solution (topically for warts) (morbidity ratio, 0.8 [95% CI, 0.3–2.0]). The morbidity ratio for lung cancer was significantly elevated (5.7 [1.6–15]) for people using formaldehyde, with four cases observed. Information on smoking was not provided. [The Working Group noted the short period of follow-up.]

Cohort and proportionate mortality studies of professional groups are summarized in Table 10.

2.3.2 Industrial groups

Several studies of industrial groups included evaluations by duration of exposure or employment, but only four contained assessments by level of exposure: a study in the United Kingdom (Acheson *et al.*, 1984a; Gardner *et al.*, 1993) and three in the United States (Blair *et al.* 1986; Stewart *et al.*, 1986; Blair *et al.*, 1990b) (Andjelkovich *et al.*, 1995) (Marsh *et al.*, 1994a). Information on tobacco use was generally absent, although Blair *et al.* (1990b) and Andjelkovich *et al.* (1995) obtained some information. The reports on industrial cohorts are not entirely independent; some publications are based on extended follow-ups (reports on the British cohort by Acheson *et al.* (1984a) and Gardner *et al.* (1993) and the Italian cohort by Bertazzi *et al.* (1986, 1989)). There is also partial overlap because of inclusion of the same workers in several studies: the two reports on the garment industry by Stayner *et al.* (1985, 1988) included two common facilities; the 10-plant study by Blair *et al.* (1986, 1990b) included workers also reported in cohort studies by Marsh (1982), Wong (1983), Liebling *et al.* (1984) and Marsh *et al.* (1994a) and in a case–control study by Fayerweather *et al.* (1983). Analyses of the data from the cohort study by Blair *et al.* (1986, 1990b) have also been published by others (Robins

Table 10. Cohort and proportionate mortality studies of cancer in professionals exposed to formaldehyde

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comments
United Kingdom (Hall *et al.*, 1991) (update of Harrington *et al.* (1984) plus new members since 1973)	Pathologists, SMR (4512), 1974–87	None	All causes	0.4 (0.4–0.5)	194 deaths
			All cancers	0.5 (0.4–0.6)	55 deaths
			Colon	1.0 (0.4–2.0)	Seven deaths
			Lung	0.2 (0.1–0.4)	Nine deaths
			Brain	2.2 (0.8–4.8)	Six deaths
			Lymphatic/haematopoietic	1.4 (0.7–2.7)	10 deaths
			Leukaemia	1.5 (0.4–3.9)	Four deaths
			Breast	1.6 (0.4–4.1)	Four deaths among women
			Prostate	3.3 (0.4–12)	Two deaths among men in Scotland
New York, USA (Walrath & Fraumeni, 1983)	Embalmers, PMR, PCMR (1132 men), 1925–80	None	All cancers	1.1 [1.0–1.3]	243 deaths, PMR
			Buccal/pharynx	1.0 [0.4–2.0]	Eight deaths, PCMR
				2.0 [0.8–4.1]	Embalmers only, seven deaths, PMR
				0.3 [0.0–1.5]	Funeral directors, one death, PMR
			Colon	1.3 [0.9–1.9]	29 deaths, PCMR
			Lung	1.1 [0.9–1.4]	70 deaths, PCMR
			Brain	1.4 [0.6–2.7]	Nine deaths, PCMR
				2.3 [0.8–5.0]	Embalmers only, six deaths, PMR
				0.9 [0.2–2.7]	Funeral directors, three deaths, PMR
			Lymphatic/haematopoietic	1.2 [0.8–1.8]	25 deaths, PMR
			Lymphoma	0.8 [0.3–1.9]	Five deaths, PCMR
			Leukaemia	1.2 [0.6–2.1]	12 deaths, PCMR
California, USA (Walrath & Fraumeni, 1984)	Embalmers, PMR, PCMR (1007 white men), 1925–80	Duration	All cancer	1.2 [1.0–1.4]	205 deaths, PMR
			Buccal/pharynx	1.3 [0.6–2.6]	Eight deaths, PMR, inverse trend with duration
			Colon	1.4 [0.9–2.0]	30 deaths, PCMR, no trend
			Lung	0.9 [0.6–1.2]	41 deaths, PCMR, no trend
			Nasal	–	0 deaths
			Prostate	1.3 [0.8–2.0]	23 deaths, PCMR, no trend
			Brain	1.9 ($p < 0.05$)	Nine deaths, PMR, no trend
			Lymphatic/haematopoietic	1.2 [0.7–1.9]	19 deaths, PMR
			Lymphoma	[1.0] [0.2–2.8]	Three deaths, PMR
			Leukaemia	1.4 [0.7–2.4]	12 deaths, PCMR, trend with duration

Table 10 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comments
Canada (Levine *et al.*, 1984a)	Embalmers, SMR (1477 men), 1950–77	None	All causes	1.0 [0.9–1.1]	319 deaths
			All cancers	0.9 [0.7–1.1]	58 deaths
			Nasal	–	0 deaths (0.2 expected)
			Buccal/pharynx	[0.5] (NA)	One death
			Lung	0.9 [0.6–1.5]	19 deaths
			Brain	[1.2] [0.2–3.4]	Three deaths
			Prostate	[0.9] [0.2–2.6]	Three deaths
			Lymphatic/haematopoietic	1.2 [0.5–2.4]	Eight deaths
			Leukaemia	[1.6] [0.4–4.1]	Four deaths
USA (Stroup *et al.*, 1986)	Anatomists, SMR (2239 men), 1925–79	Duration	All causes	0.7 (0.6–0.7)	738 deaths
			All cancers	0.6 (0.5–0.8)	118 deaths
			Buccal/pharynx	0.2 (0.0–0.8)	One death
			Colon	1.1 (0.7–1.7)	20 deaths
			Nasal	– (0.0–7.2)	0 deaths, 0.5 expected
			Lung	0.3 (0.1–0.5)	12 deaths, no trend with duration
			Prostate	1.0 (0.6–1.6)	19 deaths
			Brain	2.7 (1.3–5.0)	10 deaths, trend with duration
			Lymphatic/haematopoietic	1.2 (0.7–2.0)	18 deaths
			Lymphoma	0.7 (0.1–2.5)	Two deaths
			Leukaemia	1.5 (0.7–2.7)	10 deaths
			Other lymphatic tissue	2.0 (0.7–4.4)	Six deaths
USA (Logue *et al.*, 1986)	Pathologists, SMR (5585 men), 1962–77	None	Buccal/pharynx	0.7 (NA)	
			Digestive organs	0.8 (NA)	
			Respiratory system	0.2 ($p < 0.01$)	
			Lymphatic/haematopoietic	0.5 (NA)	
			Leukaemia	1.1 (NA)	

Table 10 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comments
USA (Hayes *et al.*, 1990)	Embalmers, PMR (3649 white men, 397 nonwhite men), 1975–85	None	All cancers	1.1 (1.0–1.2)	900 deaths among white men
				1.1 (0.9–1.3)	102 deaths among nonwhite men
			Buccal/pharynx	1.2 (0.8–1.7)	26 deaths among white men
				1.3 (0.3–3.2)	Four deaths among nonwhite men
			Nasopharynx	1.9 (0.4–5.5)	Three deaths among white men
				4.0 (0.1–22)	One death among nonwhite men
			Colon	1.2 (1.0–1.4)	95 deaths among white men
				2.3 (1.3–3.8)	16 deaths among nonwhite men
			Nasal	–	0 deaths among white and nonwhite men
			Lung	1.0 (0.9–1.1)	285 deaths among white men
				0.8 (0.5–1.1)	23 deaths among nonwhite men
			Prostate	1.1 (0.8–1.3)	79 deaths among white men
				1.4 (0.8–2.1)	19 deaths among nonwhite men
			Brain	1.2 (0.8–1.8)	24 deaths among white men
				–	0 deaths among nonwhite men
			Lymphatic/haematopoietic	1.3 (1.1–1.6)	100 deaths among white men
				2.4 (1.4–4.0)	15 deaths among nonwhite men
			Lymphoma	1.1 (0.5–1.9)	11 deaths among white men
				1.9 (0.1–11)	One death among nonwhite men
			Lymphatic leukaemia	0.6 (0.2–1.3)	Five deaths among white men
				3.0 (0.4–11)	Two deaths among nonwhite men
			Myeloid leukaemia	1.6 (1.0–2.4)	23 deaths among white men
				1.1 (0.1–5.9)	One death among nonwhite men
California, USA (Friedman & Ury, 1983)	Patients, SIR (143 574 pharmacy users), 1969–78	Use as a drug	All cancers	0.8 [0.3–2.0]	Five cases
			Lung	5.6 [1.6–15]	Four cases

CI, confidence interval; SMR, standardized mortality ratio; PMR, proportionate mortality ratio; PCMR, proportionate cancer mortality ratio; NA, not available; SIR, standardized incidence ratio

et al., 1988; Sterling & Weinkam, 1988, 1989a,b; Marsh *et al.*, 1992a,b, 1994a; Sterling & Weinkam, 1994).

Studies that provided detailed information indicate that workers had a range of levels of exposure to formaldehyde. Blair *et al.* (1986) found that 4% of their cohort was exposed to ≥ 2 ppm (≥ 2.5 mg/m^3); Acheson *et al.* (1984a) found that 35% were exposed to > 2 ppm; Andjelkovich *et al.* (1995) found 25% exposed to > 1.5 ppm (> 1.8 mg/m^3) and Marsh *et al.* (1994a) found 25% exposed to > 0.7 ppm (> 0.9 mg/m^3).

Cohort mortality studies in which cancers of the upper and lower respiratory tract are addressed may be biased by differences in the prevalence of tobacco smoking between the cohort and the referent population. Axelson and Steenland (1988), Blair *et al.* (1988), Siemiatycki *et al.* (1988) and others have shown that this potential bias is not a major problem, because the distribution of smoking habits between most occupational cohorts and referent populations differs little, if at all. Furthermore, when respiratory tract cancer rates are evaluated across a gradient of occupational exposures within the same cohort, the prevalence of smoking is generally so similar among the groups that tobacco smoking does not confound the relationship between occupation and cancer. In the present context, this theoretical lack of confounding was confirmed by Blair *et al.* (1990b) and Andjelkovich *et al.* (1995), who obtained data on the smoking habits of individual workers and found no effect on the risk estimates.

Three groups of workers were studied, which were totally or partially subsumed in the study of Blair *et al.* (1986, 1990b), described below. Marsh (1982) evaluated proportionate mortality patterns among workers engaged in the production of phenolic resins, urea–formaldehyde resins, melamine–formaldehyde resins, hexamethylenetetramine and resorcinol in the United States. He identified 603 deaths that occurred among men in 1950–76 and included 580 (132 exposed to formaldehyde for one month or more and 448 others) in the analysis. Wong (1983) studied workers employed at a formaldehyde production plant between the early 1940s and 1977. After exclusion of about 200 women, 12 blacks and two orientals, 2026 white men were included in the analysis. Tracing through 1977 was successful for all but 51 workers (2.5%), and 146 deaths were identified (death certificates were obtained for 136). Approximately 800 workers who were exposed to formaldehyde were included in the investigation of Blair *et al.* (1986, 1990b). Liebling *et al.* (1984) evaluated the proportionate mortality of 24 workers in the formaldehyde resin plant studied by Marsh (1982), who were also included by Blair *et al.* (1986, 1990b).

Blair *et al.* (1986) conducted a cohort mortality study of workers employed at 10 plants in the United States where formaldehyde was produced and used before 1966 and followed the workers up through 1979; some were included in the three studies mentioned above. The 10 plants were selected from a survey of about 200 companies because they had the most workers, the longest use of formaldehyde and the records necessary for a study. The cohort was assembled from company personnel records and verified for completeness from Social Security Quarterly Earnings reports. Relative risks were estimated from SMRs and directly standardized rate ratios. The expected numbers were calculated from rates for the general population and for the populations of the 10 counties in which the plants were located and were adjusted for race, sex, age and calendar time. Directly standardized rate ratios were adjusted to the distribution of

age and calendar-time person-years of the entire cohort for internal comparisons. Quantitative estimates of exposure were made on the basis of monitoring data available from the companies, from monitoring conducted by the study investigators and from information on tasks, plant operations, effects of controls and production levels (Stewart *et al.* (1986). On the basis of the job held with the highest exposure, 11% of the workers were in the background/unexposed category, 12% were exposed to < 0.1 ppm (< 0.12 mg/m^3), 34% to 0.1–0.5 ppm (0.12–0.6 mg/m^3), 40% to 0.5–2.0 ppm (0.6–2.5 mg/m^3) and 4% to ≥ 2.0 ppm (≥ 2.5 mg/m^3). The vital status of the 26 561 people in the cohort (20 714 white men, 1839 black men, 3104 white women, 26 black women and 878 workers of unknown race or sex) was determined successfully as of 1980 for 96% of the men and 83% of the women, yielding 4396 deaths. Death certificates were obtained for 4059 of the decedents (92%). The SMRs for all causes for workers exposed to formaldehyde were 1.0 (95% CI, 0.9–1.0) for white men, 0.9 (0.8–1.0) for white women and 0.8 (0.7–0.9) for black men. The SMRs for all cancers combined were 1.0 (0.9–1.1) for white men, 0.8 (0.6–1.0) for white women and 0.7 (0.5–1.0) for black men. Neither emphysema (SMR, 0.9; 0.7–1.3) nor cirrhosis of the liver (0.9; 0.7–1.1) occurred in excess among white men. No significant excess of mortality from any cancer was seen among exposed white men, white women or black men. Among exposed white men (the only group for which there was sufficient information), there were fewer deaths from leukaemia (0.8 [0.5–1.2]; 19 deaths) and brain cancer (0.8 [0.5–1.3]; 17 deaths) than expected, while the number of deaths from prostate cancer was about that expected (1.2 [0.8–1.6]; 33 deaths). Two nasal cancers occurred among white men, with 2.2 expected; none was observed among white women or black men. Although based on small numbers, the risk for cancer of the nasopharynx was increased ([3.2; 1.3–6.6] 7 deaths). One cancer of the nasopharynx occurred in a person who was not exposed to formaldehyde and one in a person not exposed to particulates, i.e. work environments in the formaldehyde-resin industry where the particles include urea–, phenol– and melamine–formaldehyde resins. The risk for death from nasopharyngeal cancer (5 deaths) among white men exposed to particulates rose with cumulative exposure to formaldehyde (0 deaths among unexposed; 1.9 (1 death) among those exposed for < 0.5 ppm-years; 4.0 (2 deaths) exposed for 0.5–5.5 ppm-years; and 7.5 (2 deaths) exposed for ≥ 5.5 ppm-years) (Blair *et al.*, 1987). In the same group, the SMRs for cancer of the oropharynx by cumulative exposure were 0 (no deaths) for the unexposed, 4.6 (3 deaths) for those exposed for < 0.5 ppm-years, 0 for exposure for 0.5–< 5.5 ppm-years and ≥ 5.5 ppm-years. Collins *et al.* (1988) pointed out that the excess occurred primarily at one plant and that subjects included in the analysis of Blair *et al.* (1987) were not required to have had simultaneous exposure to formaldehyde and particulates. They extended the follow-up of workers at the plant where four of the seven nasopharyngeal cancer deaths occurred and found no additional death for 13 656 person-years of follow-up. Tamburro and Waddell (1987) objected to the interpretation of the pattern of nasopharyngeal cancers as a trend in the absence of a significant exposure–response gradient. Lucas (1994) compared death certificate diagnoses of four nasopharyngeal cancers with information from a cancer registry. Because one of the four cancers was incorrectly labelled as nasopharyngeal cancer on the death certificate, Lucas (1994) suggested that corrected diagnoses should be used. Marsh *et al.* (1994b) and Blair and Stewart (1994) discussed the appropriateness of this recommendation. [The Working Group noted that

correction of the diagnoses in the cohort and not in the comparison population would bias estimates of relative risks towards the null. This bias would occur because there are deaths in the comparison population that are also incorrectly diagnosed as nasopharyngeal cancer. In fact, large surveys indicate that about 25% of death certificates coded as nasopharyngeal cancer are incorrect.] The SMRs for lung cancer among exposed and unexposed workers were 1.1 (95% CI, 1.0–1.3) and 0.9 (0.7–1.2) among white men, 1.3 (0.6–2.5) and 1.7 (0.7–3.5) among white women and 0.7 (0.4–1.3) and 0.6 (0.1–1.7) among black men. Internal comparisons resulted in directly adjusted rate ratios (compared with the unexposed category) for white men of 1.7 (35 deaths) for exposure to < 0.1 ppm (< 0.12 mg/m^3), 1.6 (70 deaths) for 0.1–0.4 ppm (0.12–0.5 mg/m^3), 1.8 (125 deaths) for 0.5–1.9 ppm (0.6–2.3 mg/m^3) and 0.8 (6 deaths) for ≥ 2.0 ppm (≥ 2.5 mg/m^3). There was a significant excess of deaths from lung cancer (1.2 [1.0–1.4] 219 observed) among white male wage workers (mainly non-managerial). Restricting analyses to wage (non-managerial) workers is valuable because it focuses on those employees likely to have had more intense exposures. Combining wage and salaried (managerial) workers in the same exposure–response analysis may introduce socioeconomic confounding, because salaried workers who have lower exposures to formaldehyde also have lower lung cancer rates. The risk was slightly higher when the analysis was restricted to events occurring 20 or more years after first exposure (1.3 [1.1–1.6] 151 observed). The SMRs for workers with a 20-year latency did not rise with cumulative exposure categories: 1.0 [0.3–2.3] (5 deaths) among unexposed; 1.4 [1.0–1.8] (49 deaths) for < 0.5 ppm-years, 1.4 [1.0–1.8] (53 deaths) for 0.5–5.5 ppm-years and 1.3 [0.9–1.7] (44 deaths) for ≥ 5.5 ppm-years.

In further analyses of the deaths from lung cancer in this cohort, Blair *et al.* (1990b) found no exposure–response gradient between the SMRs or directly-adjusted rate ratios and a variety of exposure indicators, including duration, intensity, cumulative exposure, peak, average and cumulative exposure restricted to lagged exposures (5, 10, 20 and 30 years). No exposure–response pattern was observed by duration of employment in various cumulative exposure categories or by cumulative exposure with duration of exposure categories. No increased risk for lung cancer was seen for workers exposed to formaldehyde alone (SMR, 1.0 [0.8–1.2] 88 observed). When exposures other than formaldehyde were considered, the risk for lung cancer was elevated (1.4 [1.2–1.7] 124 deaths) for workers in contact with asbestos, anti-oxidants, carbon black, dyes, melamine, phenol, urea and wood dust. Significant exposure–response trends were observed between mortality from lung cancer and duration of exposure to melamine and urea. Information on smoking was sought from medical records for 190 subjects with cancer and 950 controls. Although information was found for only about one-third of the subjects, the prevalence of smoking in this small sample did not appear to be associated with exposure to formaldehyde (80% who had ever smoked among the unexposed; 67% among those with a cumulative exposure of < 0.5 ppm-years, 84% with cumulative exposure of 0.5–< 5.5 ppm-years and 70% with cumulative exposure of ≥ 5.5 ppm-years).

Short-term workers sometimes have different mortality patterns from longer-term workers. Stewart *et al.* (1990) compared mortality among short-term (employed in the plants studied for one year or less) and long-term workers (employed for more than one year) in the cohort developed by Blair *et al.* (1986). Short-term workers had higher total mortality (SMR, 1.3;

95% CI, 1.2–1.3) than long-term workers (1.0; 0.9–1.0), and this overall excess was due to elevated rates of deaths from arteriosclerotic heart disease (1.1; 1.0–1.3), emphysema (1.7; 1.0–2.8) and cancers at all sites (1.3; 1.1–1.4). Excess rates were seen for cancers at several sites, including the stomach (1.4; 0.7–2.4), lung (1.4; 1.1–1.7) and brain (1.4; 0.7–2.5). The long-term workers had no cancer excesses. Data on nasal and nasopharyngeal cancers were not presented.

Others have re-analysed the study of Blair *et al.* (1986, 1990b). Robins *et al.* (1988), using a G-null test to adjust for the 'healthy worker survivor effect', found no indication of an association between exposure to formaldehyde and lung cancer but found a positive association with non-malignant respiratory disease. They adjusted the analysis for bias that may be created when ill workers leave the workforce: healthy workers continue to have the opportunity for exposure, while ill workers do not. This problem is most likely to occur in connection with debilitating diseases that do not lead to immediate death, such as emphysema.

Marsh *et al.* (1992a) used Poisson regression to analyse the data from the study of Blair *et al.* (1986, 1990b). They found excess mortality from lung cancer, which did not increase with level of cumulative exposure: relative risk, 1.0 for < 0.1 ppm-years, 1.4 (95% CI, 0.9–2.0) for 0.1–0.5 ppm-years, 1.2 (0.7–1.9) for 0.5–2.0 ppm-years and 1.3 (0.8–2.3) for ≥ 2.0 ppm-years, and no trend with duration of exposure. In a second report of their analyses, Marsh *et al.* (1992b) found no significant associations between lung cancer and cumulative, average or duration of exposure to formaldehyde. Significant positive associations with lung cancer were found with exposure to formaldehyde in the presence of other agents (antioxidants, hexamethylenetetramine, melamine and urea), but not in the absence of these cofactors. Finally, Marsh *et al.* (1994a) re-assessed the exposures in a five-year update of one of the plants in the study of Blair *et al.* (1986) and found a significant excess of lung cancer among short-term workers (SMR, 1.3 [95% CI, 1.1–1.8]; 63 deaths) but not among long-term workers (1.2 [0.9–1.6]; 50 deaths). Poisson regression analysis also showed larger relative risks in association with exposure to formaldehyde among short-term workers than long-term workers. No additional case of nasopharyngeal cancer was observed. Two nasopharyngeal cancers occurred among short-term workers.

Sterling and Weinkam (1988, 1989a,b, 1994) performed three re-analyses of the data and reported an exposure–response relationship between mortality from lung cancer and exposure to formaldehyde. The first two re-analyses contained errors (Blair & Stewart, 1989; Sterling & Weinkam, 1994).

Acheson *et al.* (1984a) studied 7680 British workers in six factories producing formaldehyde or formaldehyde-based resins, after excluding 7898 men who had begun work in 1965 or later, 1326 women and 689 workers for whom essential information was lacking. The date of first use of formaldehyde in the six factories ranged from the 1920s to the 1950s. Each worker was traced through 31 December 1981 from national mortality resources, and more than 98% of the cohort was successfully traced, yielding 1619 deaths. SMRs were used to estimate relative risks, and the expected numbers were based on death rates in England and Wales, adjusted for age and calendar time. Mortality rates in the areas where the factories were located were also used to generate expected numbers. Exposures were estimated on the basis of available data from monitoring (none before 1970) and information from management and labour. Exposure

was quantified in consultation with the staff of the six plants and placed in one of four categories: high (> 2.0 ppm; > 2.5 mg/m^3), moderate (0.6–2.0 ppm; 0.7–2.5 mg/m^3), low (0.1–0.5 ppm; 0.12–0.6 mg/m^3) and background/nil (< 0.1 ppm; < 0.12 mg/m^3). According to the job held with the highest exposure, 25% of the cohort were classified as having had background/nil exposure, 24% as low exposure, 9% as moderate exposure, 35% as high exposure and 6% unknown. Although the authors attempted to obtain information on tobacco use from company medical records, they were unsuccessful (Acheson *et al.*, 1984b). They point out that the workers may have had contact with other chemicals, including asbestos. Additional analyses using different approaches for dealing with exposure and death (cumulative and mortality over entire follow-up period, cumulative and mortality after leaving the factory, and cumulative at various calendar periods and subsequent mortality) (Acheson *et al.*, 1984c) yielded no further patterns.

The cohort of Acheson *et al.* (1984a) was further followed-up from 1981 through 1989 by Gardner *et al.* (1993). This follow-up includes 7660 people employed before 1965 rather than the 7680 in the original publication, because additional eligibility checks resulted in exclusion of 20 workers. The cohort also included 6357 workers who were first employed from 1965 onwards and who were thus excluded from the original report. The distribution of workers by highest formaldehyde exposure category was nil (25%), low (24%), moderate (9%), high (35%) and unknown (6%) among workers first employed before 1965 and 30%, 31%, 10%, 21% and 8%, respectively, for those first employed in 1965 or later. A further 1582 deaths were identified in the extended follow-up, for a total of 3201. SMRs are presented for workers first employed before 1965 and those first employed later. The SMRs for all causes were 1.0 (95% CI, 1.0–1.1) for workers first employed before 1965 and 1.0 (0.9–1.0) for those employed later, and the respective SMRs for all cancers were 1.1 (1.1–1.2; 802 deaths) and 1.0 (0.8–1.2; 128 deaths). One death from nasal cancer occurred (1.4 expected) in the group first employed before 1965 and none (0.3 expected) in those employed later. No deaths occurred from nasopharyngeal cancer, whereas 1.3 were expected, and no non-fatal cases were reported to the National Cancer Registry [expected number not reported]. Significant excess mortality was noted for cancers of the stomach (1.4; 1.2–1.7) and rectum (1.4; 1.0–1.9) among workers employed before 1965, although both decreased with adjustment for local rates. Non-significant SMRs greater than 2.0 were noted for cancer of the gall-bladder (2.9; 2 observed), breast (6.0; 1 observed) and other genital tumours (4.5; 1 observed) in workers employed in 1965 onwards and for bone cancer (2.4; 5 observed) in workers employed before 1965. For sites of special interest by period of first employment, the SMRs were 1.2 (1.1–1.4) and 1.1 (0.9–1.5) for lung cancer, 1.5 (0.6–3.0) and 0 deaths (1.1 expected) for pharyngeal cancer, 0.9 (0.5–1.5) and 0.9 (0.3–2.1) for brain cancer, 0.9 (0.5–1.6) and 1.9 (0.8–3.9) for non-Hodgkin's lymphoma and 0.9 (0.5–1.5) and 0.9 (0.3–2.3) for leukaemia. For background, low, moderate and high exposure categories, the relative risks for lung cancer were 1.0 (95% CI, 0.8–1.3), 1.1 (0.9–1.4), 0.9 (0.6–1.3) and 1.2 (1.1–1.4) for those first employed before 1965 and 1.4 (0.8–2.1), 1.0 (0.5–1.6), 1.0 (0.4–2.2) and 1.4 (0.8–2.3) for those first employed after 1964. There were no trends in lung cancer mortality that could be associated with level or duration of exposure.

Mortality among workers at a formaldehyde resin plant in Italy was studied by Bertazzi *et al.* (1986, 1989), who included 1330 male workers who were ever employed for at least 30 days between the start-up of the plant in 1959 and 1980. Vital status was determined as of December 1986, and 179 deaths were identified. Work histories of past employees were reconstructed from interviews with retired workers, current workers and foremen; and actual or reconstructed work histories were available for all but 16% of the cohort. Job mobility was low, and 79% of the workers had held a single job throughout their career. On the basis of their work histories, workers were placed into one of three categories: exposed to formaldehyde, exposed to compounds other than formaldehyde and exposure unknown. Individual exposures could not be estimated, but the mean levels in measurements taken between 1974 and 1979 were 0.2–3.8 mg/m^3. SMRs were used to estimate relative risks. The expected numbers were based on national and local mortality rates, adjusted for age and calendar time. The SMRs based on local rates were 0.9 ([95% CI, 0.7–1.0] 179 deaths) for all causes, 0.9 ([0.7–1.1] 62 deaths) for all cancers, 2.4 ([0.8–5.8] 5 deaths) for liver tumours, 1.0 ([0.6–1.5] 24 deaths) for lung cancer and 1.4 ([0.6–2.9] 7 deaths) for cancers of the lymphatic and haematopoietic system. The rates for lung cancer were not associated with duration of exposure, latency or age at first exposure. The SMRs for lung cancer were 0.7 ([0.3–1.5] 6 deaths) for workers exposed to formaldehyde, 0.8 ([0.4–1.5] 9 deaths) for those exposed to other chemicals and 2.1 ([1.0–4.0] 9 deaths) for those whose exposure to formaldehyde could not be determined. The risk for liver cancer was greater among workers with a latency of 20 or more years (SMR, 4.0) and among those who were first exposed at 45 years of age or older (3.8). The excess of liver cancer was seen in all three exposure categories: formaldehyde (2.4; 2 deaths), other chemicals (2.3; 2 deaths) and exposure unknown (2.9; 2 deaths). In the first report (Bertazzi *et al.*, 1986), no nasal cancer was seen (0.03 expected).

Mortality among workers in the abrasives industry in Sweden was evaluated by Edling *et al.* (1987a) in plants where grinding wheels were manufactured from abrasives held together by formaldehyde resins. The levels of formaldehyde were reported to be 0.1–1.0 mg/m^3. A cohort of 911 workers (211 women and 700 men; 521 were blue-collar workers) employed between 1955 and 1983 was traced for mortality through 1983 and cancer incidence through 1981, yielding 79 deaths and 24 incident cancers. Deaths and events occurring at the age of 75 or more were excluded because of concerns about diagnostic validity. Loss to follow-up was 2%. The expected numbers were based on rates for the general population, stratified for age, calendar year and sex. No significant excesses were seen. The relative risks for mortality were 1.0 (95% CI, 0.8–1.2; 79 deaths) for all causes, 0.9 (0.5–1.5; 17 deaths) for all cancers and 1.3 (0.3–3.2; 4 deaths) for respiratory diseases. The relative risks for cancer incidence were 0.6 (0.1–2.1; 2 cases) for lung cancer, 0.9 (0.2–2.2; 4 cases) for prostatic cancer and 2.0 (0.2–7.2; 2 cases) for non-Hodgkin's lymphoma.

Stayner *et al.* (1988) conducted a cohort study of mortality among workers who had been employed for at least three months in three garment manufacturing plants in the United States between 1955 and 1977. The cohort consisted of 11 030 workers and comprised 1602 white men, 406 nonwhite men, 6741 white women and 2281 nonwhite women. Vital status was determined through 1982, and 609 deaths were uncovered. Vital status was determined for 96%

of the cohort. The expected numbers for determining SMRs were derived from the age-, calendar time-, race- and sex-specific rates of the general population. Formaldehyde levels were monitored in each of the plants, but the data were not used in the epidemiological analyses. The geometric mean levels in various departments ranged from 0.14 to 0.17 ppm [0.17–0.21 mg/m^3]. The SMRs for most major causes of death were low, including those for all causes (0.7; 95% CI [0.7–0.8]), all cancers (0.8 [0.7–1.0]), diseases of the circulatory system (0.7 [0.6–0.8]) and diseases of the respiratory system (0.7 [0.5–1.1]). Significant excesses occurred for cancers of the buccal cavity (3.4 [0.9-8.5]) and connective tissue (3.6 [1.0-9.3]). The SMRs for other cancers were 1.1 [0.8–1.6] for lung, 0.6 [0.2–1.6] for lymphosarcoma and 1.1 [0.5–2.2] for leukaemia. The four deaths from cancer of the buccal cavity occurred among white women. Some cancers were evaluated by duration of exposure (< 4 years, 4–9 years and ≥ 10 years), resulting in SMRs of 0, 2.8 (1 death) and 7.6 [1.6–22] (3 deaths) for cancer of the buccal cavity [linear trend, $p < 0.01$]; and 1.5 [0.9–2.4] (18 deaths), 1.1 [0.5–2.0] (11 deaths) and 0.8 [0.4–1.5] (10 deaths) for cancer of the lung [linear trend, $p < 0.05$]. In a previous report, Stayner *et al.* (1985) gave the findings of a proportionate mortality study of workers in three garment plants (two of which were included in the later cohort study). Significantly increased PMRs were observed for malignant neoplasms of the buccal cavity, biliary tract and liver and 'other lymphatic and haematopoietic sites'.

Andjelkovich *et al.* (1995) reported on the mortality of a subset of a previously studied cohort of workers with potential exposure to formaldehyde in an automotive iron foundry in the United States. A cohort of 3929 men (2635 white, 1294 nonwhite) was followed from 1 January 1960 to 31 December 1989 (83 064 person-years of follow-up). For comparison, an unexposed group was also analysed, which consisted of 2032 men (1629 white, 403 nonwhite) who had worked during the same period but had not been exposed to formaldehyde (40 719 person-years of follow-up). The expected numbers of deaths were derived from rates for the general population. Men who worked predominantly in core-making and related operations were exposed to formaldehyde from 1960 through 1987, while all workers in the foundry were exposed to silica. Detailed work histories and an evaluation of occupational exposures by an industrial hygienist permitted categorization of the levels of exposure to formaldehyde (none, low, medium, high) and silica (low, medium, high) for every occupational title. Values for these exposure levels were assigned on the basis of sparse sampling data (low, 0.05; medium, 0.55; high, 1.5 ppm (formaldehyde) or mg/m^3 (silica)). Quartiles were based on each person's cumulative exposure. Basic information was obtained on the smoking habits of the exposed (ever, 1934; never, 637; unknown, 1358) and unexposed (ever, 811; never, 309; unknown, 912) men. In the exposed cohort, 608 men died during the observation period, 3263 lived, and vital status was unknown for 58. In the unexposed cohort, 422 died, 1583 lived and 27 were of unknown vital status. For the men exposed to formaldehyde, the SMRs were 0.93 (95% CI, 0.86–1.0) for all causes, 0.99 (0.82–1.2) for all cancers, 1.3 (0.48–2.9) for cancer of the buccal cavity and pharynx (no deaths from cancer of the nasopharynx [0.5 expected]), 1.2 (0.89–1.6) for lung cancer, 0.62 (0.07–2.2) for brain cancer, 0.43 (0.05–1.6) for leukaemia and 1.3 (0.47–2.8) for emphysema. No death occurred from cancer of the nasal cavity. A similar mortality pattern was seen for unexposed men, with SMRs of 0.91 (0.82–1.0) for all causes, 0.97 (0.79–

1.2) for all cancers, 1.7 (0.54–4.0) for cancer of the buccal cavity and pharynx (one death from cancer of the nasopharynx), 1.2 (0.84–1.6) for lung cancer, 0.41 (0.01–2.3) for brain cancer, 0.86 (0.17–2.5) for leukaemia and 2.3 (1.2–4.1) for emphysema. Race-specific analyses revealed no major differences from the analyses of all races, except that an excess of cancers of the buccal cavity and pharynx was seen only among nonwhites. Several comparisons, including rate ratios for exposed and unexposed men, SMRs with expected numbers based on rates in a working population and Poisson regression with adjustment for smoking, revealed no association between lung cancer and exposure to formaldehyde.

The cohort and proportionate mortality studies of cancer among industrial workers exposed to formaldehyde are summarized in Table 11. Table 12 gives an overview of the occurrence of nasal and nasopharyngeal cancer in the cohort studies of both professionals and industrial workers.

2.4 Case–control studies

The Working Group systematically reviewed case–control studies of cancers of the oral cavity, pharynx and respiratory tract. Although case–control studies of cancer at other sites sporadically contained information on exposure to formaldehyde, these studies were not reviewed systematically .

2.4.1 Cancers of the nasal cavity, paranasal sinuses, nasopharynx, oropharynx and pharynx (unclassified)

With the purpose of investigating the carcinogenic effects of exposures to wood dust, Hernberg *et al.* (1983) conducted a joint Nordic case–control study of 167 patients in Finland, Sweden and most of Denmark in whom primary malignant tumours of the nasal cavity and paranasal sinuses had been diagnosed between July 1977 and December 1980. There were 167 country-, age- and sex-matched controls in whom cancers of the colon and rectum had been diagnosed. The study subjects represented 58% of all cancers identified at these anatomical sites; the exclusions were due to early deaths or to non-responding or missing controls. Information on the occupations and smoking habits of the study subjects was obtained by telephone interview on a standardized form. A review of occupations in which exposure to formaldehyde can occur [exposure frequencies not stated] gave no indication of any association with sinonasal cancer. None of the cases or controls had worked in the particle-board or plywood industry or in the production of formaldehyde or formaldehyde-based glues. The authors considered the category 'painting, lacquering and glueing' as a possible exception, as minimal exposure to formaldehyde may occur; 18 cases and six controls had had this exposure [odds ratio, 3.2; 95% CI, 1.3–8.1]. When people with exposure to wood dust were excluded, however, the difference was in the opposite direction (three cases, six controls [odds ratio, 0.5; 0.1–1.9]. [The Working Group noted that the study was not designed to address exposure to formaldehyde and that all the cases in Denmark were also included in the study of Olsen *et al.* (1984).]

Table 11. Cohort and proportionate mortality studies of cancer and exposure to formaldehyde among industrial workers

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
United States (Blair *et al.*, 1986, 1987)	Formaldehyde producers, resin makers, other users, SMR (26 561; 20 714 white men, 1839 black men, 3104 white women, 904 others), 1934–80	Quantitative estimate, duration	All causes	1.0 (0.9–1.0)	2836 deaths, exposed white men
				0.9 (0.8–1.0)	200 deaths, exposed white women
				0.8 (0.7–0.9)	232 deaths, exposed black men
			All cancers	1.0 (0.9–1.1)	570 deaths, exposed white men
				0.8 (0.6–1.0)	50 deaths, exposed white women
				0.7 (0.5–1.0)	31 deaths, exposed black men
			Buccal/pharynx	1.0 (0.6–1.5)	18 deaths, exposed white men
				[0] (NA)	No deaths, exposed white women
				[1.5]	Three deaths, exposed black men
					With particulate exposure, white men:
			Nasopharynx	0 (0 death)	No formaldehyde
				1.9 (1 death)	< 0.5 ppm-years formaldehyde
				4.0 (2 deaths)	0.5–< 5.5 ppm-years formaldehyde
				7.5 (2 deaths)	≥ 5.5 ppm-years formaldehyde
			Colon	0.9 (0.6–1.2)	42 deaths, exposed white men
				1.1 (0.4–2.2)	Seven deaths, exposed white women
				1.9 (0.6–4.3)	Five deaths, exposed black men
			Nasal	[0.9]	Two deaths, exposed white men
				[0]	No deaths, exposed white women/black men
			Lung	1.1 (1.0–1.3)	201 deaths, exposed white men; no trend with level or duration
				1.3 (0.6–2.5)	Eight deaths, exposed white women
				0.7 (0.4–1.3)	11 deaths, exposed black men
			Breast	0.8 (0.4–1.4)	12 deaths, exposed white women
			Prostate	1.2 (0.8–1.6)	33 deaths, exposed white men
				[0.7]	Two deaths, exposed black men

Table 11 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
Blair *et al.* (contd)			Brain	0.8 (0.5–1.3)	17 deaths, exposed white men
				–	No deaths, 2 expected, exposed white women
			Lymphoma	[1.0] (NA)	One death, exposed black man
				0.5 (0.2–1.1)	Seven deaths, exposed white men
				–	No deaths, exposed white women/black men
			Leukaemia	0.8 (0.5–1.2)	19 deaths, exposed white men
				–	No deaths, exposed white men
				[1.0] (NA)	One death, exposed black man
United Kingdom (Gardner *et al.*, 1993; update of Acheson *et al.*, 1984a)	Chemical industry, SMR (7660 men employed < 1965, 6357 men employed ≥ 1965), 1941–89	Quantitative estimation, duration	Employed < 1965		
			All causes	1.0 (1.0–1.1)	2744 deaths
			All cancers	1.1 (1.1–1.2)	802 deaths
			Mouth	1.4 (0.3–4.0)	Three deaths
			Pharynx	1.5 (0.6–3.0)	Seven deaths
			Nasal	0.7	One death, 1.4 expected
			Lung	1.2 (1.1–1.4)	348 deaths, no trend with level or duration
			Prostate	0.7 (0.4–1.0)	26 deaths
			Brain	0.9 (0.5–1.5)	16 deaths
			Lymphoma	0.9 (0.5–1.6)	12 deaths
			Leukaemia	0.9 (0.5–1.5)	15 deaths
			Employed ≥ 1965		
			All causes	1.0 (0.9–1.0)	
			All cancers	1.0 (0.8–1.2)	457 deaths
			Mouth	1.9 (0.1–11)	128 deaths
			Pharynx	–	One death
			Nasal	0	0 deaths, 1.1 expected
			Lung	1.1 (0.9–1.5)	No death, 0.3 expected
					54 deaths, no trend with level or duration, slight trend with years of follow-up

Table 11 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
United Kingdom (Gardner *et al.*, 1993; update of Acheson *et al.*, 1984a) (contd)			Prostate	1.2 (0.5–2.7)	Six deaths
			Brain	0.9 (0.3–2.1)	Five deaths
			Lymphoma	1.9 (0.8–3.9)	Seven deaths
			Leukaemia	0.9 (0.3–2.3)	Four deaths
Italy (Bertazzi *et al.*, 1986, 1989)	Formaldehyde resin makers, SMR (1330 men), 1959–86	Duration of employment	All causes	0.9 [0.7–1.0]	179 deaths, local rates
			All cancers	0.9 [0.7–1.1]	62 deaths, local rates
			Alimentary tract	1.0 [0.6–1.5]	21 deaths, local rates
			Lung	1.0 [0.6–1.5]	24 deaths, local rates; no positive trend with duration
			Liver	2.4 [0.8–5.8]	Five deaths, local rates
			Lymphatic/ haematopoietic	1.4 [0.6–2.9]	Seven deaths, local rates
Sweden (Edling *et al.*, 1987a)	Abrasives industry, SMR, SIR (521 men), 1955–83	None	All causes	1.0 (0.8–1.2)	79 deaths
			All cancers	0.9 (0.5–1.5)	17 deaths
			All cancers	0.8 (0.5–1.3	24 incident cases
			Nasopharynx	– (NA)	One incident case
			Colon	1.0 (0.1–2.9)	Two incident cases
			Lung	0.6 (0.1–2.1)	Two incident cases
			Prostate	0.9 (0.2–2.2)	Four incident cases
			Lymphoma	2.0 (0.2–7.2)	Two incident cases
			Myeloma	4.0 (0.5–14)	Two incident cases

Table 11 (contd)

Country (reference)	Population, design (number), date	Exposure estimates	Cancer	Relative risk (95% CI)	Comment
United States (Stayner *et al.*, 1988)	Garment industry, SMR (11 030: 1602 white men, 406 nonwhite men, 6741 white women, 2281 nonwhite women), > 3 months, 1955–82	Duration	All causes	0.7 [0.7–0.8]	609 deaths
			All cancers	0.8 [0.7–1.0]	186 deaths
			Buccal cavity	3.4 [0.9–8.5]	Four deaths, all in white women, trend with duration
			Pharynx	1.1 [0.1–4.0]	Two deaths
			Intestine	0.7 [0.4–1.1]	15 deaths
			Lung	1.1 [0.8–1.6)	39 deaths, inverse trend with duration
			Breast	0.7 [0.5–1.0]	33 deaths
			Brain	0.7 [0.2–1.7]	Five deaths
			Connective tissue	3.6 [1.0–9.3]	Four deaths
			Lymphatic/ haematopoietic	0.9 [0.5–1.4]	18 deaths
			Lymphoma	0.6 [0.2–1.6]	Four deaths
			Leukaemia	1.1 [0.5–2.2]	Nine deaths
United States (Andjelkovich *et al.*, 1995)	Cohort in foundry, RR (2635 exposed white men, 1294 exposed nonwhite men; 1629 unexposed white men, 403 unexposed nonwhite men), 1960–89	Duration, quantitative estimate	Buccal cavity, pharynx	0.59 (0.14–2.9)	Any exposure
				1.2 (0.2–6.5)	3rd–4th quartile of exposure
			Lung	0.71 (0.43–1.2)	Any exposure
				0.59 (0.28–1.2)	3rd–4th quartile of exposure

CI, confidence interval; SMR, standardized mortality ratio; NA, not available; SIR, standardized incidence ratio; RR, relative risk

Table 12. Results for nasal and nasopharyngeal cancers in cohort studies of professionals and industrial workers exposed to formaldehyde

Reference	Study size	Nasal			Nasopharyngeal		
		RR	Obs	Exp	RR	Obs	Exp
Professional workers							
Harrington & Oakes (1984)	2 720	-	0	NR	-	0	NR
Hall *et al.* (1991)	4 512	NR			NR		
Walrath & Fraumeni (1983)	1 263	-	0	NR	-	0	NR
Walrath & Fraumeni (1984)	1 007	-	0	0.6	NR	NR	NR
Levine *et al.* (1984a)	1 477	-	0	0.2	NR	NR	NR
Stroup *et al.* (1986)	2 317	-	0	0.5	NR	NR	NR
Hayes *et al.* (1990)	4 046	-	0	1.7	2.2	4	1.9
Friedman & Ury (1983)	143 574	NR			NR		
Industrial workers							
Blair *et al.* (1986)	20 714	0.9	2	2.2	3[a]	6	2.0
Gardner *et al.* (1993)	14 017	[0.6]	1	1.7	-	0	1.3
Bertazzi *et al.* (1986)	1 330	-	0	0.03	NR		
Stayner *et al.* (1988)	11 030	NR			NR		
Edling *et al.* (1987a)	911	NR			NR		
Andjelkovich *et al.* (1995)	3 929	-	0	NR	-	0	[0.5]

NR, not reported

[a] Trend with level among those also exposed to particulates

In a case–control study conducted in four hospitals in North Carolina and Virginia, United States, in 1970–80, 193 men and women with primary malignancies of the nasal cavity and sinuses were identified (Brinton *et al.*, 1984). Two hospital controls who were alive at the date of the interview were selected for each living patient and matched on hospital, year of admission, age, sex, race and administrative area; for deceased patients, two similarly matched controls were chosen: one patient who had attended the same hospital but who was not necessarily alive at the date of the interview, and one deceased person from records of the state vital statistics offices. Patients with oesophageal and sinonasal cancers and various nasal disorders were excluded from the control group. Telephone interviews were completed with 160 of the nasal cancer patients (83%) and 290 of the controls (78%), either directly with the patients themselves (33% of cases and 39% of controls) or with their next-of-kin. Occupational exposures were assessed by the subjects' responses to a checklist of potentially high-risk industries and exposures, including formaldehyde. Exposure to formaldehyde was reported for two nasal cancer patients (one man and one woman), yielding an odds ratio of 0.35 (95% CI, 0.1–1.8). [The Working Group noted that the power of the study may have been decreased by

the high proportion of interviews that were with next-of-kin and that exposure to formaldehyde was reported by subjects or their next-of-kin.]

In a population-based study in Denmark (Olsen *et al.*, 1984), 839 men and women in whom cancer of the sinonasal cavities (525) and nasopharynx (314) was diagnosed during the period 1970–82 and reported to the national Cancer Registry were matched to 2465 controls for sex, and age and year of diagnosis, who were selected among all patients in whom cancer of the colon, rectum, prostate and breast was diagnosed during the same period. Histories of exposure to formaldehyde, wood dust and 10 other specified compounds or industrial procedures were assessed by industrial hygienists, who were unaware of the case or control status of the study subjects, on the basis of individual employment histories obtained from a national pension scheme in operation since 1964. With regard to individual compounds, the industrial hygienists determined whether a subject had not been exposed, had definitely been exposed or had probably been exposed, or whether no information could be obtained. Of the controls, 4.2% of males and 0.1% of females had had occupations with presumed exposure to formaldehyde. The results were presented only for the carcinoma subgroup of sinonasal cancer (93% of cases). The odds ratios for definite exposures to formaldehyde (unadjusted for any other occupational exposure and using the no exposure category as the reference level) were 2.8 for both men and women (95% CI, 1.8–4.3 and 0.5–14, respectively) and 3.1 (1.8–5.3) for men in whom the diagnosis was made more than 10 years after first exposure. Adjustment for exposure to wood dust reduced both risk estimates for men to 1.6, which were no longer significant. Only five men in the group of 33 workers with definite exposure to formaldehyde had not been exposed to wood dust. Probable exposure to formaldehyde was associated with a slightly increased risk for sinonasal cancer in men (odds ratio, 1.2; 0.8–1.7). There was no increase in the risk for carcinoma of the nasopharynx among men with definite exposure to formaldehyde (0.7; 0.3–1.7). [The Working Group noted that the employment histories of study subjects were restricted to 1964 or later and that the study is limited by the fact that the formaldehyde-using industries in Denmark seem to be dominated by exposure to wood dust, which makes it difficult to assess the separate effect of exposure to formaldehyde on the risk for sinonasal cancer.]

A re-analysis was performed (Olsen & Asnaes, 1986) in which data on men with squamous-cell carcinoma (215) and adenocarcinoma (39) of the sinonasal cavities were examined separately. An odds ratio (adjusted for exposure to wood dust) of 2.3 (95% CI, 0.9–5.8) for squamous-cell carcinoma was found for 13 subjects who had ever been exposed to formaldehyde; of these, four had not been exposed to wood dust (2.0; 0.7–5.9). Introduction of a 10-year latent period into the analysis yielded odds ratios of 2.4 (0.8–7.4) and 1.4 (0.3–6.4), respectively. The analysis confirmed that the risk associated with exposure to wood dust is high for adenocarcinoma (odds ratios, 16 for any exposure and 30 for exposure 10 or more years before diagnosis) and small or non-existent for squamous-cell carcinoma (odds ratio, 1.3 irrespective of period). For the 17 cases of adenocarcinoma in men who had ever been exposed to formaldehyde, the odds ratio, after adjustment for exposure to wood dust, was 2.2 (0.7–7.2), and that among men who had been exposed 10 or more years before diagnosis was 1.8 (0.5–6.0); however, only one man with an adenocarcinoma had been exposed to formaldehyde alone. Analysis of the risk for histologically specified carcinomas of the nasopharynx showed no

association with exposure to either formaldehyde or wood dust. [The Working Group noted possibly incomplete adjustment for confounding from exposure to wood dust in the assessment of the risk for adenocarcinoma associated with exposure to formaldehyde, but also noted that the assessment of risk for squamous-cell carcinoma was less likely to have been affected because squamous-cell carcinoma is not clearly associated with exposure to wood dust.]

From an examination of medical records in the six major institutions in the Netherlands for surgical and radiographic treatment of tumours of the head and neck, Hayes *et al.* (1986) identified 116 men, aged 35–79, in whom a histologically confirmed epithelial cancer of the nasal cavity and paranasal sinuses had been diagnosed in 1978–81. The cases were frequency matched on age with 259 population controls chosen randomly from among living male residents in 1982 (in a ratio of 2:1 for all patients) and from among deceased men in 1980 (in an approximate ratio of 1:1 for dead cases). Detailed histories, including information on exposure to a selected list of substances in the workplace and subjects' smoking habits, were obtained by personal interview of study subjects or their next-of-kin, with response rates of 78% for case patients and 75% for controls. Independently of one another, two industrial hygienists (A and B) evaluated possible exposure to formaldehyde on a 10-point scale, and subsequently used three categories. Exposure to wood dust was assessed similarly by one hygienist. At least some potential occupational exposure to formaldehyde was considered to have occurred for 23% of all study subjects by assessment A and 44% by assessment B; little or no exposure to wood dust was considered to have occurred in 15 and 30%, respectively. A large excess risk for adenocarcinoma (odds ratio, 26 [95% CI, 7.0-99]) was associated with high levels of exposure to wood dust; thus, there were too few cases (six) with no or limited exposure to wood dust to allow a meaningful assessment of risks associated with exposure to formaldehyde alone. Separate analyses among the 45 men with squamous-type sinonasal cancer who had had little or no exposure to wood dust showed an increase in risk with increasing level of exposure to formaldehyde, with odds ratios for moderate and high exposures of 2.7 [95% CI, 0.8–8.8] and 3.1 [0.7–13] in assessment A and 1.4 [0.4–4.4] and 2.4 [1.0–6.0] in assessment B, respectively. The overall relative risks for squamous-cell carcinoma associated with any exposure to formaldehyde were 3.0 [1.2–7.8] in assessment A and 1.9 [0.9–4.1] in assessment B. [The Working Group noted that a greater proportion of case patients than controls were dead (36% versus 14%) and variable numbers of next-of-kin were interviewed; besides, 10% of controls, but none of the case patients, were interviewed by telephone. The Group noted, however, that although assessments A and B were different both gave positive results.]

In the population of a 13-county area in western Washington State, United States, Vaughan *et al.* (1986a) studied 415 patients, aged 20–74 years, in whom cancer of the sinonasal cavities and pharynx (53 patients with sinonasal cancer, 27 with nasopharyngeal cancer and 205 with oro- or hypopharyngeal cancer) had been newly diagnosed, and 690 control subjects who were identified by random-digit dialing and were of similar age and the same sex as the cases. Medical, smoking, alcohol use, residential and occupational histories were collected in a telephone interview with study subjects or their next-of-kin. The response rates were 69% for cases and 80% for controls; interviews were conducted with next-of-kin for about half of the cases and none of the controls. Occupational exposure to formaldehyde was assessed by means

of a job–exposure linkage system, in which each job within each industry was related to the likelihood and intensity of exposure and was categorized as background, low, medium or high exposure. In addition, exposure scores were calculated for maximal and usual exposures weighted by the time spent in the relevant job. The odds ratios for sinonasal cancer, adjusted for sex, age, cigarette smoking and alcohol consumption, were 0.8 (95% CI, 0.4–1.7; nine cases) for low exposure, 0.3 (0.0–1.3; three cases) for medium or high exposure and 0.3 (0.0–2.3) for a high exposure score. The corresponding odds ratios for nasopharyngeal cancer were 1.2 (0.5–3.3), 1.4 (0.4–4.7) and 2.1 (0.6–7.8), and those for oropharyngeal cancer were 0.8 (0.5–1.4), 0.6 (0.1–2.7) [high exposure only] and 1.5 (0.7–3.0). When a latent period of 15 years or more was introduced into the analysis, the odds ratio associated with the highest exposure to formaldehyde was unchanged (2.1; 0.4–10) for nasopharyngeal cancer and was slightly reduced (1.3; 0.6–3.1) for oropharyngeal cancer; no exposed cases of sinonasal cancer remained in this latency category. [The Working Group noted that the different proportions of interviews conducted with next-of-kin of cases and controls may have affected the odds ratios.]

Vaughan *et al.* (1986b) also explored the relationships between these types of tumours and residential exposure to formaldehyde. Living in a mobile home and the presence of urea–formaldehyde foam insulation and particle-board or plywood in residences were taken as indirect measures of residential exposure. Five of the patients with sinonasal cancer had lived in a mobile home (odds ratio, 0.6; 95% CI, 0.2–1.7), all for fewer than 10 years, 25 had lived in residences constructed with particle-board or plywood, yielding odds ratios of 1.8 (0.9–3.8) for periods of < 10 years and 1.5 (0.7–3.2) for ≥ 10 years. An association was found between living in a mobile home and risk for nasopharyngeal cancer, with odds ratios of 2.1 (0.7–6.6; four exposed cases) for < 10 years and 5.5 (1.6–19; four exposed cases) for ≥ 10 years. No association was found with the risk for oropharyngeal cancer (0.9; 0.5–1.8 and 0.8; 0.2–2.7, respectively). No association was seen between the risk for oro- or hypopharyngeal cancer and reported exposure to particle-board or plywood. The risks associated with exposure to formaldehyde foam insulation could not be estimated, owing to low exposure frequencies. [The Working Group considered that living in a mobile home was a poor proxy for exposure to formaldehyde because of large variations in the use of formaldehyde-containing foams and the sharply declining release of formaldehyde to indoor air with time.]

Roush *et al.* (1987) reported on a population-based case–control study of 371 men registered at the Connecticut (United States) Tumor Registry with a diagnosis of sinonasal cancer (198) or nasopharyngeal cancer (173) and who had died (of any cause) in Connecticut in 1935–75, and 605 male controls who died in the same period and were selected randomly from the files of Connecticut death certificates, without stratification or matching. Information on the occupations of the study subjects was derived from death certificates and from annual city directories; the latter were consulted 1, 10, 20, 25, 30, 40 and 50 years before death, when available. Each occupation held by case patients and controls was assessed by an industrial hygienist with regard to the likelihood and level of work-place exposure to formaldehyde, and study subjects were subsequently categorized into one unexposed and four exposed groups according to four degrees of probable exposure to formaldehyde. The odds ratio, adjusted for age at death, year of death and availability of information on occupation for case patients with

sinonasal cancer who had probably been exposed to the same level of formaldehyde for most of their working life was 0.8 (95% CI, 0.5–1.3); for those who fulfilled the more restricted exposure criteria of being probably exposed to the same level for most of their working life and probably exposed to high levels for some years, the odds ratio was 1.0 (0.5–2.2); that for men who had probably been exposed to the same level for most of their working life and probably exposed to high levels at some point 20 or more years before death, it was 1.5 (0.6–3.9). The corresponding odds ratios for men with nasopharyngeal cancer were 1.0 (0.6–1.7), 1.4 (0.6–3.1) and 2.3 (0.9–6.0). There was no excess risk for sinonasal cancer among formaldehyde-exposed men who had also been exposed wood dust (0.9; 0.4–1.9).

Luce *et al.* (1993) conducted a case–control study of 303 men and women with primary malignancies of the nasal cavities and paranasal sinuses diagnosed in one of 27 hospitals in France between January 1986 and February 1988, and 443 control subjects selected by frequency matching for age and sex among patients in whom another cancer had been diagnosed during the same period at the same or a nearby hospital (340) or from a list of names of healthy individuals provided by the cases (103). Occupational exposures to formaldehyde and 14 other substances or groups of substances were assessed by an industrial hygienist on the basis of information obtained during a personal interview at the hospital (for the cancer patients) or at home (for the healthy controls) on job histories, a number of pre-defined occupational exposures, socioeconomic variables and smoking habits. The response rates were 68% of cases and 92% of controls. Histological confirmation was available in the medical records of all but one of the remaining 207 case patients. Study subjects were classified according to the likelihood of exposure to each of the suspected determinants of sinonasal cancer and grouped into one of four categories: none, possible, probable or definite exposure; the latter two were further split into a number of subgroups according to levels and calendar periods of exposure and combinations thereof. The risks associated with exposure to formaldehyde were reported for men only. Possible exposure to formaldehyde was considered to have occurred in 12% of the 59 men with squamous-cell carcinoma of the sinonasal cavities and 11% of the 320 control subjects (odds ratio, 1.0; 95% CI, 0.4–2.4). The corresponding proportions with probable or definite exposure to formaldehyde were 27% and 25%, respectively [1.1; 0.6–2.1]. No relationship was observed between any of the measures of exposure to formaldehyde and risk for squamous-cell carcinoma. Nearly all of the adenocarcinomas occurred in men with medium to high exposure to wood dust (77/82). For those exposed to both wood dust and formaldehyde, the odds ratio was 692 (92–5210), and for those exposed to wood dust but not formaldehyde the odds ratio was 130 (14–1191); however, the latter estimate was based on only six exposed cases. For four men who were exposed to formaldehyde but who had had no or little exposure to wood dust, the odds ratio for adenocarcinoma was 8.1 (0.9–73). [The Working Group noted that residual confounding by exposure to wood dust may have occurred.]

The etiology of nasopharyngeal carcinoma was studied in the Philippines; both viral (Hildesheim *et al.*, 1992) and non-viral (West *et al.*, 1993) risk factors were addressed. West *et al.* (1993) conducted a case–control study of 104 histologically confirmed cases of nasopharyngeal carcinoma in Rizal Province, where the incidence rates of this tumour (4.7/100 000 men and 2.6/100 000 women) are intermediate between those in China and those in western

countries. The case patients (100% response rate) were identified at the Philippines General Hospital, as were 104 hospital controls (100% response rate), who were matched to cases on sex, age and type of hospital ward, and 101 community controls (77% response rate), who were matched on sex, age and neighbourhood. A personal interview included questions on smoking habits, adult diet, demographic variables and occupational history. An industrial hygienist classified each job held by the study subjects as likely or unlikely to involve exposure to formaldehyde, solvents, exhaust fumes, wood dust, dust in general and pesticides and combined the classification with information on duration of employment in such occupations. The risk for nasopharyngeal carcinoma was associated with likely exposure to formaldehyde; the odds ratios, adjusted for the effects of dusts and exhaust fumes and other suspected risk factors, were 1.2 (0.4–3.6; 12 exposed cases) for subjects first exposed < 25 years before diagnosis and 4.0 (1.3–12; 14 exposed cases) for those first exposed ≥ 25 years before diagnosis. In the subgroup of subjects who were first exposed to formaldehyde ≥ 25 years before diagnosis and first exposed to dust and/or exhaust fumes ≥ 35 years before diagnosis, an odds ratio of 16 (2.7–91) was found relative to people exposed to neither factor [numbers exposed not given]. A reverse trend was seen, however, with increasing duration of exposure to formaldehyde, with odds ratios of 2.7 (1.1–6.6) for < 15 years and 1.2 (0.5–3.2) for ≥ 15 years of exposure. [The Working Group noted that the authors did not control for the presence of Epstein–Barr viral antibodies, which showed a strong association with nasopharyngeal cancer (odds ratio, 21) in the study of Hildesheim *et al.* (1992).]

2.4.2 Cancers of the lung and larynx

Andersen *et al.* (1982) conducted a case–control study of 79 male and five female Danish doctors with a notification of lung cancer in the files of the nationwide Danish Cancer Registry during the period 1943–77. Three times as many control subjects, matched individually on sex and age, were selected at random from among individuals on official lists of Danish doctors. Information on postgraduate specialization and places of work during the professional career of cases and controls was obtained from medical directories and supplementary files at the Danish Medical Society. Potential exposure to formaldehyde was assumed to be associated with working in pathology, forensic medicine and anatomy. None of the doctors with lung cancer had specialized in any of these fields, but one control doctor was a pathologist. Eight male case patients and 23 controls had been employed at some time in pathology, forensic medicine or anatomy, giving an odds ratio of 1.0 (95% CI, 0.4–2.4).

Fayerweather *et al.* (1983) reported on a case–control study of mortality from cancer among chemical workers in eight plants in the United States where formaldehyde was manufactured or used. All 481 active or pensioned men who were known to have died of cancer in 1957–79 were individually matched on age, pay class, sex and date of first employment to 481 men selected at random from annual payroll rosters at the plants. The cases included 181 lung cancers, 12 brain cancers and 7 cancers of the buccal cavity and pharynx. The work histories of both case and control subjects were supplied by the plants, and the categories of exposure to formaldehyde were defined, on the basis of frequency and intensity of exposure, as 'continuous direct', 'intermittent' and 'background'. Smoking histories were obtained for about 90% of subjects,

primarily by interviewing living co-workers. Of the 481 cases, 142 (30%) had had potential exposure to formaldehyde. For no cancer site examined was the odds ratio significantly greater than 1.0 in relation to any of the defined categories of exposure to formaldehyde. After allowance for a cancer induction period of 20 years, 39 patients with lung cancer and 39 controls had potentially been exposed to formaldehyde [odds ratio, 1.0; 95% CI, 0.6–1.7; unadjusted for smoking habits]; the odds ratios were 1.2 [0.6–2.8] and 0.8 [0.4–1.6] for subgroups with < 5 years and ≥ 5 years of exposure, respectively. Only one of the seven patients who died of cancer of the buccal cavity or pharynx was thought to have been exposed to formaldehyde; this was equivalent to the frequency observed among the matched controls. No death from nasal cancer was identified.

In a population-based case–control study, Coggon *et al.* (1984) used death certificates to obtain information about the occupations of all men under the age of 40 years in England and Wales who had died of bronchial carcinoma during 1975–79; 598 cases were identified, 582 of which were matched for sex, year of death, local authority district of residence and year of birth with two controls and the rest with one control who had died from any other cause. Occupations were coded according to the Office of Population Census and Surveys 1970 classification, and a job–exposure matrix was constructed by an occupational hygienist, in which the occupations were grouped according to three levels (high, low and none) of exposure to nine known or putative carcinogens, including formaldehyde. All occupations that entail exposure to formaldehyde were associated with an elevated, crude odds ratio for bronchial carcinoma of 1.5 (95% CI, 1.2–1.8); however, for occupations in which exposure was presumed to be high, the odds ratio was 0.9 (0.6–1.4). [The Working Group noted that information on occupation from death certificates is limited; they also noted the young age of the subjects and the consequent short exposure and latency.]

Partanen *et al.* (1985) conducted a case–control study in a cohort of 3805 male production workers who had been employed for at least a year in one of three particle-board factories, seven plywood factories, eight sawmills and one formaldehyde glue factory between 1944 and 1966. Of these, 57 subjects were notified to the Finnish Cancer Registry with cancer of the respiratory tract (including at least 51 cases of lung cancer), oral cavity or pharynx in 1957–80. Three controls were selected at random from the same cohort and were individually matched to the case by year of birth. Plant- and time-specific job–exposure matrices were constructed for 12 chemicals, including formaldehyde (Kauppinen & Partanen, 1988), and combined with the work histories of the subjects to yield several indicators of exposure; supplementary information on smoking was collected for 68% of cases and 76% of controls by means of a questionnaire posted to study subjects or their relatives. A slight, nonsignificant increase in risk for all cancers combined was seen among workers with any exposure to at least 0.1 ppm (0.12 mg/m^3) formaldehyde, as contrasted to workers with no exposure to formaldehyde, to give an odds ratio of 1.4 [95% CI, 0.6–3.5]; an odds ratio of 1.3 [0.5–3.5] was seen when a minimal latency of 10 years before diagnosis was assumed. No significant association was found with other indicators of exposure to formaldehyde (mean level and cumulative exposure, repeated peak exposures and 'formaldehyde in wood dust'). Adjustment for cigarette smoking did not change the overall picture.

In an expansion of the study to include a total of 35 Finnish factories and 7307 woodworkers employed in 1944–65, Partanen *et al.* (1990) identified 136 cases of newly diagnosed cancer of the respiratory tract (118 lung cancers, 12 laryngeal cancers and one sinonasal cancer), oral cavity (four cases) and pharynx (one case) from the files of the cancer registry, 1957–82. The additional factories were mainly involved in construction carpentry and furniture manufacture. Three controls were provided for each of the new cancer cases, and exposure to formaldehyde and 11 other occupational agents was assessed by the same methods as those described in the initial study (Partanen *et al.*, 1985; Kauppinen & Partanen, 1988). Of 20 cases with any exposure to formaldehyde (odds ratio, 1.4 [95% CI, 0.6–3.1]), 18 were cancers of the lung (1.3 [0.5–3.0]) and two were cancers at other sites (2.4 [0.3–18]). Adjustment for smoking reduced the odds ratios to 1.1 for all cancers combined and to 0.7 for lung cancer separately and made the odds ratio for cancers at other sites unassessable. The unadjusted odds ratios for all cancers were 1.5 [0.7–3.6] for an estimated mean level of formaldehyde of 0.1–1 ppm [0.12–1.23 mg/m^3] and 1.0 [0.1–8.2] for > 1 ppm, in comparison with no exposure. Other indicators of exposure to formaldehyde showed similar inverse dose–response relationships, i.e. the lowest risks in the highest exposure categories. Allowance for a minimal latency of 10 years further reduced the risk estimates of the subgroups with presumably the highest exposures, with odds ratios generally below 1.0. [The Working Group noted that there were too few cancers at sites other than the lung to allow meaningful analysis; consequently, this is essentially a study of lung cancer.]

Bond *et al.* (1986) conducted a case–control study in a cohort of 19 608 men employed for one year or more at a large chemical production facility in Texas, United States, between 1940 and 1980, including all 308 workers who had died from lung cancer and 588 controls chosen at random from among men in the same cohort. Two series of controls, individually matched to cases on race, year of birth and year of hire, were selected: one among men still alive when the matched subjects died of lung cancer, and one among men who had died ≤ 5 years after the matched subjects. Exposures (ever or never) to 171 chemical and physical agents, including formaldehyde, were assessed by an industrial hygienist on the basis of a review of documentation on the subject's employment history at the facility and industrial hygiene records; six exposures, excluding formaldehyde, were assessed in greater detail. Only nine men with lung cancer (3%) were judged ever to have been exposed to formaldehyde, and a negative association was seen between this exposure and mortality from lung cancer (not adjusted for other exposure variables), with an odds ratio of 0.6 (95% CI, 0.3–1.3); incorporation into the analysis of a 15-year minimal latency gave an odds ratio of 0.3 (0.1–0.9).

In a population-based case–control study in the area of Montréal, Canada, 857 men with histologically confirmed primary lung cancer diagnosed during 1979–85, were identified (Gérin *et al.*, 1989). Two groups of control subjects were established, one composed of 1523 men diagnosed during the same years with cancers of other organs (oesophagus, stomach, colorectum, liver, pancreas, prostate, bladder, kidney, melanoma and lymphoid tissue), the other composed of 533 men selected from electoral lists of the Montréal area. Interviews or completed questionnaires, yielding lifelong job history and information on potential nonoccupational confounders, were obtained from the cancer patients or their next-of-kin and from the population

controls, with response rates at 82 and 72%, respectively. Each job was translated by a group of chemists and hygienists into a list of 300 potential exposures, including formaldehyde, which were categorized according to the likelihood, intensity and frequency of exposure. Nearly one-quarter of all men had been exposed to formaldehyde in at least one of the jobs they had held during their working life; however, only 3.7% were considered to be definitely exposed and only 0.2% were considered to have had high exposure, defined as more than 1.0 ppm [1.23 mg/m^3] of formaldehyde in the ambient air. Odds ratios, adjusted for age, ethnic group, socioeconomic status, cigarette smoking, the 'dirtiness' of the jobs held and other potential workplace exposure, were 0.8 (95% CI, 0.6–1.2) for < 10 years of exposure to formaldehyde, 0.5 (0.3–0.8) for ≥ 10 years of presumed exposure to < 0.1 ppm [0.12 mg/m^3], 1.0 (0.7–1.4) for ≥ 10 years of presumed exposure to 0.1–1.0 ppm [0.12–1.23 mg/m^3] and 1.5 (0.8–2.8), for ≥ 10 years of presumed exposure to ≥ 1.0 ppm formaldehyde, in relation to controls with other cancers. In comparison with the population controls, the equivalent odds ratios were 1.0 (0.6–1.8), 0.5 (0.3–0.8), 0.9 (0.5–1.6), and 1.0 (0.4–2.4), respectively. Marginally increased risks were seen for subjects with the adenocarcinoma subtype of lung cancer who had had long exposure to a high concentration of formaldehyde, with odds ratios of 2.3 (0.9–6–0) and 2.2 (0.7–7.6) in comparison with the cancer and population control groups, respectively; however, the estimates were based on only seven exposed cases.

Wortley *et al.* (1992) studied 291 male and female residents of a 13-county area of western Washington State, United States, in whom laryngeal cancer was diagnosed in 1983–87 and notified to a population-based cancer registry in the area; 81% were interviewed. Control subjects were identified by random-digit dialing and selected to be similar in age and sex to the cases; 80% of eligible subjects were interviewed, leaving 547 for analysis. Lifetime occupational, smoking and drinking histories were obtained by personal interview, and each job held for least six months was coded according to the United States census codes for industries and occupations. Codes for exposure to formaldehyde and five other agents were assigned to each classified job held by the study subjects, using a job–exposure matrix assessing both likelihood and degree of exposure and created *ad hoc*, and combined with information on duration of exposure; finally, three summary variables for presumed exposure were derived. The risk for laryngeal cancer, adjusted for age, smoking and drinking habits and length of education, was not associated with exposure to formaldehyde to a significant degree. The odds ratios were 1.0 (95% CI, 0.6–1.7) for patients with any 'low' exposure, 1.0 (0.4–2.1) for any 'medium' exposure and 2.0 (0.2–20; two exposed cases) for any 'high' exposure. Odds ratios of 0.8 (0.4–1.3) and 1.3 (0.6–3.1) were seen for exposure < 10 years and ≥ 10 years and of 1.0 (0.5–2.0) and 1.3 (0.5–3.3) for a medium and high formaldehyde score, respectively; the latter were calculated as the sum of years exposed weighted by the level of exposure in each of the years.

2.4.3 Cancers at other sites

In a study of 578 male leukaemia cases, 622 male non-Hodgkin's lymphoma cases and 1245 population-based controls in Iowa and Minnesota (United States), Linos *et al.* (1990) observed elevated risks for both leukaemia (odds ratio, 2.1 [95% CI, 0.4–10]) and non-Hodgkin's lymphoma (3.2 [0.8–13]) among subjects who had been employed in funeral homes

and crematoria, indicating some degree of professional exposure to formaldehyde and other compounds. The risks were particularly high for the acute myeloid subtype of leukaemia (6.7 [1.2–36]) and the follicular subtype of non-Hodgkin's lymphoma (6.7 [1.2–37]), however, these estimates were each based on only three exposed cases.

In the study of Gérin *et al.* (1989) in Montréal, Canada (see p. 274), 206 cases of non-Hodgkin's lymphoma were compared with cases of other cancer. No association was found with estimated exposure to formaldehyde.

Merletti *et al.* (1991) reported a case–control study of 103 male residents of Turin, Italy, with a diagnosis of cancer of the oral cavity or oropharynx notified to the population-based cancer registry of the city, and a random sample of 679 males, stratified by age, chosen from files of residents of Turin. Detailed occupational (since 1945) and lifelong smoking and drinking histories were obtained by personal interview, with response rates of 84% for cases and 57% for controls. Each job held for at least six months was coded according to the International Standard Classification of Occupations and the International Standard Industrial Classification, and a job–exposure matrix for 13 agents (including formaldehyde) which are known or suspected respiratory tract carcinogens and three non-specific exposures (including dust) were applied to the occupation–industry code combination of study subjects; the matrix was developed at the International Agency for Research on Cancer for use in a similar study of laryngeal cancer. Study subjects were grouped into three categories of presumed frequency and intensity of exposure to formaldehyde, with a 'no exposure' group (exposure not higher than that of the general population) as the reference level. An association was suggested between cancer of the oral cavity or oropharynx and exposure to formaldehyde, with odds ratios of 1.6 (95% CI, 0.9–2.8) for any exposure and 1.8 (0.6–5.5) for 'probable or definite' exposure; however, only 25 and six cases were exposed, respectively. No relationship was seen with duration of exposure to formaldehyde: non-significantly raised odds ratios were estimated of 1.7 for 1–15 years of exposure and 1.5 for ≥ 16 years within the 'any exposure' category, and 2.1 and 1.4, respectively, within the 'probable or definite' exposure category. Separate results in association with exposure to formaldehyde were not reported for the 12 men with oropharyngeal cancer.

Goldoft *et al.* (1993) interviewed nine of 14 patients with nasal or nasopharyngeal melanoma as part of a population-based case–control study of sinonasal cancer described above (Vaughan *et al.*, 1986a,b; see pp. 269–270). The frequency of exposure to formaldehyde was compared with the frequency of exposure of the control subjects included in the study of Vaughan *et al.* One subject had lived in a residence insulated with formaldehyde-based foam ([0.3 expected] not significant). None of the melanoma patients reported specific occupational exposure to formaldehyde (0.3 expected), and none reported having been employed in industries likely to result in exposure to formaldehyde (0.8 expected).

The case–control studies of cancer and exposure to formaldehyde are summarized in Table 13.

Table 13. Case–control studies of formaldehyde by cancer site

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Sinonasal cancer				
Hernberg *et al.* (1983) Denmark, Finland, Sweden	167 patients (distribution by sex not given) 167 controls	Employment in particle-board or plywood industry	–	No exposed subjects
Brinton *et al.* (1984) United States	160 patients (93 men, 67 women) 290 controls	Ever	0.4 (0.1–1.8)	Control for tobacco use did not change results
Olsen *et al.* (1984) Denmark	488 patients (distribution by sex not given) 2465 controls	Probably exposed ≥ 10 years previously (men)	3.1 (1.8–5.3)	Unadjusted
		Probably exposed ≥ 10 years previously (men)	1.6 (0.7–3.6)	Adjusted for exposure to wood dust
Olsen & Asnaes (1986) Denmark	215 men with squamous-cell carcinoma 2465 controls	Probably exposed ≥ 10 years previously	2.4 (0.8–7.4)	Adjusted for exposure to wood dust
	39 men with adenocarcinoma 2465 controls	Probably exposed ≥ 10 years previously	1.8 (0.5–6.0)	Adjusted for exposure to wood dust
Hayes *et al.* (1986) Netherlands	63 male patients 161 controls	Any, with no or little exposure to wood dust		
		Industrial hygienist A	2.5 [1.0–5.9]	
		Industrial hygienist B	1.6 [0.8–3.1]	
	28 male patients 34 controls	Any, with moderate or high exposure to wood dust		
		Industrial hygienist A	1.9 [0.6–6.5]	
		Industrial hygienist B	NR	
	45 male patients with squamous-cell carcinoma 161 controls	Any, with no or little exposure to wood dust		Controlling for cigarette use did not change the result
		Industrial hygienist A	3.0 [1.2–7.8]	
		Industrial hygienist B	1.9 [0.9–4.1]	
Vaughan *et al.* (1986a) United States	53 patients (distribution by sex not given) 552 controls	Low	0.8 (0.4–1.7)	Occupational exposure; adjusted for sex, age, cigarette smoking and alcohol consumption
		Medium or high	0.3 (0.0–1.3)	
		High exposure score (exposure level weighted by period of exposure)	0.3 (0.0–2.3)	

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Sinonasal cancer (contd)				
Vaughan *et al.* (1986b) United States	53 patients (distribution by sex not given) 552 controls	Any, from 'mobile home' Any from particle-board or plywood < 10 years ≥ 10 years	0.6 (0.2–1.7) 1.8 (0–9–3.8) 1.5 (0.7–3.2)	Residential exposure; adjusted for sex, age, cigarette smoking and alcohol consumption
Roush *et al.* (1987) United States	169 male patients 509 male controls	Probably exposed for most of working life Plus exposure ≥ 20 years before death Plus exposure to high level in some year Plus exposure to high level ≥ 20 years before death	0.8 (0.5–1.3) 1.0 (0.5–1.8) 1.0 (0.5–2.2) 1.5 (0.6–3.9)	Information on histological subtypes not available; information on occupation obtained from death certificates and city directories; adjusted for age and calender period
Luce *et al.* (1993) France	77 patients (59 men, 18 women) with squamous-cell carcinoma 407 controls	Possible (men) Probable or definite (men) < 20 years ≥ 20 years	1.0 (0.4–2.4) 1.1 (0.5–2.5) 0.8 (0.3–2.0)	Adjusted for age, exposure to wood dust, glues and adhesives
Nasopharyngeal cancer				
Olsen *et al.* (1984) Denmark	266 patients (distribution by sex not given) 2465 controls	Possible or probable exposure Men Women	 0.7 (0.3–1.7) 2.6 (0.3–22)	Unadjusted
Vaughan *et al.* (1986a) United States	27 patients (distribution by sex not given) 552 controls	Low Medium or high High exposure score (exposure level weighted by period of exposure)	1.2 (0.5–3.3) 1.4 (0.4–4.7) 2.1 (0.6–7.8)	Occupational exposure; adjusted for cigarette smoking and race

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Nasopharyngeal cancer (contd)				
Vaughan *et al.* (1986b) United States	27 patients (distribution on sex not given) 552 controls	Any, from 'mobile home' < 10 years ≥ 10 years Any, from particle-board or plywood < 10 years ≥ 10 years	 2.1 (0.7–6.6) 5.5 (1.6–19) 1.4 (0.5–3.4) 0.6 (0.2–2.3)	Residential exposure; adjusted for cigarette smoking and ethnic origin
Roush *et al.* (1987) United States	147 male patients 509 male controls	Probably exposed for most of working life Plus exposure ≥ 20 years before death Plus exposure to high level in some year Plus exposure to high level ≥ 20 years before death	1.0 (0.6–1.7) 1.3 (0.7–2.4) 1.4 (0.6–3.1) 2.3 (0.9–6.0)	Information on occupation obtained from death certificates and city directories; adjusted for age and calender period
West *et al.* (1993) Philippines	104 patients (76 male, 28 female) 193 controls	< 15 years ≥ 15 years First exposure < 25 years before diagnosis First exposure ≥ 25 years before diagnosis	2.7 (1.1–6.6) 1.2 (0.5–3.2) 1.3 (0.6–3.2) 2.9 (1.1–7.6)	Adjusted for other occupational exposure
Cancer of the oral cavity, oro- and hypopharynx				
Vaughan *et al.* (1986a)	205 patients with oro- or pharyngeal cancer (distribution by sex not given) 552 controls	Low Medium High High exposure score (exposure level weighted by period of exposure)	0.8 (0.5–1.4) 0.8 (0.4–1.7) 0.6 (0.1–2.7) 1.5 (0.7–3.0)	Occupational exposure; adjusted for sex, age, cigarette smoking and alcohol consumption
Vaughan *et al.* (1986b)	205 patients with oro- or pharyngeal cancer (distribution by sex not given) 552 controls	Any, from 'mobile home' < 10 years ≥ 10 years Any, from particle-board or plywood < 10 years ≥ 10 years	 0.9 (0.5–1.8) 0.8 (0.2–2.7) 1.1 (0.7–1.9) 0.8 (0.5–1.4)	Residential exposure; adjusted for sex, age, cigarette smoking and alcohol consumption

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
Cancer of the oral cavity, oro- and hypopharynx (contd)				
Merletti *et al.* (1991) Italy	86 male patients with oral or oropharyngeal cancer 373 controls	Any Probable or definite	1.6 (0.9–2.8) 1.8 (0.6–5.5)	Adjusted for age, level of education, area of birth, tobacco smoking and alcohol drinking
Lung cancer				
Andersen *et al.* (1982) Denmark	84 cases among doctors (79 men and five women) 252 controls	Ever employed in exposed speciality	1.0 (0.4–2.4)	Both cases and controls were medical doctors
Fayerweather *et al.* (1983) United States	181 male cases 181 controls	Any, < 5 years Any, ≥ 5 years	1.2 [0.6–2.8] 0.8 [0.4–1.6]	Estimates but not CIs adjusted for smoking habits
Coggon *et al.* (1984) England and Wales	598 male patients 1180 controls	Any High	1.5 (1.2–1.8) 0.9 (0.6–1.4)	Matched analysis, but unadjusted for smoking habits; all subjects < 40 years at death
Bond *et al.* (1986) United States	308 male patients 588 controls	Any Any, ≥ 15 years before death	0.6 (0.3–1.3) 0.3 (0.1–0.9)	Unadjusted
Gérin *et al.* (1989) Canada	857 male patients 1523 male cancer controls (*a*) 533 male population controls (*b*)	Any, < 10 years ≥ 10 years Low Medium High	0.8 (0.6–1.2) (*a*) 1.0 (0.6–1.8) (*b*) 0.5 (0.3–0.8) (*a*) 0.5 (0.3–0.8) (*b*) 1.0 (0.7–1.4) (*a*) 0.9 (0.5–1.6) (*b*) 1.5 (0.8–2.8) (*a*) 1.0 (0.4–2.4) (*b*)	Adjusted for age, ethnic group, socioeconomic status, cigarette smoking, dirtiness of job and other occupational risk factors

Table 13 (contd)

Authors and country	Subjects	Exposure estimates	Odds ratio (95% CI)	Comments
***Lung cancer* (contd)**				
Gérin *et al.* (1989)	Adenocarcinoma subtype	Any, < 10 years	0.6 (0.3–1.3) (*a*)	
Canada (contd)	162 male patients		0.8 (0.3–2.0) (*b*)	
	1523 male cancer controls (*a*)	≥ 10 years		
	533 male population controls (*b*)	Low	0.5 (0.2–1.2) (*a*)	
		0.5 (0.2–1.3) (*b*)		
		Medium	0.8 (0.4–1.6) (*a*)	
		1.0 (0.4–2.5) (*b*)		
		High	2.3 (0.9–6.0) (*a*)	
		2.2 (0.7–7.6) (*b*)		
Partanen *et al.* (1990)	118 male woodworkers	Any	0.7 [0.2–2.8]	Adjusted for vital status
Finland	354 controls	Any, ≥ 10 years since first exposure	0.9 [0.2-3.8]	and smoking
Laryngeal cancer				
Wortley *et al.* (1992)	235 patients	Any		
United States	(185 men, 50 women)	Low	1.0 (0.6–1.7)	Adjusted for age,
	547 controls	Medium	1.0 (0.4–2.1)	smoking, drinking and
		High	2.0 (0.2–20)	level of education
		≥ 10 years previously	1.0 (0.3–3.0)	

CI, confidence interval

2.5 Meta-analyses

Recent reviews (Purchase & Paddle, 1989; McLaughlin, 1994) and meta-analyses (Blair *et al.*, 1990a; Partanen, 1993) summarize most of the available data. Some differences exist between the analyses of Blair *et al.* (1990a) and Partanen (1993). Partanen (1993) used lagged and confounder-adjusted inputs, whenever available, and developed summary relative risks using a log-Gaussian, fixed-effects model. Blair *et al.* (1990a) simply summed observed and expected numbers. Partanen (1993) also included three studies not incorporated by Blair *et al.* (1990a) and used only the values for men; there were also differences in exposure contrasts. The two meta-analyses were in overall agreement with regard to the risks for lung cancer, nasopharyngeal carcinoma and miscellaneous cancers of the upper respiratory tract but differed with regard to the risk for cancer of the nasal cavities and paranasal sinuses: Blair *et al.* (1990a) found a relative risk of 1.1 (95% CI, 0.7–1.5) for the more highly exposed category, while Partanen (1993) found a risk of 1.7 (1.0–2.8). For the mixed category of cancers of the oropharynx, lip, tongue, salivary glands and mouth, the aggregated data did not suggest associations with exposure to formaldehyde.

The results of the two meta-analyses are summarized in Table 14.

3. Studies of Cancer in Experimental Animals

3.1 Inhalation

3.1.1 Mouse

Groups of 42–60 C3H mice [sex and age unspecified] were started on a regimen of exposure to formaldehyde (USP grade) vapour at concentrations of 0, 0.05, 0.1 or 0.20 mg/L [0, 50, 100 or 200 mg/m^3] for 1 h per day, three times a week, ostensibly for 35 weeks. Treatment of mice with the highest concentration was discontinued after the eleventh exposure because of severe toxicity, and 36 of the mice exposed to 0.05 mg/L for 35 weeks were subsequently exposed to 0.15 mg/L [150 mg/m^3] for a further 29 weeks. Surviving animals in the initial groups were killed at 35 weeks and those on extended treatment at 68 weeks. The nasal epithelium was not examined, either grossly or microscopically. There was no evidence of induction of pulmonary tumours at any dose. Basal-cell hyperplasia, squamous-cell metaplasia and atypical metaplasia were seen in the trachea and bronchi of most of the exposed mice but not in untreated controls (Horton *et al.*, 1963). [The Working Group noted the high doses used, the short intervals of exposure, the short duration of the experiment and the lack of pathological examination of the nose.]

Groups of 119–120 male and 120–121 female B6C3F1 mice, six weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm [0, 2.5, 6.9, 17.6 mg/m^3] formaldehyde (> 97.5% pure) vapour by whole-body exposure for 6 h per day on five days per week, for up to 24 months, followed by a six-month observation period with no further exposure. Ten males and 10 females

Table 14. Aggregated risk ratios (RR), 95% confidence intervals (95% CI) and observed (O) and expected (E) frequencies of respiratory cancers in the meta-analyses of Blair *et al.* (1990a) and Partanen (1993)

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

Blair *et al.* (1990a) included the following studies in their analysis: Harrington & Shannon (1975), Petersen & Milham (1980), Jensen & Andersen (1982), Fayerweather *et al.* (1983), Friedman & Ury (1983), Marsh (1983), Milham (1983), Walrath & Fraumeni (1983), Wong (1983), Acheson *et al.* (1984a,c), Coggon *et al.* (1984), Harrington & Oakes (1984), Levine *et al.* (1984), Liebling *et al.* (1984), Malker & Weiner (1984), Olsen *et al.* (1984), Walrath & Fraumeni (1984), Stayner *et al.* (1985), Partanen *et al.* (1985), Walrath *et al.* (1985), Bertazzi *et al.* (1986), Blair *et al.* (1986), Bond *et al.* (1986), Gallagher *et al.* (1986), Hayes *et al.* (1986), Logue *et al.* (1986), Stroup *et al.* (1986), Vaughan *et al.* (1986a,b), Blair *et al.* (1987), Roush *et al.* (1987), Stayner *et al.* (1988), Bertazzi *et al.* (1989), Gérin *et al.* (1989), Blair *et al.* (1990b), Hayes *et al.* (1990)

Partanen (1993) included in his analysis both the above studies and: Brinton *et al.* (1984), Partanen *et al.* (1990), Merletti *et al.* (1991)

[a] Anatomists, pathologists, forensic medicine specialists

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

from each group were killed at 6 and 12 months, 0–20 of each sex at 18 months, 17–41 at 24 months and 0–16 at 27 months. Between 0 and 24 months, 78 male and 30 female controls, 77 and 34 exposed to 2 ppm formaldehyde vapour, 81 and 19 exposed to 5.6 ppm and 82 and 34 exposed to 14.3 ppm died; all animals that died or were killed were examined grossly. Thorough histopathological examinations were performed on control and high-dose mice, on multiple sections of the nasal cavity and on all lesions identified grossly in the other two groups. Squamous-cell carcinomas occurred in the nasal cavities of 2/17 male mice at the high dose killed at 24 months. There were no nasal cavity tumours in males mice treated with the lower doses of formaldehyde, in females at any dose or among 21 male or 31 female control mice killed at 24 months ($p > 0.05$). A variety of non-neoplastic lesions (such as squamous-cell hyperplasia, squamous-cell metaplasia and dysplasia) were commonly found in the nasal cavities of mice exposed to formaldehyde, particularly at 14.3 ppm (Kerns *et al.*, 1983a,b; Gibson, 1984).

3.1.2 Rat

Groups of 119–120 male and 120 female Fischer 344 rats, seven weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm [0, 2.5, 6.9, 17.6 mg/m^3] formaldehyde (> 97.5% pure) vapour by whole-body exposure for 6 h per day on five days per week for up to 24 months and were then observed for six months with no further exposure. Ten males and 10 females from each group were killed at 6 and 12 months, 19–20 of each sex at 18 months, 13–54 at 24 months, 0–10 at 27 months and 0–6 at 30 months. Between 0 and 24 months, 6 males and 13 females in the control group, 10 and 16 exposed to 2 ppm, 19 of each sex exposed to 5.6 ppm and 57 and 67 exposed to 14.3 ppm died; all animals that died or were killed were examined grossly. Histopathological examinations were performed on multiple sections of the nasal cavity, on all lesions identified grossly and on all major tissues of each organ system (approximately 40/animal) from control and high-dose rats. The findings for the nasal cavity are summarized in Table 15. While no nasal cavity malignancies were found in rats exposed to 0 or 2.0 ppm formaldehyde, two squamous-cell carcinomas (one among 119 males and one among 116 females examined) occurred in the group exposed to 5.6 ppm and 107 (51 among 117 males and 52 among 115 females examined) in those exposed to 14.3 ppm ($p < 0.001$). Five additional nasal cavity tumours (classified as carcinoma, undifferentiated carcinoma/sarcoma and carcinosarcoma) were identified in rats exposed to 14.3 ppm; two of these tumours were found in rats that also had squamous-cell carcinomas of the nasal cavity. There was a significant overall increase in the incidence of polypoid adenomas in treated animals (males and females combined) when compared with controls [$p = 0.02$, Fisher's exact test]. The incidences of polypoid adenomas were marginally significantly elevated in females at the low dose and in males at the middle dose (see also Table 15). A variety of non-neoplastic lesions were commonly found in the nasal cavities of rats exposed to formaldehyde, particularly at 14.3 ppm (Kerns *et al.*, 1983a,b; Gibson, 1984). More than half (57%) of the squamous-cell carcinomas in rats exposed to 14.3 ppm formaldehyde were observed on the anterior portion of the lateral side of the nasoturbinate and the adjacent lateral wall, 26% were located on the midventral nasal

septum, 10% on the dorsal septum and roof of the dorsal meatus and a small number (3%) on the maxilloturbinate (Morgan *et al.*, 1986a).

Table 15. Neoplastic lesions in the nasal cavities of Fischer 344 rats exposed to formaldehyde vapour

Lesion	Exposure (ppm)							
	0		2.0		5.6		14.3	
	M	F	M	F	M	F	M	F
(No. of nasal cavities examined	118	114	118	118	119	116	117	115)
Squamous-cell carcinoma	0	0	0	0	1	1	51[a]	52[a]
Nasal carcinoma	0	0	0	0	0	0	1[b]	1
Undifferentiated carcinoma or sarcoma	0	0	0	0	0	0	2[b]	0
Carcinosarcoma	0	0	0	0	0	0	1	0
Osteochondroma	1	0	0	0	0	0	0	0
Polypoid adenoma[e]	1	0	{ 4	4[c]	6[d]	0	4	1 }[e]

From Morgan *et al.* (1986a)

[a] $p < 0.001$, pair-wise comparisons

[b] One animal also had a squamous-cell carcinoma.

[c] [$p = 0.07$, Fisher's exact test in comparison with female controls]

[d] [$p = 0.06$, Fisher's exact test in comparison with male controls]

[e] [$p = 0.02$, Fisher's exact test in comparison of all treated rats with controls]

In a study to investigate the carcinogenicity of bis(chloromethyl)ether formed *in situ* in inhalation chambers, by mixing formaldehyde and hydrogen chloride gas at high concentrations before introduction into the chamber in order to maximize formation of bis(chloromethyl)ether, 99 male Sprague–Dawley rats, eight weeks of age, were exposed to a mixture of 14.7 ppm [18.1 mg/m^3] formaldehyde vapour [purity unspecified] and 10.6 ppm [15.8 mg/m^3] hydrogen chloride gas for 6 h per day on five days per week for life. The average level of bis(chloromethyl)ether was 1 ppb [4.7 μg/m^3]. Groups of 50 rats were sham-exposed to air or were untreated. The animals were allowed to die naturally and were then necropsied. Histological sections of nasal cavities, respiratory tract, major organs and gross lesions were prepared. No nasal cancers were found in the controls, but 28 of the treated rats developed tumours of the nasal cavity, 25 of which were squamous-cell carcinomas [$p < 0.001$, Fisher's exact test] and three of which were papillomas. Mortality was greater in the treated group than in controls throughout the experiment; about 50% of the exposed rats were still alive at 223 days, when the first nasal carcinoma was observed. About two-thirds of the exposed rats showed squamous-cell metaplasia of the nasal mucosa; these lesions were not seen in controls (Albert *et al.*, 1982).

In the sames series of experiments, groups of 99–100 male Sprague-Dawley rats, nine weeks of age, were exposed for 6 h per day on five days per week for life to: (1) 14.3 ppm [17.6 mg/m^3] formaldehyde [purity unspecified] and 10 ppm [14.9 mg/m^3] hydrogen chloride

gas mixed before dilution in the exposure chamber to maximize formation of bis(chloromethyl)ether; (2) 14.1 ppm [17.3 mg/m^3] formaldehyde and 9.5 ppm [14.2 mg/m^3] hydrogen chloride gas not mixed before introduction into the exposure chamber; (3) 14.2 ppm [17.5 mg/m^3] formaldehyde vapour alone; (4) 10.2 ppm [15.2 mg/m^3] hydrogen chloride gas alone; or (5) air (sham-exposed controls). A control group of 99 rats was also available. The findings in the nasal cavity are summarized in Table 16. At the end of the experiment, 38 squamous-cell carcinomas of the nasal cavities and 10 polyps or papillomas were observed in rats exposed to formaldehyde alone; none were seen in the controls (p = 0.001, Fisher's exact test). No differences were reported between groups in the incidences of tumours outside the nasal cavity (Albert *et al.*, 1982; Sellakumar *et al.*, 1985.)

Table 16. Neoplastic lesions in the nasal cavities of rats exposed to formaldehyde (HCHO) and/or hydrogen chloride (HCl) vapour

Lesion	Group 1: Premixed HCl (10 ppm) and HCHO (14.3 ppm)	Group 2: Non-premixed HCl (9.5 ppm) and HCHO (14.1 ppm)	Group 3: HCHO (14.2 ppm)	Group 4: HCl (10.2 ppm)	Group 5: Air controls	Colony controls
(No. of rats examined	100	100	100	99	99	99)
Squamous-cell carcinoma	45	27	38	0	0	0
Adenocarcinoma	1	2	0	0	0	0
Mixed carcinoma	0	0	1	0	0	0
Fibrosarcoma	1	0	1	0	0	0
Aesthesioneuroepithelioma	1	0	0	0	0	0
Polyps or papillomas	13	11	10	0	0	0
Tumours in organs outside the respiratory tract	22	12	10	19	25	24

From Sellakumar *et al.* (1985)

Nine groups of 45 male Wistar rats [age unspecified], initially weighing 80 g, were exposed to 0, 10 or 20 ppm [0, 12.3 or 25 mg/m^3] of formaldehyde vapour [purity unspecified] starting one week after acclimatization. Whole-body exposures for 6 h per day on five days per week were continued for four, eight or 13 weeks; thereafter, the rats were observed during recovery periods of 126, 122 or 117 weeks, respectively, when all survivors were killed. All rats were autopsied and examined by gross pathology; histological examination was limited to six cross-sections of the nose of each rat. Hyperplasia and metaplasia of the nasal epithelium were found to persist in rats exposed to formaldehyde. Significant tumour incidences are presented in Table 17. In control rats, the only nasal tumours reported were two squamous-cell carcinomas among 45 rats that were exposed to air for eight weeks: One was a small tumour found at 130 weeks which appeared to involve a nasolachrymal duct; the second was a large squamous-cell carcinoma in a rat killed at week 94, which formed a large mass outside the nasal cavity and was thought to have arisen in a nasolachrymal duct or maxillary sinus. The tumours were considered

by the authors not to resemble those observed in the rats exposed to formaldehyde. Rats exposed to 10 ppm formaldehyde also had two squamous-cell carcinomas: One was reported to be a small nasolachrymal-duct tumour in a survivor at 130 weeks, and the second occurred largely outside the nasal cavity in association with an abnormal incisor tooth in a rat killed at week 82. Rats exposed to 20 ppm formaldehyde had 10 tumours: Polypoid adenomas of the nasal cavity were found in one rat exposed for four weeks and killed at 100 weeks and in another rat exposed for eight weeks and killed at 110 weeks; and there were six squamous-cell carcinomas, two of which were thought to originate in the nasolachrymal ducts, one of which appeared to be derived from the palate, and the three others, all in the group exposed for 13 weeks, appeared to arise from the naso- or maxillo-turbinates and formed large tumours that invaded the bone and subcutaneous tissues. The other two neoplasms observed in treated animals were an ameloblastoma found at week 73 and an exophytic tumour of the nasal septum of doubtful malignancy, which was designated a carcinoma *in situ*, in a rat that died at 81 weeks. The authors concluded that the nasal tumours were induced by formaldehyde only at 20 ppm, at an incidence of 4.5% (6 tumors/132 rats) [$p = 0.01$, Fisher's exact test] (Feron *et al.*, 1988). [The Working Group noted that positive findings were made in spite of the short duration of exposure.]

Table 17. Nasal tumours in rats exposed to formaldehyde for various periods followed by observation up to 126 weeks

Exposure time; no. of rats	Tumour	Dose (ppm [mg/m^2])		
		0	10 [12.3]	20 [25]
4 weeks				
No. of rats		44	44	45
	Polypoid adenoma	0	0	1[a]
	Squamous-cell carcinoma	0	0	1
8 weeks				
No. of rats		45	44	43
	Polypoid adenoma	0	0	1[a]
	Squamous-cell carcinoma	2	1	1
13 weeks				
No. of rats		45	44	44
	Squamous-cell carcinoma	0	1	3[a]
	Cystic squamous-cell carcinoma	0	0	1
	Carcinoma *in situ*	0	0	1[a]
	Ameloblastoma	0	0	1

From Feron *et al.* (1988)
[a]Considered by the authors to be causally related to exposure to formaldehyde

A total of 720 male specific pathogen-free Wistar rats initially weighing 30–50 g were acclimatized for one week, and then the nasal mucosa of 480 of the rats was severely injured

bilaterally by electrocoagulation. One week later, groups of 180 rats were exposed to 0, 0.1, 1.0 or 10 ppm [0, 0.123, 1.23 or 12.3 mg/m^3] of formaldehyde [purity unspecified] vapour by whole-body exposure for 6 h per day on five days per week. One-half of the animals (30 undamaged, 60 damaged rats) were exposed for 28 months, and the other half (30 undamaged, 60 damaged) were exposed for only three months and then allowed to recover for 25 months with no further treatment. All surviving rats were killed at 29 months, autopsied and examined grossly; histological examination was restricted to six cross-sections of the nose of each rat. The neoplastic lesions found in the nasal cavity are summarized in Table 18. A high incidence of nasal tumours (17/58) was found in rats with damaged noses and exposed to 10 ppm formaldehyde for 28 months; only one was found in 54 controls [$p < 0.001$; Fisher's exact test], and only one of the 26 rats with undamaged noses that were exposed to 10 ppm formaldehyde for 28 months developed a nasal tumour. The tumour incidences in the other groups were low (0–4%). Eight additional squamous-cell carcinomas found in this study that appeared to be derived from the nasolachrymal ducts were excluded from the analysis (Woutersen *et al.*, 1989).

Table 18. Nasal tumours in male Wistar rats with damaged or undamaged noses and exposed to formaldehyde vapour for 28 or three months, followed by a 25-month recovery period

Exposure time; no. of rats	Tumour	Exposure (ppm [mg/m^3])							
		0		0.1 [0.123]		1.0 [1.23]		10.0 [12.3]	
		U	D	U	D	U	D	U	D
28 months									
Effective number		26	54	26	58	28	56	26	58
	Squamous-cell carcinoma	0	1	1	1	1	0	1	15
	Adenosquamous carcinoma	0	0	0	0	0	0	0	1
	Adenocarcinoma	0	0	0	0	0	0	0	1
3 months									
Effective number		26	57	30	57	29	53	26	54
	Squamous-cell carcinoma	0	0	0	2	0	2	1	1
	Carcinoma *in situ*	0	0	0	0	0	0	0	1
	Polypoid adenoma	0	0	0	0	0	0	1	0

From Woutersen *et al.* (1989)
U, undamaged; D, damaged nose

In a study to explore the interaction between formaldehyde and wood dust (see also p. 165 of the monograph on wood dust), two groups of 16 female Sprague-Dawley rats, 11 weeks of age, were exposed either to air or to formaldehyde [purity unspecified] at an average concentration of 12.4 ppm [15.3 mg/m^3]. Exposures were for 6 h per day for five days a week for a total of 104 weeks. At the end of the experiment, surviving animals were killed, and

histological sections were prepared from five cross-sections of the nose of each rat. Pronounced squamous-cell metaplasia or metaplasia with dysplasia was observed in 10/16 rats exposed to formaldehyde and in 0/15 controls. One exposed rat developed a squamous-cell carcinoma [not significant]. Neither the frequency nor the latent periods of induction of tumours outside the nasal cavity differed from those in controls (Holmström *et al.*, 1989a). [The Working Group noted the small numbers of animals used in the study.]

3.1.3 Hamster

A group of 88 male Syrian golden hamsters [age unspecified] were exposed to 10 ppm [12.3 mg/m^3] formaldehyde [purity unspecified] for 5 h a day on five days a week for life; 132 untreated controls were available. At necropsy, all major tissues were preserved, and histological sections were prepared from two transverse sections of the nasal turbinates of each animal, longitudinal sections were taken of the larynx and trachea, and all lung lobes were cut through the major bronchus. No tumours of the nasal cavities or respiratory tract were found in either the controls or the animals exposed to formaldehyde (Dalbey, 1982).

In a second study in the same report, 50 male Syrian golden hamsters [age unspecified] were exposed to 30 ppm [36.9 mg/m^3] formaldehyde [purity unspecified] for 5 h once per week for life. A group of 50 untreated hamster served as controls. When the animals died, their respiratory tract tissues were preserved, stained with Wright's stain, rendered semitransparent and evaluated for 'subgross' evidence of tumours. Areas of dense staining of 1 mm or more were scored as tumours. Multiple transverse sections of the nasal turbinates were evaluated similarly. No nasal tumours were observed in control or treated hamsters (Dalbey, 1982).

3.2 Oral administration

Rat: In a lifetime study, formaldehyde was administered in drinking-water to male and female Sprague-Dawley rats beginning at various ages. Groups of 50 male and 50 female rats received 10, 50, 100, 500, 1000 or 1500 ppm [mg/L] formaldehyde from seven weeks of age for life; two control groups of 50 males and 50 females and 100 males and 100 females received 15 mg/L (ppm) methanol or nothing, respectively, in their drinking water. Two groups of 18–20 male and female breeder rats, 25 weeks old, were given formaldehyde at 0 or 2500 ppm for life. The offspring of these breeders, 36–59 males and 37–49 females, were initially exposed to 0 or 2500 ppm formaldehyde via their mothers starting on day 13 of gestation and then received these levels in the drinking-water for life. The survival rates in the treated groups were similar to those of controls. All animals were necropsied, and extensive histological examinations were performed. The authors reported an increased, dose-related incidence of leukaemias in the treated groups (see Table 19). They also observed a variety of malignant and benign tumours of the stomach and intestines in the treated animals. Although the incidences of intestinal tract tumours were low, there were no comparable tumours in the control groups in this study, and some of these tumours were reported to be uncommon among historical controls (Soffritti *et al.*, 1989).

Table 19. Incidences of leukaemia and gastrointestinal tract tumours after administration of formaldehyde to rats in drinking-water (males and females combined)

Treatment	No. of tumours (benign and malignant)		
	Leukaemia	Gastrointestinal tract	
		Stomach	Intestine
7 weeks old			
(0 ppm + 15 ppm methanol)	8/100	0	0
0 ppm	7/200	0	0
10 ppm	3/100	2/100	1/100
50 ppm	9/100	0	2/100
100 ppm	9/100	0	0
500 ppm	12/100 *a*	0	0 *a*
1000 ppm	13/100	1/100	1/100
1500 ppm	18/100	2/100	6/100
25 weeks old (breeders)			
0 ppm	1/40	0/40	0/40
2500 ppm	4/36	2/36	0/36
Offspring			
0 ppm	6/108 *b*	0/108 *b*	0/108 *b*
2500 ppm	4/73	5/73	8/73

From Soffritti *et al.* (1989)

[a][Significant linear dose–response relationship when formaldehyde-treated groups are compared with water controls, $p < 0.001$, or water-methanol controls, $p < 0.01$, Cochran–Mantel-Haenszel test]

[b][$p = 0.01$; Fisher's exact test]

Concerns about the results in this study and their interpretation have been published by Feron *et al.* (1990). They noted that leukaemia incidences in untreated Sprague-Dawley rats vary widely and that incidences similar to those seen in the group receiving the highest dose of formaldehyde have been reported previously among controls in the same laboratory and others. The Working Group, however, noted the absence of gastric or intestinal tumours among the 300 control animals, while, on the basis of the authors' report of historical incidences, three gastric and one intestinal tumour would have been expected. Furthermore, the reporting of the data was limited. The Group subjected the available data from this study to statistical analysis, despite the above reservations. The groups treated at seven weeks were found to differ significantly with regard to both leukaemia and intestinal tumour incidence from the 300 combined controls [$p < 0.05$, Fisher's exact test]. The incidence of leukaemia in the treated groups also differed significantly [$p < 0.001$, Fisher's exact test] from that in the untreated controls; however, the difference in intestinal tumours was only marginally significant

[$p = 0.055$, Fisher's exact test]. When the groups treated at seven weeks were compared with the controls given methanol, the differences were not significant. A significant, linear dose–response relationship was found for the incidences of both leukaemia and intestinal tumours, in comparison with either the untreated [$p < 0.01$] or the methanol controls [$p < 0.01$] [Cochran–Mantel Haenszel test].

Wistar rats, obtained at five weeks of age and acclimatized for nine days, were divided into four groups of 70 males and 70 females and were treated for up to 24 months with drinking-water containing formaldehyde generated from 95% pure paraformaldehyde and 5% water. The mean doses of formaldehyde were 0, 1.2, 15 or 82 mg/kg bw per day for males and 0, 1.8, 21 or 109 mg/kg bw per day for females. Selected animals were killed at 53 and 79 weeks, and all surviving animals were killed at 102 weeks. Thorough necropsies were done on all animals. Extensive histological examinations were made of animals in the control and high-dose groups; somewhat less extensive examinations were made of animals receiving the low and middle doses, but the liver, lung, stomach and nose were examined in each case. Treatment-related hyperplastic lesions, ulceration and atrophy were found in the stomachs, but the incidence of tumours did not vary notably between groups. Two benign gastric papillomas were observed—one in a male at the low dose and the other in a female control. The authors noted that the other tumours observed were common in this strain of rat and that there was no indication of a treatment-related response (Til *et al.*, 1989).

Four groups of 20 male and 20 female Wistar rats, four weeks of age, were given formaldehyde (prepared from 80% pure paraformaldehyde) in their drinking-water at concentrations of 0, 0.02, 0.1 or 0.5% for up to 24 months. Six rats were chosen at random from each group and killed after 12 and 18 months of treatment; surviving animals were killed at 24 months and necropsied, and histological examinations were performed on major organs. [The Working Group noted that gross or microscopic examination of the nasal cavities was not mentioned specifically.] Rats given the high dose had reduced body weight gain and high mortality. Non-neoplastic lesions, such as squamous- and basal-cell hyperplasia, erosion and ulceration, were seen in the stomachs and forestomachs of rats given 0.5% at 12 months. The incidences of tumours in all groups were similar to those occurring spontaneously in this strain of rat. The authors reported that there were no significant differences in the incidences of any tumours from those in the control groups (Tobe *et al.*, 1989). [The Working Group noted the lack of detailed reporting of tumours and the small numbers of animals used.]

In a study to evaluate the effects of formaldehyde on gastric carcinogenesis induced by oral administration of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) (see below), two groups of 10 male Wistar rats, seven weeks of age, received tap water for the first eight weeks of the study. During weeks 8–40, one group then received pure water and the other group received 0.5% formaldehyde in the drinking-water. Animals still alive at 40 weeks were killed, rats surviving beyond 30 weeks being considered as effective animals for the study. Necropsy was performed on most animals that died and all animals that were killed, and the stomach and other abdominal organs were examined grossly and histologically. Eight of 10 animals that had received formaldehyde in drinking-water and none of the controls developed forestomach papillomas ($p < 0.01$, Fisher's exact test) (Takahashi *et al.*, 1986).

3.3 Skin application

Mouse: Two groups of 16 male and 16 female Oslo hairless mice [age unspecified] received topical applications of 200 µl of 1 or 10% formaldehyde in water on the skin of the back twice a week for 60 weeks. All of the animals treated with 10% formaldehyde were necropsied and the brain, lungs, nasal cavities and all tumours of the skin and other organs were examined histologically. Virtually no changes were found in the mice treated with 1% formaldehyde. The higher dose induced slight epidermal hyperplasia and a few skin ulcers. There were no benign or malignant skin tumours or tumours in other organs in either group (Iversen, 1986). [The Working Group noted the incomplete reporting of the data.]

3.4 Subcutaneous injection

Rat: In a study reported as an abstract, 10 rats [strain, age and sex unspecified] were injected subcutaneously once a week for 15 months with 1 ml of a 0.4% aqueous solution of formaldehyde and then observed for life. Spindle-cell sarcomas were found in three rats: two in the skin at the injection site and one in the peritoneal cavity (Watanabe *et al.*, 1954). [The Working Group noted the lack of controls.]

3.5 Administration with known carcinogens and other modifying factors

3.5.1 Mouse

Two groups of 50 female CBA × C57Bl6 mice, weighing 10–12 g, received drinking-water containing *N*-nitrosodimethylamine (NDMA) at a concentration of 10 mg/L and formaldehyde at a concentration of 0.5 mg/L for 26 or 39 weeks. Other groups of mice were treated either with NDMA alone for 26 and 39 weeks or formaldehyde alone for 39 weeks. Animals were killed after completion of treatment and necropsied, and the liver, kidney, lung, spleen and all gross lesions were examined histologically. No tumours were observed in the group receiving formaldehyde alone for 39 weeks. Combined administration of NDMA and formaldehyde increased the proportions of surviving mice bearing tumours in the liver, kidney and/or lung in the groups treated for 26 weeks and for 39 weeks, as compared with mice treated with NDMA alone (11/15 versus 17/30 and 19/19 versus 20/25) ($p = 0.049$, Fisher's exact test). The effect was not associated with obvious changes in the relative incidence of tumours at any site (Litvinov *et al.*, 1984).

Oslo hairless mice [age unspecified] each received a single application of 51.2 µg 7,12-dimethylbenz[*a*]anthracene (DMBA) in 100 µl of reagent-grade acetone on the skin of the back. Nine days later, the first group of 16 male and 16 females mice received twice weekly applications of 200 µl 10% formaldehyde in water (technical-grade formalin) on the skin of the back. A second group of 16 males and 16 females received 17 nmol 12-*O*-tetradecanoylphorbol-13-acetate (TPA) on the skin of the back twice a week. A third group, of 176 mice [sex unspecified], was given no further treatment. Animals were observed weekly for 60 weeks (groups 1 and 2) or 80 weeks (group 3). All of the animals treated with 10% formaldehyde were

necropsied, and the brain, lungs, nasal cavities and all tumours of the skin and other organs were examined histologically. In group 1, 3/32 mice had lung adenomas and 11/32 (34%) had 25 neoplasms of the skin, including three squamous-cell carcinomas and 22 papillomas. In mice receiving DMBA alone, 225 skin tumours (including six squamous-cell carcinomas) occurred in 85/176 (48%) animals. Statistical analysis of the results for these two groups was reported by the authors to show no significant effect of formaldehyde on the skin tumour yield initiated by DMBA ($p > 0.30$, Gail test), but formaldehyde significantly enhanced the rate of skin tumour induction ($p = 0.01$, Peto's test), thus reducing the latent period for the tumours (Iversen, 1986). [The Working Group noted the incomplete reporting of the tumours.]

3.5.2 Rat

Two groups of 30 and 21 male Wistar rats, seven weeks of age, received MNNG in the drinking-water at a concentration of 100 mg/L and a standard diet containing 10% sodium chloride for eight weeks. Thereafter, the rats received the standard diet with 0 or 0.5% formaldehyde in the drinking-water for a further 32 weeks. Animals still alive at 40 weeks were killed, rats surviving 30 weeks or more being considered effective animals for the study. Necropsies were performed on most animals that died and on all animals killed at week 40. Malignant tumours of the stomach and duodenum were found in 5/17 (29%) rats that received both MNNG and formaldehyde and in 4/30 (13%) rats that received MNNG [not significant]. Adenocarcinomas of the glandular stomach were found in 4/17 (23.5%) rats given the combined treatment and in 1/30 rats given MNNG alone ($p < 0.05$, Fisher's exact test). Papillomas of the forestomach were found in 15/17 rats given the combined treatment, in 0/30 given MNNG alone ($p < 0.01$, Fisher's exact test) and in 8/10 given formaldehyde alone (not significant; see section 3.2). The incidence of adenomatous hyperplasia of the fundus of the glandular stomach was significantly greater in the group given the combined treatment (15/17) than in those given MNNG alone (0/3) ($p < 0.01$, Fisher's exact test) (Takahashi *et al.*, 1986).

3.5.3 Hamster

Groups of male Syrian golden hamsters [age unspecified] were treated in various ways: 50 were exposed by inhalation to 30 ppm [36.9 mg/m^3] formaldehyde [purity unspecified] for 5 h per day once a week for life; 100 hamsters were injected subcutaneously with 0.5 mg *N*-nitrosodiethylamine (NDEA) once a week for 10 weeks and then given no further treatment; 50 hamsters were injected with NDEA once a week for 10 weeks, exposed to 30 ppm formaldehyde for 5 h 48 h before each injection of NDEA and then received weekly exposure to 30 ppm formaldehyde for life; and the fifth group of [presumably 50] hamsters was injected with NDEA once a week for 10 weeks and then exposed to 30 ppm formaldehyde for 5 h per day once a week for life, beginning two weeks after the last NDEA injection. A group of 50 animals were untreated. After the animals had died, the respiratory tract tissues were removed, stained with Wright's stain, rendered semitransparent and evaluated for 'subgross' evidence of tumours. Areas of dense staining greater than 1 mm in 2–3-mm transverse-step sections of nasal turbinates were scored as tumours. No tumours were observed in untreated hamsters or those exposed only to formaldehyde, but 77% of hamsters treated with NDEA alone had tumours at

one or more sites in the respiratory tract. Ten or more such lesions from each tissue were examined histologically, and all were found to be adenomas. Lifetime exposure of NDEA-treated hamsters to formaldehyde did not increase the number of tumour-bearing animals. The incidences of nasal tumours in NDEA-treated groups were low (0–2%). The only significant increase was in the multiplicity of tracheal tumours in the group receiving formaldehyde concurrently with and subsequent to NDEA injection as compared with that in animals receiving NDEA alone ($p < 0.05$, Kolmogorov–Smirnoff test) (Dalbey, 1982).

4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Absorption, distribution, metabolism and excretion

4.1.1 Humans

In humans, as in other animals, formaldehyde is an essential metabolic intermediate in all cells. It is produced endogenously from serine, glycine, methionine and choline, and it is generated in the demethylation of *N*-, *O*- and *S*-methyl compounds. It is an essential intermediate in the biosynthesis of purines, thymidine and certain amino acids.

The endogenous concentration of formaldehyde, determined by gas chromatography–mass spectrometry (Heck *et al.*, 1982) in the blood of human subjects not exposed to formaldehyde, was 2.61 ± 0.14 μg/g of blood (mean ± SE; range, 2.05–3.09 μg/g) (Heck *et al.*, 1985), i.e. about 0.1 mmol/L (assuming that 90% of the blood volume is water and the density of human blood is 1.06 g/cm^3 (Smith *et al.*, 1983)). This concentration represents the total concentration of endogenous formaldehyde in the blood, both free and reversibly bound.

The possibility that gaseous formaldehyde may be adsorbed to respirable particles, inhaled and subsequently released into the lung has been examined. Risby *et al.* (1990) developed and validated a model to describe the adsorption of formaldehyde to and release from respirable carbon black particles. They concluded that of an airborne concentration of 6 ppm [7.4 mg/m^3], only 2 ppb [0.0025 mg/m^3] would be adsorbed to carbon black. Rothenberg *et al.* (1989) investigated the adsorption of formaldehyde to dust particles in homes and offices and concluded that, even with a concentration of 1 ppm formaldehyde (1.2 mg/m^3), the particle-associated dose to the pulmonary compartment of an adult human would be approximately 0.05 μg/h, whereas the dose of vapour-phase formaldehyde delivered to the upper respiratory tract would be 500 μg/h, i.e. four orders of magnitude larger.

Since formaldehyde can induce allergic contact dermatitis in humans (section 4.2.1), it can be concluded that formaldehyde or its metabolites penetrate human skin (Maibach, 1983). The kinetics of this penetration were determined *in vitro* using a full-thickness skin sample mounted in a diffusion cell at 30 °C (Lodén, 1986). The rate of 'resorption' of ^{14}C-formaldehyde (defined as the uptake of ^{14}C into phosphate-buffered saline, pH 7.4, flowing unidirectionally beneath the sample) was 16.7 μg/cm^2 per h when a 3.7% solution of formaldehyde was used, and increased

to 319 μg/cm^2 per h when a 37% solution was used. The presence of methanol in both of these solutions (at 3.3–4.9% and 10–15%, respectively) may have affected the uptake rate, and it is unclear whether the resorbed ^{14}C was due only to formaldehyde. Skin retention of formaldehyde represented a significant fraction of the total amount of formaldehyde absorbed.

The concentration of formaldehyde was measured in the blood of six human volunteers immediately after exposure by inhalation to 1.9 ppm [2.3 mg/m^3] for 40 min. The measured value was 2.77 ± 0.28 μg/g, which was not different from the pre-exposure concentration due to metabolically formed formaldehyde (see above). The absence of an increase is understandable, since formaldehyde is rapidly metabolized by human erythrocytes (Malorny *et al.*, 1965), which contain formaldehyde dehydrogenase (Uotila & Koivusalo, 1987) and aldehyde dehydrogenase (Inoue *et al.*, 1979).

A gas chromatographic method was used to examine the urinary excretion of formate by veterinary medical students exposed to low concentrations of formaldehyde, in order to determine whether monitoring of formate is a useful biomarker for human exposure to formaldehyde (Gottschling *et al.*, 1984). The average baseline level of formate in the urine of 35 unexposed subjects was 12.5 mg/L, but the level varied considerably both within and among subjects (range, 2.4–28.4 mg/L). No significant changes in concentration were detected over a three-week period of exposure to formaldehyde at a concentration in air of less than 0.4 ppm [0.5 mg/m^3]. The authors concluded that biological monitoring of formic acid in the urine to determine exposure to formaldehyde is not a feasible technique at this concentration.

4.1.2 Experimental systems

The steady-state concentrations of endogenous formaldehyde have been determined by gas chromatography–mass spectrometry (Heck *et al.*, 1982) in the blood of Fischer 344 rats (2.24 ± 0.07 μg/g of blood (mean ± SE)) (Heck *et al.*, 1985) and three rhesus monkeys (2.04 ± 0.40 μg/g of blood; range, 1.24–2.45 μg/g) (Casanova *et al.*, 1988). These concentrations are similar to those measured in humans by the same method (see section 4.1.1). The blood concentrations of formaldehyde immediately after exposure of rats once to 14.4 ppm [17.6 mg/m^3] (2 h) or exposure of monkeys subacutely to 6 ppm [7.3 mg/m^3] (6 h/day, five days/week, four weeks) were indistinguishable from those before exposure.

As reported in an abstract, more than 93% of a dose of inhaled formaldehyde was absorbed readily by the tissues of the respiratory tract (Patterson *et al.*, 1986). In rats, formaldehyde is absorbed almost entirely in the nasal passages (Chang *et al.*, 1983; Heck *et al.*, 1983). In rhesus monkeys, absorption occurs primarily in the nasal passages but also in the trachea and proximal regions of the major bronchi (Monticello *et al.*, 1989; Casanova *et al.*, 1991). The efficiency and sites of formaldehyde uptake are determined by nasal anatomy, which differs greatly among species (Schreider, 1986). The structure of the nose gives rise to complex airflow patterns, which have been correlated with the location of formaldehyde-induced nasal lesions in both rats and monkeys (Morgan *et al.*, 1991).

After exposure by inhalation, absorbed formaldehyde can be oxidized to formate and carbon dioxide or can be incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways (see Figure 1). The fate of inhaled formaldehyde

was studied in Fischer 344 rats exposed to ^{14}C-formaldehyde (at 0.63 or 13.1 ppm [0.8 or 16.0 mg/m^3]) for 6 h. About 40% of the inhaled ^{14}C was eliminated as expired ^{14}C-carbon dioxide over a 70-h period; 17% was excreted in the urine, 5% was eliminated in the faeces and 35–39% remained in the tissues and carcass. Elimination of radioactivity from the blood of rats after exposure by inhalation to 0.63 ppm or 13.1 ppm ^{14}C-formaldehyde is multiphasic. The terminal half-time of the radioactivity was approximately 55 h (Heck *et al.*, 1983), but the half-time of formaldehyde in rat plasma after intraperitoneal administration is reported to be approximately 1 min (Rietbrock, 1965). Analysis of the time course of residual radioactivity in plasma and erythrocytes after inhalation or intravenous injection of ^{14}C-formaldehyde or intravenous injection of ^{14}C-formate showed that the radioactivity is due to incorporation of ^{14}C (as ^{14}C-formate) into serum proteins and erythrocytes and subsequent release of labelled proteins and cells into the circulation (Heck *et al.*, 1983).

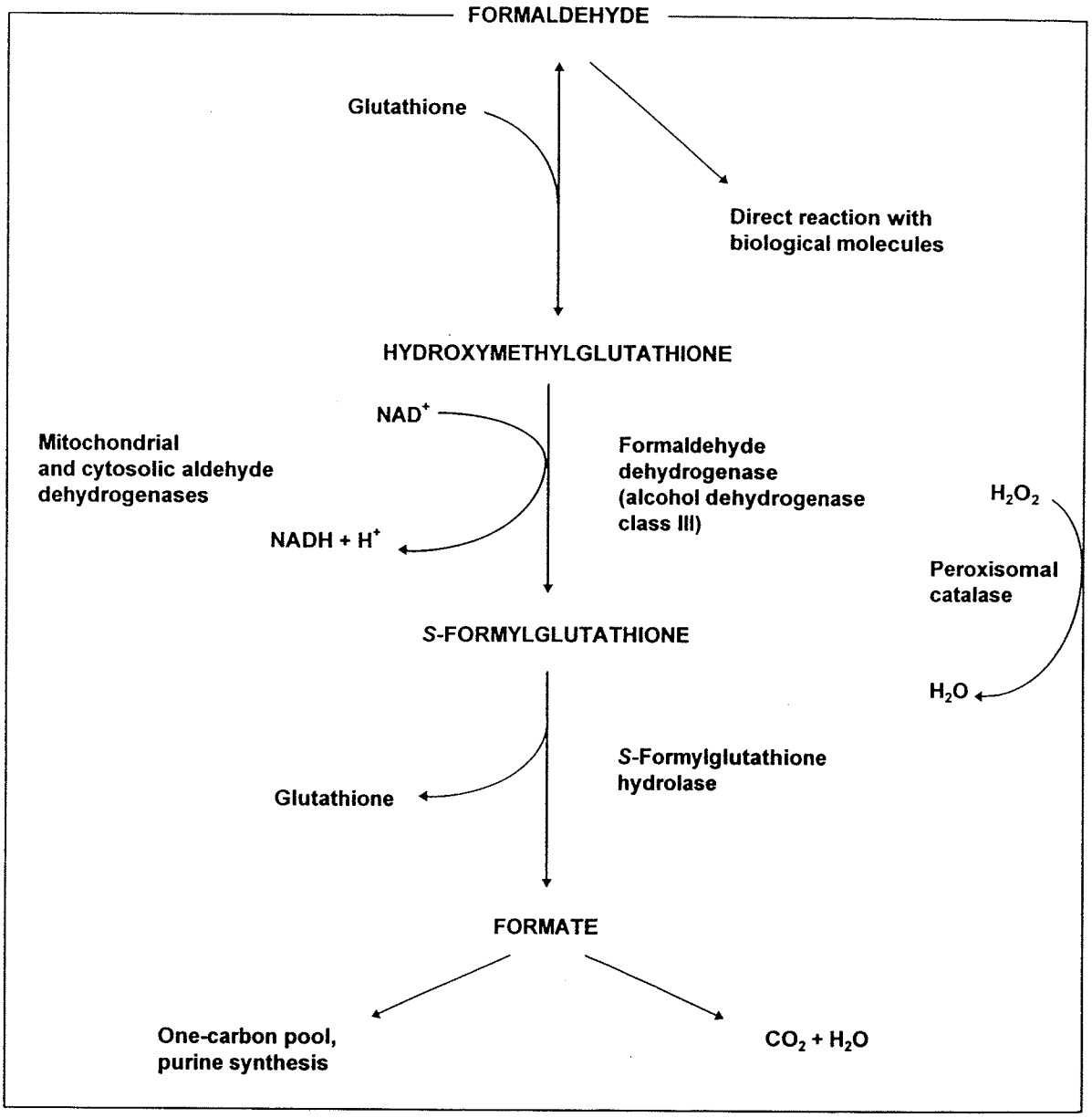
The fate of ^{14}C-formaldehyde after topical application to Fischer 344 rats, Dunkin–Hartley guinea-pigs and cynomolgus monkeys was described by Jeffcoat *et al.* (1983). Aqueous formaldehyde was applied to a shaven area of the lower back, and the rodents were placed in metabolism cages for collection of urine, faeces, expired air and ^{14}C-formaldehyde evaporated from the skin. Monkeys were seated in a restraining chair and were fitted with a plexiglass helmet for collection of exhaled ^{14}C-carbon dioxide. The concentrations of ^{14}C in tissues, blood and carcass of rodents were determined at the end of the experiment. Rodents excreted about 6.6% of the dermally applied dose in the urine over 72 h, while 21–28% was collected in the air traps. It was deduced that almost all of the air-trapped radioactivity was due to evaporation of formaldehyde from the skin, since less than 3% of the radioactivity (i.e. 0.6–0.8% of the applied ^{14}C) was due to ^{14}C-carbon dioxide. Rodent carcass contained 22–28% of the ^{14}C and total blood about 0.1%; a substantial fraction of ^{14}C (3.6–16%) remained in the skin at the site of application. In monkeys, only 0.24% of the dermally applied ^{14}C-formaldehyde was excreted in the urine, and 0.37% was accounted for as ^{14}C-carbon dioxide in the air traps; about 0.015% of the radioactivity was found in total blood and 9.5% in the skin at the site of application. Less than 1% of the applied dose was excreted or exhaled, in contrast to rodents in which nearly 10% was eliminated by these routes. Coupled with the observation of lower blood levels of ^{14}C in monkeys than in rodents, the results suggest that the skin of monkeys may be less permeable to aqueous formaldehyde than that of rodents.

Formaldehyde is absorbed rapidly and almost completely from the rodent intestinal tract (Buss *et al.*, 1964). In rats, about 40% of an oral dose of ^{14}C-formaldehyde (7 mg/kg) was eliminated as ^{14}C-carbon dioxide within 12 h, while 10% was excreted in the urine and 1% in the faeces. A substantial portion of the radioactivity remained in the carcass as products of metabolic incorporation.

Formaldehyde reacts rapidly with glutathione, forming a hemithioacetal, *S*-hydroxymethylglutathione, which is a substrate for the cytosolic enzyme, formaldehyde dehydrogenase [formaldehyde:NAD$^+$ oxidoreductase (glutathione-formylating), EC 1.2.1.1] (Uotila & Koivusalo, 1974a). With NAD$^+$ as a cofactor, this enzyme catalyses the oxidation of *S*-hydroxymethylglutathione to *S*-formylglutathione. The latter compound is hydrolysed to formate by

S-formylglutathione hydrolase [EC 3.1.2.12], regenerating free glutathione (Uotila & Koivusalo, 1974b).

Figure 1. Metabolism and fate of formaldehyde



Formaldehyde dehydrogenase has been identified in a number of tissues in several species (Koivusalo *et al.*, 1982). The activity of formaldehyde dehydrogenase is similar in the respiratory and olfactory mucosa of rats (Casanova-Schmitz *et al.*, 1984a; Bogdanffy *et al.*, 1986; Keller *et al.*, 1990). This enzyme is structurally identical to another well-characterized enzyme, class III alcohol dehydrogenase [alcohol:NAD^+ oxidoreductase, EC 1.1.1.1] (Kaiser *et al.*, 1991; Danielsson & Jörnvall, 1992), which catalyses the oxidation of long-chain primary

alcohols to aldehydes; in contrast to the well-characterized class I alcohol dehydrogenase, however, it has low affinity for ethanol and is not inhibited by 4-methylpyrazole. Class III alcohol dehydrogenase does not require glutathione when catalysing the oxidation of primary alcohols, but a thiol group is essential for the oxidation of formaldehyde, presumably because a hemithioacetal is formed which is structurally similar to a primary alcohol (Holmquist & Vallee, 1991). Numerous other thiols perform this function at nearly the same rate as glutathione (Holmquist & Vallee, 1991). Aldehydes other than formaldehyde are not oxidized by the enzyme.

Because formaldehyde dehydrogenase and class III alcohol dehydrogenase are identical, it cannot be concluded that the normal function of 'formaldehyde dehydrogenase' *in vivo* is solely to catalyse the oxidation of formaldehyde. Lam *et al.* (1985) and Casanova and Heck (1987) found that depletion of glutathione, either by inhalation of acrolein or by intraperitoneal injection of phorone, increased the amount of DNA–protein cross-links in the nasal mucosa of rats exposed to formaldehyde, implying that formaldehyde oxidation (detoxification) was partially inhibited. The authors postulated that depletion of glutathione had decreased the concentration of *S*-hydroxymethylglutathione, resulting in an increase in the tissue concentration of formaldehyde. Dicker and Cederbaum (1985, 1986) showed, however, that phorone not only depletes glutathione but can also inhibit a mitochondrial low-K_m aldehyde dehydrogenase, which may also be important for the oxidation of formaldehyde. The low-K_m mitochondrial aldehyde dehydrogenase [aldehyde:NAD^+ oxidoreductase, EC 1.2.1.3] catalyses the oxidation of both formaldehyde and acetaldehyde, although acetaldehyde is the preferred substrate of both. This enzyme is strongly inhibited by cyanamide, which acts by inhibiting the uptake and oxidation of formaldehyde by mitochondria and isolated rat hepatocytes (Dicker & Cederbaum, 1984). Inhibition of formaldehyde oxidation in hepatocytes was incomplete, however, presumably because formaldehyde was also being oxidized by the cytosolic formaldehyde dehydrogenase. The authors concluded that both formaldehyde dehydrogenase and the low-K_m mitochondrial aldehyde dehydrogenase contribute to the overall metabolism of formaldehyde in isolated rat hepatocytes, but, as the two enzymes have different K_m values, the importance of each is dependent on the formaldehyde concentration (Dicker & Cederbaum, 1986).

The experiments of Dicker and Cederbaum (1984, 1985, 1986) are useful for understanding the metabolism of formaldehyde in general and in hepatocytes in particular, but their relevance to the toxicology of inhaled formaldehyde is uncertain. Although aldehyde dehydrogenase activity was identified in rat nasal mucosa (Casanova-Schmitz *et al.*, 1984a; Bogdanffy *et al.*, 1986), it is not known whether this activity is due to the low-K_m mitochondrial aldehyde dehydrogenase. Moreover, the subcellular location of the low-K_m enzyme within the mitochondria might restrict its accessibility to exogenous formaldehyde and, therefore, impair its ability to metabolize the compound. Thus, the role of this dehydrogenase in the detoxification of inhaled formaldehyde is presently unknown.

Oxidation of formaldehyde to formate may also be mediated by catalase, which is located in peroxisomes. In this reaction, formaldehyde acts as a hydrogen donor for the peroxidative decomposition of the catalase–hydrogen peroxide complex. This reaction contributes less to the overall metabolism of formaldehyde in isolated, perfused rat liver than other pathways, owing to

the rate-limiting generation of hydrogen peroxide (Waydhas *et al.*, 1978). The latter compound is also decomposed by the glutathione peroxidase system, resulting in depletion of glutathione and the production of oxidized glutathione. In hepatocytes in which glutathione has been depleted, hydrogen peroxide production is increased, which may result in increased metabolism of formaldehyde via catalase (Jones *et al.*, 1978).

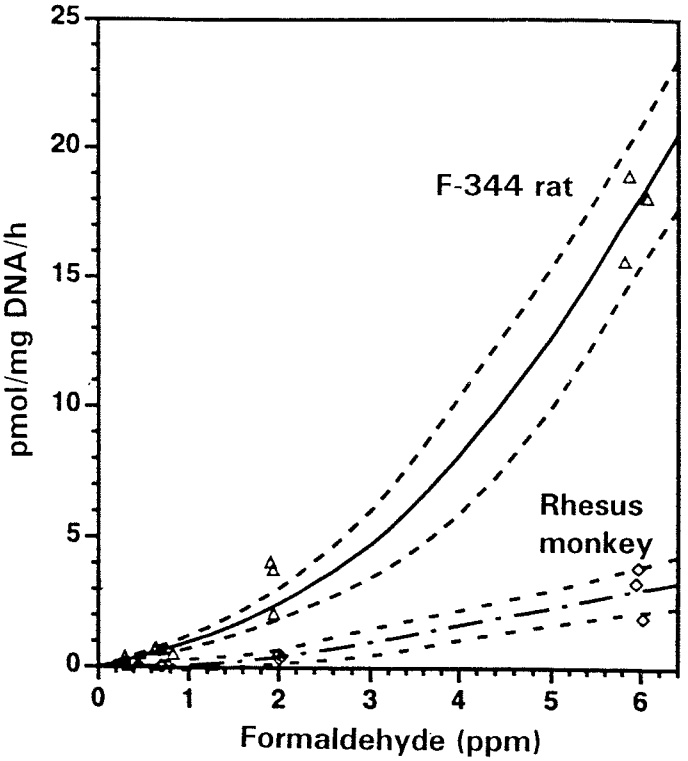
Incubation of formaldehyde with human nasal mucus *in vitro* resulted in the reversible formation of protein adducts, primarily with albumin, suggesting that a portion of the inhaled formaldehyde is retained in the mucous blanket (Bogdanffy *et al.*, 1987). No adducts were found in high relative-molecular-mass glycoproteins. Absorbed formaldehyde may react with nucleophiles (e.g. amino and sulfhydryl groups) at or near the absorption site, or it can be oxidized to formate and exhaled as carbon dioxide or incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways.

Several of the urinary excretion products of formaldehyde in rats have been identified after intraperitoneal administration of ^{14}C-formaldehyde. After injecting Wistar rats with 0.26 mg/kg bw, Hemminki (1984) detected formate and a sulfur-containing metabolite (thought to be a derivative of thiazolidine-4-carboxylic acid) and products presumed to result from one-carbon metabolism. Thiazolidine-4-carboxylate, which is formed via the nonenzymatic condensation of formaldehyde with cysteine, was not detected in urine.

After Sprague–Dawley rats were injected intraperitoneally with 4 or 40 mg/kg bw of ^{14}C-formaldehyde, formate (80% of the total radioactivity in urine), *N*-(hydroxymethyl)- and *N,N'*-bis(hydroxymethyl)urea (15% of urinary radioactivity) (which appeared to have resulted from the condensation of formaldehyde with urea) and an unidentified product (5% of the total) were identified (Mashford & Jones, 1982). As the urine of the Sprague–Dawley rat contains little, if any, cysteine, formation of thiazolidine-4-carboxylate is precluded and urea-containing adducts can be formed. The existence of these adducts suggests that, at least in Sprague–Dawley rats administered large doses of formaldehyde, a portion of the injected material (about 3–5% at a dose of 40 mg/kg bw) is excreted unchanged in the urine. After exposure by inhalation, however, it is questionable whether a significant amount of formaldehyde is excreted unchanged in the urine, since such high dose levels are not attainable by this route.

The formation of DNA–protein cross-links by formaldehyde in the nasal respiratory mucosa of rats after exposure to 6 ppm [7.3 mg/m^3] and more has been demonstrated by a variety of techniques, including decreased extractability of DNA from proteins (Casanova-Schmitz & Heck, 1983), double-labelling studies with ^{3}H- and ^{14}C-formaldehyde (Casanova-Schmitz *et al.*, 1984b; Casanova & Heck, 1987; Heck & Casanova, 1987) and isolation of DNA from respiratory mucosal tissue and quantification of cross-links by high-performance liquid chromatography after exposure to ^{14}C-formaldehyde (Casanova *et al.*, 1989, 1995). The formation of DNA–protein cross-links is a nonlinear function of concentration (Casanova & Heck, 1987; Casanova *et al.*, 1989, 1995; Heck & Casanova, 1995; see Figure 2). Cross-links were not detected in the olfactory mucosa or in the bone marrow of rats (Casanova-Schmitz *et al.*, 1984b; Casanova & Heck, 1987).

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



Reproduced, with permission, from Casanova *et al.* (1991)
All animals were exposed for 6 h. Dashed lines are the 95% confidence limits around the mean for each species.

DNA–protein cross-links were also measured in the respiratory tracts of groups of three rhesus monkeys immediately after single, 6-h exposures to airborne ^{14}C-formaldehyde (0.7, 2 or 6 ppm [0.9, 2.4 or 7.3 mg/m^3]) (Casanova *et al.*, 1991). The concentrations of cross-links in the nose of monkeys decreased in the order: middle turbinates > lateral wall–septum > nasopharynx, and this order is consistent with the location and severity of lesions in monkeys exposed to 6 ppm (Monticello *et al.*, 1989). Very low levels of cross-links were also found in the trachea and carina of some monkeys, but none were detected in the maxillary sinus. The yield of cross-links in the nose of monkeys was approximately an order of magnitude lower than that in the nose of rats, due largely to species differences in minute volume and quantity of exposed tissue (Casanova *et al.*, 1991; Figure 2). A pharmacokinetic model based on these results indicated that the concentrations of DNA–protein cross-links in the human nose would be lower than those in the noses of monkeys and rats (Casanova *et al.*, 1991).

The yields of DNA–protein cross-links produced in rats exposed to formaldehyde (at 0.7, 2, 6 or 15 ppm [0.9, 2.4, 7.3 or 18.3 mg/m^3] for 6 h/day, five days/week for 11 weeks and four days) were compared with those produced in naive (previously unexposed) rats (Casanova *et al.*,

1995). The acute yields of cross-links (pmol/mg DNA) were determined in the lateral meatus (susceptible tumour site; see section 3.1 (Morgan *et al.*, 1986a)) and in the medial and posterior meatuses (low susceptibility site (Morgan *et al.*, 1986a)) after a single 3-h exposure of pre-exposed and naive rats to the same concentration of ^{14}C-formaldehyde. At 0.7 and 2 ppm, the acute yields of cross-links in the lateral meatus of pre-exposed rats were indistinguishable from those of naive rats; at 6 and 15 ppm, the acute yields in pre-exposed rats were approximately half those of naive rats, and the difference was significant (Figure 3). Pre-exposed animals had lower concentrations of cross-links than naive rats at 6 and 15 ppm partly because of an increase in total DNA in the target tissue caused by cell proliferation (Heck & Casanova, 1995; see section 4.2.2). The acute yields of DNA–protein cross-links in the medial and posterior meatuses were similar in pre-exposed and naive rats at all concentrations and were lower than the acute yields in the lateral meatus. This result is consistent with the location and severity of lesions in the rat nose (Morgan *et al.*, 1986a).

In order to determine whether DNA–protein cross-links accumulate with repeated exposure, the cumulative yield was investigated using reduced DNA extractability as a measure of cross-linking. Rats were exposed subchronically to unlabelled formaldehyde (6 or 10 ppm [7.3 or 12.2 mg/m^3]; 6 h/day, five days/week, 11 weeks and four days) (Casanova *et al.*, 1995), and the cumulative yields of DNA–protein cross-links in the nasal mucosa of pre-exposed rats were compared with those in naive rats after a single 3-h exposure to the same concentration of unlabelled formaldehyde. A concentration-dependent increase in the yield of DNA–protein cross-links over that in unexposed controls was seen in both pre-exposed and naive rats. The yield was not higher in pre-exposed than in naive rats, suggesting that no accumulation had occurred in pre-exposed rats. The results suggest that DNA–protein cross-links in the rat nasal mucosa are rapidly repaired.

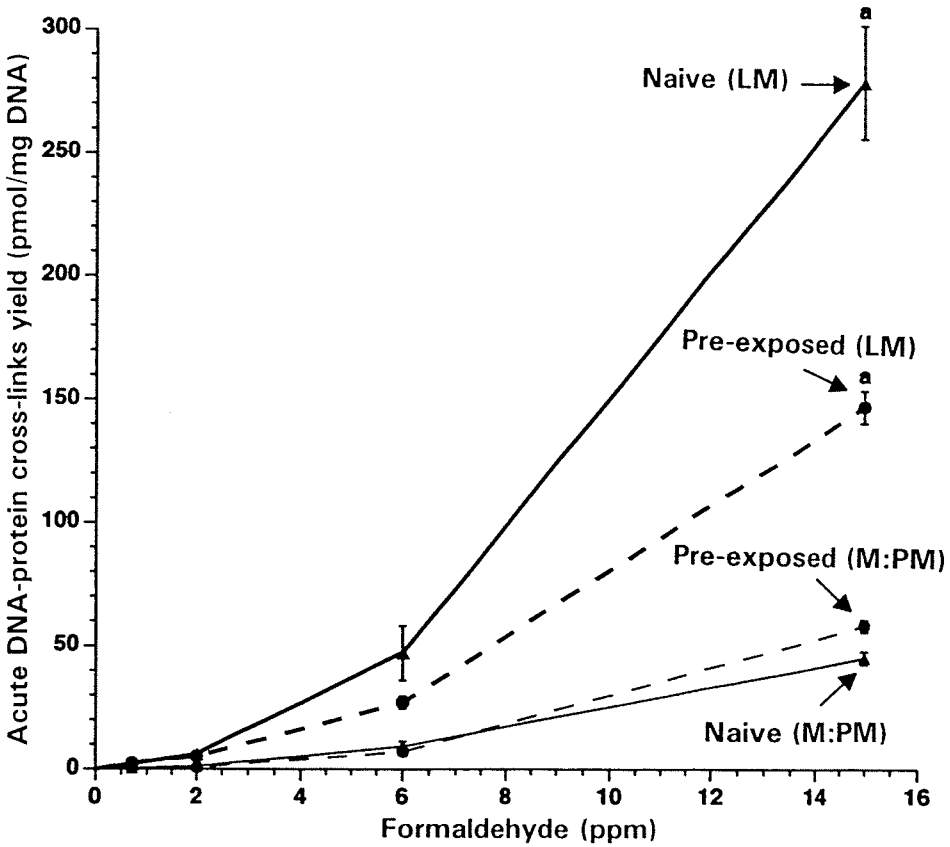
An anatomically based pharmacokinetic model was developed for determining the site-specificity of cross-link formation in the nasal mucosa of Fischer 344 rats (Heck & Casanova, 1995) and rhesus monkeys (Casanova *et al.*, 1991). The model is based on the assumption that the site-specificity of cross-links is due to nasal airflow and absorption patterns, rather than to site-specific differences in metabolism (Casanova *et al.*, 1991; Heck & Casanova, 1995). Parameter estimation indicates that at concentrations of less than about 3 ppm [3.7 mg/m^3], about 90% of a dose of inhaled formaldehyde is eliminated by saturable metabolism, 10% is eliminated by nonsaturable pathways and only $1/10^6$ (i.e. 10^{-4} %) exists as DNA–protein cross-links immediately after exposure. The amount bound to DNA increases sublinearly with respect to concentration but linearly with respect to time during exposure (Heck & Casanova, 1995). Computer simulations of nasal airflow and formaldehyde absorption patterns at specific sites in the nose of rats are generally consistent with the experimental results on the site-specificity of DNA–protein cross-links (Kimbell *et al.*, 1993).

4.2 Toxic effects

The toxicity of formaldehyde in humans and experimental systems has been reviewed (IARC, 1982; Heck & Casanova-Schmitz, 1984; Feinman, 1988; WHO, 1989; Heck *et al.*, 1990;

American Conference of Governmental Industrial Hygienists, 1991; Bardana & Montanaro, 1991; Restani & Galli, 1991; Vaught, 1991; Leikauf, 1992).

Figure 3. Acute yields of DNA–protein cross-links (mean ± SE) in the lateral meatus (LM) and medial and posterior meatuses (M:PM) of pre-exposed and naive (previously unexposed) Fischer 344 rats immediately after a single 3-h exposure to ^{14}C-formaldehyde



Adapted, with permission, from Casanova *et al.* (1995)
Pre-exposed rats were exposed subchronically to the same concentrations of unlabelled formaldehyde (6 h/day, five days/week, for 11 weeks and four days), while naive rats were exposed to room air. Exposure to ^{14}C-formaldehyde occurred on the fifth day of the twelfth week, and the acute yields pertain to the DNA–protein cross-links produced at that time.

4.2.1 Humans

(a) Acute effects

(i) Odour detection

The threshold for detection of formaldehyde odour was determined among 22 nonsmokers and 22 aged-matched, heavy smokers (all female) (Berglund & Nordin, 1992). Odour was detected at 25–144 ppb (31–177 μg/m^3) by nonsmokers and at 20–472 ppb (25–581 μg/m^3) by smokers ($p < 0.01$).

(ii) Irritation

The following studies of healthy humans given short-term exposures to formaldehyde under controlled conditions indicate that the irritation threshold for eyes, nose and throat is 0.5–1 ppm (0.6–1.2 mg/m^3).

Irritation thresholds were determined in subjects exposed to steadily increasing (0–3.2 ppm [0–3.9 mg/m^3] over 37 min) or to constant formaldehyde concentrations (0, 1, 2, 3 or 4 ppm [0, 1.2, 2.4, 3.7 or 4.9 mg/m^3], 1.5 min per exposure). The thresholds for eye and nose irritation were between 1 and 2 ppm (1.2–2.5 mg/m^3); the threshold for throat irritation was > 2 ppm (Weber-Tschopp *et al.*, 1977)..

Workers exposed to 0.35–1.0 ppm [0.43–1.2 mg/m^3] for 6 min had a significant irritation response at 1.0 ppm; nonsignificant responses were reported at 0.7 and 0.9 ppm [0.9 and 1.1 mg/m^3] (Bender *et al.*, 1983).

Among nonsmokers exposed to 0.5–3.0 ppm [0.6–3.7 mg/m^3], some subjects reported eye irritation at 1.0 ppm, and one reported nose and throat irritation at 0.5 ppm (Kulle *et al.*, 1987). Tolerance to the irritating effects of formaldehyde developed during prolonged exposure to concentrations above 1 ppm (Andersen & Mølhave, 1983).

Respiratory and ocular irritation has been reported by occupants of mobile homes (see section 1) and offices where there are low levels of formaldehyde (Hanrahan *et al.*, 1984; Bracken *et al.*, 1985; Ritchie & Lehnen, 1987; Broder *et al.*, 1988a,b,c; Liu *et al.*, 1991) and by medical students, histology technicians and embalmers, who may be exposed briefly to higher concentrations (Kilburn *et al.*, 1985; Holness & Nethercott, 1989; Uba *et al.*, 1989). In general, the reported thresholds for irritation in uncontrolled environments are lower than those in controlled exposures. The answers to a questionnaire indicated that a few individuals experienced sensory irritation at concentrations as low as 0.1 ppm [0.12 mg/m^3]; however, the contribution of other substances is unknown.

(iii) Pulmonary function

Fifteen healthy nonsmokers and 15 asthmatic subjects were exposed to 2 ppm [2.4 mg/m^3] formaldehyde for 40 min to determine whether acute exposures could induce asthmatic symptoms (Schachter *et al.*, 1986; Witek *et al.*, 1987). On separate days, the subjects either remained at rest or engaged in moderate exercise, and pulmonary function was measured before, during, immediately after or 24 h after exposure. No significant airway obstruction or changes in pulmonary function were noted. Neither healthy nor asthmatic subjects had bronchial hyperreactivity, as shown by responsiveness to methacholine.

Similar observations were made on a group of 15 hospital laboratory workers who had been exposed to formaldehyde (Schachter *et al.*, 1987). The subjects were exposed in an environmental chamber to 2.0 ppm [2.4 mg/m^3] for 40 min on four occasions, during two of which the subjects were at rest and during two of which they performed moderate exercise. Lung function was unaltered on all four days, and there were no delayed obstructive changes or increased reactivity to methacholine.

Healthy nonsmokers (nine subjects for 3 h, 22 for 1 h) and asthmatic subjects (nine subjects for 3 h, 16 for 1 h) were exposed to 3.0 ppm [3.7 mg/m^3] formaldehyde, either at rest or when

engaged in intermittent heavy exercise. Pulmonary function and nonspecific airway reactivity were assessed before, during and up to 24 h after exposure. No significant changes were observed among asthmatic subjects. Small decreases (< 5%) in pulmonary function (forced expiratory volume at one second, forced vital capacity) were observed in healthy nonsmokers exposed to formaldehyde while engaging in heavy exercise. Two normal and two asthmatic subjects had decrements greater than 10% at two times. There were no changes in nonspecific airway reactivity (as judged by the methacholine challenge test) (Sauder *et al.*, 1986; Green *et al.*, 1987; Sauder *et al.*, 1987).

Healthy nonsmokers were exposed for 3 h at rest to 0, 0.5, 1.0, 2.0 or 3.0 ppm [0, 0.6, 1.2, 2.4 or 3.7 mg/m^3] formaldehyde; they were also exposed to 2.0 ppm while exercising. Nasal flow resistance was increased at 3.0 ppm but not at 2.0 ppm. There was no significant decrement in pulmonary function or increase in bronchial reactivity to methacholine with exposure to 3.0 ppm at rest or to 2.0 ppm with exercise (Kulle *et al.*, 1987).

A group of 24 healthy nonsmokers were exposed while engaged in intermittent heavy exercise for 2 h to formaldehyde at 3 ppm [3.7 mg/m^3] or to a mixture of formaldehyde and 0.5 mg/m^3 of respirable carbon aerosol, in order to determine whether adsorption of formaldehyde on respirable particles elicits a pulmonary response. Small (< 5%) decreases were seen in forced vital capacity and forced expiratory volume, but these effects were not considered to be clinically significant (Green *et al.*, 1989). As noted previously, Risby *et al.* (1990) and Rothenberg *et al.* (1989) estimated that the amount of formaldehyde adsorbed onto carbon black or dust particles and delivered to the deep lung by particle inhalation is minuscule in relation to the amount that remains in the vapour phase and is adsorbed in the upper respiratory tract.

In a study of controlled exposure to formaldehyde, 18 subjects, nine of whom had complained of adverse effects from urea–formaldehyde foam insulation installed in their homes, were exposed to 1 ppm [1.2 mg/m^3] formaldehyde or to off-gas products of urea–formaldehyde foam insulation containing 1.2 ppm [1.5 mg/m^3] formaldehyde, for 90 min (Day *et al.*, 1984). No statistically or clinically significant change in pulmonary function was seen either during or 8 h after exposure, and no evidence was obtained that urea–formaldehyde foam insulation off-gas acts as a lower airway allergen. When 15 asthmatic subjects were exposed for 90 min to concentrations of 0.008–0.85 mg/m^3 formaldehyde, no change in pulmonary function was seen, and there was no evidence of an increase in bronchial reactivity (Harving *et al.*, 1990).

(b) Chronic effects

(i) Effects on the nasal mucosa

The possibility that formaldehyde may induce pathological or cytogenetic changes in the nasal mucosa has been examined in subjects exposed either in residential environments or in occupational settings. Samples of cells were collected with a swab inserted 2–3 cm into the nostrils of subjects living in urea–formaldehyde foam-insulated homes and of subjects living in homes without this type of insulation and were examined cytologically. Small but significant increases were observed in the prevalence of squamous metaplastic cells in the samples from the occupants of urea–formaldehyde foam-insulated homes (Broder *et al.*, 1988a,b,c). A follow-up

study one year later (Broder *et al.*, 1991) showed a decrease in nasal signs that was unrelated to any decrease in formaldehyde levels.

Cell smears were collected with a swab inserted 6–8 cm into the nose from 42 workers employed in two phenol–formaldehyde plants and 38 controls with no known exposure to formaldehyde. The formaldehyde concentrations in the plants were 0.02–2.0 ppm [0.02–2.4 mg/m^3], with occasional peaks as high as 9 ppm [11.0 mg/m^3], and the average length of employment in the plants was about 17 years. Atypical squamous metaplasia was detected as a function of age > 50, but there was no association with exposure to formaldehyde (Berke, 1987).

Biopsy samples were taken from the anterior edge of the inferior turbinate of the nose of 37 workers in two particle-board plants, 38 workers in a laminate plant and 25 controls of similar ages. The formaldehyde concentrations in the three plants were 0.1–1.1 mg/m^3, with peak concentrations up to 5 mg/m^3. Simultaneous exposure to wood dust occurred in the particle-board plants but not in the laminate plant. The average length of employment was 10.5 years. Exposure to formaldehyde appeared to be associated with squamous metaplasia and mild dysplasia, but no concentration–response relationship was observed, and the histological score was not related to years of employment. There was no detectable difference in the nasal histology of workers exposed to formaldehyde alone and to formaldehyde and wood dust (Edling *et al.*, 1987b, 1988).

Biopsy samples were collected from the medial or inferior aspect of the middle turbinate, 1 cm behind the anterior border, from 62 workers engaged in the manufacture of resins for laminate production, 89 workers employed in furniture factories who were exposed to particle-board and glue, and 32 controls, who were mainly clerks in a local government office. The formaldehyde concentrations in the resin manufacturing plant were 0.05–0.5 mg/m^3, with frequent peaks over 1 mg/m^3. The concentrations in the furniture factories were 0.2–0.3 mg/m^3, with rare peaks to 0.5 mg/m^3; these workers were also exposed to wood dust (1–2 mg/m^3). The control group was exposed to concentrations of formaldehyde of 0.09–0.17 mg/m^3. The average length of employment was about 10 years. The histological scores of workers exposed to formaldehyde alone were slightly but significantly higher than those of controls, but the histological scores of workers exposed to formaldehyde and wood dust together did not differ from those of controls. No correlation was found between histological score and either duration or concentration of exposure (Holmström *et al.* (1989b). [The possible effect of age on nasal cytology, as noted by Berke (1987), was not determined.]

A nasal biopsy sample was taken from the anterior curvature of the middle turbinate from 37 workers exposed at a chemical company where formaldehyde resins were produced and from 37 age-matched controls. The formaldehyde concentrations in the company ranged from 0.5 to > 2 ppm [0.6–> 2.4 mg/m^3], and the average length of employment was 20 years. Hyperplasia and squamous metaplasia were commoner among the exposed workers than the controls, but the difference was not significant. The histological scores increased with age and with exposure concentration and duration, but the changes were not significant (Boysen *et al.*, 1990).

Histopathological abnormalities of respiratory nasal mucosa cells were determined in 15 nonsmokers (seven women, eight men) who were exposed to formaldehyde released from a urea–formaldehyde glue in a plywood factory. Each subject was paired with a control matched

for age and sex. The mean age of the controls was 30.6 ± 8.7 years and that of exposed workers was 31.0 ± 8.0 years. The mean levels of exposure to formaldehyde (8-h time-weighted) were about 0.1 mg/m^3 in the sawmill and shearing-press department and 0.39 mg/m^3 in the warehouse area. Peak exposure levels were not given. There was concurrent exposure to low levels of wood dust (respirable mass, 0.23 mg/m^3 in the warehouse, 0.73 mg/m^3 during sawing). Nasal respiratory cell samples were collected from near the inner turbinate with an endocervical cytology brush. The exposed group had chronic inflammation of the nasal respiratory mucosa and a higher frequency of squamous metaplasia than the controls (mean scores, 2.3 ± 0.5 in the exposed group, 1.6 ± 0.5 in the control group; $p < 0.01$, Mann–Whitney U test) (Ballarin *et al.*, 1992).

The effects of formaldehyde, other than cancer, on the nasal mucosa are summarized in Table 20.

(ii) Pulmonary function

Pulmonary function has been assessed in residents of mobile and conventional homes (Broder *et al.*, 1988a,b,c) and mobile offices (Main & Hogan, 1983) exposed to concentrations of 0.006–1.6 ppm [0.007–2.0 mg/m^3]. No changes were seen in pulmonary function or airway resistance.

Lung function tests were performed on particle-board and plywood workers (Holmström & Wilhelmsson, 1988; Horvath *et al.*, 1988; Imbus & Tochilin, 1988; Malaka & Kodama, 1990), workers using acid-hardening paints (Alexandersson & Hedenstierna, 1988, 1989), embalmers (Levine *et al.*, 1984b; Holness & Nethercott, 1989), urea–formaldehyde resin producers (Holmström & Wilhelmsson, 1988; Nunn *et al.*, 1990), medical students (Uba *et al.*, 1989) and anatomy and histology workers (Khamgaonkar & Fulare, 1991). These groups were often exposed to formaldehyde in combination with other substances. The formaldehyde concentrations were < 0.02–> 5 ppm [< 0.02–> 6.0 mg/m^3]. In most of the studies, formaldehyde alone or in combination with other agents caused transient, reversible declines in lung function, but there was no evidence that formaldehyde induces a chronic decrement in lung function.

(iii) Effects on the skin

Formaldehyde is a skin irritant and can cause allergic contact dermatitis. It is difficult to distinguish between these two effects (Maibach, 1983). The estimated percentages of people with positive reactions in patch tests were 8.4% in the United States, 7.4% in Saskatoon, Canada, 9.2% in Cologne, Germany, and 5.5% of men and 12.4% of women in Hamburg, Germany (Cronin, 1991). Maibach (1983), however, indicated that these estimates may be considerably inflated, as they are usually uncorrected for the 'excited skin state' and are often unconfirmed. He estimated that the results of more than 40% of patch tests are unreproducible, especially for substances such as formaldehyde, as the concentrations that evoke an allergic response and an irritant response are similar.

In order to determine whether specific immunoglobulin (Ig) E antibodies are involved in contact dermatitis after exposure to formaldehyde, 23 patients with a history of a positive epicutaneous test to formaldehyde were studied. Fifteen (65%) showed a positive reaction on re-testing. The findings do not support the hypothesis that specific IgE antibodies are active in the

Table 20. Findings in nasal mucosa of people with occupational exposure to formaldehyde

Reference	Industry	Concentration of formaldehyde (mg/m^3)	No. of exposed	No. of controls	Method	Findings
Edling *et al.* (1987b)	Formaldehyde (laminate plant)	0.5-1.1	38	25	Nasal biopsy	Histological score: exposed 2.8, controls 1.8 ($p < 0.05$) Four exposed men had mild dysplasia
Edling *et al.* (1988)	Formaldehyde Wood dust (laminated particle-board)	0.1–1.1 (peaks to 5) 0.6–1.1	75	25	Nasal biopsy	Histological score: exposed 2.9, controls 1.8 ($p < 0.05$) Six men had mild dysplasia
Berke (1987)	Formaldehyde (phenol?) (laminate)	0.02–2.4 (peaks to 11–18.5)	42	38	Swab smears	No positive correlation between exposure to formaldehyde and abnormal cytology
					Clinical examination	More mucosal abnormalities in non-smoking exposed workers ($p = 0.004$)
Boysen *et al.* (1990)	Formaldehyde (production of formaldehyde and formaldehyde resins)	0.6–> 2.4	37	37	Nasal biopsy	Histological score: exposed 1.9, controls, 1.7 ($p > 0.05$) Three exposed and none of the controls had dysplasia
Holmström *et al.* (1989b)	Formaldehyde (resins for laminate production)	0.05–0.5 (peaks to > 1)	62	32	Nasal biopsy	Histological score: exposed 2.16, controls 1.56 ($p < 0.05$) No case of dysplasia
Ballarin *et al.* (1992)	Formaldehyde Wood dust (plywood factory)	0.1–0.39 0.23–0.73	15	15	Nasal scrapes	Micronuclei in nasal mucosal cells: exposed 0.90, controls 0.25 ($p < 0.010$) Cytological score: exposed 2.3, controls 1.6 ($p < 0.01$) One exposed had mild dysplasia

pathogenesis of contact sensitivity to formaldehyde, in either atopic or nonatopic patients (Lidén *et al.*, 1993).

Contact urticaria has also, but rarely, been associated with exposure to formaldehyde. Cases have been reported in a nonatopic histology technician (Rappaport & Hoffman, 1941), a worker exposed through contact with formaldehyde-treated leather (Helander, 1977) and a worker in a pathology laboratory (Lindskov, 1982). Information about the mechanisms of contact urticaria is limited (Maibach, 1983).

(c) Allergy

Immunological tests were performed on 23 asthmatic subjects who lived in urea–formaldehyde foam-insulated homes and on four asthmatic subjects living in conventionally insulated homes. The authors concluded that long-term exposure to formaldehyde had not affected the six immune parameters measured, but that short-term acute exposure resulted in minor immunological changes (Pross *et al.*, 1987).

No IgE-mediated sensitization could be attributed to formaldehyde in 86 individuals at risk of exposure to formaldehyde (Kramps *et al.*, 1989), and none of 63 practising pathologists had allergen-specific IgE directed against formaldehyde, although 29 subjects complained of sensitivityy to formaldehyde (Salkie, 1991).

The immune responses of a large number of people exposed to formaldehyde were investigated, including people living in mobile homes or working in buildings insulated with urea–formaldehyde foam, patients undergoing haemodialysis with formaldehyde-sterilized dialysers, physicians and dialysis nurses exposed to formaldehyde, histology technicians, medical and pathology students, and workers in an aircraft factory who were exposed to formaldehyde and other substances (including phenol and solvents) (Patterson *et al.*, 1989; Grammer *et al.*, 1990; Dykewicz *et al.*, 1991). The authors of the last paper stated that none of their studies indicated an immunological basis for respiratory or conjunctival symptoms (conjunctivitis, rhinitis, coughing, wheezing, shortness of breath) seen after exposure to gaseous formaldehyde.

Elevated serum levels of IgE, IgG or IgM antibodies were observed in several individuals exposed to formaldehyde (Thrasher *et al.*, 1987, 1988, 1990). The experimental design and methods used have been criticized, however, for lack of adequate controls, lack of a correlation between disease and immunological abnormalities, lack of information about the diseased and comparison populations and use of unproven diagnostic tests (Beavers, 1989; Greenberg & Stave, 1989).

4.2.2 Experimental systems

Formaldehyde has been shown to be toxic *in vitro* in a variety of experimental systems, including human cells. It decreased growth rate, cloning efficiency and the ability of cells to exclude trypan blue while inducing squamous differentiation of cultured human bronchial epithelial cells (Grafström, 1990). These effects occurred simultaneously with elevated levels of intracellular calcium ion, decreased levels of free low-relative-molecular-mass thiols, including glutathione, and the appearance of genotoxicity (see section 4.4).

(a) Acute effects

(i) Irritation

A quantitative measure of sensory irritation in rodents is provided by the reflex decrease in respiratory rate of mice or rats caused by stimulation of trigeminal nerve receptors in the nasal passages. In comparison with other aldehydes (Steinhagen & Barrow, 1984), formaldehyde is a potent respiratory tract irritant, eliciting a 50% decrease in respiratory frequency in B6C3F1 mice at 4.9 ppm [6.0 mg/m^3] and Fischer 344 rats at 31.7 ppm [38.7 mg/m^3] (Chang *et al.*, 1981). Swiss–Webster mice exposed to the concentration that elicits a 50% decrease in respiratory frequency (3.1 ppm [3.8 mg/m^3]) for five days (6 h/day) developed mild histopathological lesions in the anterior nasal cavity, but no lesions were found in the posterior nasal cavity or in the lung (Buckley *et al.*, 1984).

In addition to decreasing the respiratory rate, formaldehyde may also alter the tidal volume, resulting in a decrease in minute ventilation. Exposure to formaldehyde over a 10-min test period induced prompt reductions in both respiratory rates and minute volumes of mice and rats, whether or not they were exposed before testing to 6 ppm [7.4 mg/m^3] formaldehyde for 6 h per day for four days (Fig. 4). These effects were observed at lower concentrations of formaldehyde in mice than in rats (Chang *et al.*, 1983). A similar effect has been demonstrated in C57Bl6/F1 mice and CD rats (Jaeger & Gearhart, 1982).

Rats exposed to 28 ppm [34.1 mg/m^3] formaldehyde for four days developed tolerance to its sensory irritancy, but rats exposed to 15 ppm [18.3 mg/m^3] for one, four or 10 days did not (Chang & Barrow, 1984).

(ii) Pulmonary hyperreactivity

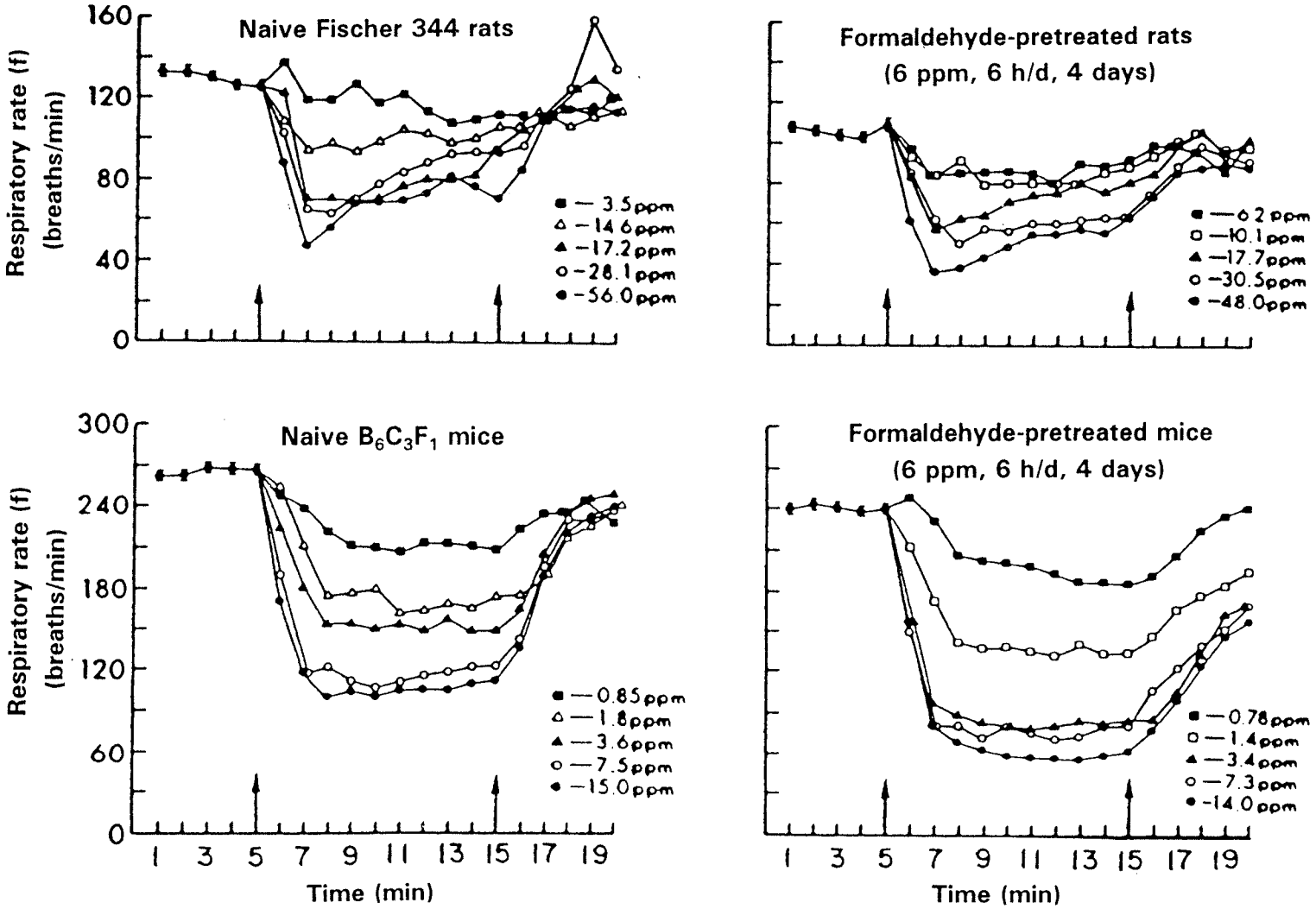
Formaldehyde induced pulmonary hyperreactivity in guinea-pigs: exposure to 0.03 ppm [0.04 mg/m^3] caused transient bronchoconstriction and hyperreactivity to infused acetylcholine when the duration of exposures was 8 h, but higher concentrations (10 ppm [12.2 mg/m^3]) were required to induce bronchoconstriction when the duration was 2 h. These effects occurred with no evidence of tracheal epithelial damage after exposure to 3.4 ppm [4.1 mg/m^3] for 8 h. The mechanism by which they occur is unknown (Swiecichowski *et al.*, 1993).

The effects of formaldehyde (vaporized formalin) on pulmonary flow were determined in cynomolgus monkeys, which were tranquilized before exposure and received an endotracheal tube transorally. Pulmonary flow resistance was increased at a concentration of 2.5 ppm [3.0 mg/m^3]. Airway narrowing was not correlated with methacholine reactivity (Biagini *et al.*, 1989). [The Working Group questioned the relevance of these findings, in view of the method of administration.]

(iii) Cytotoxicity and cell proliferation in the respiratory tract

The acute and subacute effects of formaldehyde in experimental animals are summarized in Table 21. A critical issue for the mechanism of carcinogenesis is whether low concentrations of formaldehyde increase the rate of cell turnover in the nasal epithelium. Subacute exposure to a low concentration of formaldehyde (1 ppm [1.2 mg/m^3], 6 h/day, three days) has been reported to induce a small, transient increase in nasal epithelial cell turnover in Wistar rats (Zwart *et al.*,

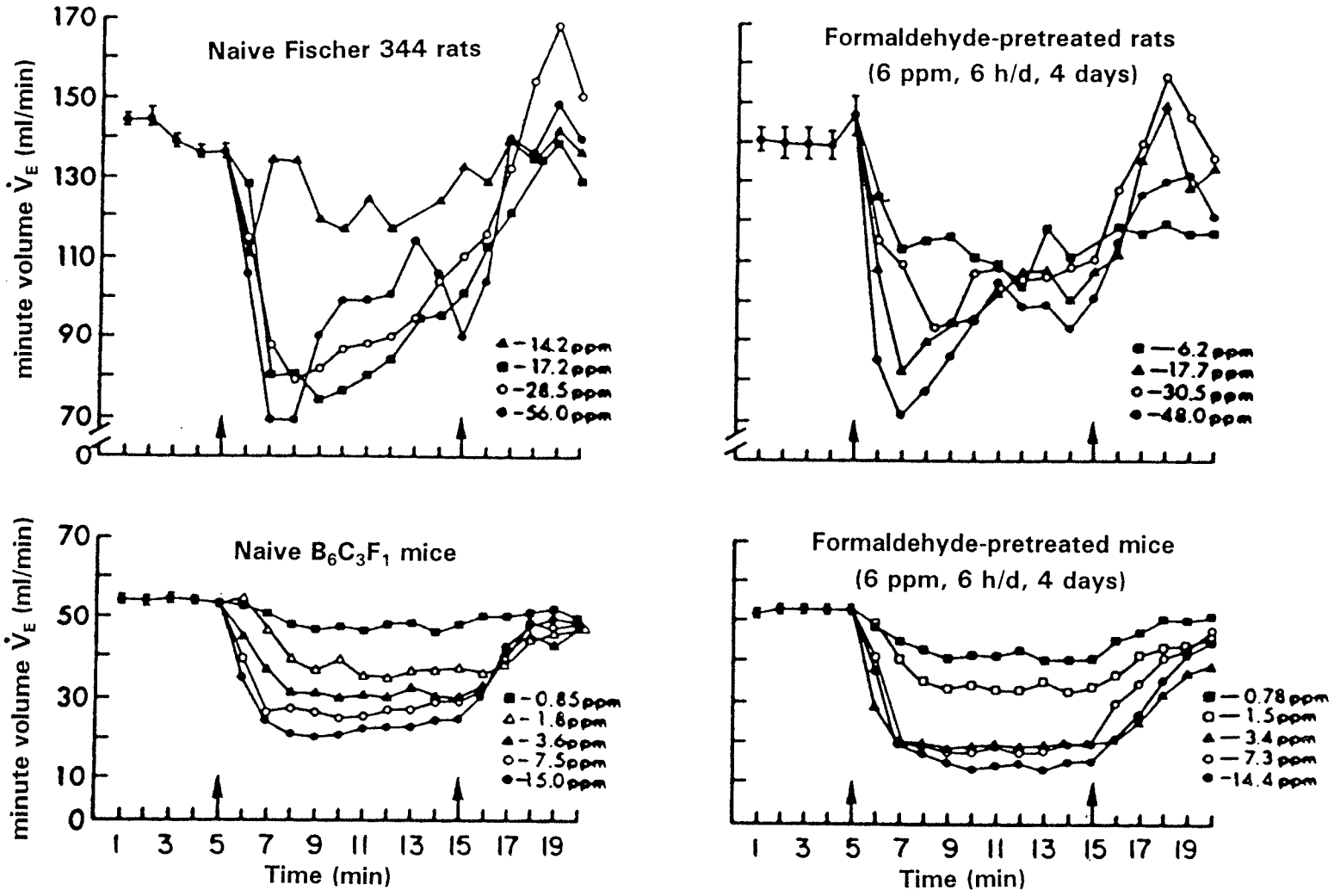
Figure 4. Representative time–response curves for the minute volume of naive and formaldehyde-treated mice and rats during 10-min exposures to various concentrations of formaldehyde



From Chang *et al.*(1981)

Data for the pre-exposure period are means ± SE of 19 or (A) 22 or (B) 28 animals, and the points for each concentration are means for four animals. Arrows indicate beginning and end of exposure.

Figure 4 (contd)



1988), but the apparent increase was not shown to be significant, and it was not confirmed in later studies (Reuzel *et al.*, 1990). Other investigators did not detect an increase in cell turnover in the nasal epithelium of Fischer 344 rats exposed to 0.7 or 2 ppm [0.9 or 2.4 mg/m^3] (6 h/day, one, four or nine days) (Monticello *et al.*, 1991) or to 0.5 or 2 ppm [0.6 or 2.4 mg/m^3] (6 h/day, three days) (Swenberg *et al.*, 1983). Low concentrations of formaldehyde (0.5 or 2 ppm; 6 h/day, one, two, four, nine or 14 days) also did not inhibit mucociliary function in the nasal passages of Fischer 344 rats (Morgan *et al.*, 1986b,c), and no injury to the nasal epithelium of rats of this strain was detected ultrastructurally after exposure to 0.5 or 2 ppm (6 h/day, one or four days) (Monteiro-Riviere & Popp, 1986).

Wistar rats exposed to 3 ppm [3.7 mg/m^3] (6 h/day, three days (Zwart *et al.*, 1988) or 22 h/day, three days (Reuzel *et al.*, 1990)) had a transient increase in cell replication. Higher formaldehyde concentrations (≥ 6 ppm [7.3 mg/m^3]) induced erosion, epithelial hyperplasia, squamous metaplasia and inflammation in a site-specific manner in the nasal mucosa (Monticello *et al.*, 1991). Mice are less responsive than rats, probably because they are better able than rats to reduce their minute ventilation when exposed to high concentrations of formaldehyde (Chang *et al.*, 1983; Swenberg *et al.*, 1983). Fischer 344 rats exposed to 6, 10 or 15 ppm [7.3, 12.2 or 18.3 mg/m^3] (6 h/day, one, four or nine days, or 6 h/day, five days/week, six weeks) had an enhanced rate of cell turnover (Monticello *et al.*, 1991). The severity of nasal epithelial responses at 15 ppm was much greater than at 6 ppm (Monteiro-Riviere & Popp, 1986). Rhesus monkeys exposed to 6 ppm (6 h/day, five days) developed similar nasal lesions to rats. Mild lesions, characterized as multifocal loss of cilia, were also detected in the larynx, trachea and carina (Monticello *et al.*, 1989).

The relative importance of concentration and total dose on cell proliferation was examined in Fischer 344 and Wistar rats exposed to a range of concentrations for various lengths of time, such that the total inhaled dose was constant. Exposures were for three or 10 days (Swenberg *et al.*, 1983) or four weeks (Wilmer *et al.*, 1987). All of the investigators concluded that concentration, not total dose, is the primary determinant of the cytotoxicity of formaldehyde. A similar conclusion was reached when rats were exposed for 13 weeks (Wilmer *et al.*, 1989).

The effects of simultaneous exposure to formaldehyde and ozone were investigated in Wistar rats exposed to 0.3, 1 or 3 ppm [0.4, 1.2 and 3.7 mg/m^3] formaldehyde, 0.2, 0.4 or 0.8 ppm [0.4, 0.8 or 1.6 mg/m^3] ozone or mixtures of 0.4 ppm ozone with 0.3, 1 or 3 ppm formaldehyde or 1 ppm formaldehyde with 0.2, 0.4 or 0.8 ppm ozone (22 h/day, three days). Both formaldehyde (3 ppm) and ozone (0.4 or 0.8 ppm) induced cell proliferation in the most anterior region of the respiratory epithelium. In a slightly more posterior region, ozone had no effect on cell replication, but formaldehyde either enhanced cell proliferation (3 ppm) or appeared to inhibit it slightly (0.3 or 1 ppm). Combined exposures to low concentrations (0.4 ppm ozone and 0.3 ppm formaldehyde, 0.4 or 0.8 ppm ozone and 1 ppm formaldehyde) induced less cell proliferation than ozone alone; however, more than additive increases in cell proliferation were detected in the anterior nose after exposure to 0.4 ppm ozone in combination with 3 ppm formaldehyde, and in a slightly more posterior region after exposure to 0.4 ppm ozone with 1 or 3 ppm formaldehyde. The results suggested to the authors a complex response of the nasal epithelium to low (just nonirritating) concentrations of these irritants but a

Table 21. Cytotoxicity and cell proliferation induced by acute and subacute exposure to formaldehyde

Species	Exposure	Effects	Reference
Fischer 344 rat, male; B6C3F1 mouse, male	0, 0.6, 2.4, 7.4, 18.5 mg/m^3, 6 h/day, 3 days	0.6, 2.4: No increase in cell replication rate in nasal mucosa 7.4: Increased cell turnover (rats only) 18.5: Cell proliferation (rats and mice)	Swenberg *et al.* (1983)
Fischer 334 rat, male; B6C3F1 mouse, male	0, 18.5 mg/m^3, 6 h/day, 1 or 5 days	18.5: Cell proliferation induced in nasal mucosa of both species; rat responses exceeded mouse responses	Chang *et al.* (1983)
Fischer 344 rat, male	3.7 mg/m^3 × 12 h/day, 7.4 mg/m^3 × 6 h/day, 14.4 mg/m^3 × 3 h/day ($C \times t$ = 44 mg/m^3-h/day), 3 or 10 days	Cell proliferation related more closely to concentration than to time; proliferation less after 10 than after 3 days of exposure, indicating adaptation	Swenberg *et al.* (1983)
Fischer 344 rat, male	0, 0.6, 2.4, 7.4, 18.5 mg/m^3, 6 h/day, 1, 2, 4, 9 or 14 days	0.6: No effects on mucociliary function 2.4: Minimal effects 7.4: Moderate inhibition 18.5: Marked inhibition	Morgan *et al.* (1986c)
Fischer 344 rat, male	0, 2.4, 18.5 mg/m^3, 10, 20, 45 or 90 min or 6 h	2.4: No effect on mucociliary function 18.5: Inhibition of mucociliary function, marked recovery 1 h after exposure	Morgan *et al.* (1986b)
Fischer 344 rat, male	0, 0.6, 2.4 mg/m^3, 6 h/day, 1 or 4 days; 7.4 mg/m^3, 6 h/day, 1, 2 or 4 days; 18.5 mg/m^3, 6 h/day, 1 or 2 days	0.6, 2.4: No lesions 7.4, 18.5: Non-cell-specific, dose-related injury, including hypertrophy, nonkeratinized squamous cells, nucleolar segregation	Monteiro-Riviere & Popp (1986)
Wistar rat, male	0, 6.2 mg/m^3 × 8 h/day, 12.3 mg/m^3 × 8 h/day ($C \times t$ = 49 or 98 mg/m^3-h/day); 2.13 mg/m^3 × 8 × 0.5 h/day, 25 mg/m^3 × 8 × 0.5 h/day ($C \times t$ = 49 or 98 mg/m^3-h/day), 5 days/week, 4 weeks	Labelling index increased at all concentrations; cell proliferation more closely related to concentration than to total dose	Wilmer *et al.* (1987)
Wistar rat, male and female	0, 0.37, 1.2, 3.7 mg/m^3, 6 h/day, 3 days	0.37, 1.2: Small increase in cell turnover at 1.2 ppm, but significance not shown and not confirmed in later studies (Reuzel *et al.*, 1990); 3.7: significant, transient increase in cell turnover	Zwart *et al.* (1988)

Table 21 (contd)

Species	Exposure	Effects	Reference
Rhesus monkey, male	0, 7.4 mg/m^3, 6 h/day, 5 days/week, 1 or 6 weeks	Lesions similar to those in rats (Monticello *et al.*, 1991) but more widespread, extending to trachea and major bronchi; increased cell replication in nasal passages, trachea and carina; percentage of nasal surface area affected increased between 1 and 6 weeks	Monticello *et al.* (1989)
Wistar rat, male	0, 0.37, 1.2, 3.7 mg/m^3, 22 h/day, 3 days Also investigated effect of simultaneous exposure to 0.4, 0.8 or 1.6 mg/m^3 ozone	0.37, 1.2: Either no increase or inhibition of cell proliferation 3.7: Increased cell replication 0.8 mg/m^3 ozone + 1.2 or 3.7 mg/m^3 formaldehyde: Synergistic increase in cell turnover 1.6 mg/m^3 ozone + 1.2 mg/m^3 formaldehyde: Inhibition of cell turnover	Reuzel *et al.* (1990)
Fischer 344 rat, male	0, 0.86, 2.4, 7.4, 12.3, 18.5 mg/m^3, 6 h/day, 1, 4, or 9 days or 6 weeks	0.86, 2.4: No effect on cell turnover 7.4, 12.3, 18.5: Concentration- and site-dependent cell proliferation induced at all exposure times	Monticello *et al.* (1991)

C, concentration; *t*, time

synergistic increase in cell proliferation at irritating concentrations. To induce a synergistic effect on cell proliferation, at least one of the compounds must be present at a cytotoxic concentration (Reuzel *et al.*, 1990).

(iv) Enzyme induction

No increase in the activity of formaldehyde or aldehyde dehydrogenase was seen in the nose of Fischer 344 rats exposed to 15 ppm [18.3 mg/m^3] (6 h/day, five days/week, two weeks) (Casanova-Schmitz *et al.*, 1984a). A large increase in the activity of rat pulmonary cytochrome P450 was seen, however, after exposure to 0.5, 3 or 15 ppm formaldehyde [0.6, 3.7 or 18.3 mg/m^3] (6 h/day, four days) (Dallas *et al.*, 1986), although Dinsdale *et al.* (1993), using the same rat strain, could not confirm these results and found no increase in pulmonary cytochrome P450 activity after exposure to 10 ppm [12.2 mg/m^3] formaldehyde (6 h/day, four days).

(b) Chronic effects

(i) Cytotoxicity and cell proliferation in the respiratory tract

The subchronic and chronic effects of formaldehyde in different animal species exposed by inhalation are summarized in Table 22. No increases in cell turnover or DNA synthesis were found in the nasal mucosa after subchronic or chronic exposure to concentrations ≤ 2 ppm [≤ 2.4 mg/m^3] (Rusch *et al.*, 1983; Zwart *et al.*, 1988; Monticello *et al.*, 1993; Casanova *et al.*, 1995). Small, site-specific increases in the rate of cell turnover were noted at 3 ppm [3.7 mg/m^3] (6 h/day, 5 days/week, 13 weeks) in Wistar rats (Zwart *et al.*, 1988) and in the rate of DNA synthesis at 6 ppm [7.3 mg/m^3] (6 h/day, 5 days/week, 12 weeks) in Fischer 344 rats (Casanova *et al.*, 1995). At these concentrations, however, an adaptive response occurs in rat nasal epithelium, as cell turnover rates after six weeks (Monticello *et al.*, 1991) or 13 weeks (Zwart *et al.*, 1988) are lower than those after one to four days of exposure. Monticello *et al.* (1993) detected no increase in cell turnover in the nasal passages of Fischer 344 rats exposed to 6 ppm [7.3 mg/m^3] formaldehyde for three months (6 h/day, 5 days/week), but, as already noted, Casanova *et al.* (1995) detected a small increase in DNA synthesis under these conditions. Large, sustained increases in cell turnover were observed at 10 and 15 ppm [12.2 and 18.3 mg/m^3] (6 h/day, 5 days/week, 3, 6, 12 or 18 months) (Monticello *et al.*, 1993). The effects of subchronic exposure to various concentrations of formaldehyde on DNA synthesis in the rat nose are illustrated in Figure 5.

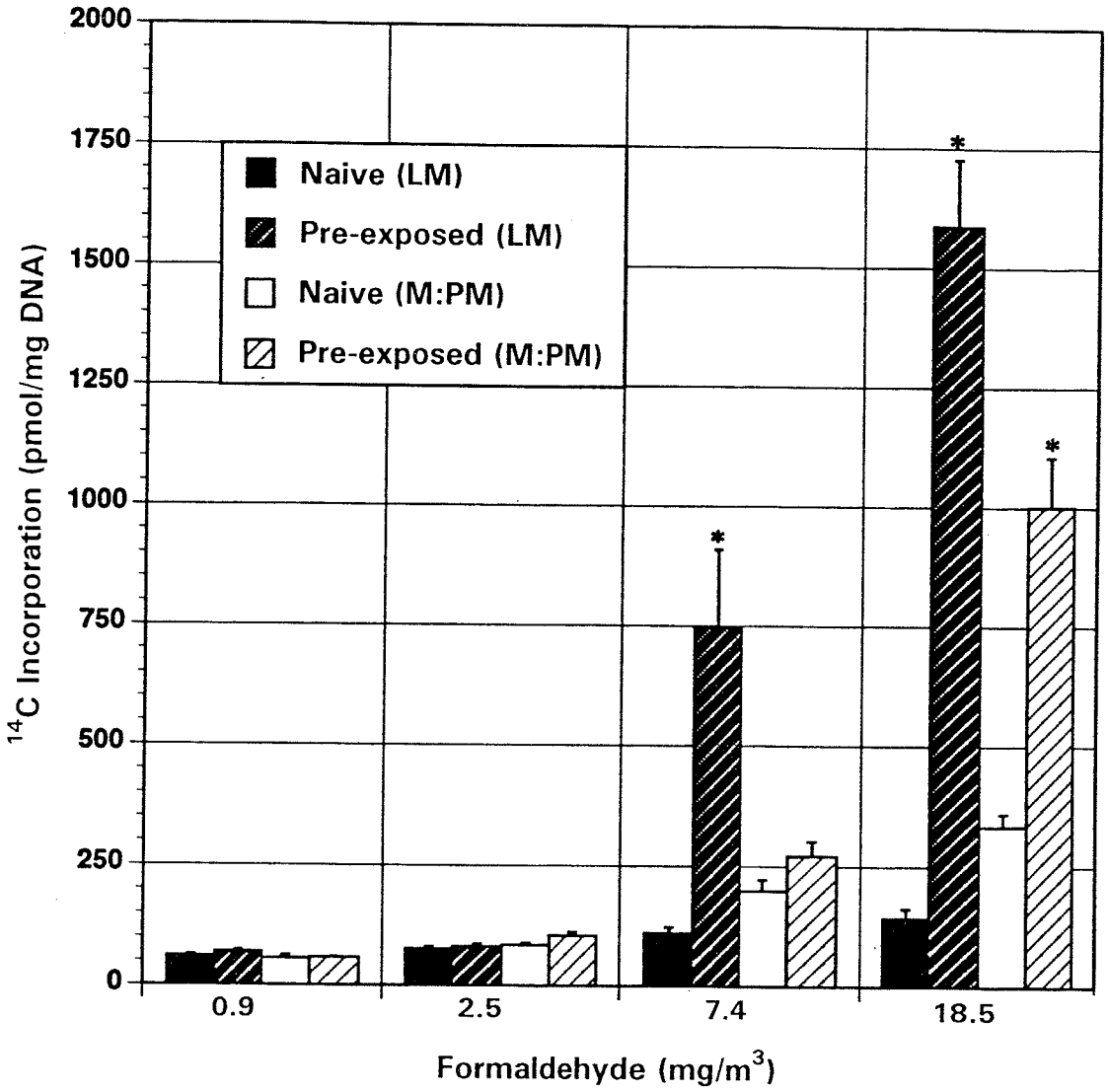
Additional studies have shown the importance of increased cell turnover in the induction of rat nasal tumours (Appelman *et al.*, 1988; Woutersen *et al.*, 1989). The investigators damaged the nasal mucosa of Wistar rats by bilateral intranasal electrocoagulation and evaluated the susceptibility of the rats to formaldehyde at concentrations of 0.1, 1 or 10 ppm [0.1, 1.2 or 12.2 mg/m^3] (6 h/day, 5 days/week, 13 or 52 weeks, 28 months, or three months of exposure followed by a 25-month observation period). In rats with undamaged mucosa, the effects of exposure were seen only at 10 ppm; these effects were limited to degenerative, inflammatory and hyperplastic changes. These noncancerous effects were increased by electrocoagulation. In the group exposed to 10 ppm for 28 months, nasal tumours were induced in 17/58 rats. No compound-related tumours were induced at 0.1 or 1 ppm. It was concluded that the damaged

Table 22. Cytotoxicity and cell proliferation induced by subchronic and chronic exposures to formaldehyde

Species	Exposure	Effects	Reference
Fischer 344 rat, Syrian hamster, male and female; cynomolgus monkey, male	0, 0.25, 1.2, 3.7 mg/m^3, 22 h/day, 7 days/week, 26 weeks	Rats: Squamous metaplasia in nasal turbinates at 3.7 mg/m^3 only Hamsters: No significant toxic response Monkey: Squamous metaplasia in nasal turbinates at 3.7 mg/m^3 only	Rusch *et al.* (1983)
B6C3F1 mouse, male	0, 2.5, 4.9, 12.3, 24.7, 49.2 mg/m^3, 6 h/day, 5 days/week, 13 weeks	2.5, 4.9: No lesion induced 12.3, 24.7, 49.2: Squamous metaplasia, inflammation of nasal passages, trachea and larynx; 80% mortality at 49.2 mg/m^3	Maronpot *et al.* (1986)
Wistar rat, male and female	0, 0.37, 1.2, 3.7 mg/m^3, 6 h/day, 5 days/week, 13 weeks	0.37, 1.2: No increase in cell replication 3.7: Increased cell turnover in nasal epithelium but cell proliferation lower than after 3 days	Zwart *et al.* (1988)
Wistar rat, male and female	0, 1.2, 12.3, 24.7 mg/m^3, 6 h/day, 5 days/week, 13 weeks	1.2: Results inconclusive 12.3, 24.7: Squamous metaplasia, epithelial erosion, cell proliferation in nasal passages and larynx; no hepatotoxicity	Woutersen *et al.* (1987)
Wistar rat, male	0, 0.12, 1.2, 12.3 mg/m^3, 6 h/day, 5 days/week, 13 or 52 weeks Nasal mucosa of some rats injured by bilateral intranasal electrocoagulation to induce cell proliferation	0: Electrocoagulation induced hyperplasia and squamous metaplasia, still visible after 13 weeks but slight after 52 weeks 0.12, 1.2: Focal squamous metaplasia after 13 or 52 weeks; no adverse effects in animals with undamaged nasal mucosa 12.3: Squamous metaplasia and degeneration in respiratory epithelium (both intact and damaged nose) and olfactory epithelium (damaged nose only)	Appelman *et al.* (1988)
Wistar rat, male	0, 1.2 mg/m^3 × 8 h/day, 2.4 mg/m^3 × 8 h/day ($C \times t$ = 9.8 or 19.7 mg/m^3-h/day), 5 days/week, 13 weeks; 2.4 mg/m^3 × 8 × 0.5 h/day, 4.9 mg/m^3 × 8 × 0.5 h/day ($C \times t$ = 9.8 or 19.7 mg/m^3 h/day), 5 days/week, 13 weeks	1.2, 2.5: No observed toxic effect 4.9: Epithelial damage, squamous metaplasia, occasional keratinization; concentration, not total dose, determines severity of toxic effect	Wilmer *et al.* (1989)
Fischer 344 rat, male	0, 0.86, 2.5, 7.4, 12.3, 18.5 mg/m^3, 6 h/day, 5 days/week, 3 months	0.86, 2.5, 7.4: No increase in cell replication detected 12.3, 18.5: Sustained cell proliferation	Monticello *et al.* (1993)
Fischer 334 rat, male	0, 0.86, 2.5, 7.4, 18.5 ppm, 6 h/day, 5 days/week, 12 weeks	0.86, 2.5: DNA synthesis rates in nasal mucosa similar in naive (previously unexposed) and subchronically exposed rats 7.4, 18.5: DNA synthesis rates higher in subchronically exposed than in naive rats, especially at 18.5 mg/m^3	Casanova *et al.* (1995)

C, concentration; *t*, time

Figure 5. Cell turnover in the lateral meatus (LM) and medial and posterior meatuses (M:PM) of pre-exposed and naive (previously unexposed) Fischer 344 rats, as measured by incorporation of ^{14}C derived from inhaled ^{14}C-formaldehyde into nucleic acid bases (deoxyadenosine, deoxyguanosine and thymidine) and thence into DNA, during a single 3-h exposure to 0.7, 2, 6 or 15 ppm [0.86, 2.5, 7.4 or 18.5 mg/m^3]



Reproduced, with permission, from Casanova *et al.* (1995)

Pre-exposed rats were exposed subchronically to the same concentrations of unlabelled formaldehyde (6 h/day, 5 days/week, 11 weeks and four days), while naive rats were exposed to room air. The exposure to ^{14}C-formaldehyde occurred on the fifth day of the twelfth week. The asterisk denotes a significant difference between pre-exposed and naive rats.

mucosa was more susceptible to the cytotoxic effects of formaldehyde and that severe damage contributes to the induction of nasal tumours.

Rhesus monkeys exposed to 6 ppm [7.3 mg/m^3] formaldehyde (6 h/day, 5 days/week) had a larger percentage of the nasal mucosal surface area affected after six weeks than after five days. Cell proliferation was detected in the nasal passages, larynx, trachea and carina, but the effects in the lower airways were minimal in comparison with the effects in the nasal passages (Monticello *et al.*, 1989). Other studies showed that Fischer 344 rats exposed to 1 ppm [1.2 mg/m^3] (22 h/day, 7 days/week, 26 weeks) developed no detectable nasal lesions (Rusch *et al.*, 1983), but Fischer 344 rats exposed to 2 ppm [2.4 mg/m^3] (6 h/day, 5 days/week, 24 months) developed mild squamous metaplasia in the nasal turbinates (Kerns *et al.*, 1983b). Although the total dose received by the former group was 2.5 times higher than that received by the latter, the incidence and severity of lesions was less, again demonstrating the greater importance of concentration than total dose (Rusch *et al.*, 1983).

(ii) Toxicity in the gastrointestinal tract after oral administration

The toxic effects of formaldehyde given by oral administration have been reviewed (Restani & Galli, 1991).

Formaldehyde was administered orally to rats and dogs at daily doses of 50, 100 or 150 mg/kg bw (rats) or 50, 75 or 100 mg/kg bw (dogs) for 91 consecutive days. Significant changes in body weight were observed at the higher doses, but clinical and pathological studies revealed no specific treatment-related effects on the kidney, liver or lung, which were considered possible target organs, or on the gastrointestinal mucosa (Johannsen *et al.*, 1986).

Formaldehyde was administered in the drinking-water to male and female Wistar rats for up to two years. In the chronic portion of the study, the mean daily doses of formaldehyde were 1.2, 15 or 82 mg/kg bw (males) and 1.8, 21 or 109 mg/kg bw (females). Controls received drinking-water either *ad libitum* or in an amount equal to that consumed by the highest-dose group, which had a marked decrease in water consumption. Pathological changes after two years were essentially restricted to the highest-dose group and consisted of a thickened and raised limiting ridge of the forestomach and gastritis and hyperplasia of the glandular stomach. The no-adverse-effect level was estimated to be 82 mg/kg bw per day (males) or 109 mg/kg bw per day (females) (Til *et al.*, 1988, 1989).

In another experiment in which formaldehyde was administered in the drinking-water to male and female Wistar rats, fixed concentrations (0, 0.02, 0.1 and 0.5%) were given for up to two years. Estimated from the water intake, these concentrations corresponded, on average, to 0, 10, 50 and 300 mg/kg bw per day. All rats that received the highest dose died during the study. The lesions induced in the stomach were similar to those reported by Til *et al.* (1988, 1989). No treatment-related tumour was found. The no-effect level was estimated to be 0.02% (10 mg/kg bw per day), as forestomach hyperkeratosis was observed in a small number of rats (2/14) receiving 0.1% formaldehyde (50 mg/kg bw per day) (Tobe *et al.*, 1989).

(c) Immunotoxicity

The possibility that formaldehyde may induce changes in the immune response was examined in B6C3F1 mice exposed to 15 ppm [18.3 mg/m^3] formaldehyde (6 h/day, 5 days/week, 3 weeks). A variety of immune function tests revealed no significant changes, except for an increase in host resistance to challenge with the bacterium, *Listeria monocytogenes*, implying an increased resistance to infection. Exposure did not alter the number or impair the function of resident peritoneal macrophages, but it increased the competence for release of hydrogen peroxide from peritoneal macrophages (Dean *et al.*, 1984; Adams *et al.*, 1987).

Sprague–Dawley rats were exposed to 12.6 ppm [15.4 mg/m^3] formaldehyde (6 h/day, 5 days/week, 22 months) and then vaccinated with pneumococcal polysaccharide antigens and tetanus toxoid. They were tested three to four weeks later for the development of antibodies. An IgG response to pneumococcal polysaccharides and to tetanus toxoid and an IgM response to tetanus toxoid were found in both exposed and control groups. No evidence was obtained that long-term exposure to a high concentration of formaldehyde impairs B-cell function, as measured by antibody production (Holmström *et al.*, 1989c).

In order to investigate the induction of sensitivity to formaldehyde, undiluted formalin was painted on shaven and epilated dorsal sites on guinea-pigs; a second application was administered two days later at naive sites, to give a total dose of 74 mg/animal. Other animals received diluted formalin at doses of 12–9.3 mg/animal. All animals receiving 74 mg developed skin sensitivity when tested seven days after exposure. A significant dose–response relationship was observed for degree of sensitization and for percentage of animals sensitized; however, pulmonary sensitivity was not induced when formaldehyde was administered dermally, by injection or by inhalation, and no cytophilic antibodies were detected in blood (Lee *et al.*, 1984).

4.3 Reproductive and developmental effects

4.3.1 Humans

The incidence of spontaneous abortion was studied among hospital staff in Finland who used ethylene oxide (see IARC, 1994b), glutaraldehyde and formaldehyde for sterilizing instruments. Potentially exposed women were identified in 1980 with the help of supervising nurses at all of the approximately 80 general hospitals of the country, and an equal number of control women were selected by the supervising nurse from among nursing auxiliaries in the same hospitals who had no exposure to sterilizing agents, anaesthetic gases or X-rays. Study subjects were administered a postal questionnaire which requested personal data and information on smoking habits, intake of alcohol, reproductive history, including number of pregnancies and their outcome, and occupation at the time of each pregnancy. Information about exposure to chemical sterilizing agents was obtained from the supervising nurses. The crude rates of spontaneous abortions were 16.7% for sterilizing staff who were considered to have been exposed during the first trimester of pregnancy, 6.0% for sterilizing staff who left employment when they learnt they were pregnant (the difference being significant) and 10.6% among controls. When adjusted for age, parity, decade of pregnancy, smoking habits and alcohol and

coffee consumption, the rate associated with exposure to ethylene oxide, with or without other agents, was 12.7%, which was significantly increased ($p < 0.05$), and that associated with formaldehyde, with or without other agents, was 8.4%, which was comparable to the reference level of 10.5% (Hemminki *et al.*, 1982).

In a nationwide record linkage study in Finland, all nurses who had been pregnant between the years 1973 and 1979 and who had worked in anaesthesia, surgery, intensive care, operating rooms or internal departments of a general hospital (and in paediatric, gynaecological, cancer and lung departments for the part of the study concerned with malformations) were identified. Each of the 217 women treated for spontaneous abortion according to the files of the Finnish hospital discharge register and the 46 women notified to the Register of Congenital Malformations was individually matched on age and hospital with three control women, who were selected at random from the same population of nurses and matched for age and hospital where they were employed. Information was obtained from supervising nurses by postal questionnaires on the exposure of cases and controls to sterilizing agents (ethylene oxide, glutaraldehyde and formaldehyde), anaesthetic gases, disinfectant soaps, cytostatic drugs and X-radiation. Exposure to formaldehyde during pregnancy was reported for 3.7% of the nurses who were later treated for spontaneous abortion and for 5.2% of their controls, yielding a crude odds ratio of 0.7 [95% CI, 0.28–1.7]. Exposure to formaldehyde was also reported for 8.8% of nurses who gave birth to a malformed child and to 5.3% matched controls, to give an odds ratio of 1.7 [95% CI, 0.39–7.7]; the latter analysis was based on eight exposed subjects (Hemminki *et al.*, 1985).

The occurrence of spontaneous abortions among women working in laboratories in Finland and congenital malformations and birth weights of the children were investigated in a matched retrospective case–control study. The final population in the study of spontaneous abortion was 206 cases and 329 controls; that in the study of congenital malformations was 36 cases and 105 controls. Information on occupational exposure, health status, medication, contraception, smoking and alcohol consumption during the first trimester of the pregnancy was collected by postal questionnaire. The odds ratio for spontaneous abortion was increased among women who had been exposed to formalin for at least three days per week (odds ratio, 3.5; 95% CI, 1.1–11). A greater proportion of the cases (8/10) than the controls (4/7) who had been exposed to formalin had been employed in pathology and histology laboratories. Most of the cases (8/10) and controls (5/7) who were exposed to formalin were also exposed to xylene (see IARC, 1989c). The authors stated that the results for individual chemicals should be interpreted cautiously because laboratory personnel are often exposed to several solvents and other chemicals simultaneously. No association was observed between exposure to formalin and congenital malformations [data not shown] (Taskinen *et al.*, 1994).

4.3.2 Experimental systems

The reproductive and developmental toxicity of formaldehyde has been reviewed (Feinman, 1988; WHO, 1989).

Whether administered by inhalation, ingestion or the skin to various rodent species, formaldehyde did not exert adverse effects on reproductive parameters or fetal development (Marks *et al.*, 1980; Feinman, 1988). Additional studies have confirmed this assessment. Groups

of 25 pregnant Sprague–Dawley rats were exposed to formaldehyde (0, 5, 10, 20 or 40 ppm [0, 6, 12, 24 or 49 mg/m^3]; 6 h/day, days 6–20 of gestation). On day 21, the rats were killed and maternal and fetal parameters were evaluated. The authors concluded that formaldehyde was neither embryolethal nor teratogenic when given under these conditions. The mean fetal body weight at 20 ppm was 5% less than that of controls ($p < 0.05$) in males but was not reduced in females; at 40 ppm, mean fetal body weight was about 20% less than that in controls ($p < 0.01$) in both males and females. The decrease in fetal weight in the group given the high dose was attributable to maternal toxicity (Saillenfait *et al.*, 1989).

Groups of 25 mated female Sprague–Dawley rats were exposed to formaldehyde at 2, 5 or 10 ppm [2.5, 6 or 12 mg/m^3] (6 h/day) on days 6–15 of gestation. At 10 ppm, there was a significant decrease in maternal food consumption and weight gain. None of the parameters of pregnancy, including numbers of corpora lutea, implantation sites, live fetuses, dead fetuses and resorptions, or fetal weights were affected by treatment (Martin, 1990).

Formaldehyde was applied topically to pregnant Syrian hamsters on day 8, 9, 10 or 11 of gestation by clipping the hair on the dorsal body and applying 0.5 ml formalin (37% formaldehyde) with a syringe directly onto the skin. In order to prevent grooming, the animals were anaesthetized with nembutal (13 mg intraperitoneally) during the 2-h treatment. On day 15, fetuses were removed from four to six hamsters per group and examined. The number of resorptions was increased, but no teratogenic effects or effects on fetal weight or length were detected. The authors suggested that the increase in resorptions may have been caused by stress (Overman, 1985).

4.4 Genetic and related effects

The mutagenicity of formaldehyde has been reviewed (IARC, 1982, 1987d; Ma & Harris, 1988; WHO, 1989; Feron *et al.*, 1991).

4.4.1 Humans

(a) DNA–protein cross-links

No data were available to the Working Group.

(b) Mutation and allied effects

The effects of formaldehyde on the frequencies of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes of people occupationally exposed to formaldehyde were reviewed previously (IARC, 1987d). Both positive and negative results were obtained, but their interpretation was difficult because of the small number of subjects studied and inconsistencies in the findings. Since then, further data on the cytogenetic effects of formaldehyde in humans have been published.

In a study of workers exposed to formaldehyde in a factory manufacturing wood-splinter materials, short-term cultures of peripheral lymphocytes were examined from a group of 20 workers aged 27–57 (mean, 42.3 years), of whom 10 were men and 10 were women. They had been exposed to formaldehyde at 8-h time-weighted concentrations of 0.55–10.36 mg/m^3 for

periods of 5–≥ 16 years. The control group consisted of 19 people [sex and age unspecified] employed in the same plant whose habits and social status were similar to those of the exposed group but who had unknown occupational contact with chemicals. No significant difference was observed between control and exposed groups with respect to any of the chromosomal anomalies (including chromatid and chromosome gaps, breaks, exchanges, breaks per cell, percentage of cells with aberrations) scored in the study (controls: 3.6% aberrant cells, 0.08 breaks per cell; exposed: 3.08% aberrant cells, 0.045 breaks per cell). The authors noted that the frequency of aberrations in the control group was higher than that seen in the general population (1.2–2% aberrant cells) (Vargová *et al.*, 1992). [The Working Group noted that, although the text states that there were 20 people in the exposed group, Table II of the paper gives a figure of 25. The Group also noted the lack of detail on the smoking habits of the subjects.]

In the study of Ballarin *et al.* (1992), described on p. 306, the frequency of micronuclei in respiratory nasal mucosa cells was also investigated. At least 6000 cells from each individual were scored for micronuclei. A significant excess of micronucleated cells was seen in the exposed group (mean percentage of micronucleated cells, 0.90 ± 0.47; range, 0.17–1.83 in exposed group; 0.25 ± 0.22; range, 0.0–0.66 in controls; Mann–Whitney U test: $p < 0.01$). The authors noted the absence of a dose–response relationship between exposure to formaldehyde and the frequency of micronuclei and that concurrent exposure to wood dust could have contributed to the excess of micronucleated cells seen in the exposed group.

In a prospective study of the effect of formaldehyde on the frequency of micronuclei in oral and nasal mucosal cells and peripheral lymphocytes from a group of 29 student morticians, samples of blood and epithelial cells were taken before the students started the course (baseline samples) and again after the first nine weeks in an embalming laboratory. During the 85-day study period, the subjects had average cumulative formaldehyde exposures of 14.8 ppm-h [17.8 mg/m^3-h], with an average air concentration of 1.4 ppm [1.7 mg/m^3]. Epithelial cells were taken with a cytopathology brush from each inner cheek and from the inferior turbinate of each nostril. Weakly positive results were found in lymphocytes, positive results in buccal epithelium and negative results in nasal epithelium (Suruda *et al.*, 1993). [The Working Group noted the inadequate reporting of the data in this study and was unable to evaluate it.]

(c) Sperm abnormalities

Eleven hospital autopsy service workers and 11 matched controls were evaluated for sperm count, abnormal sperm morphology and the frequency of one or two fluorescent bodies. Subjects were matched for sex, age and use of alcohol, tobacco and marijuana; additional information was collected on health, medications and other exposure to toxins. Exposed and control subjects were sampled three times at two- to three-month intervals. Ten exposed subjects had been employed for 4.3 months (range, 1–11 months) before the first sample was taken, and one had been employed for several years. Exposure to formaldehyde was intermittent, with a time-weighted average of 0.61–1.32 ppm [0.73–1.58 mg/m^3] (weekly exposure, 3–40 ppm-h [3.6–48 mg/m^3-h]). No significant difference was observed between the exposed and control groups with regard to sperm parameters (Ward *et al.*, 1984).

(d) Urinary mutagenicity

Hospital autopsy service workers in Galveston, TX (United States), consisting of 15 men and four women aged < 30–> 50, and a control group from the local medical school, consisting of 15 men and five women in the same age range and matched for consumption of tobacco, marijuana, alcohol and coffee, were studied for urinary mutagenicity (Connor *et al.*, 1985). Individuals were sampled three times at approximately two-month intervals. The time-weighted average exposures to formaldehyde in the work areas were estimated to be 0.61–1.32 ppm [0.73–1.58 mg/m^3]. Urine (150–200 ml from each subject) was treated with β-glucuronidase and passed through an XAD-2 column, which was then washed with water. The fraction that eluted with acetone was assayed for mutagenicity in *Salmonella typhimurium* TA98 and TA100 in the presence and absence of an exogenous metabolic activation system from livers of Aroclor-1254-induced rats. No increase in mutagenicity was seen in the autopsy workers as compared with the control group.

4.4.2 Experimental systems

(a) DNA–protein cross-links

Formaldehyde induces DNA–protein cross-links in mammalian cells *in vitro* and *in vivo* (see Table 23). The precise nature of these cross-links is unknown. Studies of the repair of DNA–protein cross-links caused by formaldehyde *in vitro* showed that they are removed from several types of normal cells and xeroderma pigmentosum cells, with a half-time of 2–3 h. These removal rates were similar at non-toxic and toxic concentrations of formaldehyde. In formaldehyde-exposed normal cells, active removal of DNA adducts by DNA excision repair was indicated by formation of DNA single-strand breaks, which could be accumulated in the presence of DNA repair synthesis inhibitors (Grafström *et al.*, 1984).

Groups of four male Fischer 344 rats were exposed for 6 h to 0.3, 0.7, 2, 6 or 10 ppm [0.4, 0.9, 2.4, 7.3 or 12.2 mg/m^3] ^{14}C-formaldehyde in a nose-only inhalation chamber. Individual male rhesus monkeys (*Macaca mulatta)* were exposed for 6 h to 0.7, 2 or 6 ppm ^{14}C-formaldehyde in a mouth-only inhalation chamber. DNA–protein cross-links induced by exposure to formaldehyde were measured in the nasal mucosa of several regions of the upper respiratory tract of exposed animals. The concentration of cross-links increased non-linearly with the airborne concentration in both species. The concentrations of cross-links in the turbinates and anterior nasal mucosa were significantly lower in monkeys than in rats. Cross-links were also formed in the nasopharynx and trachea of monkeys, but they were not detected in the sinus, proximal lung or bone marrow. The authors suggested that the differences between the species with respect to DNA–protein cross-link formation may be due to differences in nasal cavity deposition and in the elimination of absorbed formaldehyde (Heck *et al.*, 1989; Casanova *et al.*, 1991).

(b) Mutation and allied effects (see also Table 23 and Appendices 1 and 2*)*

Formaldehyde induced mutation and DNA damage in bacteria and mutation, gene conversion, DNA strand breaks and DNA–protein cross-links in fungi. In *Drosophila*

Table 23. Genetic and related effects of formaldehyde

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
*	Misincorporation of DNA bases into synthetic polynucleotides *in vitro*	+	0	30	Snyder & Van Houten (1986)
PRB	Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	0	0.0075	Kuykendall & Bogdanffy (1992)
PRB	Prophage induction, SOS repair test, DNA strand breaks, cross-links or related damage	+	0	20	Le Curieux *et al.* (1993)
ECB	*Escherichia coli* (or *E. coli* DNA) strand breaks, cross-links or related damage; DNA repair	+	0	600	Wilkins & MacLeod (1976)
ECB	*Escherichia coli* (or *E. coli* DNA) strand breaks, cross-links or related damage; DNA repair	+	0	60	Poverenny *et al.* (1975)
ECD	*Escherichia coli polA*/W31110-P3478, differential toxicity (spot test)	+	0	10	Leifer *et al.* (1981)
ECL	*Escherichia coli* K12 KS160-KS66 *pol*AI, differential toxicity	+	0	60	Poverenny *et al.* (1975)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	0	60	Zijlstra (1989)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	0	18.8	Graves *et al.* (1994)
ECK	*Escherichia coli* K12, forward or reverse mutation	+	0	120	Crosby *et al.* (1988)
SAF	*Salmonella typhimurium*, forward mutation	+	+	10	Temcharoen & Thilly (1983)
SA0	*Salmonella typhimurium* TA100, reverse mutation	(+)	0	25	Marnett *et al.* (1985)
SA0	*Salmonella typhimurium* TA100, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA0	*Salmonella typhimurium* TA100, reverse mutation	-	+	16.6	Haworth *et al.* (1983)
SA0	*Salmonella typhimurium* TA100, reverse mutation	(+)	+	30 (toxic above 125 µg/plate)	Connor *et al.* (1983)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	0	7.5	Takahashi *et al.* (1985)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	+[c]	4.5	Pool *et al.* (1984)
SA0	*Salmonella typhimurium* TA100, reverse mutation	+	0	9.3	O'Donovan & Mee (1993)
SA0	*Salmonella typhimurium* TA100, reverse mutation	(+)	+	3	Schmid *et al.* (1986)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	10	Marnett *et al.* (1985)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	10	Le Curieux *et al.* (1993)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	35.7	O'Donovan & Mee (1993)
SA4	*Salmonella typhimurium* TA104, reverse mutation	+	0	10	Marnett *et al.* (1985)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	-	-	50	Haworth *et al.* (1983)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	0	-[c]	9	Pool *et al.* (1984)

Table 23 (contd)

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
SA5	*Salmonella typhimurium* TA1535, reverse mutation	-	0	143	O'Donovan & Mee (1993)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	-	-	50	Haworth *et al.* (1983)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	-	0	143	O'Donovan & Mee (1993)
SA8	*Salmonella typhimurium* TA1538, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA8	*Salmonella typhimurium* TA1538, reverse mutation	-	0	143	O'Donovan & Mee (1993)
SA9	*Salmonella typhimurium* TA98, reverse mutation	+	0	5	Marnett *et al.* (1985)
SA9	*Salmonella typhimurium* TA98, reverse mutation	-	-	30	Gocke *et al.* (1981)
SA9	*Salmonella typhimurium* TA98, reverse mutation	-	(+)	16.6	Haworth *et al.* (1983)
SA9	*Salmonella typhimurium* TA98, reverse mutation	-	(+)	30 (toxic above 100 µg/plate)	Connor *et al.* (1983)
SA9	*Salmonella typhimurium* TA98, reverse mutation	0	(+)[c]	3	Pool *et al.* (1984)
SA9	*Salmonella typhimurium* TA98, reverse mutation	+	0	17.9	O'Donovan & Mee (1993)
SAS	*Salmonella typhimurium* TA97, reverse mutation	+	0	5	Marnett *et al.* (1985)
SAS	*Salmonella typhimurium* (other miscellaneous strains), reverse mutation	-	-	100 (toxic at 250 µg/ml)	Connor *et al.* (1983)
ECW	*Escherichia coli* WP2 *uvr*A, reverse mutation	+	0	15	Takahashi *et al.* (1985)
ECW	*Escherichia coli* WP2 *uvr*A(pKM101), reverse mutation	+	0	17.9	O'Donovan & Mee (1993)
EC2	*Escherichia coli* WP2, reverse mutation	+	0	1.2	Nishioka (1973)
EC2	*Escherichia coli* WP2(pKM101), reverse mutation	+	0	35.7	O'Donovan & Mee (1993)
EC2	*Escherichia coli* WP2, reverse mutation	+	0	60	Takahashi *et al.* (1985)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	900	Panfilova *et al.* (1966)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	80	Demerec *et al.* (1951)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	30	Takahashi *et al.* (1985)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	990	Magaña-Schwencke *et al.* (1978)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	500	Magaña-Schwencke & Ekert (1978)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	500	Magaña-Schwencke & Moustacchi (1980)
SCH	*Saccharomyces cerevisiae*, gene conversion	+	0	540	Chanet *et al.* (1975)
SCH	*Saccharomyces cerevisiae*, homozygosis by mitotic recombination or gene conversion	+	0	18.5	Zimmermann & Mohr (1992)

Table 23 (contd)

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
NCF	*Neurospora crassa*, forward mutation	+	0	100	de Serres *et al.* (1988)
NCR	*Neurospora crassa*, reverse mutation	-	0	732	Dickey *et al.* (1949)
NCR	*Neurospora crassa*, reverse mutation	+	0	37 500	Jensen *et al.* (1952)
NCR	*Neurospora crassa*, reverse mutation	-	0	300	Kölmark & Westergaard (1953)
PLM	Plants (other), mutation	+	0	0.0	Auerbach *et al.* (1977)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		2700	Ratnayake (1970)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		420	Alderson (1967)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		1260	Sobels & van Steenis (1957)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		420	Alderson (1967)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		1940	Ratnayake (1968)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		2380	Ratnayake (1970)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1940	Auerbach & Moser (1953)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1080	Kaplan (1948)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		420	Khan (1967)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		270	Stumm-Tegethoff (1969)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1260	Sobels & van Steenis (1957
DMH	*Drosophila melanogaster*, heritable translocation	+		2700	Ratnayake (1970)
DMH	*Drosophila melanogaster*, heritable translocation	+		420	Khan(1967)
DML	*Drosophila melanogaster*, dominant lethal mutation	+		1940	Auerbach & Moser (1953)
DML	*Drosophila melanogaster*, dominant lethal mutation	+		1400	Šrám (1970)
*	*Caenorhabditis elegans*, recessive lethal mutations	+		700	Johnsen & Baillie (1988)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	6	Ross & Shipley (1980)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	3.75	Ross *et al.* (1981)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	22.5	Demkowicz-Dobrzanski & Castonguay (1992)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	7.5	O'Connor & Fox (1987)
G9H	Gene mutation, Chinese hamster V79 cells, *hprt* locus	+	0	9	Grafström *et al.* (1993)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	0	1	Obe & Beek (1979)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	3.2	Natarajan *et al.* (1983)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	1.8	Basler *et al.* (1985)
CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*	+	+	6.5	Natarajan *et al.* (1983)
CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*	+	0	18	Ishidate *et al.* (1981)

Table 23 (contd)

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
TCM	Cell transformation, C3H10T1/2 mouse cells	+[d]	0	0.5	Ragan & Boreiko (1981)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	24	Fornace *et al.* (1982)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	1.5	Craft *et al.* (1987)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Grafström *et al.* (1986)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Snyder & Van Houten (1986)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Saladino *et al.* (1985)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Grafström *et al.* (1984)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	12	Grafström (1990)
UIH	Unscheduled DNA synthesis, human bronchial epithelial cells *in vitro*	-	0	3 (> 0.1 mmol/L was lethal)	Doolittle *et al.* (1985)
GIH	Gene mutation, human cells *in vitro*	+	0	3	Grafström *et al.* (1985)
GIH	Gene mutation, human cells *in vitro*	+	0	3.9	Goldmacher & Thilly (1983)
GIH	Gene mutation, human cells *in vitro*	+	0	0.9	Craft *et al.* (1987)
GIH	Gene mutation, human cells *in vitro*	+	0	4.5	Crosby *et al.* (1988)
GIH	Gene mutation, human cells *in vitro*	+	0	4.5	Liber *et al.* (1989)
GIH	Gene mutation, human cells *in vitro*	+	0	3	Grafström (1990)
RIH	DNA repair exclusive of unscheduled DNA synthesis, human cells *in vitro*	+	0	6	Grafström *et al.* (1984)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	0	5.4	Obe & Beek (1979)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	0	5	Kreiger & Garry (1983)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	+	3.75	Schmid *et al.* (1986)
CHF	Chromosomal aberrations, human fibroblasts *in vitro*	+	0	60	Levy *et al.* (1983)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	0	10	Miretskaya & Shvartsman (1982)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	+	7.5	Schmid *et al.* (1986)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	0	3.75	Dresp & Bauchinger (1988)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		1.5 inhal. 6 h	Casanova-Schmitz *et al.* (1984b)
DVA	DNA–protein cross-links, rat cells *in vivo*	(+)		1.5 inhal. 6 h	Lam *et al.* (1985)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0.25 inhal. 3 h	Heck *et al.* (1986)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0.25 inhal. 3 h	Casanova & Heck (1987)
DVA	DNA–protein cross-links, rat cells *in vivo*	+		0.08 inhal. 6 h	Casanova *et al.* (1989)
DVA	DNA–protein cross-links, rhesus monkey nasal turbinate cells *in vivo*	+		0.05 inhal. 6 h	Heck *et al.* (1989)

Table 23 (contd)

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
DVA	DNA–protein cross-links, rhesus monkey nasal turbinate cells *in vivo*	+		0.05 inhal. 6 h	Casanova *et al.* (1991)
*	DNA–protein cross-links, rat tracheal implant cells *in vivo*	+		2 mg/ml instil.	Cosma *et al.* (1988)
SVA	Sister chromatid exchange, rat cells *in vivo*	-		3.9 inhal. 6 h/d × 5	Kligerman *et al.* (1984)
*	Micronucleus induction, newt (*Pleurodeles waltl*) *in vivo*	-		5 µg/ml, 12 d	Siboulet *et al.* (1984)
MVM	Micronucleus induction, mouse *in vivo*	-		25 ip × 1	Natarajan *et al.* (1983)
MVM	Micronucleus induction, mouse *in vivo*	-		30 ip × 1	Gocke *et al.* (1981)
MVR	Micronucleus induction, rat (gastrointestinal tract) *in vivo*	+		200 po × 1	Migliore *et al.* (1989)
CBA	Chromosomal aberrations, mouse bone-marrow cells *in vivo*	-		25 ip × 1	Natarajan *et al.* (1983)
CBA	Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		0.07 inhal. 4 h/d, 4 months	Kitaeva *et al.* (1990)
CBA	Chromosomal aberrations, rat bone-marrow cells *in vivo*	-		3.9 inhal. 6 h/d × 5, 8 weeks	Dallas *et al.* (1992)
CLA	Chromosomal aberrations, rat leukocytes *in vivo*	-		3.9 inhal. 6 h/d × 5	Kligerman *et al.* (1984)
CCC	Chromosomal aberrations, mouse spermatocytes treated *in vivo*, spermatocytes observed	-		50 ip × 1	Fontignie-Houbrechts (1981)
CVA	Chromosomal aberrations, mouse spleen cells *in vivo*	-		25 ip × 1	Natarajan *et al.* (1983)
CVA	Chromosomal aberrations, rat pulmonary lavage cells *in vivo*	+		3.9 inhal. 6 h/d × 5	Dallas *et al.* (1992)
GVA	Gene mutation, rat cells *in vivo* (*p53* point mutations in nasal carcinomas)	+		3.9 inhal. 6 h/d, 2 years	Recio *et al.* (1992)
MST	Mouse spot test	-		3.9 inhal. 6 h/d × 3	Jensen & Cohr (1983) [Abstract]
DLM	Dominant lethal mutation, mouse	(+)		50 ip × 1	Fontignie-Houbrechts (1981)
DLM	Dominant lethal mutation, mouse	-		20 ip × 1	Epstein *et al.* (1972)
DLR	Dominant lethal mutation, rat	(+)		0.2 inhal. 4 h/d × 120	Kitaeva *et al.* (1990)
DLM	Dominant lethal mutation, mouse	-		20 ip × 1	Epstein & Shafner (1968)
MVH	Micronucleus formation, human lymphocytes *in vivo*	(+)		0.06[e] inhal. 8-h TWA	Suruda *et al.* (1993)
MVH	Micronucleus formation, human cells (buccal epithelium) *in vivo*	+		0.06[e] inhal. 8-h TWA	Suruda *et al.* (1993)
MVH	Micronucleus formation, human cells (nasal epithelium) *in vivo*	-		0.06[e] inhal. 8-h TWA	Suruda *et al.* (1993)
MVH	Micronucleus formation, human cells (nasal epithelium) *in vivo*	+		0.06[e] inhal. 8-h TWA	Ballarin *et al.* (1992)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	-		0.5 inhal. 8-h TWA	Thomson *et al.* (1984)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	-		0.5 inhal. 8-h TWA	Bauchinger & Schmid (1985)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	+		0.2 inhal. 8-h TWA	Yager *et al.* (1986)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	-		0.06[e] inhal. 8-h TWA	Suruda *et al.* (1993)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	-		0.5 inhal. 8-h TWA	Thomson *et al.* (1984)

Table 23 (contd)

Test system		Result[a]		Dose[b] (LED/HID)	Reference
		Without exogenous metabolic system	With exogenous metabolic system		
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	-		0.8 inhal. 8-h TWA	Fleig *et al.* (1982)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	+		0.5 inhal. 8-h TWA	Bauchinger & Schmid (1985)
CLH	Chromosomal aberrations, human lymphocytes *in vivo*	-		0.4 inhal.	Vargová *et al.* (1992)
SPR	Sperm morphology, rats *in vivo*	+		200 po × 1	Cassidy *et al.* (1983)
SPM	Sperm morphology, mice *in vivo*	-		100 po × 5	Ward *et al.* (1984)
SPH	Sperm morphology, humans *in vivo*	-		0.2 inhal. 8-h TWA	Ward *et al.* (1984)

*Not on profile

[a] +, positive; (+) weak positive; -, negative; 0, not tested; ?, inconclusive (variable response in several experiments within an adequate study)

[b] In-vitro tests, µg/ml; in-vivo tests, mg/kg bw

[c] Tested with S9 without co-factors

[d] Positive only in presence of 12-*O*-tetradecanoylphorbol 13-acetate (TPA)

[e] Based on a mean 8-h time-weighted average of 0.33 ppm (range, 0.1–0.96 ppm); peak exposures up to 6.6 ppm

melanogaster, administration of formaldehyde in the diet induced sex-linked recessive lethal mutations, dominant lethal effects, heritable translocations and crossing-over in spermatogonia. In a single study, it induced recessive lethal mutations in a nematode. It induced chromosomal aberrations, sister chromatid exchange, DNA strand breaks and DNA–protein cross-links in animal cells and, in single studies, gene mutation in Chinese hamster V79 cells and transformation of mouse C3H10T1/2 cells *in vitro*. It induced DNA–protein cross-links, chromosomal aberrations, sister chromatid exchange and gene mutation in human cells *in vitro*. Experiments in human and Chinese hamster lung cells indicate that formaldehyde can inhibit repair of DNA lesions caused by the agent itself or by other mutagens (Grafström, 1990; Grafström *et al.*, 1993).

While there is conflicting evidence that formaldehyde can induce chromosomal anomalies in the bone marrow of rodents exposed by inhalation *in vivo*, recent studies have shown that it induces cytogenetic damage in the cells of tissues that are more locally exposed, either by gavage or by inhalation. Thus, groups of five male Sprague–Dawley rats were given 200 mg/kg bw formaldehyde orally, were killed 16, 24 or 30 h after treatment and were examined for the induction of micronuclei and nuclear anomalies in cells of the gastrointestinal epithelium. The frequency of mitotic figures was used as an index of cell proliferation. Treated rats had significant (greater than five fold) increases in the frequency of micronucleated cells in the stomach, duodenum, ileum and colon; the stomach was the most sensitive, with a 20-fold increase in the frequency of micronucleated cells 30 h after treatment, and the colon the least sensitive. The frequency of nuclear anomalies was also significantly increased at these sites. These effects were observed in conjunction with signs of severe local irritation (Migliore *et al.*, 1989).

In the second experiment, male Sprague–Dawley rats were exposed to 0, 0.5, 3 or 15 ppm [0, 0.62, 3.7 or 18.5 mg/m^3] formaldehyde for 6 h per day on five days per week, for one and eight weeks. There was no significant increase in chromosomal abnormalities in the bone-marrow cells of formaldehyde-exposed rats relative to controls, but there was a significant increase in the frequency of chromosomal aberrations in pulmonary lavage cells (lung alveolar macrophages) from rats that inhaled 15 ppm formaldehyde. Aberrations, which were predominantly chromatid breaks, were seen in 7.6 and 9.2% of the scored pulmonary lavage cells from treated animals and in 3.5 and 4.8% of cells from controls, after one and eight weeks, respectively (Dallas *et al.*, 1992).

Assays for dominant lethal mutations in rodents *in vivo* gave inconclusive results. In single studies, formaldehyde induced sperm-head anomalies in rats but not in mice.

(c) Mutational spectra

The spectrum of mutations induced by formaldehyde was studied in human lymphoblasts *in vitro*, in *Escherichia coli* and in naked pSV2gpt plasmid DNA (Crosby *et al.*, 1988). Thirty TK6 X-linked *hprt*$^-$ human lymphoblast colonies induced by eight treatments with 150 μmol/L formaldehyde were characterized by Southern blot analysis. Fourteen (47%) of these mutants had visible deletions of some or all of the X-linked *hprt* bands, indicating that formaldehyde can induce large losses of DNA in human TK6 lymphoblasts. The remainder of the mutants showed normal restriction patterns, which, according to the authors, probably consisted of point

mutations or smaller insertions or deletions that were too small to detect by Southern blot analysis. In *E. coli,* the mutations induced by formaldehyde were characterized in the xanthine guanine phosphoribosyl transferase (*gpr*) gene. Exposure of *E. coli* to 4 mmol/L formaldehyde for 1 h induced large insertions (41%), large deletions (18%) and point mutations (41%). DNA sequencing revealed that most of the point mutations were transversions at GC base-pairs. In contrast, exposure of *E. coli* to 40 mmol/L formaldehyde for 1 h produced 92% point mutations, 62% of which were transitions at a single AT base-pair in the gene. Therefore, formaldehyde produced different genetic alterations in *E. coli* at different concentrations. When naked pSV2gpt plasmid DNA was exposed to 3.3 or 10 mmol/L formaldehyde and transformed into *E. coli*, most of the resulting mutations were frameshifts, again suggesting a different mechanism of mutation.

Sixteen of the 30 formaldehyde-induced human lymphoblast TK6 X-linked *hprt* mutants referred to above which were not attributable to deletion were examined by Southern blot, northern blot and DNA sequence analysis (Liber *et al.*, 1989). Of these, nine produced mRNA of normal size and amount, three produced mRNA of normal size but in reduced amounts and three produced no detectable mRNA. Sequence analyses of cDNA prepared from *hprt* mRNA were performed on one spontaneous and seven formaldehyde-induced mutants by normal northern blotting. The spontaneous mutant was caused by an AT→GC transition. Six of the formaldehyde-induced mutants were base substitutions, all of which occurred at AT base-pairs. There was an apparent hot spot, in that four of six independent mutants were AT→CG transversions at a specific site. The remaining mutant had lost exon 8.

Table 24. DNA sequence analysis of *p53* cDNA (polymerase chain reaction fragment D) from squamous-cell carcinomas of nasal passages induced in rats by formaldehyde

DNA sequence[a]	Mutation (codon)[b]	Equivalent human *p53* codon no.	Location in conserved region
$_{396}$C→A	TTC→TTA (132) phe→leu	134	II
$_{398}$G→T	TGC→TTC (133) cys→phe	135	II
$_{638}$G→T	AGC→ATC (213) ser→ile	215	
$_{812}$G→A	CGT→CAT (271) arg→his	273	V
$_{842}$G→C	CGG→CCG (281) arg→pro	283	V

From Recio *et al.* (1992)
[a]The A in the start codon is designated as base position 1.
[b]The start codon ATG is designated as codon 1.

DNA sequence analysis of polymerase chain reaction-amplified cDNA fragments containing the evolutionarily conserved regions II–V of the rat *p53* gene was used to examine *p53* mutations in 11 primary nasal squamous-cell carcinomas induced in rats by formaldehyde. The rats has been exposed by inhalation to 15 ppm [18.5 mg/m^3] formaldehyde for up to two years. Point mutations at GC base-pairs in the *p53* complementary DNA sequence were found in five of the tumours (Table 24). The authors pointed out that all five human counterparts of the mutated *p53* codons listed in the Table have been identified as mutants in a variety of human cancers; the CpG dinucleotide at codon 273 (codon 271 in the rat) is a mutational hot spot occurring in many human cancers (Recio *et al.*, 1992).

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Formaldehyde is produced worldwide on a large scale by catalytic, vapour phase oxidation of methanol. Annual world production is about 12 million tonnes. It is used mainly in the production of phenolic, urea, melamine and acetal resins, which have wide use in the production of adhesives and binders for the wood, plastics, textiles, leather and related industries. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals, such as 1,4-butanediol and 4,4′-diphenylmethane diisocyanate (for polyurethanes and particle-board), pentaerythritol (for surface coatings and explosives) and hexamethylene tetramine (for phenol–formaldehyde resins and explosives). Formaldehyde is used as such in aqueous solution (formalin) as a disinfectant and preservative in many applications.

Formaldehyde occurs as a natural product in most living systems and in the environment. Common nonoccupational sources of exposure include vehicle emissions, some building materials, food, tobacco smoke and its use as a disinfectant. Levels of formaldehyde in outdoor air are generally below 0.001 mg/m^3 in remote areas and below 0.02 mg/m^3 in urban settings. The levels of formaldehyde in the indoor air of houses are typically 0.02–0.06 mg/m^3; average levels of 0.5 mg/m^3 or more have been measured in 'mobile homes' constructed with particle-board or in houses with urea–formaldehyde insulation, but the levels have declined in recent years as a result of changes in building materials.

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

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

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

5.2 Human carcinogenicity data

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

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

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

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

5.3 Animal carcinogenicity data

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

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

In experiments to test the effect of formaldehyde on the carcinogenicity of known carcinogens, oral administration of formaldehyde concomitantly with *N*-nitrosodimethylamine to mice increased the incidence of tumours at various sites; skin application in addition to 7,12-dimethylbenz[*a*]anthracene reduced the latency of skin tumours. In rats, concomitant administration of formaldehyde and *N*-methyl-*N*′-nitro-*N*-nitrosoguanidine in the drinking-water increased the incidence of adenocarcinoma of the glandular stomach. Exposure of hamsters by inhalation to formaldehyde increased the multiplicity of tracheal tumours induced by subcutaneous injections of *N*-nitrosodiethylamine.

5.4 Other relevant data

The concentration of endogenous formaldehyde in human blood is about 2–3 mg/L; similar concentrations are found in the blood of monkeys and rats. Exposure of humans, monkeys or rats to formaldehyde by inhalation does not alter the concentration of formaldehyde in the blood.

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

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

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

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

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

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

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

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

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

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

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

5.5 Evaluation[1]

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

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

Overall evaluation

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

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

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