# FORMALDEHYDE

This substance was considered by previous working groups in October 1981 (IARC, 1982), March 1987 (IARC, 1987a) and October 1994 (IARC, 1995). 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; 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 (2003), unless otherwise specified
(*a*)  *Description*: Colourless gas with a pungent odour (Reuss *et al.*, 2003)
(*b*)  *Boiling-point*: –19.1 °C
(*c*)  *Melting-point*: –92 °C
(*d*)  *Density*: 0.815 at –20 °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*: Soluble in water, ethanol and chloroform; miscible with acetone, benzene and diethyl ether

(*g*)  *Stability*: Commercial formaldehyde–alcohol solutions are stable; the gas is stable in the absence of water; incompatible with oxidizers, alkalis, acids, phenols and urea (IARC, 1995; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

(*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) (IARC, 1995; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

(*i*)  *Octanol/water partition coefficient (P)*: log P = 0.35 (Hansch *et al.*, 1995)

(*j*)  *Conversion factor*: mg/m$^3$ = 1.23 × ppm[1]

### 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; Super-lysoform

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 glycols 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 that contain up to 95% formaldehyde are also available, but the temperature necessary to maintain the solution and 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 (WHO, 1991; IARC, 1995; Reuss *et al.*, 2003).

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

1.1.5    *Analysis*

Selected methods for the determination of formaldehyde in various matrices are presented in Table 1.

The most widely used methods for the determination of the concentration of formaldehyde in air 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 (HPLC), polarography, gas chromatography (GC), infrared detection and gas detector tubes. Most methods require the formation of a derivative for separation and detection.

HPLC is the most sensitive method (limit of detection, 2 µg/m$^3$ or less). Gas detector tubes (Draeger Safety, undated; Sensidyne, undated; WHO, 1989; MSA, 1998; Matheson Tri-Gas®, 2004; Sensidyne, 2004; SKC®, 2005) that have sensitivities of about $0.05–0.12$ mg/m$^3$ [0.04–0.1 ppm] and infrared analysers (Interscan Corporation, undated; Environmental Protection Agency, 1999a,b; MKS Instruments, 2004a,b; Thermo Electron Corporation, 2005) that have sensitivities of about $1.2–230$ µg/m$^3$ [1–110 ppb] are often used to monitor workplace atmospheres.

Based on these methods, several standards have been established to determine levels of formaldehyde emissions from wood products (European Commission, 1989; ASTM International, 1990; Groah *et al.*, 1991; Jann, 1991; Deutsche Norm, 1992, 1994, 1996; Standardiseringen i Sverige, 1996; Composite Panel Association, 1999; ASTM International, 2000; Japanese Standards Association, 2001; ASTM International, 2002a,b; Composite Panel Association, 2002).

Sandner *et al.* (2001) reported a modification of the existing method 1 of the Deutsche Forschungsgemeinschaft (1993) to monitor formaldehyde in the workplace that uses adsorption to 2,4-dinitrophenylhydrazine-coated sorbents followed by HPLC with ultraviolet (UV)/diode array detection. The detection limit decreased from approximately 15 µg/m$^3$ for the original method to 0.07 µg/m$^3$ for the modified method.

In the development of new methods to monitor formaldehyde in air, emphasis has been on direct optical sensors and on increased sensitivity (Friedfeld *et al.*, 2000; Lancaster *et al.*, 2000; Chan *et al.*, 2001; Mathew *et al.*, 2001; Alves Pereira *et al.*, 2002; Werle *et al.*, 2002).

Methods for the analysis of formaldehyde in biological matrices (e.g. blood and urine) have been reviewed (ATSDR, 1999), and new methods continue to be reported (Carraro *et al.*, 1999; Spanel *et al.*, 1999; Luo *et al.*, 2001; Kato *et al.*, 2001). Formaldehyde has been measured in blood by gas chromatography–mass spectrometry (GC–MS) after derivatization to pentafluorophenylhydrazone (Heck *et al.*, 1982, 1985). Formic acid or formate is produced from formaldehyde and can be measured in blood and urine (Baumann & Angerer, 1979). However, biological monitoring of exposure to formaldehyde is not common practice.

**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 | Spectrometry | $10\ \mu g/m^3$ | 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 | Spectrometry | $0.5\ \mu g/sample$ | NIOSH (1994a) [Method 3500] |
| | Draw air through solid sorbent tube treated with 10% 2-(hydroxymethyl) piperidine on XAD-2; desorb with toluene | GC/FID | $1\ \mu g/sample$ | NIOSH (1994b) [Method 2541] |
| | | GC/FID & GC/MS | $2\ \mu g/sample$ | NIOSH (1994c) [Method 2539] |
| | | GC/NSD | $20\ \mu g/m^3$ | Occupational Safety and Health Administration (1990a) [Method 52] |
| | Draw air through impinger containing hydrochloric acid/2,4-dinitrophenylhydrazine reagent and isooctane; extract with hexane/dichloromethane | HPLC/UV | $2\ \mu g/m^3$ | Environmental Protection Agency (1988) [Method TO5] |
| | Draw air through a glassfibre filter impregnated with 2,4-dinitrophenyl-hydrazine; extract with acetonitrile | HPLC/UV | $15\ \mu g/m^3$ | Deutsche Forschungs-gemeinschaft (1993) [Method 1] |
| | Draw air through silica gel coated with acidified 2,4-dinitrophenyl-hydrazine reagent | HPLC/UV | $2\ \mu g/m^3$ $(0.6-123\ \mu g/m^3)$ | Environmental Protection Agency (1999c); INRS (2003) [Method TO11A] |
| | Draw air through a cartridge containing silica gel coated with 2,4-dinitrophenylhydrazine; extract with acetonitrile | HPLC/UV | $0.07\ \mu g/m^3$ | Sandner et al. (2001) |
| | Draw air through a cartridge containing silica gel coated with 2,4-dinitrophenylhydrazine; extract with acetonitrile | HPLC/UV | $0.07\ \mu g/sample$ | NIOSH (2003a) [Method 2016] |

**Table 1 (contd)**

| Sample matrix | Sample preparation | Assay procedure | Limit of detection | Reference |
|---|---|---|---|---|
| | Expose passive monitor containing bisulfite-impregnated paper; desorb with deionized water; acidify; add chromotropic acid; read absorbance at 580 nm | Chromo-tropic acid test | 0.14 µg/m$^3$ | Occupational Safety and Health Administration (1990b) [Method ID-205] |
| | Collect gases with portable direct-reading instrument; compare spectra with references | FTIRS | 0.49 µg/m$^3$ | NIOSH (2003b) [Method 3800] |
| Dust (textile or wood) | Draw air through inhalable dust sampler containing a PVC filter; extract with distilled water and 2,4-dinitrophenylhydrazine/acetonitrile | HPLC/UV | 0.08 µg/ sample | NIOSH (1994d) [Method 5700] |
| Food | Distil sample; add 1,8-dihydroxy-naphthalene-3,6-disulfonic acid in sulfuric acid; purple colour indicates presence of formaldehyde | Chromo-tropic acid test | NR | AOAC (2003) [Method 931.08] |
| | Distil sample; add to cold sulfuric acid; add aldehyde-free milk; add bromine hydrate solution; purplish-pink colour indicates presence of formaldehyde | Hehner-Fulton test | NR | AOAC (2003) [Method 931.08] |

FTIRS, Fourier transform infrared spectrometry; GC/FID, gas chromatography/flame ionization detection; GC/MS, gas chromatography/mass spectrometry; GC/NSD, gas chromatography/nitrogen selective detection; HPLC/UV, high-performance liquid chromatography/ultraviolet detection; NR, not reported; PTFE, polytetrafluoroethylene; PVC, polyvinyl chloride

## 1.2     Production and use

### 1.2.1     *Production*

Formaldehyde has been produced commercially since 1889 by the catalytic oxidation of methanol. Various specific methods were used in the past, but only two are widely used currently: the silver catalyst process and the metal oxide catalyst process (Bizzari, 2000; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

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 at 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 (Bizzari, 2000; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

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, dimethyl ether and small amounts of carbon dioxide and formic acid (Bizzari, 2000; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

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, the value of $n$ and product specifications; the remainder is bound or free water. As a convenient source of formaldehyde for certain applications, paraformaldehyde is prepared commercially by the concentration of aqueous formaldehyde solutions under vacuum in the presence of small amounts of formic acid and metal formates. An alternative solid source of formaldehyde is the cyclic trimer of formaldehyde, 1,3,5-trioxane, which is prepared commercially by strong acid-catalysed condensation of formaldehyde in a continuous process (Bizzari, 2000; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

Available information indicates that formaldehyde was produced by 104 companies in China, 19 companies in India, 18 companies in the USA, 15 companies each in Italy and Mexico, 14 companies in Russia, 11 companies each in Brazil and Japan, eight companies each in Canada and Germany, seven companies each in China (Province of Taiwan), Malaysia and the United Kingdom, six companies each in Argentina and Spain, five companies in Belgium, four companies each in Colombia, France, Iran, the Netherlands and Thailand, three companies each in Chile, Israel, Poland, Portugal, the Republic of Korea, Sweden, Turkey and the Ukraine, two companies each in Australia, Austria, Ecuador, Egypt, Pakistan, Peru, Romania and Serbia and Montenegro, and one company each in Algeria, Azerbaijan, Bulgaria, Denmark, Estonia, Finland, Greece, Hungary, Indonesia, Ireland, Lithuania, Norway, Saudi Arabia, Singapore, Slovakia, Slovenia, South Africa, Switzerland, Uzbekistan and Venezuela (Chemical Information Services, 2004).

Available information indicates that paraformaldehyde was produced by eight companies in China, four companies each in Germany and India, three companies each in Russia and the USA, two companies each in China (Province of Taiwan), Iran, Mexico and Spain and one company each in Canada, Egypt, Israel, Italy, Japan, the Netherlands, the Republic of Korea, Romania, Saudi Arabia and the United Kingdom (Chemical Information Services, 2004).

Available information indicates that 1,3,5-trioxane was produced by three companies in Germany, two companies each in China, India and the USA and one company in Poland (Chemical Information Services, 2004).

Production of formaldehyde in selected years from 1983 to 2000 and in selected countries is shown in Table 2. Worldwide capacity, production and consumption of formaldehyde in 2000 are shown in Table 3.

**Table 2. Production of 37% formaldehyde in selected regions (thousand tonnes)**

| Country or region | 1983 | 1985 | 1990 | 1995 | 2000 |
|---|---|---|---|---|---|
| North America | | | | | |
|   Canada | 256 | 288 | 288 | 521 | 675 |
|   Mexico | 79 | 106 | 118 | 139 | 136 |
|   USA | 2520[a] | 2663 | 3402 | 3946 | 4650 |
| Western Europe[b] | 3757 | 3991 | 4899 | 5596 | 6846[c] |
| Japan | 1089 | 1202 | 1444 | 1351 | 1396 |

From Bizzari (2000)
[a] Data for 1980
[b] Includes Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom
[c] Data for 1999

### 1.2.2    *Use*

Worldwide patterns of use for formaldehyde in 2000 are shown in Table 4. The most extensive use of formaldehyde is in the production of resins with urea, phenol and melamine, and of polyacetal resins. Formaldehyde-based resins are used as adhesives and impregnating resins in the manufacture of particle-board, plywood, furniture and other wood products; 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 also 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 (WHO, 1989; IARC, 1995; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

Another major use of formaldehyde is as an intermediate in the synthesis of other industrial chemical compounds, such as 1,4-butanediol, trimethylolpropane and neopentyl glycol, that are used in the manufacture of polyurethane and polyester plastics, synthetic resin coatings, synthetic lubricating oils and plasticizers. Other compounds produced from formaldehyde include pentaerythritol, which is used primarily in raw materials for surface coatings and explosives, and hexamethylenetetramine, which is 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. Formaldehyde is used for the production of 4,4′-methylenediphenyl diisocyanate (see IARC, 1979), which is a constituent of polyurethanes that are used in the production of soft and rigid foams, as adhesives and to bond particle-board (WHO, 1989; IARC, 1995; Reuss *et al.*, 2003; Gerberich & Seaman, 2004).

Polyacetal plastics produced by the polymerization of formaldehyde are incorporated into automobiles to reduce weight and fuel consumption, and are used to make functional

**Table 3. World supply and demand for 37% formaldehyde in 2000 (thousand tonnes)**

| Country/region | Production | Consumption |
|---|---|---|
| North America | | |
|    Canada | 675 | 620 |
|    Mexico | 136 | 137 |
|    USA | 4 650 | 4 459 |
| South and Central America[a] | 638 | 636 |
| Western Europe[b] | 7 100 | 7 054 |
| Eastern Europe[c] | 1 582 | 1 577 |
| Middle East[d] | 454 | 438 |
| Japan | 1 396 | 1 395 |
| Africa[e] | 102 | 102 |
| Asia | | |
|    China | 1 750 | 1 752 |
|    Indonesia | 891 | 892 |
|    Malaysia | 350 | 350 |
|    Republic of Korea | 580 | 580 |
|    Other[f] | 789 | 795 |
| Australia and New Zealand | 304 | 304 |
| Total | 21 547 | 21 091 |

From Bizzari (2000)

[a] Includes Argentina, Brazil, Chile, Colombia, Ecuador, Peru, Uruguay and Venezuela

[b] Includes Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom

[c] Includes Bulgaria, the Czech Republic, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia, the Ukraine and Yugoslavia

[d] Includes Iran, Israel, Saudi Arabia and Turkey

[e] Includes Algeria, Nigeria, South Africa and Tunisia

[f] Includes Bangladesh, Cambodia, China (Province of Taiwan), Democratic People's Republic of Korea, India, Laos, Myanmar, Pakistan, the Philippines, Singapore, Sri Lanka, Thailand and Viet Nam

components of audio and video electronic equipment. Formaldehyde is also the basis for products that are used to manufacture dyes, tanning agents, precursors of dispersion and plastics, extraction agents, crop protection agents, animal feeds, perfumes, vitamins, flavourings and drugs (WHO, 1989; Reuss *et al*., 2003).

Formaldehyde itself is used to preserve and disinfect, for example, human and veterinary drugs and biological materials (viral vaccines contain 0.05% formalin as an inactivating agent), to disinfect hospital wards and to preserve and embalm biological specimens. Formaldehyde and medications that contain formaldehyde are also used in dentistry (Lewis, 1998). Formaldehyde is used as an antimicrobial agent in many cosmetics products,

**Table 4. Worldwide use patterns (%) of formaldehyde in 2000**

| Region or country | Use (million tonnes) | UFR | PFR | PAR | MFR | BDO | MDI | PE | HMTA | TMP | Other[a] |
|---|---|---|---|---|---|---|---|---|---|---|---|
| USA | 4.5 | 24.2 | 16.6 | 12.7 | 3.1 | 11.2 | 6.8 | 5.0 | 2.6 | | 17.8[b] |
| Canada | 0.62 | 51.3 | 32.3 | | 3.2 | | | 12.9 | | | |
| Mexico | 0.14 | 70.8 | 11.7 | | 5.1 | | | | 11.7 | | 0.7 |
| South and Central America[c] | 0.64 | 55.8 | 18.9 | | 7.9 | | 1.6 | 10.8 | | | 5.0 |
| Western Europe[d] | 7.1 | 44.4 | 8.6 | 7.1 | 7.5 | 6.7 | 5.4 | 5.4 | 2.0 | 2.1 | 10.9 |
| Eastern Europe[e] | 1.6 | 71.5 | 5.1 | | 3.2 | | | 4.4 | 8.8 | | 6.9 |
| Africa[f] | 0.10 | 70.6 | 14.7 | | 7.8 | | | | | | 6.9 |
| Middle East[g] | 0.43 | 75.1 | 4.6 | | 14.8 | | | | | | 5.5 |
| Japan | 1.4 | 12.3 | 7.7 | 32.9 | 4.8 | 2.1 | 8.4 | 6.7 | 2.2 | 2.2 | 20.7[h] |
| Asia[i] | 4.4 | 54.2 | 9.8 | 8.4 | 8.7 | | | 5.8 | 2.9 | | 10.2 |
| Oceania[j] | 0.30 | 67.4 | 12.2 | | 20.4 | | | | | | |

From Bizzari (2000)

UFR, urea–formaldehyde resins; PFR, phenol–formaldehyde resins; PAR, polyacetal resins; MFR, melamine–formaldehyde resins; BDO, 1,4-butane-diol; MDI, 4,4′-diphenylmethane diisocyanate; PE, pentaerythritol; HMTA, hexamethylenetetramine; TMP, trimethylolpropane

[a] Not defined

[b] Including chelating agents, trimethylolpropane, trimethylolethane, paraformaldehyde, herbicides, neopentyl glycol, pyridine chemicals, nitroparaffin derivatives, textile treating and controlled-release fertilizer

[c] Includes Argentina, Brazil, Chile, Colombia, Ecuador, Peru, Uruguay and Venezuela

[d] Includes Austria, Belgium, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom

[e] Includes Bulgaria, the Czech Republic, Hungary, Lithuania, Poland, Romania, Russia, Slovakia, Slovenia, the Ukraine and Yugoslavia

[f] Includes Algeria, Nigeria, South Africa and Tunisia

[g] Includes Iran, Israel, Saudi Arabia and Turkey

[h] Including 6.4% for paraformaldehyde

[i] Includes Bangladesh, Cambodia, China, China (Province of Taiwan), Democratic People's Republic of Korea, India, Indonesia, Laos, Malaysia, Myanmar, Pakistan, the Philippines, Republic of Korea, Singapore, Sri Lanka, Thailand and Viet Nam

[j] Includes Australia and New Zealand

including soaps, shampoos, hair preparations, deodorants, lotions, make-up, mouthwashes and nail products (Cosmetic Ingredient Review Expert Panel, 1984; Reuss *et al*., 2003).

Formaldehyde is also used directly to inhibit corrosion, in mirror finishing and electro-plating, in the electrodeposition of printed circuits and in the development of photographic films (Reuss *et al*., 2003).

Paraformaldehyde is used in place of aqueous solutions of formaldehyde, 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), the preparation of disinfectants and deodorants (Reuss *et al*., 2003) and in selected pesticide applications (Environmental Protection Agency, 1993).

## 1.3     Occurrence

Formaldehyde is a gaseous pollutant from many outdoor and indoor sources. Out-doors, major sources of formaldehyde include power plants, manufacturing facilities, inci-nerators and automobile exhaust emissions. Forest fires and other natural sources of com-bustion also introduce formaldehyde into the ambient air. Other than in occupational settings, the highest levels of airborne formaldehyde have been detected indoors where it is released from various building materials, consumer products and tobacco smoke. Form-aldehyde may be present in food, either naturally or as a result of contamination (Suh *et al*., 2000).

Natural and anthropogenic sources of formaldehyde in the environment, and environ-mental levels in indoor and outdoor air, water, soil and food have been reviewed (WHO, 1989; IARC, 1995; ATSDR, 1999).

### 1.3.1     *Natural occurrence*

Formaldehyde is ubiquitous in the environment; it is an 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 that are emitted by foliage react with hydroxyl radicals to form formaldehyde as an intermediate product. Because of their short half-life, these sources of formaldehyde are important only in the vicinity of vegetation. Formal-dehyde is one of the volatile compounds that are formed in the early stages of decompo-sition of plant residues in the soil, and occurs naturally in fruit and other foods (WHO, 1989; IARC, 1995).

An overview of the formation and occurrence of formaldehyde in living organisms has been reported (Kalász, 2003). The reader is referred to Section 4.1 for a discussion of blood levels of endogenously formed formaldehyde in humans.

### 1.3.2    *Occupational exposure*

Estimates of the number of persons who are occupationally exposed to formaldehyde worldwide are not available. However, an estimate of the number of people who were exposed in the European Union in the early 1990s is available from the International Information System on Occupational Exposure to Carcinogens (more commonly referred to as CAREX) (Kauppinen *et al*., 2000). Approximate numbers of persons who were exposed to levels of formaldehyde above 0.1 ppm [0.12 mg/m$^3$] are presented by major industry sector in Table 5. While these are not precise estimates, they do indicate that exposure to formaldehyde, at least at low levels, may occur in a wide variety of industries.

Three main sets of circumstances may lead to occupational exposure to formaldehyde. The first is related to the production of aqueous solutions of formaldehyde (formalin) and their use in the chemical industry, e.g. for the synthesis of various resins, as a preservative in medical laboratories and embalming fluids and as a disinfectant. A second set is related to its release from formaldehyde-based resins in which it is present as a residue and/or through their hydrolysis and decomposition by heat, e.g. during the manufacture of wood products, textiles, synthetic vitreous insulation products and plastics. In general, the use of phenol–formaldehyde resins results in much lower emissions of formaldehyde than that of urea- and melamine-based resins. A third set of circumstances is related to the pyrolysis or combustion of organic matter, e.g. in engine exhaust gases or during firefighting.

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

Concentrations of formaldehyde measured in the 1980s during the manufacture of formaldehyde and formaldehyde-based resins are summarized in Table 6. More recent data were not available to the Working Group.

Mean levels during the manufacture of formaldehyde were below 1 ppm [1.2 mg/m$^3$]. These workers may also be exposed to methanol (starting material), carbon monoxide, carbon dioxide and hydrogen (process gases) (Stewart *et al*., 1987).

The reported mean concentrations in the air of factories that produce formaldehyde-based resins vary from < 1 to > 10 ppm [< 1.2 to > 12.3 mg/m$^3$]. There are obvious differences between factories (the earliest measurements date from 1979) but no consistent seasonal variation. Chemicals other than formaldehyde to which exposure may occur depend on the types of resin manufactured: urea, phenol, melamine and furfural alcohol are the chemicals most commonly reacted with liquid formaldehyde (formalin). Some processes require the addition of ammonia, and alcohols are used as solvents in the production of liquid resins (Stewart *et al*., 1987).

**Table 5. Approximate number of workers exposed to formaldehyde above background levels (0.1 ppm) in the European Union, 1990–93**

| Industry | Estimate |
|---|---|
| Manufacture of furniture and fixtures, except primarily of metal | 179 000 |
| Medical, dental, other health and veterinary services | 174 000 |
| Manufacture of wearing apparel, except footwear | 94 000 |
| Manufacture of wood and wood and cork products, except furniture | 70 000 |
| Personal and household services | 62 000 |
| Construction | 60 000 |
| Manufacture of textiles | 37 000 |
| Iron and steel basic industries | 29 000 |
| Manufacture of fabricated metal products, except machinery | 29 000 |
| Manufacture of other non-metallic mineral products | 23 000 |
| Manufacture of machinery, except electrical | 20 000 |
| Manufacture of industrial chemicals | 17 000 |
| Manufacture of other chemical products | 17 000 |
| Manufacture of plastic products not classified elsewhere | 16 000 |
| Agriculture and hunting | 16 000 |
| Manufacture of paper and paper products | 13 000 |
| Printing, publishing and allied industries | 13 000 |
| Wholesale and retail trade and restaurants and hotels | 13 000 |
| Manufacture of transport equipment | 11 000 |
| Manufacture of electrical machinery, apparatus and appliances | 10 000 |
| Manufacture of footwear | 9 000 |
| Manufacture of glass and glass products | 8 000 |
| Research and scientific institutes | 7 000 |
| Non-ferrous metal basic industries | 6 000 |
| Manufacture of leather and products of leather or of its substitutes | 6 000 |
| Beverage industries | 4 000 |
| Manufacture of instruments, photographic and optical | 4 000 |
| Other manufacturing industries | 3 000 |
| Food manufacturing | 3 000 |
| Crude petroleum and natural gas production | 2 000 |
| Manufacture of rubber products | 4 000 |
| Financing, insurance, real estate and business services | 3 000 |
| Education services | 2 000 |
| Sanitary and similar services | 2 000 |
| Services allied to transport | 2 000 |
| Manufacture of miscellaneous products of petroleum and coal | 1 000 |
| Other industries | 2 000 |
| Total (all industries) | 971 000 |

From Kauppinen *et al*. (2000); CAREX (2003)

**Table 6. Concentrations of formaldehyde in the workroom air in formaldehyde and resin manufacturing plants**

| Industry and operation | No. of measurements | Mean[a] (ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| Special chemical manufacturing plant (USA) | 8 | NR | < 0.03–1.6 [0.04–2.0] | NR | Blade (1983) |
| Production of formaldehyde (Sweden) | 9 | 0.3 [0.3] | NR | 1980s | Rosén *et al.* (1984) |
| Resin manufacture (Sweden) | 22 | 0.5 [0.6] | NR | 1980s | Rosén *et al.* (1984) |
| Formaldehyde manufacture (USA) | | | | 1983 | Stewart *et al.* (1987) |
| 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 manufacture (USA) | | | | 1983–84 | Stewart *et al.* (1987) |
| Plant no. 1, summer | 24 | 3.4[b] [4.2] | 0.2–13.2 [0.3–16.2] | | |
| Plant no. 6, summer[c] | 6 | 0.2[b] [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[c,d] | 13 | 0.4[b] [0.7] | 0.2–0.8 [0.3–1.0] | | |
| Plant no. 8, winter[c,d] | 9 | 0.1[b] [0.1] | 0.1–0.2 [0.1–0.3] | | |
| Plant no. 9, summer[c,d] | 8 | 14.2[b] [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[d] | 23 | 0.7[b] [0.9] | 0.3–1.2 [0.4–1.5] | | |
| 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) |
| 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 [0.9] | 0.6–0.8 [0.7–1.1] | 1981 | |

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 that contained nascent formaldehyde (leading to high values).

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

### (b)    Histopathology and disinfection in hospitals

Formalin is commonly used to preserve tissue samples in histopathology laboratories. Concentrations of formaldehyde are sometimes high, e.g. during tissue disposal, preparation of formalin and changing of tissue processor solutions (Belanger & Kilburn, 1981). The usual mean concentration during exposure is approximately 0.5 ppm [0.6 mg/m$^3$]. Other agents to which pathologists and histology technicians may be exposed include xylene (see IARC, 1989a), toluene (see IARC, 1989b), chloroform (see IARC, 1987c) and methyl methacrylate (see IARC, 1994a) (Belanger & Kilburn, 1981). Concentrations of airborne formaldehyde in histopathology laboratories and during disinfection in hospitals are presented in Table 7.

Levels of formaldehyde were measured in 10 histology laboratories using area samplers for 1–4 h for a study of neurobehavioural and respiratory symptoms. Concentrations of formaldehyde in areas where tissue specimens were prepared and sampled were 0.25–2.3 mg/m$^3$ (Kilburn et al., 1985). In two studies in Israel, pathology staff were divided into two groups: those who had low exposure (mean, 0.5 mg/m$^3$), which included laboratory assistants and technicians, and those who had high exposure (mean, 2.8 mg/m$^3$), which included physicians and hospital orderlies, based on 15-min samples (Shaham et al., 2002, 2003). Another study by the same group [it is not clear whether these are the same data or not] reported 15-min area measurements of 1.7–2.0 mg/m$^3$ and personal measurements of 3.4–3.8 mg/m$^3$ during exposure (Shaham et al., 1996a,b).

Formaldehyde has also been used extensively in hospitals for disinfection (IARC, 1995; see Table 7).

### (c)    Embalming and anatomy laboratories

Formaldehyde is used as a tissue preservative and disinfectant in embalming fluids (Table 7). Some parts of bodies that are 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 its content in the embalming fluid, the type of body, ventilation and work practices; mean levels are approximately 1 ppm [1.2 mg/m$^3$]. Embalming of a normal intact body usually takes approximately 1 h. Disinfectant sprays are occasionally used, and these may release small amounts of solvent, such as isopropanol (Williams et al., 1984). Methanol is used as a stabilizer in embalming fluids, and concentrations 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).

Skisak (1983) measured levels of formaldehyde in the breathing zone at dissecting tables and in the ambient air in a medical school in the USA for 12 weeks. Concentrations of > 1.2 mg/m$^3$ formaldehyde were found in 44% of the breathing zone samples and

**Table 7. Concentrations of formaldehyde in the workroom air of mortuaries, hospitals and laboratories**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| **Histopathology laboratories** | | | | | |
| Pathology laboratory (Sweden) | 13 | 0.5 [0.7] | NR | 1980s | Rosén *et al.* (1984) |
| Histology laboratory, tissue specimen preparation and sampling (USA) | NR | NR | 0.2–1.9 [0.25–2.3] | NR | Kilburn *et al.* (1985) |
| Pathology laboratories (Germany) | 21 | 0.5[b] [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) |
| Histology laboratory (Israel) | | | | | Shaham *et al.* (1996a,b) |
| Area samples | NR | NR | 1.4–1.6 [1.7–2.0] | NR | |
| Personal samples | NR | NR | 2.8–3.1 [3.4–3.8] | | |
| Teaching laboratory (USA) | 16 | 0.3 [0.4] | | NR | Tan *et al.* (1999) |
| Pathology laboratories (Turkey) | 10 | NR | max., < 2 [< 2.5] | NR | Burgaz *et al.* (2001) |
| Histology laboratory (Israel) | NR | | | NR | Shaham *et al.* (2002) |
| Laboratory assistants/technicians (15 min) | | 0.4 [0.5] | 0.04–0.7 [0.05–0.9] | | |
| Physicians and orderlies (15 min) | | 2.2 [2.8] | 0.7–5.6 [0.9–7.0] | | |
| **Disinfection in hospitals** | | | | | |
| Cleaning hospital floors with detergent containing formaldehyde (Italy) Personal samples (38–74 min) | 4 | 0.18 [0.22] | 0.15–0.21 [0.18–0.26] | NR | Bernardini *et al.* (1983) |
| 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) |
| Disinfecting operating theatres (Germany) | 43 | 0.4[c] [0.5] | 0.04–1.4 [0.05–1.7] | NR | Elias (1987) |
| Bedrooms in hospital (Germany) | 14 | 0.05 [0.06] | < 0.01–0.7 [< 0.01–0.9] | 1980–88 | Triebig *et al.* (1989) |
| Disinfecting operating theatres (Germany)[d] | | | | 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 [0.2] | 0.01–0.4 [0.01–0.5] | | |
| Disinfection in hospitals (Finland) | 18 | 0.1 [0.1] | 0.03–0.2 [0.04–0.3] | 1981–86 | Heikkilä *et al.* (1991) |

**Table 7 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range (ppm [mg/m³]) | Year | Reference |
|---|---|---|---|---|---|
| **Embalming** | | | | | |
| Embalming, six funeral homes (USA) | NR | 0.7 [0.9] | 0.09–5.3 [0.1–6.5] | NR | Kerfoot & Mooney (1975) |
| Autopsy service (USA)[d] | | | | NR | Coldiron *et al.* (1983) |
|    Personal samples | 27 | 1.3[c] [1.7] | 0.4–3.3 [0.5–4.0] | | |
|    Area samples | 23 | 4.2 [5] | 0.1–13.6 [0.1–16.7] | | |
| Museum, taxidermy (Sweden) | 8 | 0.2 [0.3] | NR | 1980s | Rosén *et al.* (1984) |
| 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] | 0–2.1 [0–2.6] | | |
| Embalming, 23 mortuaries (USA) | NR | 1.1 [1.4] | 0.03–3.2 [0.04–3.9] | NR | Lamont Moore & |
|    8-h TWA | | 0.2 [0.2] | 0.01–0.5 [0.01–0.6] | | Ogrodnik (1986) |
| Autopsy (Finland) | 5 | 0.7 [0.8] | < 0.1–1.4 [< 0.1–1.7] | 1981–86 | Heikkilä *et al.* (1991) |
| Embalming (USA) | | | | NR | Stewart *et al.* (1992) |
|    Personal samples | 25 | 2.6 [3.2] | 0.3–8.7 [0.4–10.7] | | |
|    Area 1 | 25 | 2.0 [3.0] | 0.2–7.5 [0.3–9.2] | | |
|    Area 2 | 25 | 2.2 [2.7] | 0.3–8.2 [0.3–10.0] | | |
| Embalming (Canada) | | | | NR | Korczynski (1994) |
|    Intact bodies (personal samples) | 24 | 0.6 [0.8] | 0.1–4.6 [0.1–5.6] | | |
|    Autopsied bodies (personal samples) | 24 | 0.6 [0.8] | 0.09–3.3 [0.1–4.1] | | |
|    Area samples | 72 | 0.5 [0.6] | 0.04–6.8 [0.05–8.4] | | |
| Funeral home, embalming (USA) | | | | NR | Korczynski (1996) |
|    Area samples | 4 | NR | < 0.1–0.15 [< 0.1–0.19] | | |
|    Personal samples | 4 | 0.16 [0.19] | NR | | |
| **Anatomy laboratories** | | | | | |
| Anatomy laboratory, dissecting (USA) Personal samples | 54 | NR | 0.3–2.6 [0.4–3.2] | NR | Skisak (1983) |

**Table 7 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range (ppm [mg/m³]) | Year | Reference |
|---|---|---|---|---|---|
| Anatomy laboratory, dissecting (USA) | | | | 1982–83 | Korky (1987) |
|     Laboratory | NR | NR | 7–16.5 [8.6–20.3] | | |
|     Stock room | NR | NR | 2.0–2.6 [2.4–3.2] | | |
|     Public hallway | NR | NR | max., < 1 [< 1.2] | | |
| Anatomical theatre (Germany) | 29 | 1.1[b] [1.4] | 0.7–1.7 [0.9–2.2] | 1980–88 | Triebig et al. (1989) |
| Anatomy laboratory, dissecting (USA) | | | | NR | Akbar-Khanzadeh et al. |
|     Personal samples (1.2–3.1 h) | 32 | 1.2 [1.5] | 0.07–2.9 [0.09–3.6] | | (1994) |
|     Personal samples (TWA) | NR | 0.4 [0.5] | 0.09–0.95 [0.11–1.17] | | |
|     Area samples (2.5 min) | 13 | 1.4 [1.7] | 0.9–1.8 [1.1–2.2] | | |
|     Area samples (TWA) | 2 | 1.7 [2.0] | 1.0–2.3 [1.2–2.8] | | |
| Anatomy laboratory, dissecting (USA) | | | | NR | Akbar-Kahnzadeh & |
|     Personal samples | 44 | 1.9 [2.3] | 0.3–4.5 [0.4–5.5] | | Mlynek (1997) |
|     Area samples | 76 | 1.0 [1.2] | 0.6–1.7 [0.7–2.1] | | |
| Anatomy laboratory, dissecting (China) | 25 | 0.4 [0.5] | 0.06–1.04 [0.07–1.28] | NR | Ying et al. (1997, 1999) |
| Anatomy laboratory, dissecting (China) | NR | 2.4 [2.9] | NR | NR | He et al. (1998) |
| Anatomy/histology laboratory, dissecting | 48 | 3.0 [3.7] | 0.2–9.1 [0.2–11.2] | NR | Kim et al. (1999) |
| Anatomy laboratory, dissecting (Austria) | NR | 0.22 [0.27] | 0.11–0.33 [0.13–0.41] | NR | Wantke et al. (2000) |
|     Two locations in a room over 4 weeks | NR | 0.12 [0.15] | 0.06–0.22 [0.07–0.27] | NR | Wantke et al. (1996b) |
| Anatomy laboratory, dissecting (Turkey) | NR | NR | max., < 4 [< 5] | NR | Burgaz et al. (2001) |
| Anatomy laboratory, dissecting (USA) | 15 | 0.9 [1.1] | 0.3–2.6 [0.3–3.1] | NR | Keil et al. (2001) |
| Biology laboratory, dissecting (Canada) | | | | NR | Dufresne et al. (2002) |
|     Laboratory 1 | 18 | 0.20 [0.25] | 0.08–0.62 [0.11–0.76] | | |
|     Laboratory 2 | 18 | 0.51 [0.63] | 0.3–1.2 [0.3–1.5] | | |
| Anatomy laboratory, dissecting (Japan) | NR | NR | 0.11–0.62 [0.14–0.76] | NR | Tanaka et al. (2003) |

NR, not reported; TWA, time-weighted average
[a] Arithmetic means unless otherwise specified
[b] Median
[c] Mean of arithmetic means
[d] 8-h TWA

11 ambient air samples; the levels in breathing zone samples were in the range of 0.4–3.2 mg/m³, and 50% of the samples contained 0.7–1.2 mg/m³.

Korky *et al*. (1987) studied the dissecting facilities at a university in the USA during the 1982–83 academic year. Airborne concentrations of formaldehyde were 7–16.5 ppm [8.6–20.3 mg/m³] in the laboratory, 1.97–2.62 ppm [2.4–3.2 mg/m³] in the stockroom and < 1 ppm [< 1.2 mg/m³] in the public hallway.

Concentrations of formaldehyde in the breathing zone of two embalmers in the USA were measured during the embalming of an autopsied body, which generally results in higher exposures than that of non-autopsied bodies. The average was 0.19 mg/m³ [duration of measurement not provided] (Korczynski, 1996).

Samples (1–2-h) taken in an anatomy/histology laboratory in the Republic of Korea for a cross-sectional study of serum antibodies showed concentrations of formaldehyde that ranged from 0.19 to 11.25 mg/m³ with a mean of 3.74 mg/m³ (Kim *et al*., 1999).

In a cross-sectional study of immunoglobulin (Ig)E sensitization in Austria, concentrations of formaldehyde were measured in two locations in a dissection room for the full period that students were present. The mean level was 0.15 mg/m³ (Wantke *et al*., 1996a,b). The windows were open and the ventilation was working continuously. In a second study in the same laboratories, medical students were exposed to an average indoor concentration of 0.27 mg/m³ formaldehyde (Wantke *et al*., 2000).

Levels of formaldehyde measured in anatomy laboratories in China for a cytogenetic study averaged 0.51 mg/m³ over a 3-h period; the peak occurred while cadavers were being dissected (Ying *et al*., 1997, 1999).

A cross-sectional study on the cytogenetic effects of formaldehyde on anatomy students in China found personal exposures of 2.92 mg/m³ (He *et al*., 1998).

In a study of respiratory function, 34 personal samples and short-term area samples were collected in a gross anatomy laboratory in the USA. The mean concentration of formaldehyde in the room was 1.53 mg/m³ during the 1.2–3.1-h dissecting period. The direct-reading short-term area samples (2.5-min) averaged 1.68 mg/m³. Eight-hour time-weighted average (TWA) personal exposures ranged from 0.11 to 1.17 mg/m³, with a mean of 0.52 mg/m³ (96% of subjects were exposed to levels of formaldehyde above the 0.38 mg/m³ ceiling, and the 8-h TWA exposure of 3% of them was above 0.94 mg/m³) (Akbar-Khanzadeh *et al.*, 1994). A subsequent study of respiratory function was conducted in the same laboratory because, among other reasons, the concentration of formaldehyde in the embalming solution was increased. The mean concentration of formaldehyde in the personal samples was 2.31 mg/m³ (duration, 2.5 h) (Akbar-Khanzadeh & Mlynek, 1997). In the same laboratory, area measurements were taken in the centre of and at various locations in the room over a 16-week period; each measurement lasted for the time the students were active during a session (3–4 h per day). The average concentration in the centre of the room was 1.13 mg/m³ (15 measurements) (Keil *et al*., 2001). Breathing zone concentrations were expected to be higher because of the proximity of the students to the cadaver during dissection. Although the room had mechanical air supply and exhaust systems, the ventilation system served the entire building and intake air was contaminated with formaldehyde.

The concentration of formaldehyde in the air in pathology and anatomy laboratories in Turkey did not exceed 2 and 4 mg/m$^3$, respectively [no other information available], when measured in a study of cytogenetic responses (Burgaz *et al*., 2001).

In a study of two biological laboratories in Canada where dissection of animal specimens was performed, 3-h personal samples showed mean concentrations of 0.25 mg/m$^3$ and 0.63 mg/m$^3$ formaldehyde, respectively (Dufresne *et al*., 2002). The first laboratory had a general mechanical ventilation system, whereas the second had no ventilation system.

Measurements in an anatomy class in Japan rose to 0.76 mg/m$^3$ after 10 min of class; 30 min later, the formaldehyde concentration had decreased to 0.14 mg/m$^3$ (Tanaka *et al*., 2003).

### (*d*)     *Manufacture of wood products and paper*

Exposure to formaldehyde may occur in several sectors of the wood-related industries because of the use of formaldehyde-based resins. Table 8 summarizes the concentrations of formaldehyde observed in the wood product and pulp and paper industries.

Exposure to formaldehyde is typically monitored by measuring its gaseous form; slight additional exposure may occur through the inhalation of formaldehyde bound to wood dust, although this was considered to be negligible in one study (Gosselin *et al*., 2003). For example, at a plant in the USA that constructed products made of particle-board, measurements were taken for 4.5 h at the sawing operation. A back-up impinger was positioned behind an inhalable dust sampler or a closed-face cassette to capture both dust-bound and gaseous formaldehyde. Levels of formaldehyde gas behind the inhalable dust sampler averaged [132 µg/m$^3$ (standard deviation [SD], 14 µg/m$^3$; four samples)] and those of bound formaldehyde from inhalable dust averaged [11 µg/m$^3$ (SD, 4 µg/m$^3$; 12 samples)]. Respective measurements for the closed cassettes averaged [147 µg/m$^3$ (SD, 9 µg/m$^3$; four samples)] and [8 µg/m$^3$ (SD, 2 µg/m$^3$; 12 samples)] (Kennedy *et al*., 1992).

### (i)     *Veneer and plywood mills*

Plywood consists of three or more veneers glued together or a core of solid wood strips or particle-board with veneered top and bottom surfaces. The dried panels may also be patched or spliced by applying a liquid formaldehyde-based adhesive to the edges, pressing the edges together and applying heat to cure the resin. To produce panels, veneers are roller- or spray-coated with formaldehyde-based resins, then placed between unglued veneers. The plywood industry has used formaldehyde-based glues in assembling of plywood for over 50 years. Before the introduction of formaldehyde-based resins in the 1940s, soya bean and blood–albumen adhesives were used, and cold pressing of panels was common. Exposure to formaldehyde from resins may occur among workers during the preparation of glue, during splicing, patching, sanding and hot-pressing operations and among nearby workers. Urea-based resins release formaldehyde more readily during curing than phenol-based resins; however, improvements in the formulation of resins have reduced exposures.

**Table 8. Concentrations of formaldehyde in the workroom air of plywood mills, particle-board mills, furniture factories, other wood product plants, paper mills and the construction industry**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range (ppm [mg/m³]) | Year | Reference |
|---|---|---|---|---|---|
| **Plywood mills** | | | | | |
| Plywood production (Sweden) | 47 | 0.3 [0.4] | NR | 1980s | Rosén *et al.* (1984) |
| 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 panelling manufacture (USA) | | | | 1983–84 | Stewart *et al.* (1987) |
|   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] | | |
| Plywood mill (Indonesia) | 40 | 0.6 [0.8] | 0.2–2.3 [0.3–2.8] | NR | Malaka & Kodama (1990) |
| Plywood factory (Italy) | | | | NR | Ballarin *et al.* (1992) |
|   Warehouse | 3 | 0.3 [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 mill (Finland) | | | | 1996–97 | Mäkinen *et al.* (1999) |
|   Personal samples | | | | | |
|     Patching | 6 | 0.06 [0.07] | 0.02–0.08 [0.03–0.10] | | |
|     Feeding of drying machine | 6 | 0.05 [0.06] | 0.01–0.12 [0.01–0.15] | | |
|     Forklift driving | 6 | 0.06 [0.07] | 0.02–0.16 [0.02–0.20] | | |
|     Scaring | 6 | 0.11 [0.14] | 0.06–0.20 [0.07–0.24] | | |
|     Assembly (machine I) | 4 | 0.24 [0.30] | 0.08–0.66 [0.10–0.81] | | |
|     Assembly (machine II) | 6 | 0.12 [0.15] | 0.08–0.22 [0.10–0.27] | | |
|     Hot pressing (machine I) | 5 | 0.11 [0.13] | 0.07–0.19 [0.08–0.23] | | |

**Table 8 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| Glue preparation | 2 | 0.12 [0.15] | 0.06–0.19 [0.07–0.23] | | |
| Finishing (puttying) | 4 | 0.07 [0.09] | 0.06–0.11 [0.07–0.14] | | |
| Carrying plywood piles | 2 | 0.05 [0.06] | 0.04–0.06 [0.05–0.07] | | |
| Finishing (sanding) | 2 | 0.04 [0.05] | 0.01–0.06 [0.01–0.07] | | |
| Plywood mill (New Zealand) | | | | [2000] | Fransman *et al.* (2003) |
| Dryers | 14 | 0.06[b] [0.07] | GSD, [3.2] | | |
| Composers | 2 | 0.02[b] [0.03] | GSD, [1.0] | | |
| Pressing | 5 | 0.13[b] [0.16] | GSD, [2.7] | | |
| Finishing end | 1 | 0.03[b] [0.04] | NA | | |
| **Particle- and other board mills** | | | | | |
| Particle-board production (Sweden) | 21 | 0.3 [0.4] | NR | 1980s | Rosén *et al.* (1984) |
| Medium-density fibre board (Sweden) | 19 | 0.2 [0.3] | NR | 1980s | Rosén *et al.* (1984) |
| Particle-board mills (Finland) | | | | | Kauppinen & Niemelä |
| Glue preparation | 10 | 2.2 [2.7] | 0.3–4.9 [0.4–6.0] | 1975–84 | (1985) |
| 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 | |
| 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 | |
| Chip-board production (Germany) | 24 | 1.5 [1.9] | < 0.01–8.4 [< 0.01–10] | 1980–88 | Triebig *et al.* (1989) |
| Particle-board mill (Indonesia) | 9 | 2.4 [3.0] | 1.2–3.5 [1.5–4.3] | NR | Malaka & Kodama (1990) |
| Block-board mill (Indonesia) | 6 | 0.5 [0.6] | 0.4–0.6 [0.5–0.7] | NR | Malaka & Kodama (1990) |

**Table 8 (contd)**

| Industry and operation (location)<br>    Type of sample | No. of measurements | Mean[a]<br>(ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| Oriented strand board plant (Canada) | | | | 1990s | Herbert *et al.* (1995) |
|     Debarking | 5 | ≤ 0.05 [0.06] | NR | | |
|     Pre-heat conveyor | 5 | ≤ 0.05 [0.06] | NR | | |
|     Post-heat press conveyor | 5 | ≤ 0.05 [0.06] | NR | | |
|     Packaging/storage | 5 | ≤ 0.05 [0.06] | NR | | |
| Fibreboard, sawing and sanding (United Kingdom) | | | | 1990s | Chung *et al.* (2000) |
|     Standard MDF (Caberwood) | | | | | |
|         Gaseous form | 5 | 0.06 [0.07] | 0.04–0.07 [0.05–0.09] | | |
|         Extracted from dust | 6 | 0.08 [0.10] | 0.06–0.11 [0.07–0.13] | | |
|     Moisture resistant (Medite MR) | | | | | |
|         Gaseous form | 5 | 0.05 [0.06] | 0.01–0.10 [0.01–0.12] | | |
|         Extracted from dust | 6 | 0.10 [0.13] | 0.04–0.14 [0.05–0.17] | | |
|     Zero added formaldehyde (Medite ZF) | | | | | |
|         Gaseous form | 6 | 0.04 [0.04] | 0.02–0.06 [0.03–0.07] | | |
|         Extracted from dust | 6 | 0.03 [0.04] | 0.02–0.06 [0.03–0.07] | | |
|     Medite exterior grade (Medex) | | | | | |
|         Gaseous form | 6 | 0.03 [0.04] | 0.01–0.07 [0.01–0.08] | | |
|         Extracted from dust | 6 | 0.04 [0.05] | 0.04–0.06 [0.05–0.07] | | |
| **Furniture factories** | | | | | |
| Furniture factories (Sweden) | | | | 1980s | Rosén *et al.* (1984) |
|     Varnishing with acid-cured varnishes | 32 | 0.7 [0.9] | NR | | |
| Furniture factories (Finland) | | | | 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] | | |

**Table 8 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range (ppm [mg/m³]) | Year | Reference |
|---|---|---|---|---|---|
| Cabinet-making (Canada) | 48 | NR | max., < 0.1 [< 0.1] | NR | Sass-Kortsak *et al.* (1986) |
| 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 [0.4] | 0.1–0.9 [0.1–1.1] | | |
|     Varnishing | 150 | 1.1 [1.4] | 0.1–6.3 [0.1–7.9] | | |
| Manufacture of furniture (Denmark) | | | | NR | Vinzents & Laursen (1993) |
|     Painting | 43 | 0.16 [0.20][b] | GSD, [2.25] | | |
|     Glueing | 68 | 0.12 [0.15][b] | GSD, [2.87] | | |
| Wood-working shops (Egypt) | | | | 1990s | Abdel Hameed *et al.* (2000) |
|     Ventilated workshop | 14 | 0.42 [0.52] | 0.28–0.54 [0.34–0.66] | | |
|     Unventilated workshop | 14 | 0.64 [0.79] | 0.48–0.84 [0.59–1.03] | | |
| **Other wood product plants** | | | | | |
| Glueing in wood industry (Sweden) | 65 | 0.2 [0.3] | NR | 1980s | Rosén *et al.* (1984) |
| 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 [0.4] | 0.1–0.8 [0.1–0.9] | | |
| Manufacture of wooden bars (Finland) | | | | 1983 | Heikkilä *et al.* (1991) |
|     Glueing | 33 | 0.6 [0.7] | 0.2–1.9 [0.2–2.4] | | |
|     Machining | 7 | 1.2 [1.5] | 0.2–2.2 [0.3–2.7] | | |

**Table 8 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range (ppm [mg/m³]) | Year | Reference |
|---|---|---|---|---|---|
| Match mill, impregnation of matchbox parts (Finland) Short-term | 2 | 2.0 [2.5] | 1.9–2.1 [2.3–2.6] | 1963 | Finnish Institute of Occupational Health (1994) |
| Wooden container mill, glueing and sawing (Finland) | 6 | 0.3 [0.4] | 0.2–0.4 [0.3–0.5] | 1961 | Finnish Institute of Occupational Health (1994) |
| **Paper mills** | | | | | |
| Laminated paper production (Sweden) | 23 | 0.3 [0.4] | NR | 1980s | Rosén *et al.* (1984) |
| Manufacture of offset paper (Sweden) | 8 | 0.2 [0.2] | NR | 1980s | Rosén *et al.* (1984) |
| Lamination and impregnation of paper with melamine and phenol resins (USA) | | | | 1983 | Stewart *et al.* (1987) |
| Plant no. 6, summer[c,d] | 53 | 0.7[b] [0.9] | < 0.01–7.4 [< 0.01–9.1] | | |
| Plant no. 6, winter[d] | 39 | 0.3[b] [0.4] | 0.05–0.7 [0.06–0.9] | | |
| 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] | | |
| 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 | |
| Pulp and paper industries (12 countries) | | | | 1950–94 | Korhonen *et al.* (2004) |
| Pulping, refining of stock (8 mills) | 25 | 0.5 [0.6] | 0–3.1 [0–3.8] | | |
| Newsprint and uncoated paper machine (2 mills) | 7 | 0.15 [0.18] | 0.04–0.46 [0.05–0.57] | | |
| Fine and coated paper machine (6 mills) | 51 | 1.1 [1.4] | 0.01–9.9 [0.01–12.2] | | |

**Table 8 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range (ppm [mg/m³]) | Year | Reference |
|---|---|---|---|---|---|
| Paperboard machine (1 mill) | 8 | 0.5 [0.6] | 0.2–2.2 [0.2–2.7] | | |
| Paper/paperboard machine from more than one of above categories (24 mills) | 228 | 0.4 [0.5] | 0–6.6 [0–8.1] | | |
| Calendering or on-machine coating (10 mills) | 166 | 4.2 [5.2] | 0–50 [0–61.5] | | |
| Winding, cutting and grading (17 mills) | 111 | 0.2 [0.3] | 0–1.1 [0–1.4] | | |
| Recycled paper industry (12 countries) | | | | | |
| Re-pulping of waste paper (2 mills) | 8 | 0.2 [0.3] | 0.05–0.4 [0.06–0.5] | | |
| **Construction industry** | | | | | |
| Insulating buildings with urea–formaldehyde foam (Sweden) | 6 | 0.1 [0.2] | NR | 1980s | Rosén et al. (1984) |
| Insulating buildings with urea–formaldehyde foam (USA) | 66 | 1.3[e] [1.6] | 0.3–3.1 [0.4–3.8] | NR | WHO (1989) |
| 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) |
| Sawing particle-board at construction site (Finland) | 5 | < 0.5 [< 0.6] | NR | 1967 | Finnish Institute of Occupational Health (1994) |

GSD, geometric standard deviation; NA, not applicable; NR, not reported
[a] Arithmetic mean unless otherwise specified
[b] Geometric mean
Some of the results in the Stewart et al. (1987) study were affected by the simultaneous occurrence in the samples of:
[c] phenol (leading to low values)
[d] particulates that contained nascent formaldehyde (leading to high values).
[e] Mean of arithmetic means

Recent studies conducted in these industries in Finland and New Zealand (Mäkinen *et al*., 1999; Fransman *et al*., 2003) found mean concentrations of formaldehyde to be less than 0.5 mg/m$^3$. In contrast, mean levels of 2 ppm [2.5 mg/m$^3$] have been observed historically in some operations in the Finnish industry (Kauppinen, 1986).

### (ii)    *Manufactured board mills*

Both phenol–formaldehyde and urea–formaldehyde resins are used in mills that produce particle- and other manufactured boards, including oriented strand boards and medium-density fibre boards. Phenolic resins are more liable to be used for panels that are destined for applications that require durability under adverse conditions, while urea-based resins are used for less demanding, interior applications. Melamine–formaldehyde resins may also be used to increase durability, but rarely are because they are more expensive. Exposure to formaldehyde and other resin constituents is possible during the mixing of glues, the laying of mat and hot-pressing operations.

Herbert *et al*. (1995) and Chung *et al*. (2000) found levels of formaldehyde below 0.2 mg/m$^3$ in recent studies in Canada and the United Kingdom, respectively, in oriented strand-board and fibre-board plants. Mean exposures greater than 1 ppm [1.2 mg/m$^3$] have been observed in the past in particle- and chip-board mills (Kauppinen & Niemelä, 1985; Triebig *et al*., 1989; Malaka & Kodama, 1990).

### (iii)    *Furniture factories*

Furniture varnishes may contain acid-cured urea–formaldehyde resins dissolved in organic solvents. In Finland, workers were exposed to an average level of about 1 ppm [1.23 mg/m$^3$] formaldehyde in most facilities (Priha *et al*., 1986; Heikkilä *et al*., 1991).

In a recent study in wood-working shops in Egypt, the levels of formaldehyde were found to average 0.42 and 0.64 ppm [0.52 and 0.79 mg/m$^3$] in ventilated and unventilated workplaces, respectively (Abdel Hameed *et al*., 2000). [The origin of the formaldehyde was not stated.]

### (iv)    *Paper mills*

Some paper mills produce special products that are coated with formaldehyde-based phenol, urea or melamine resins. Coating agents and other chemicals used in paper mills may also contain formaldehyde as a bactericide.

As part of an IARC international epidemiological study of workers in the pulp and paper industry, measurements were carried out in the production departments of paper and paperboard mills and recycling plants in 12 countries. The highest exposures were observed during calendering or on-machine coating (Korhonen *et al*., 2004).

### (e)    *Building and construction industry*

Exposure to formaldehyde may also occur in the construction industry (Table 8). 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 ranged between 2 and 5 ppm [2.5–6.2 mg/m$^3$]. 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. Other chemical agents to which parquetry workers are usually exposed include wood dust from sanding (see IARC, 1995) and solvent vapours from varnishes, putties and adhesives. Operations that may have resulted in exposure to formaldehyde in the building trades are insulation with urea–formaldehyde foam and machining of particle-board, but these have now largely been discontinued. 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. Formaldehyde may be released when synthetic vitreous fibre-based insulation is applied to hot surfaces, i.e. high-temperature insulation in power plants, due to decomposition of the phenol–formaldehyde binder at temperatures > 150 °C (International Labour Office, 2001) (see also under (*f*)).

### (*f*)    *Manufacture of textiles and garments*

The use of formaldehyde-based resins to produce crease-resistant fabrics began in the 1950s. The early resins contained substantial amounts of extractable formaldehyde: over 0.4% by weight of fabric. The 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 contain agents that release formaldehyde (Heikkilä *et al.*, 1991). The cutting and sewing of fabrics release low levels of textile dust, and small amounts of chlori-nated organic solvents are used to clean spots. Pattern copying machines may emit ammonia and dimethylthiourea in some plants (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 (see IARC, 1990b).

Measurements of formaldehyde in the air of textile mills are summarized in Table 9. In the late 1970s and 1980s, levels of formaldehyde in the garment industry averaged 0.2–2 ppm [0.25–2.5 mg/m$^3$]. However, exposures in the past were generally higher, probably because of the higher content of free formaldehyde in fabrics. For example, the concentrations of formaldehyde were 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 manufacturing plants in the USA in 1966 (Elliott *et al.*, 1987). Goldstein (1973) reported that concentrations of formaldehyde in cutting rooms decreased from over 10 ppm [12 mg/m$^3$] in 1968 to less than 2 ppm [2.4 mg/m$^3$] in 1973 as a result of improve-ments in the processes of resin treatment. The mean formaldehyde concentration in air increased from 0.1 to 1.0 ppm [0.12 to 1.23 mg/m$^3$] in a study in the USA when the formaldehyde content of the fabric increased from 0.015 to 0.04% (Luker & Van Houten, 1990). Measurements from the late 1980s onwards indicate lower levels, usually averaging 0.1–0.2 ppm [0.12–0.25 mg/m$^3$].

Full-shift personal (for 5.7–6.4 h; eight samples) and area (for 6.3–7.3 h; 12 samples) measurements were taken at a pre-cured permanent-press garment manufacturing plant in

# Table 9. Concentrations of formaldehyde in the workroom air of textile mills and garment factories

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m³]) | Range or SD in ppm [mg/m³] | Year | Reference |
|---|---|---|---|---|---|
| **Textile mills** | | | | | |
| Textile plants (Finland) | | | | 1975–78 | Nousiainen & |
|   Finishing department, mixing | 8 | 0.8 [1.1] | < 0.2–>5 [< 0.2–> 6] | | Lindqvist (1979) |
|   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] | max., 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 [0.2] | NR | | |
|   Flame-retardant treatment | 2 | 1.2 [1.5] | NR | | |
| **Garment factories** | | | | | |
| Manufacture from crease-resistant cloth (USA) | 181 | NR | < 0.1–0.9 [< 0.1–1.1] | NR | 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 [0.03–0.1] | | |
|   Pressing | 32 | 0.2 [0.3] | 0.02–0.7 [0.03–0.9] | | |
|   Sewing | 15 | 0.1 [0.1] | 0.02–0.3 [0.03–0.3] | | |
| Sewing plant (USA) | | | | NR | Luker & Van Houten |
|   Processing of 0.04% formaldehyde fabric | 9 | 1.0 [1.2] | 0.5–1.1 [0.6–1.4] | | (1990) |
|   Processing of 0.015% formaldehyde fabric | 9 | 0.1 [0.1] | < 0.1–0.2 [< 0.1–0.3] | | |
| Garment manufacturing (USA) | | | | NR | Echt & Burr (1997) |
|   Sewers, cutters and bundlers | | | | | |
|     Personal samples | | | | | |
|       8-h TWA | 8 | 0.21 [0.26] | 0.18–0.23 [0.22–0.28] | | |
|     Area samples | 8 | 0.16 [0.19] | 0.14–0.17 [0.17–0.21] | | |
|       8-h TWA | 8 | 0.24 [0.30] | 0.17–0.30 [0.21–0.37] | | |
| | 8 | 0.21 [0.26] | 0.16–0.25 [0.20–0.31] | | |

**Table 9 (contd)**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m$^3$]) | Range or SD in ppm [mg/m$^3$] | Year | Reference |
|---|---|---|---|---|---|
| Cut and spread | | | | NR | Kennedy *et al.* (1992) |
|   Formaldehyde gas (inhalable dust) | 6 | 0.03 | SD, 0.01 | | |
|   Bound formaldehyde (inhalable dust) | 6 | < 0.01 | SD, < 0.01 | | |
|   Formaldehyde gas (total dust) | 6 | 0.04 | SD, 0.01 | | |
|   Bound formaldehyde (total dust) | 6 | < 0.01[b] | SD, < 0.01 | | |
| Turn and ticket | | | | | |
|   Formaldehyde gas (inhalable dust) | 6 | < 0.01 | SD, < 0.01 | | |
|   Bound formaldehyde (inhalable dust) | 6 | < 0.01 | SD, < 0.01 | | |
|   Formaldehyde gas (total dust) | 6 | 0.03 | SD, 0.01 | | |
|   Bound formaldehyde (total dust) | 6 | < 0.01 | SD, < 0.01 | | |
| Retail dress shops (USA) | NR | NR | 0.1–0.5 [0.1–0.6] | 1959 | Elliott *et al.* (1987) |
| Fabric shops (Finland) | 3 | 0.17 [0.21] | 0.12–0.24 [0.15–0.30] | 1985–87 | Priha *et al.* (1988) |
| Fabric stores (USA) | 77 | 0.14 [0.17] | 0.03–0.28 [0.04–0.34] | NR | McGuire *et al.* (1992) |
|   24-h area samples | | | | | |
|     Independent stores | 33 | 0.10 [0.13] | 0.03–0.28 [0.04–0.34] | | |
|     Chain stores | 44 | 0.19 [0.24] | 0.09–0.27 [0.11–0.33] | | |

NR, not reported; SD, standard deviation
[a] Arithmetic mean
[b] Five samples with non-detectable levels

the USA. Levels of exposure to formaldehyde for sewers, cutters and bundlers ranged from 0.22 to 0.28 mg/m³ (8-h TWA, 0.17–0.21 mg/m³). Area measurements of formaldehyde at cutting, sewing, pressing, spreading and receiving (storage) locations ranged from 0.21 to 0.37 mg/m³ (8-h TWA; 0.20–0.31 mg/m³). Full-shift (for 5.8–6.4 h; eight samples) personal measurements of formaldehyde in inhalable dust showed levels of up to 29 µg/mg dust; settled dust samples showed concentrations of 0.7 and 0.8 µg/mg dust (Echt & Burr, 1997). In another garment production facility in the USA, formaldehyde gas and formaldehyde bound to dust were detected at levels of 26–36 µg/m³ and 0.2–0.7 µg/m³, respectively (Kennedy *et al.*, 1992).

The use of formaldehyde-based resin to finish textiles and some garments may also result in exposure in retail shops. Measurements in dress shops in the USA in the 1950s showed levels up to 0.5 ppm [0.62 mg/m³] (Elliott *et al.*, 1987). The air in three Finnish fabric shops in the 1980s contained 0.15–0.3 mg/m³ formaldehyde (Priha *et al.*, 1988). In fabric stores in the USA that were monitored by placing samplers on a shelf in the store for 24 h, the average concentration of formaldehyde was 0.17 mg/m³ (McGuire *et al.*, 1992).

### (g)   *Foundries*

Formaldehyde-based resins are commonly used as core binders in foundries (Table 10). 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). 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 concentrations of formaldehyde measured during core-making and operations following core-making in the 1980s in Sweden and Finland were usually below 1 ppm [1.2 mg/m³]; 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 (see IARC, 1987d) and other mineral dusts, polycyclic aromatic hydrocarbons (see IARC, 1983), asbestos (see IARC, 1987e), metal fumes and dusts, carbon monoxide, isocyanates (see IARC, 1986), phenols (see IARC, 1989c), organic solvents and amines (see IARC, 1999). These exposures have been described in a previous monograph (IARC, 1984).

### (h)   *Synthetic vitreous fibre production*

Formaldehyde resins are commonly used to bind man-made vitreous fibre products. Measurements of formaldehyde in the air of plants manufacturing synthetic vitreous fibres are summarized in Table 10.

Measurements in glasswool and stonewool plants in the 1980s showed mean concentrations of 0.1–0.2 ppm [0.12–0.25 mg/m³] formaldehyde. Very high levels were measured

**Table 10. Concentrations of formaldehyde in the workroom air of foundries and during the manufacture of synthetic vitreous fibres and plastics**

| Industry and operation (location)<br>　Type of sample | No. of measurements | Mean[a]<br>(ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| **Foundries** | | | | | |
| Foundry (Sweden) | | | | 1980s | Rosén *et al.* |
| 　Hot-box method | 5 | 1.5 [1.9] | NR | | (1984) |
| 　Moulding | 17 | 0.1 [0.1] | NR | | |
| Foundries (Sweden) | | | | | Åhman *et al.* |
| 　Moulders and core-maker handling furan resin sand<br>　　8-h TWA | 36 | 0.1 [0.1] | 0.02–0.22 [0.02–0.27] | NR | (1991) |
| Foundries (Finland) | | | | Before 1975 | Heikkilä *et al.* |
| 　Core-making | 43 | 2.8 [3.4] | < 0.1–> 10 [< 0.1–> 11] | | (1991) |
| 　Core-making | 17 | 0.3 [0.4] | 0.02–1.4 [0.03–1.8] | 1981–86 | |
| 　Casting | 10 | 0.2 [0.2] | 0.02–0.2 [0.03–0.8] | 1981–86 | |
| 　Moulding | 25 | 0.3 [0.4] | 0.04–2.0 [0.05–2.5] | 1981–86 | |
| **Synthetic vitreous fibre plants** | | | | | |
| (Sweden) | | | | 1980s | Rosén *et al.* |
| 　Production | 16 | 0.15 [0.19] | NR | | (1984) |
| 　Form pressing | 4 | 0.16 [0.20] | NR | | |
| (Finland) | | | | 1981–86 | Heikkilä *et al.* |
| 　Production | 36 | 0.20 [0.25] | 0.02–1.5 [0.03–1.7] | | (1991) |
| 　Form pressing | 24 | 0.09 [0.11] | 0.01–0.3 [0.01–0.4] | | |
| **Fibrous glass manufacturing plant (USA)** | | | | NR | Milton *et al.* |
| 　Fixed location workers (*n* = 17) | 97 | 0.07; 0.05[b] | GSD, 4.0 | | (1996) |
| 　　Forming attendant (*n* = 2) | 11 | 0.07; 0.03[b] | GSD, 8.2 | | |
| 　　Forming attendant leader (*n* = 3) | 18 | 0.09; 0.07[b] | GSD, 1.9 | | |
| 　　Binder water leader (*n* = 1) | 4 | 0.05; 0.01[b] | GSD, 10.9 | | |
| 　　Binder water operator (*n* = 1) | 6 | 0.06; 0.05[b] | GSD, 2.1 | | |
| 　　Pipefitter (*n* = 1) | 5 | 0.05; 0.05[b] | GSD, 1.4 | | |
| 　　Forehearth operator (*n* = 6) | 35 | 0.07; 0.05[b] | GSD, 4.4 | | |
| 　　Curing oven machine operator (*n* = 3) | 18 | 0.08; 0.07[b] | GSD, 1.7 | | |

**Table 10 (contd)**

| Industry and operation (location) <br> Type of sample | No. of measurements | Mean[a] (ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| Mobile workers ($n = 20$) | < 100 | 0.03; 0.02[b] | GSD, 3.1 | | |
| Crew (packaging) ($n = 2$) | 12 | 0.02; 0.01[b] | GSD, 4.1 | | |
| Washwater tender ($n = 1$) | 3 | 0.04; 0.04[b] | GSD, 1.5 | | |
| Mechanical repair ($n = 7$) | 35 | 0.02; 0.01[b] | GSD, 3.4 | | |
| Electrician ($n = 5$) | 25 | 0.03; 0.02[b] | GSD, 3.1 | | |
| Sheet metal worker ($n = 2$) | 10 | 0.03; 0.02[b] | GSD, 2.7 | | |
| Welder ($n = 2$) | 10 | 0.04; 0.03[b] | GSD, 2.6 | | |
| Pipefitter ($n = 1$) | 5 | 0.03; 0.02[b] | GSD, 1.9 | | |
| **Plastics production** | | | | | |
| Production of moulded plastic products (USA) | | | | 1983–84 | Stewart *et al.* |
| Plant no. 8, phenol resin, summer | 10 | 0.5[b] [0.6] | 0.1–0.9 [0.1–1.1] | | (1987) |
| Plant no. 9, melamine resin, summer | 13 | 9.2[b] [11.3] | < 0.01–26.5 [< 0.01–32.6] | | |
| Moulding compound manufacture (USA) | | | | | |
| Plant no. 9, winter | 9 | 2.8[b] [3.4] | 0.04–6.7 [0.05–8.2] | | |
| Plant no. 9, summer[c] | 18 | 38.2[b] [47.0] | 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] | | |
| Plastics production (Finland) | | | | 1981–86 | Heikkilä *et al.* |
| Casting of polyacetal resin | 10 | 0.3 [0.4] | 0.06–0.7 [0.08–0.8] | | (1991) |
| Casting of urea–formaldehyde resin | 4 | 0.4 [0.5] | 0.2–0.5 [0.3–0.6] | | |
| Casting of other plastics | 29 | < 0.1 [< 0.1] | < 0.1–0.2 [< 0.1–0.3] | | |
| Plastics manufacturing (Canada) | | | | | Tikuisis *et al.* |
| Polyethylene extrusion | 9 | NR | max., [< 0.12] | NR | (1995) |

GSD, geometric standard deviation; NR, not reported; TWA, time-weighted average

[a] Arithmetic mean unless otherwise specified

[b] Geometric mean

[c] Some of the results were affected by the simultaneous occurrence in the samples of particulates that contained formaldehyde (leading to high values).

occasionally in factories close to cupola ovens and hardening chambers (Heikkilä *et al.,* 1991). Other exposures in man-made vitreous fibre production have been described in a previous monograph (IARC, 2002).

Personal measurements of maintenance and production workers were taken in a fibreglass insulation manufacturing plant. The average level of exposure to formaldehyde for all fixed location workers (basement workers, forehearth operators and curing oven operators; 17 samples) was 0.07 mg/m$^3$. The mean of the measurements for all mobile workers (packaging crew, washwater tender, mechanical repairer, electrician, sheet metal workers, welder and pipefitter; 20 samples) was 0.03 mg/m$^3$. No measurement was below the limit of detection (Milton *et al*., 1996).

### (*i*)    *Plastics production*

Formaldehyde-based plastics are used in the production of electrical parts, dishware and various other plastic products (Table 10).

The concentrations of formaldehyde measured in such industries have usually been < 1 ppm [1.2 mg/m$^3$], but much higher exposures may occur. Plastic dust and fumes may be present in the atmospheres of moulded plastic 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 USA where moulding compounds were used. Some workers may have been exposed to pigments, lubricants and fillers (e.g. historically, asbestos and wood flour) that were used as constituents of moulding compounds (Stewart *et al.*, 1987).

An experimental scenario was created in Canada to evaluate thermal decomposition products that are emitted from the extrusion of polyethylene into a variety of products. Eight-hour area samples, collected at worst-case locations at typical operator locations, and 8-h personal samples were collected. All levels of formaldehyde were below 0.12 mg/m$^3$ (Tikuisis *et al*., 1995).

### (*j*)    *Firefighters*

Measurements of the exposure of firefighters to formaldehyde are given in Table 11. One study measured personal exposures to formaldehyde outside a self-contained breathing apparatus (if worn) while fighting fires in two cities in the USA. Formaldehyde was detected in six of 24 samples. Concentrations ranged from 0.1 to 8.3 ppm [0.12–10.2 mg/m$^3$], with a second highest concentration of 3.3 ppm [4.1 mg/m$^3$] (Brandt-Rauf *et al*., 1988). In another study in the USA, levels of formaldehyde ranged from the limit of detection (0.13 mg/m$^3$) to 9.8 mg/m$^3$ during knockdown (when the main body of the fire is brought under control), and formaldehyde was detected in 73% of the samples, from the limit of detection to 0.5 mg/m$^3$, during overhaul (searching for and extinguishing hidden fires) for 22 fires (Jankovic *et al*., 1991). Exposure levels inside the self-contained breathing masks ranged from the limit of detection to 0.4 mg/m$^3$. Two of the measurements during knockdown exceeded the 15-min short-term exposure limit (STEL) of 2.5 mg/m$^3$.

**Table 11. Concentrations of formaldehyde during firefighting and exposure to engine exhausts**

| Industry and operation (location) Type of sample | No. of measurements | Mean[a] (ppm [mg/m$^3$]) | Range (ppm [mg/m$^3$]) | Year | Reference |
|---|---|---|---|---|---|
| **Firefighting** | | | | | |
| City fire (USA) | 24 | 0.55 [0.68][b] | 0.1–8.3 [0.1–10.2][b] | 1986 | Brandt-Rauf *et al.* (1988) |
| City fire (USA) | 22 fires | | | NR | Jankovic *et al.* (1991) |
| Knockdown[c] | | NR | ND–8 [ND–9.8] | | |
| Overhaul[c] | | NR | ND–0.4 [ND–0.5] | | |
| Inside mask | | NR | ND–0.3 [ND–0.4] | | |
| Wildland fire (USA) | 5 | 0.05 [0.06] | 0.02–0.07 [0.02–0.09] | 1990 | Reh *et al.* (1994) |
| Wildland fire (USA) | 30 | 0.13 [0.16] | 0.04–0.3 [0.05–0.4] | 1989 | Materna *et al.* (1992) |
| City fire (USA) | 96 | 0.25 [0.31] | 0.02–1.2 [0.02–1.5] | 1998 | Bolstad-Johnson *et al.* (2000) |
| **Engine exhaust** | | | | | |
| Chain-sawing (Sweden) | NR | 0.05 [0.06] | 0.02–0.11 [0.03–0.13] | NR | Hagberg *et al.* (1985) |
| Chain-sawing (Finland) 8-h TWA | NR | < 0.1 [< 0.1] | < 0.1–0.5 [< 0.1–0.6] | NR | Heikkilä *et al.* (1991) |
| Automobile garage Personal samples | 53 | 0.03 [0.04] | NR | NR | Zhang *et al.* (2003) |

ND, not detected; NR, not reported; TWA, time-weighted average

[a] Arithmetic mean

[b] Excluding 18 values noted as 0

[c] See text for definitions

A comprehensive study that monitored air was conducted to characterize exposures of firefighters during 25 structure fires. Exposures of firefighters during overhaul, when they look for hidden fire inside attics, ceilings and walls often without respiratory protection, were measured. Ceiling values for formaldehyde (National Institute for Occupational Safety and Health [NIOSH]; 0.1 ppm [0.12 mg/m$^3$]) were exceeded at 22 fires (Bolstad-Johnson *et al.*, 2000).

Limited studies of exposure to aldehydes that is related to forest and wildland fires indicate lower exposures. Formaldehyde was detected in all 30 samples collected during a study of wildland fires. Concentrations ranged from 0.048 to 0.42 mg/m$^3$; the mean was 0.16 mg/m$^3$ (Materna *et al.*, 1992). A smaller study by NIOSH also detected formaldehyde in each of five samples collected during wildfire. Concentrations ranged from 0.02 to 0.07 ppm [0.02–0.09 mg/m$^3$] and the mean was 0.05 ppm [0.06 mg/m$^3$] (Reh *et al.*, 1994).

(*k*)    *Automobile and engine exhausts*

Engine exhausts are a source of exposure to formaldehyde (see Section 1.3.3; Table 11).

Maître *et al.* (2002) evaluated individual airborne exposures to gaseous and particulate pollutants of a group of policemen who worked close to traffic in the centre of Grenoble, France. Personal active air samples were collected during the workshifts of eight policemen in summer and winter during the occurrence of a thermal inversion phenomenon for 4 days at each period. Stationary air samples were taken in the policemen's work area during the same period. The median concentration of the personal samples for formaldehyde was 14 µg/m$^3$ in the summer and 21 µg/m$^3$ in the winter.

Zhang *et al.* (2003) examined whether work in an automobile garage and tobacco smoke can significantly affect personal exposure to a number of important carbonyl compounds, including formaldehyde. The study was carried out on 22 garage workers (nine smokers and 13 nonsmokers) and 15 non-garage workers (four smokers and 11 non-smokers). Daily exposure was estimated using 48-h integrated measurements of breathing zone concentrations. The mean formaldehyde concentrations were: 40.6 µg/m$^3$ for smoking garage workers, 41.1 µg/m$^3$ for nonsmoking garage workers, 34.6 µg/m$^3$ for smoking non-garage workers and 30.2 µg/m$^3$ for nonsmoking non-garage workers (total range, 14.1–80.1 µg/m$^3$).

(*l*)    *Offices and public buildings*

Concentrations of formaldehyde in offices and public buildings (museums, geriatric homes) are given in Table 12.

In Australia, measurements of formaldehyde over 3–4 days were found to average 0.03 mg/m$^3$ in conventional offices and 1.4 mg/m$^3$ in portable office buildings (Dingle *et al.*, 2000).

Exposure measurements were taken for an epidemiological study of nasal symptoms in a Swedish office building that had recently been painted with low-emitting products [the

**Table 12. Concentrations of formaldehyde in offices and miscellaneous other workplaces**

| Industry and operation (location)<br>Type of sample | No. of measurements | Mean (ppm [mg/m³])[a] | Range (ppm [mg/m³])[a] | Year | Reference |
|---|---|---|---|---|---|
| **Offices** | | | | | |
| Offices (USA) | 25 | 80.0[b] µg/m³ | NR | 1981–84 | Shah & Singh (1988) |
| Non-industrial office workplaces and restaurants (Brazil) | 12 | 20.4 µg/m³ | 4.7–60.7 µg/m³ | 1993 | Miguel *et al*. (1995) |
| Four offices on several floors of an office building (Brazil) | 11 | 40 µg/m³ | 12.2–99.7 µg/m³ | 1995 | Brickus *et al*. (1998) |
| Offices (Sweden) | | | | 1995–96 | Wieslander *et al*. (1999a) |
|    Recently painted with low-emitting paint | NR | 18 µg/m³ | 16–20 µg/m³ | | |
|    Three months later | NR | 8 µg/m³ | 7–10 µg/m³ | | |
|    Control (at the time and 3 months later) | NR | 8 µg/m³ | 8–9 µg/m³ | | |
| Offices (Australia) | | | | NR | Dingle *et al*. (2000) |
|    Conventional offices (18 sites) | NR | 27 µg/m³ | 12–96 µg/m³ | | |
|    Portable office buildings (20 sites) | 40 | 1400 µg/m³ | 516–2595 µg/m³ | | |
| Six office buildings (USA) | [72] | 1.7–13.3 µg/m³ [c] | NR | 1996–97 | Reynolds *et al*. (2001) |
| Five office buildings (Taiwan, China)<br>  8-h average during working time from measurements conducted continuously ≥ 24 h | 54 | 140–1190 µg/m³ [d] | NR | NR | Wu *et al*. (2003) |
| **Miscellaneous** | | | | | |
| Coal coking plant (former Czechoslovakia) | NR | 0.05[e] [0.06] | < 0.01–0.25 [< 0.01–0.3] | NR | Mašek (1972) |
| Pitch coking plant (former Czechoslovakia) | NR | 0.4[e] [0.5] | 0.05–1.6 [0.07–2.0] | NR | Mašek (1972) |
| Electrical machinery manufacture (Finland) | | | | 1977–79 | Niemelä & Vainio (1981) |
|    Soldering | 47 | < 0.1 [< 0.1] | NR | | |
|    Lacquering and treatment of melamine plastics | 8 | 0.35 [0.4] | NR | | |
| Rubber processing (USA) | NR | NR | 0.4–0.8 [0.5–0.98] | 1975 | IARC (1982) |
| Painting with bake-drying paints (Sweden) | 13 | < 0.1 [< 0.1] | NR | 1980s | Rosén *et al*. (1984) |
| Abrasive production (Sweden) | 20 | 0.2 [0.3] | NR | 1980s | Rosén *et al*. (1984) |

**Table 12 (contd)**

| Industry and operation (location)<br>    Type of sample | No. of<br>measurements | Mean<br>(ppm [mg/m³])[a] | Range (ppm [mg/m³])[a] | Year | Reference |
|---|---|---|---|---|---|
| Sugar mill (Sweden) | | | | 1980s | Rosén *et al.* (1984) |
|     Preservation of sugar beets | 26 | 0.4 [0.5] | NR | | |
| Fur processing | 16 | NR | 0.8–1.6 [1.0–2.0] | 1980s | Rosén *et al.* (1984) |
|     8-h TWA | | | | | |
| Photographic film manufacture (USA) | | | | 1983–84 | Stewart *et al.* (1987) |
|     Plants no. 4 and 5, summer | 49 | 0.1[e] [0.1] | < 0.01–0.4 [< 0.01–0.5] | | |
|     Plants no. 4 and 5, winter | 29 | 0.3[e] [0.4] | 0.02–0.9 [0.03–1.1] | | |
| Agriculture (Finland) | | | | | Heikkilä *et al.* (1991) |
|     Handling of fodder | NR | NR | 0.02–0.4 [0.03–0.5] | 1982 | |
|     Disinfection of eggs | 11 | 2.6 [3.2] | 0.2–7.8 [0.3–9.6] | 1981–86 | |
| Metalware plant, bake painting (Finland) | 18 | 0.3 [0.4] | 0.03–0.7 [0.04–0.9] | 1981–86 | Heikkilä *et al.* (1991) |
| Print (Finland) | | | | 1981–86 | Heikkilä *et al.* (1991) |
|     Development of photographs | 11 | 0.04 [0.05] | 0.02–0.1 [0.03–0.13] | | |
| 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] | | |
| Photographic laboratories (Finland) | 10 | 0.07 [0.09] | 0.02–0.3 [0.03–0.40] | 1981–86 | Heikkilä *et al.* (1991) |
| Fish hatchery (USA) | | | | NR | Lee & Radtke (1998) |
|     Treating fish eggs (6 sites) | 6 | 0.02 [0.02] | 0.006–0.038 [0.007–0.05] | | |
|         8-h TWA | | | | | |

NR, not reported; TWA, time-weighted average
[a] Arithmetic mean unless otherwise specified; values in ppm [mg/m³], unless stated otherwise
[b] Median
[c] Range of geometric means
[d] Range of arithmetic means
[e] Mean of arithmetic means

recency was not identified but appeared to be within a few months]. The measurements taken at that time showed average levels of formaldehyde of 18 μg/m³ (range, 16–20 μg/m³); those taken 3 months later averaged 8 μg/m³ (range, 7–10 μg/m³) (Wieslander *et al.*, 1999a). The latter were equivalent to the levels found in the same office complex in an area that had not been redecorated (mean, 8–9 μg/m³).

Laser-jet printers have been found to be a source of formaldehyde, as a result of the ozonolysis reactions of volatile organic compounds emitted from the toner powder (Wolkoff *et al.*, 1992; Tuomi *et al.*, 2000). In a study in an office environment in Finland (Tuomi *et al.*, 2000), the emission rate of formaldehyde of three printers that used traditional corona-discharge technology (dating from approximately 1990) ranged from 9 to 46 μg/m³, whereas a newer technology printer did not produce detectable levels of formaldehyde.

In another study in Sweden, average levels of formaldehyde in four geriatric homes ranged from 2 to 7 μg/m³ (Wieslander *et al.*, 1999b).

### (*m*)    *Miscellaneous*

Formaldehyde is used in agriculture as a preservative for fodder and as a disinfectant (Table 12). For example, fodder was preserved with a 2% formalin solution several times per year from the late 1960s until the early 1980s on farms in Finland. As the air concentration during preservation was < 0.5 ppm [0.6 mg/m³], the annual mean exposure was 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/m³], but annual exposure from this source probably remains very low (Heikkilä *et al.*, 1991).

One worker in each of six different fish hatcheries in the USA was monitored once over the 15–90-min period it took to treat fish eggs with a formalin solution to control infection. Concentrations ranged from not quantifiable to 1 mg/m³. Area measurements during treatment were < 0.062–0.84 mg/m³, and 8-h TWAs were reported to be < 0.01–0.05 mg/m³ (mean, 0.02 mg/m³) (Lee & Radtke, 1998).

Formaldehyde is also used or formed during many other industrial operations, such as treatment of fur and leather, preservation of barley and sugar beets, coal and pitch coking, rubber processing and production of abrasives (Table 12). 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 TWA concentration of formaldehyde was assessed to be 0.8–1.6 ppm [1.0–2.0 mg/m³] and high peak exposures occurred many times per day (Rosén *et al.*, 1984).

Heating of bake-drying paints and soldering may release some formaldehyde in plants where metalware and electrical equipment are produced, but the measured concentrations are usually well below 1 ppm [1.2 mg/m³] (Rosén *et al.*, 1984).

The mean concentrations of formaldehyde measured during the coating of photographic films and during development of photographs are usually well below 1 ppm [1.2 mg/m³]

(Table 12). Methanol, ethanol, acetone and ammonia are other volatile agents that may occur in film manufacturing facilities (Stewart *et al.*, 1987).

Formaldehyde has been found consistently in spacecraft atmospheres at concentrations that exceed the 180-day spacecraft maximum allowable concentration of 0.05 mg/m$^3$. The source is thought to be hardware off-gassing and possibly leakage from experiments that involve fixatives. Small amounts could also be present from human metabolism and exhalation (James, 1997).

### 1.3.3   *Ambient (outdoor) air*

Measurements of indoor and outdoor levels of formaldehyde have been generated in many countries for several decades. Standard sampling and analytical methodologies are sufficiently sensitive to detect formaldehyde in most samples of ambient (outdoor) air. Concentrations of formaldehyde in urban, suburban and rural areas are presented in Table 13.

Although formaldehyde is a natural component of ambient air, anthropogenic sources usually contribute most to the levels of formaldehyde in populated regions, since 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 (De Serves, 1994; IARC, 1995; Environment Canada/ Health Canada, 2001).

Outdoor air concentrations of formaldehyde in urban environments are more variable and depend on local conditions. They are usually in the range of 1–20 µg/m$^3$ (Preuss *et al*., 1985; IARC, 1995; Jurvelin, 2001). Urban air concentrations in heavy traffic or during severe inversions can range up to 100 µg/m$^3$ (Báez *et al.*, 1995; IARC, 1995; Williams *et al.*, 1996; de Andrade *et al.*, 1998).

A major source of formaldehyde in urban air is incomplete combustion of hydrocarbon fuels, especially from vehicle emissions (Vaught, 1991; Pohanish, 2002). Combustion processes account directly or indirectly for most of the formaldehyde that enters the atmosphere, particularly from engines that are not equipped with catalytic converters (WHO, 1989; Pohanish, 2002). In the USA, emissions of formaldehyde from automobiles were estimated to be about 277 million kg each year just prior to the introduction of the catalytic converter in 1975 (Environmental Protection Agency, 1976) and to have decreased since (Zweidinger *et al.*, 1988). In Mexico, a comparison of exhaust emissions from light-duty vehicles in the early 1990s showed a 10–30-fold decrease in emissions of formaldehyde from vehicles that were equipped with a catalytic converter compared with those with no catalyst (Schifter *et al*., 2001). In contrast, emissions of formaldehyde from automobile exhaust have been reported to have risen again with the introduction of oxygenated fuels (Kirchstetter *et al*., 1996). Gaffney *et al*. (1997) found that, in Albuquerque (NM, USA), the introduction of oxygenated fuels was associated with higher ambient air levels of formaldehyde during the winter, the season during which these fuels were used. Levels of

**Table 13. Occurrence of formaldehyde in outdoor (ambient) air**

| Country | Location/region | Settings | Sampling period | No. of samples | Mean concentration or range of means ($\mu g/m^3$)[a] | Range ($\mu g/m^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| Algeria | Algiers | Urban | 2000–01 | 10 | 12.7 | 5.2–27.1 | | Cecinato et al. (2002) |
| | Ouargla | Urban | | 4 | 4.0 | 2.6–5.2 | | |
| | Algiers | Suburban | | 14 | 11.9 | 6.0–21.2 | | |
| Austria | Exelberg | Semi-rural | 1986–87 | 21 | 6.4–13.4 ppb | NR | Measured in July and August | Puxbaum et al. (1988) |
| | Raasdorf | Semi-rural | | 18 | 6.6–11.1 ppb | NR | Measured in July and August | |
| | Schoeneben | Rural | | 20 | 4.0–8.9 ppb | NR | Measured in September | |
| Brazil | São Paulo and Rio de Janeiro | Urban | 1993 | 12 | 10.7 | 4.0–27.7 | Measured outside non-industrial office workplaces and restaurants | Miguel et al. (1995) |
| | Salvador, Bahia | Urban | NR | 68 | 2.9–80 ppb | 1.3–88 ppb | Collected at six sites around the city | de Andrade et al. (1998) |
| | Rio de Janeiro | Rural | 1995 | 37 | 1.2–1.5 ppb | 0.2–4.6 ppb | Collected at two sites in rural area | Brickus et al. (1998) |
| | | Urban | | 11 | 14.5 ppb | 7.1–21.0 ppb | Measured outside of an office building | |
| | São Paulo | Urban | 1999 | 37 | | | Collected in winter at two sites: | Montero et al. (2001) |
| | | | | | 16.4–18.0 ppb | 1.1–46.3 ppb | Morning | |
| | | | | | 10.7–13.1 ppb | 1.2–28.3 ppb | Midday | |
| | | | | | 9.8–10.7 ppb | 2.7–38.1 ppb | Evening | |
| | São Paulo | Urban | 1997 | 11 | 5.0 ppb | 1.4–9.7 ppb | Measured in February during use of alcohol fuel | Nguyen et al. (2001) |
| | Theobroma | Rural | 1995 | 15 | 12.8 ppb daytime, 16.5 ppb nighttime, 8.6 ppb | 5–25 ppb | Measured during 1 week of an open agricultural and silvi-cultural biomass burning period | Reinhardt et al. (2001) |
| | Rio de Janeiro | Urban | 2000 | 13 | 10.8 | NR | Collected from May to November during morning commute | Grosjean et al. (2002) |
| | Rio de Janeiro | Urban | 1998–2001 | 28 | 13.7 ppb | 1.5–54.3 ppb | Measured on a high traffic street in the downtown area | Corrêa et al. (2003) |

**Table 13 (contd)**

| Country | Location/region | Settings | Sampling period | No. of samples | Mean concentration or range of means ($\mu g/m^3$)[a] | Range ($\mu g/m^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| Canada | Ontario | Rural | 1988 | 49<br>47 | 1.6 ppb<br>1.8 ppb | 0.6–4.4 ppb<br>0.7–4.2 ppb | Dorset site<br>Egbert site | Shepson *et al.* (1991) |
| | Alert, Nunavut | Remote | 1992 | NR | 0.48<br>NR | 0.04–0.74<br>0.12–0.86 | Polar night<br>Sunlit period | De Serves (1994) |
| | Nova Scotia | Remote | 1993 | 108 | NR | < 0.6–4.2 | Summer measurements | Tanner *et al.* (1994), cited in Environment Canada/Health Canada (2001) |
| | Six provinces | Various | 1989–98 | NR<br>NR<br>NR | NR<br>NR<br>NR | ND–27.5<br>ND–12.0<br>ND–9.9 | Measured at eight urban sites<br>Measured at two suburban sites<br>Measured at six rural sites | Environment Canada (1999), cited in Environment Canada/Health Canada (2001) |
| | | Rural | 1995–96<br>Spring<br>Summer<br>Winter | NR | NR | <br>max., 3.0<br>max., 1.7<br>max., 4.4 | Near a forest product plant | Environment Canada (1997), cited in Environment Canada/Health Canada (2001) |
| | Prince Rupert, BC | Urban, residential, and industrial areas | 1994–95 | 96 | 0.7–3.9 | 0.08–14.7 | Collected from the roofs at four sites | Environment Canada/Health Canada (2001) |
| | Various | Urban and suburban | 1990–98 | 2819 | 3.3 (2.8)[b] | | Four urban and four suburban sites from the National Air Pollution Survey programme | Liteplo & Meek (2003) |

**Table 13 (contd)**

| Country | Location/region | Settings | Sampling period | No. of samples | Mean concentration or range of means ($\mu g/m^3$)[a] | Range ($\mu g/m^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| China | Hong Kong | Urban | 1997–2000 | 182 | 3.6–4.2<br>4.8–5.1 | 0.6–10<br>1.9–11 | Residential and commercial<br>Residential, commercial and light industrial | Sin *et al.* (2001) |
| | Hong Kong | Urban | 1999–2000 | 41 | 4.1<br>5.9<br>2.6 | 1.0–11.3<br>NR<br>NR | Overall average (12 months)<br>Summer average (May–August)<br>Winter average (November–February) | Ho *et al.* (2002) |
| | Guangzhou | Urban | 2002 | 25 | 12.4 | 6.4–29.0 | Measured outside a hotel in the evening on 7 consecutive days | Feng *et al.* (2004) |
| Denmark | Copenhagen | Urban | 1994 | 37 | 2.6 ppb | 0.2–6.4 ppb | Winter measurements (February) | Granby *et al.* (1997) |
| | Lille Valby | Semi-rural | | 18 | 0.9 ppb | 0.1–2.8 ppb | Winter measurements (February) | |
| | | | | 28 | 0.8 ppb | 0.3–1.8 ppb | Spring measurements (April) | |
| | Lille Valby | Semi-rural | 1995 | 244 | 1.2 ppb | 0.1–4.7 ppb | Measured in May–July | Christensen *et al.* (2000) |
| Egypt | Cairo | Urban | 1999 | 98<br>49<br>49 | 33 ppb<br>29 ppb<br>37 ppb | SD, 8.6<br>SD, 7.1<br>SD, 9.5 | Residential area<br>    Spring<br>    Summer | Khoder *et al.* (2000) |
| France | Grenoble | Urban | 1995 | NR | NR | 2–18 ppb | Measured during 1 week in May | Ferrari *et al.* (1998) |
| | Paris | Urban and semi-urban | 1985 | NR | 2–32 ppb | NR | Measured at one urban site and three rural sites with some urban influence | Kalabokas *et al.* (1988) |

**Table 13 (contd)**

| Country | Location/region | Settings | Sampling period | No. of samples | Mean concentration or range of means $(\mu g/m^3)^a$ | Range $(\mu g/m^3)^a$ | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| Germany | Mainz-Finthen | Semi-rural | 1979 | 14 | 1.9 ppb | 0.7–5.1 ppb | Measured during July–October | Neitzert & Seiler (1981) |
| | Deuselbach | Rural | | 14 | 1.7 ppb | 0.4–3.8 ppb | Measured during November | |
| | The Alps | Rural | 1991 | NR | 1.3 ppb | 0.4–3.3 ppb | Measurement at summit of Wank mountain in October | Slemr & Junkermann (1992) |
| | Schauinsland | Rural | 1992 | 22 | 1.0 ppb | 0.4–2.3 ppb | Measured continuously over 11 days | Slemr *et al.* (1996) |
| Hungary | Budapest | Urban | 1987–89 | 185 | 14.9 ppb 34.6 ppb | ND–58 ppb 7–176 ppb | Measured at downtown site Measured at the border of downtown with a possible local emission source | Haszpra *et al.* (1991) |
| Italy | Rome | Urban | 1994–95 | 56 57 | 17.0 ppb 11.2 ppb | 8.8–27.7 ppb 8.2–17.0 ppb | Measured in summer 1994 Measured in winter 1995 | Possanzini *et al.* (1996) |
| | Milan | Urban | 1998–99 | NR | NR 5.9 8.0–15.7 | 4.1–53.4 NR NR | Winter measurements (six sites) Rural-industrial (one site) Urban (five sites) | Andreini *et al.* (2000) |
| Japan | Takasaki | Urban | 1984 | 38 | NR | 2.5–11.4 ppb | Measured during July and August | Satsumabayashi *et al.* (1995) |
| | Osaka | Urban | 1997 | NR | 1.9 ppb | 0.1–4.3 ppb | Measured in October–December | Nguyen *et al.* (2001) |
| | Nagoya | NR | 1998 | 37 | 5.8[c] | GSD, 1.5 | Measured in February | Sakai *et al.* (2004) |
| Lithuania | Kaunas | NR | 1998 | NR | 3.1 | 1.4–5.3 | Measured at 12 municipal monitoring sites | Maroziene & Grazuleviciene (2002) |
| Mexico | Mexico City | Urban | 1993 | 48 | 35.5 ppb | 5.9–110 ppb | Measured at the University of Mexico campus | Báez *et al.* (1995) |
| | Mexico City and Xalapa | Urban | 1996–98 | 145[d] | 4–32 | 2–63 | Measured outside two houses, three museums and two offices | Báez *et al.* (2003) |

**Table 13 (contd)**

| Country | Location/region | Settings | Sampling period | No. of samples | Mean concen-tration or range of means ($\mu g/m^3$)[a] | Range ($\mu g/m^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| Norway | Drammen | Urban | 1994–97<br>1998–2000 | 974<br>973 | 8.9<br>2.9 | NR<br>NR | Reduction of mean levels attributed to increase in vehicles with catalysts | Hagen *et al.* (2000); Oftedal *et al.* (2003) |
| South Africa | Cape Point | Semi-rural | 1979 | 5 | 0.5 ppb | 0.2–1.0 ppb | Measured during December | Neitzert & Seiler (1981) |
| Spain | Madrid | Urban | 1996 | NR | 9.0 | 4.7–20 | Air sampling in September–October from 8 h to 16 h | García-Alonso & Pérez-Pastor (1998) |
| Sweden | Uppsala | Urban | 1998 | 27 | 1.3[c] | GSD, 1.8 | Measured in February–May near 22 houses and five apartments | Sakai *et al.* (2004) |
| Taiwan, China | Taipei | Urban | 1999 | NR | 7.2–9.8 ppb | range of max., 20.6–34.8 ppb | Measured from February–June at five locations | Mathew *et al.* (2001) |
| United Kingdom | London | Urban | 1991–92 | 9<br>7 | 19.2 ppb<br>7.4 ppb | ND–98 ppb<br>0.8–13.5 ppb | West London, residential area<br>North London, residential area | Williams *et al.* (1996) |
| USA | Country-wide | Various<br>Urban<br>Suburban<br>Rural | 1975–85 | 629<br>332<br>281<br>12 | 8.3 ppb (4.1 ppb)[b]<br>6.5 ppb[b]<br>2.7 ppb[b]<br>2.7 ppbv[b] | NR<br>NR<br>NR<br>NR | All sites combined[e] | Shah & Singh (1988)[f] |
| | Atlanta, GA | Urban | 1992 | 217 | 2.7–3.0 ppb | max., 8.3 ppb | Measured at four locations during July and August | Grosjean *et al.* (1993) |
| | Albany, NY | Semi-urban | 1991 | NR | NR | 0.6–3.7 ppb | Measured during October | Khwaja (1995) |
| | Boston, MA | Residential | 1993 | 8 | 3.1 ppb | 0–3.1 ppb | Winter measurements, outside four residences | Reiss *et al.* (1995) |
| | | | | 18 | 2.6 ppb | 1.2–5.9 ppb | Summer measurements, outside nine residences | |

**Table 13 (contd)**

| Country | Location/region | Settings | Sampling period | No. of samples | Mean concen- tration or range of means (µg/m$^3$)[a] | Range (µg/m$^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|---|
| USA (contd) | Denver, CO | Urban | 1987–91 | NR | 3.9 ppb 2.3 ppb 2.7 ppb | NR NR NR | Measured in winter Measured in spring Measured in summer | Anderson *et al.* (1996) |
| | Los Angeles, CA | Urban | 1993 | 32 | 5.3 ppb | 1.4–10.6 ppb | Measured during the smog season (September) | Grosjean *et al.* (1996) |
| | | Rural | | | 0.8 ppb | 0.7–1.0 ppb | Background location | |
| | Eniwetok Atoll | Remote | 1980 | 7 | 0.4 ppb | max., 0.8 ppb | South Pacific | Preuss *et al.* (1985) |
| | Minnesota | Mixed | 1991–99 | 2494 | 1.7 (1.37)[b] | < 0.05–21 | Collected at 25 sites throughout the state for varying periods of time | Pratt *et al.* (2000) |
| | New York City, NY | Urban | 1999 | 36 36 | 2.1 5.3 | | Winter measurements Summer measurements | Kinney *et al.* (2002) |
| | Los Angeles County, CA | Semi-urban | 1999–2000 | 69 | 7.2 ppb | 4.3–14.0 ppb | | Delfino *et al.* (2003) |
| | California | Urban | 1990–2002 | NR | 2.0–4.3 | NR | Range of annual averages | California Air Resources Board (2004) |

GSD, geometric standard deviation; NR, not reported; SD, standard deviation
[a] Unless otherwise specified
[b] Median
[c] Geometric mean
[d] Number of indoor and outdoor measurements combined (see Table 14)
[e] Includes urban, suburban, rural, remote and source-dominated sources.
[f] Data collected from literature searches, direct contacts with individuals and organisations, reports, computer tapes and direct electronic transfers

formaldehyde in vehicle emissions in 1994 were found to increase by 13% within 2 months after the average oxygen content of fuels sold in the San Francisco Bay (CA, USA) area increased from 0.3 to 2.0% by weight (Kirchstetter *et al*., 1996). In the Denver (CO, USA) area, use of oxygenated fuels was associated with a 20–75% increase in ambient air levels of formaldehyde, although nearly all ambient air measurements remained below 6 $\mu$g/m$^3$ (Spitzer, 1997). Local air concentrations as high as 35.4, 41.8 and 44.2 $\mu$g/m$^3$ have been reported inside vehicles, in parking garages and at service stations, respectively (Spitzer, 1997).

Formaldehyde was detected (detection limit, 0.05 $\mu$g/m$^3$) in 3810 of 3842 24-h samples from rural, suburban and urban areas in Canada that were collected at 16 sites in six provinces surveyed from August 1989 to August 1998 (Environment Canada, 1999, cited in Environment Canada/Health Canada, 2001). Concentrations ranged from below the detection limit to a maximum of 27.5 $\mu$g/m$^3$ for eight urban sites, a maximum of 12.03 $\mu$g/m$^3$ for two suburban sites and a maximum of 9.88 $\mu$g/m$^3$ for six rural sites. Long-term (1 month–1 year) mean concentrations for the rural sites ranged from 0.78 to 8.76 $\mu$g/m$^3$. Monthly mean concentrations were highest during the summer, but there was no apparent long-term trend in concentrations of formaldehyde at these sites over this 9-year period (Environment Canada/Health Canada, 2001).

In addition to primary emissions of formaldehyde in vehicle exhaust, secondary formation of formaldehyde by oxidation of alkenes in the atmosphere is also an important source (Altshuller, 1993; Seila *et al.*, 2001). Patterns of diurnal and seasonal variation in levels of formaldehyde and formaldehyde:acetaldehyde ratios have led to the suggestion that natural sources of alkenes add significantly to anthropogenic emissions, particularly during the summer months (Gaffney *et al*., 1997; Viskari *et al*., 2000). Photo-oxidation is also a primary degradation pathway for formaldehyde in the atmosphere, with an estimated half-life in the range of a few hours (ATSDR, 1999).

### 1.3.4   *Residential indoor air*

The occurrence of formaldehyde in indoor air in private housing and public settings is summarized in Table 14.

Levels of formaldehyde in indoor air are often higher by one order of magnitude or more than those outdoors. The concentrations in dwellings depend on the sources of formaldehyde that are present, the age of the source materials, ventilation, temperature and humidity. Indoor sources include pressed wood products (e.g. plywood, particle-board), some insulation materials, carpets, paints and varnishes, clothing and fabrics, cooking, tobacco smoke and the use of formaldehyde as a disinfectant (Gammage & Gupta, 1984; IARC, 1995; Dingle *et al*., 2000; Hodgson *et al*., 2000, 2002; Jurvelin, 2003). Off-gassing of urea–formaldehyde foam insulation and particle-board has been reported historically to be a major source of formaldehyde in some dwellings.

In a study on indoor emissions of formaldehyde, quasi steady-state emission rates of formaldehyde from new carpets were measured in a large-scale environmental chamber

**Table 14. Occurrence of formaldehyde in indoor air in residential and public settings**

| Country | Location/ region | Sampling period | No. of samples | Mean concentration or range of means ($\mu g/m^3$)[a] | Range ($\mu g/m^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|
| **Residential** | | | | | | | |
| Australia | Victoria | 1994–95 | NR | 12.6 ppb[b] | | Eighty households | Garrett et al. |
| | | | | 13.8 ppb[b] | < 0.3–105 | Bedroom | (1997, 1999) |
| | | | | 11.3 ppb[b] | < 0.3–108 | Living-room | |
| | | | | 11.4 ppb[b] | < 0.3–108 | Kitchen | |
| Austria | Burgenland, Carinthia and Styria | 1988–89 | 234 apartments | < 30–100 ppb | | Measured in 33% of the apartments | Koeck et al. (1997) |
| | | | | 100–500 ppb | | Measured in 48% of the apartments | |
| | | | | > 500 ppb | | Measured in 19% of the apartments | |
| Canada | Quebec City, QC | NR | 28 | 7.3 | max., 20.2 | Basement, with combustion appliance | Lévesque et al. |
| | | | 3 | 9.2 | max., 19.7 | Basement, without combustion appliance | (2001) |
| | | | 34 | 8.2 | max., 23.4 | Ground floor, with combustion appliance | |
| | | | 6 | 9.9 | max., 19.5 | Ground floor, without combustion appliance | |
| | Various | 1989–95 | 151 | 35.9 (29.8[b]) | NR | Pooled data from five studies at various locations | Liteplo & Meek (2003) |
| Egypt | Cairo | 1999 | 294 | | | Seven apartments | Khoder et al. |
| | | | | 89 ppb | 35–192 ppb | Kitchen | (2000) |
| | | | | 100 ppb | 30–213 ppb | Bedroom | |
| | | | | 100 ppb | 28–225 ppb | Living room | |
| | | | 147 | 87.6 ppb | NR | Measured in spring | |
| | | | 147 | 105.6 ppb | NR | Measured in summer | |
| France | Paris | 2001 | | | | Sixty-one dwellings in Paris and suburbs | Clarisse et al. |
| | | | 61 | 21.7[c] | NR | Kitchen | (2003) |
| | | | 61 | 24.2[c] | NR | Living room | |
| | | | 61 | 24.5[c] | NR | Bedroom | |
| Hungary | | 1998 | 123 | 17.5 | 0.6–56.7 | Homes in six medium-sized cities | Erdei et al. (2003) |

**Table 14 (contd)**

| Country | Location/region | Sampling period | No. of samples | Mean concentration or range of means ($\mu g/m^3$)[a] | Range ($\mu g/m^3$)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|
| Japan | Country-wide | 1998–2001 | 1642 | 120 (95.7[b]) | max., 979 | From 1422 homes distributed throughout the country | Park & Ikeda (2003) |
| | NR | 2000 | 171 | 110 ppb 120 ppb | 20–872 ppb 11–840 ppb | Rooms from 81 houses Active DNPH method Detector tube method | Azuma et al. (2003) |
| | Niigata Prefecture | 1999 | 104 | NR | 0–740 | Data from figure; 29% greater than 100 $\mu g/m^3$ | Sakaguchi & Akabayashi (2003) |
| | Nagoya | 1998 | 37 | 17.6[c] | max., 73 | Dwelling factors and airborne concentrations were also compared | Sakai et al. (2004) |
| Mexico | Mexico City and Xalapa | 1996–98 | 50[d] | 37–47 | 12–81 | Measured in two houses | Báez et al. (2003) |
| Sweden | Uppsala | 1998 | 27 | 8.3[c] | max., 19 | Dwelling factors and airborne concentrations were also compared | Sakai et al. (2004) |
| United Kingdom | London | 1991–92 | 17 40 | 15.0 ppb 3.4 ppb | ND–93.1 ppb ND–10.3 ppb | West London, residential area North London, residential area | Williams et al. (1996) |
| USA | San Francisco Bay Area, CA | 1984 | 48 45 | 41 ppb 36 ppb | NR NR | Kitchen Main bedroom | Sexton et al. (1986) |
| | Various | 1981–84 | 273 | 44.0[b] | NR | Mixed locations | Shah & Singh (1988)[e] |
| | Colorado | 1992–93 | 9 | 26[d] 49[d] | 8–66 33–81 | Prior to occupancy After 5 months of occupancy | Lindstrom et al. (1995) |
| | Boston, MA | 1993 | 14 26 | 11.1 ppb 16.1 ppb | 6.0–16.1 ppb 5.9–53.8 ppb | Winter measurements, four residences Summer measurements, nine residences | Reiss et al. (1995) |
| | Louisiana | NR | 419 | 460 | ND–6600 | Measured in 53 houses (75% urban, 25% rural); also measured seasonal differences | Lemus et al. (1998) |

**Table 14 (contd)**

| Country | Location/region | Sampling period | No. of samples | Mean concentration or range of means (μg/m³)[a] | Range (μg/m³)[a] | Comments | Reference |
|---|---|---|---|---|---|---|---|
| USA (contd) | East and South-East | 1997–98 | 4 | 34 ppb[d] | 21–47 ppb | Manufactured houses | Hodgson et al. (2000) |
| | | | 7 | 36 ppb[d] | 14–58 ppb | Site–built houses | |
| | Florida | 2000 | NR | 94.9 | NR | New manufactured house | Hodgson et al. (2002) |
| | New York City, NY | 1999 | 38 | 12.1 | NR | Winter measurements | Kinney et al. (2002) |
| | | | 41 | 20.9 | NR | Summer measurements | |
| **Public settings** | | | | | | | |
| China | Hotel ballroom | 2002 | 28 | 29.7 | 26.3–63.0 | Measured in four hotel ballrooms in the evening on 7 consecutive days | Feng et al. (2004) |
| Italy | Library | 1995–96 | 16 | 32.7 | 1.7–67.8 | Sixteen libraries at the University of Modena; 10 samples with detectable levels | Fantuzzi et al. (1996) |
| Mexico | Museum | 1996–98 | 60[d] | 11–34 | 4–59 | Three museums | Báez et al. (2003) |
| Sweden | Hospital | 1997 | 4 | 5 | 2–7 | Geriatric hospitals built in 1925, 1985, 1993 and 1994 | Wieslander et al. (1999b) |
| | Primary school | 1993, 1995 | 48 | 9.5 | 3–16 | Twelve randomly selected primary schools | Norbäck et al. (2000) |

ND, not detected; NR, not reported
[a] Unless stated otherwise
[b] Median
[c] Geometric mean
[d] Number of indoor and outdoor measurements combined (see Table 13)
[e] Data collected from literature searches, direct contacts with individuals and organisations, reports, computer tapes and direct electronic transfers

(Hodgson *et al.*, 1993). The emission rates in single samples were 57.2 and 18.2 $\mu g/m^2/h$ at 24 and 168 h, respectively, after the start of each experiment. Similar results were observed in a Swedish study in which indoor levels of formaldehyde were found to be higher in homes that had wall-to-wall carpeting (Norbäck *et al.*, 1995).

The release of formaldehyde and volatile organic compounds from newly painted indoor surfaces was investigated in a sample of 62 dwellings in Uppsala, Sweden, in 1991–92. Concentrations of formaldehyde were significantly increased in dwellings where wood paint had been used, but were not related to other types of painting. Wall-to-wall carpeting and wood painting made approximately equal contributions of 13 $\mu g/m^3$ and 16 $\mu g/m^3$ formaldehyde, respectively (Wieslander *et al.*, 1997). The adsorption of formaldehyde to dust particles on wipe samples from homes and offices was investigated to evaluate the extent to which such particles could act as carriers for volatile pollutants and contribute to exposure to formaldehyde. A person exposed to an ambient concentration of 1 ppm [1.2 $mg/m^3$] formaldehyde would inhale about 1 mg/h formaldehyde vapour when breathing normally (15 L/min). In the presence of 1 $mg/m^3$ dust (that contains 10 ng/mg formaldehyde based on analysis of the dust samples), the amount of particle-associated formaldehyde inhaled would be approximately 10 ng/h, i.e. five orders of magnitude lower (Rothenberg *et al.*, 1989). The dose of particle-associated formaldehyde to the lower respiratory tract is predicted to be at least four orders of magnitude smaller than the vapour-phase dose to the upper respiratory tract. [The Working Group noted that the conditions of this investigation are also relevant to industrial environments.]

Data on concentrations of formaldehyde in residential indoor air from five studies conducted in Canada between 1989 and 1995 were examined (Health Canada, 2000). Despite differences in sampling mode and duration (i.e. active sampling for 24 h or passive sampling for 7 days), the distribution of concentrations was similar in the five studies. The median, arithmetic mean, 95th percentile and 99th percentile concentrations of the pooled data (151 samples) were 29.8, 35.9, 84.6 and 116 $\mu g/m^3$, respectively (Health Canada, 2000). Similar concentrations have been measured in non-workplace indoor air in other countries.

Personal 48-h exposures of 15 randomly selected participants as well as microenvironment concentrations in each participant's residence and workplace were measured for 16 carbonyl compounds, including formaldehyde, during the summer and autumn of 1997 as part of the Air Pollution Exposure of Adult Urban Populations in Europe (EXPOLIS) study in Helsinki, Finland. The mean personal exposure concentration of formaldehyde was 21.4 ppb [26.3 $\mu g/m^3$]; the mean indoor residential concentration was 33.3 ppb [41.0 $\mu g/m^3$]; the mean outdoor residential concentration was 2.6 ppb [3.2 $\mu g/m^3$]; and the mean workplace concentration was 12.0 ppb [14.8 $\mu g/m^3$] (Jurvelin *et al.*, 2003).

In earlier studies summarized by Preuss *et al.* (1985), the mean concentrations in conventional homes with no urea–formaldehyde foam insulation were 25–60 $\mu g/m^3$. Since the late 1970s, many studies have reported formaldehyde levels in 'mobile homes' (caravans) (see, for example, the review of Gammage & Travis, 1989). The levels appear to decrease as the mobile home ages, with a half-life of 4–5 years (Preuss *et al.*, 1985). In

the early 1980s, mean concentrations of 0.4 ppm [0.5 mg/m³] and individual values as high as several parts per million were measured in new mobile homes. As a result of new standards and regulations established in the mid-1980s for building materials and voluntary reductions by the manufacturers, concentrations of formaldehyde in mobile homes have decreased to approximately 0.1 ppm [0.12 mg/m³] or less (Gammage & Travis, 1989; Sexton *et al*., 1989; Gylseth & Digernes, 1992; Lehmann & Roffael, 1992).

Formaldehyde may also occur in indoor air through the degradation of other organic compounds. Naturally occurring unsaturated hydrocarbons, such as limonene and pinene (which may also be released from consumer products), anthropogenic compounds, such as 4-vinylcyclohexene (an emission from carpet padding), and other alkenes that are commonly found in indoor air have been found to produce formaldehyde via their initial reaction with ozone (Zhang *et al*., 1994; Weschler & Shields, 1996). Reiss *et al*. (1995) estimated that the effective average rate of emissions of formaldehyde from this process in four residences in Boston (MA, USA) was about three times higher in the summer than in the winter.

In a study conducted at the Inhalation Toxicology Research Institute, release rates of formaldehyde were measured for six types of consumer product (Pickrell *et al*., 1983, 1984). Release rates calculated per unit surface area ($\mu$g/m² per day) were used to rank the products in the following order: pressed wood products >> clothes ~ insulation products ~ paper products > fabric > carpet. Release rates from pressed wood products ranged from below the limit of detection for an exterior plywood to 36 000 $\mu$g/m² per day for some panelling. Other release rates were 15–550 $\mu$g/m² per day for articles of new clothing that had not previously been washed, 52–620 $\mu$g/m² per day for insulation products, 75–1000 $\mu$g/m² per day for paper plates and cups, from below the limit of detection to 350 $\mu$g/m² per day for fabrics and from below the limit of detection to 65 $\mu$g/m² per day for carpets.

In a follow-up study that was performed as a result of changes in product manufacturing processes, many of these release rates were re-investigated (Kelly *et al*., 1999). Release rates of formaldehyde were reported to range typically from 9 to 1578 $\mu$g/m²/h for a variety of bare urea–formaldehyde wood products, from 1 to 461 $\mu$g/m²/h for coated urea–formaldehyde wood products, from 42 to 214 $\mu$g/m²/h for permanent press fabrics, from 4 to 50 $\mu$g/m²/h for decorative laminates, from 16 to 32 $\mu$g/m²/h for fibreglass products and from 4 to 9 $\mu$g/m²/h for bare phenol–formaldehyde wood products (Kelly *et al*., 1999). Paper grocery bags and towels had emission rates of < 0.5 and < 0.6 $\mu$g/m²/h, respectively. For wet products, the emission rates were: latex paint, 326–854 $\mu$g/m²/h; fingernail hardener, 178 000–354 000 $\mu$g/m²/h; nail polish, 20 700 $\mu$g/m²/h; and commercially applied urea–formaldehyde floor finish, 1 050 000 and 421 000 $\mu$g/m²/h for base and topcoats, respectively (Kelly *et al*., 1999).

1.3.5    *Other exposures*

According to the Environmental Protection Agency Toxics Release Inventory (TRI), in 2001, approximately 9500 tonnes of formaldehyde were released into the environment from 800 domestic manufacturing and processing facilities in the USA. This number represents the sum of all releases of formaldehyde to air (4800 tonnes), water (160 tonnes), soil (70 tonnes) and underground injection wells (4500 tonnes). The TRI data should be used with caution because not all facilities are required to report releases of formaldehyde into the environment (National Library of Medicine, 2004).

Cigarette smoke has been reported to contain levels of a few to over 100 µg formaldehyde per cigarette (IARC, 2004). A 'pack-a-day' smoker may inhale as much as 0.4–2.0 mg formaldehyde (IARC, 1995; ACGIH® Worldwide, 2003).

Cosmetic products that contain 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, nail creams and lotions). Use of aerosol products (e.g. shaving creams) may result in potential inhalation of formaldehyde (Cosmetic Ingredient Review Expert Panel, 1984). A Swedish study on indoor emissions reported that oil-based skin care products that are known to contain formaldehyde precursors (donors) still release formaldehyde into the air after storage for 1 year (Karlberg *et al*., 1998).

Formaldehyde occurs naturally in foods, and foods may be contaminated as a result of fumigation (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). Fruit and vegetables typically contain 3–60 mg/kg, milk and milk products contain about 1 mg/kg, meat and fish contain 6–20 mg/kg and shellfish contain 1–100 mg/kg. Drinking-water generally contains < 0.1 mg/L (WHO, 1989).

Formaldehyde can also be emitted into indoor air during the cooking of fish. Amounts of formaldehyde that formed in a headspace when various kinds of fish flesh were heated to 200 °C ranged from 0.48 µg/g for mackerel to 5.31 µg/g for sardine (Yasuhara & Shibamoto, 1995). Free formaldehyde was found in fish at levels ranging from 1.4 to 40.3 ppm [1.7 to 49.6 mg/m³]; the high levels were attributed to the processes used to freeze the fish products (Nielsen, 2002). When cooking oils are heated to high temperatures (240–280 °C) that are typical of Chinese wok cooking, several volatile mutagenic organic compounds are released, including formaldehyde. Emissions of formaldehyde from several cooking oils (rapeseed, canola, soya bean, peanut) ranged from 23 to 71 µg/L (Shields *et al*., 1995).

Composting of household waste was also found to generate formaldehyde (Eitzer *et al*., 1997). [Composting may also be of concern for occupational exposures.]

In some regions, mosquito coils are burned in residences for mosquito control. In a study of the combustion products from two common brands of mosquito coil, formaldehyde

was generated at a level of approximately 2–4 mg/g of mosquito coil, which would result in air concentrations in the range of 0.16–0.40 ppm [0.19–0.49 mg/m³] (Chang & Lin, 1998).

Formaldehyde has been used as a chemical germicide to control bacterial contamination in water distribution systems and in the dialysis fluid pathways of artificial kidney machines. In addition, formaldehyde has been used to disinfect hollow fibre dialysers (artificial kidneys) that are reprocessed and re-used only by the same patient (Centers for Disease Control, 1986).

When formalin-sterilized dialysers were rinsed by the technique used in many dialysis centres in the 1970s, undesirable concentrations of formaldehyde were found in the apparatuses at the start of dialysis. When the technique was modified by passing part of the saline through the blood compartment immediately before connection and discarding the saline left in the dialyser at the time of connection, the concentration of formaldehyde infused into the patient fell to below 2 µg/mL. However, the dialysers still contained up to 13 mg formaldehyde which leached slowly during simulated dialysis. Some residual formaldehyde was found in several components of the dialyser, but the majority was contained in the cellulose membrane (Lewis *et al.*, 1981).

Stragier *et al.* (1995) studied the influence of the type of disinfecting agent used on the necessary rinsing time and rebound release after rinsing re-used dialysers. The rinsing time required to reach undetectable levels of disinfecting agent was longest for formaldehyde and the rebound release 30 min after completion of rinsing was the highest for formaldehyde.

In the USA, the proportion of dialysis centres that use formaldehyde to reprocess dialysers decreased from 94 to 31% during 1983–2000 (Tokars *et al.*, 2000).

## 1.4    Regulations and guidelines

Occupational exposure limits and guidelines for formaldehyde are presented in Table 15. International regulations and guidelines related to emissions of and exposures to formaldehyde in occupational settings, indoor air and building materials have been reviewed (IARC, 1995; Paustenbach *et al.*, 1997; ATSDR, 1999).

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% by weight or volume (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). Labels of cosmetic products 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).

The Food and Drug Administration (2003) in the USA identifies formaldehyde: as a secondary direct food additive that is permitted in food for human consumption; for use as a preservative in defoaming agents; as an indirect food additive for use only as a component of adhesives; as an indirect food additive for use only as paper and paperboard

**Table 15. Occupational exposure standards and guidelines for formaldehyde**

| Country or region | Concentration (mg/m$^3$) [ppm] | Interpretation | Carcinogen classification |
|---|---|---|---|
| Australia | 1.2 [1] | TWA | 2; Sen |
| | 2.5 [2] | STEL | |
| Belgium | 0.37 [0.3] | Ceiling | |
| Brazil | 2 [1.6] | Ceiling | |
| China | 0.5 | Ceiling | |
| Canada | | | |
|   Alberta | 2.5 [2] | Ceiling | |
|   Ontario | 0.37 [0.3] | Ceiling | |
|   Quebec | 2.5 [2] | Ceiling | A2[a] |
| Denmark | 0.4 [0.3] | STEL | L, K |
| Finland | 0.37 [0.3] | TWA | |
| | 1.2 [1] | Ceiling | |
| France | 0.6 [0.5] | TWA | |
| | 1.2 [1] | STEL | |
| Germany | 0.37 [0.3] | TWA (MAK) STEL | 4; Sh; I |
| | 0.7 [0.6] | Ceiling | |
| | 1.2 [1] | | |
| Hong Kong | 0.37 [0.3] | Ceiling | A2[b] |
| Ireland | 2.5 [2] | TWA | |
| | 2.5 [2] | STEL | |
| Japan | 0.6 [0.5] | TWA | 2A |
| Malaysia | 0.37 [0.3] | Ceiling | |
| Mexico | 2.5 [2] | Ceiling | A2[b] |
| Netherlands | 1.2 [1] | TWA | |
| | 2.5 [2] | STEL | |
| New Zealand | 1.2 [1] | Ceiling | A2[b] |
| Norway | 0.6 [0.5] | TWA | Ca[c]; Sen |
| | 1.2 [1] | Ceiling | |
| Poland | 0.5 | TWA | |
| | 1 | STEL | |
| South Africa | 2.5 [2] | TWA | |
| | 2.5 [2] | STEL | |
| Spain | 0.37 [0.3] | STEL | |
| Sweden | 0.6 [0.5] | TWA | Ca[d]; Sen |
| | 1.2 [1] | Ceiling | |
| Switzerland | 0.37 [0.3] | TWA | Sen |
| | 0.74 [0.6] | STEL | |
| United Kingdom (MEL) | 2.5 [2] | TWA | |
| | 2.5 [2] | STEL | |

**Table 15 (contd)**

| Country or region | Concentration (mg/m$^3$) [ppm] | Interpretation | Carcinogen classification |
|---|---|---|---|
| USA |  |  |  |
|   ACGIH (TLV) | 0.37 [0.3] | Ceiling | A2[b]; Sen |
|   NIOSH (REL) | 0.02 [0.016] | TWA | Ca[d] |
|  | 0.12 [0.1] | Ceiling |  |
|   OSHA (PEL) | 0.9 [0.75] | TWA | Ca[d] |
|  | 2.5 [2] | STEL |  |

From Arbejdstilsynet (2002); Health & Safety Executive (2002); Työsuojelu-säädöksiä (2002); ACGIH® Worldwide (2003); Deutsche Forschungsgemein-schaft (2003); Suva (2003); INRS (2005)

I, local irritant; K, carcinogenic; L, substance with ceiling value; MEL, maximum exposure limit; PEL, permissible exposure limit; REL, recommended exposure limit; Sen, sensitizer; Sh, skin sensitizer; STEL, short-term exposure limit; TLV, threshold limit value; TWA, time-weighted average; 2, probable human carcinogen; 2A, probably carcinogenic to humans (IARC classification); 4, carcinogenic potential with no or little genotoxicity

[a] A2: carcinogenic effects suspected in humans
[b] A2: suspected human carcinogen
[c] Ca: potential cancer-causing agent
[d] Ca: Substance is carcinogenic.

components; as an indirect food additive for use as a preservative in textile and textile fibre polymers; as an indirect food additive for use as an adjuvant in animal glue; and, under specified conditions, as an animal drug and in the manufacture of animal feeds.

Guidelines for levels of formaldehyde in ambient air in living spaces have been set in several countries and range from 0.05 to 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).

Some European countries have established maximum limits for emissions of formaldehyde from particle-boards, other wood products, furniture and insulation foam: for instance, Denmark, Finland and Sweden have set a maximum of 0.15 mg/m$^3$, measured in a test room of 225 L under standard conditions; in France, the content of formaldehyde that arises from walls insulated with urea–formaldehyde foam should not exceed 0.2 ppm (European Union, 1989).

In the USA, all plywood and particle-board materials that are bonded with a resin system or coated with a surface finish that contains formaldehyde cannot exceed the following formaldehyde emission levels when installed in manufactured homes, as expressed as air concentrations using standard conditions: plywood materials and particle-board flooring products (including urea–formaldehyde-bonded particle-board), 0.25 mg/m$^3$; particle-board materials and medium-density fibre-board, 0.37 mg/m$^3$ (Composite Panel Association, 1999, 2002; Department of Housing and Urban Development, 2003).

# 2.   Studies of Cancer in Humans

## 2.1      Cohort studies

More than 25 cohort studies have examined the association between formaldehyde and cancer. Since the previous IARC monograph in 1994 (IARC, 1995), three of these have been updated, and six new studies have been published. The following review divides the studies into those that concern professionals (e.g. pathologists, anatomists and embalmers) and those that concern industrial workers (e.g. formaldehyde producers, formaldehyde resin makers, plywood and particle-board manufacturers, garment workers and workers in the abrasives industry). This division was also made in the previous IARC monograph because of differences between these studies with regard to their findings, the nature of the exposure to formaldehyde and the potential for exposures to other carcinogens or other factors that might confound the findings.

The following discussion is focused largely on the results for sites that may come into direct contact with airborne formaldehyde (cancers of the respiratory tract including cancers of the trachea, bronchus and lung, laryngeal cancer, sinonasal cancer, nasopharyngeal cancer, oral cancer and other pharyngeal cancers) and on leukaemia and brain cancer, for which excess mortality has been reported in several studies.

### 2.1.1   *Cohorts of industrial workers*

Key study features and findings from the cohort and nested case–control studies of industrial workers are summarized chronologically in Table 16, based on the year of publication of the first report of the cohort. Studies have been conducted on workers who were exposed to formaldehyde in the chemical, garment, fibreglass, iron, wood-working, plastics and paper, pulp and plywood industries. Several of these cohort studies have recently been updated, and the results presented below are largely limited to the updated data, grouped by industry.

### (*a*)     *The National Cancer Institute (NCI) Cohort*

Blair *et al.* (1986, 1990a) at the NCI, USA, conducted the largest of the cohort studies, which included over 25 000 workers (88% men) who had first been employed before 1966 in one of 10 industrial facilities in the USA. These facilities manufactured formaldehyde (three plants), formaldehyde resins (six plants), moulding compounds (six plants), moulded plastic products (two plants), photographic films (two plants) and plywood (one plant). Among all of the workers, 11% were considered to be unexposed.

This study included workers from facilities that were also included in studies by Marsh (1982), Wong (1983) and Liebling *et al.* (1984) and in a case–control study by Fayerweather

**Table 16. Cohort studies of industrial workers exposed to formaldehyde**

| Reference, location, years of study | Cohort description Type of analysis (cohort size) | Exposure assessment | Organ site (ICD code)[a] | No. of cases/ deaths | SMR (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Coggon *et al.* (2003), United Kingdom, 1941–2000 (update of Acheson *et al.*, 1984a; Gardner *et al.*, 1993) | Chemical factories that used or produced formaldehyde Standardized mortality (14 014 men) | Level of exposure (background, low, moderate, high); among highly exposed, time period and duration of exposure | All cancers | 1511 deaths | 1.10 (1.04–1.16) | |
| | | | Nasopharynx | 1 death | NR | 2.0 expected |
| | | | Nose and nasal sinuses | 2 deaths | 0.87 (0.11–3.14) | Two additional cases identified from registry that could not be used in the analysis |
| | | | Lymphohaematopoietic | NR | NR | |
| | | | Leukaemia | 31 deaths | 0.91 (0.47–1.59) | |
| | | | Mouth (ICD-9, 143–145) | 6 deaths | 1.28 (0.47–2.78) | |
| | | | Lung | 594 deaths | 1.22 (1.12–1.32) | Increased risk among highly exposed (1.58; 95% CI, 1.40–1.78); inverse trend with duration of exposure |
| | | | Brain and central nervous system | 30 deaths | 0.85 (0.57–1.21) | |
| Hauptmann *et al.* (2003, 2004), USA, 1966–94 (update of Blair *et al.*, 1986, 1987) | Manufacturer of formaldehyde, formaldehyde resins, moulding compounds, moulded plastic products, photographic films and plywood Standardized mortality (25 619 workers; 22 493 men, 3126 women) | Duration; quantitative estimates of cumulative, average and highest peak exposure | All cancers | 1723 deaths | 0.90 (0.86–0.95) | 15-year lag for solid cancers; 2-year lag for lymphohaematopoietic cancers |
| | | | Nasopharynx | 8 deaths | 2.10 (1.05–4.21) | The authors noted that the exact CI is 0.91–4.14; statistically significant trend with highest peak exposure; weaker trends observed with duration of, cumulative and average exposures |
| | | | Nose and nasal sinuses | 3 deaths | 1.19 (0.38–3.68) | |
| | | | Lymphohaematopoietic | 161 deaths | 0.80 (0.69–0.94) | |
| | | | Leukaemia | 65 deaths | 0.85 (0.67–1.09) | Statistically significant trend with peak exposure, particularly for myeloid leukaemia; weaker trend with average exposure; no trend with duration of or cumulative exposure |
| | | | Buccal cavity | 49 deaths | 1.01 (0.77–1.34) | |
| | | | Lung | 641 deaths | 0.97 (0.90–1.05) | |
| | | | Brain and central nervous system | 43 deaths | 0.92 (0.68–1.23) | |

**Table 16 (contd)**

| Reference, location, years of study | Cohort description Type of analysis (cohort size) | Exposure assessment | Organ site (ICD code)[a] | No. of cases/ deaths | SMR (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Bertazzi *et al.* (1986, 1989), Italy, 1959–86 | Formaldehyde resin makers Standardized mortality (1332 men) | Duration of exposure, latency, age at employment, year of employment, time since beginning of employment | All cancers | 62 deaths | 1.23 [0.94–1.58][b] | Mortality was close to expected when local rates were used as the referent (1.00 [95% CI, 0.64–1.49]) |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | 0 deaths | NA | |
| | | | Lymphohaematopoietic | 7 deaths | 1.77 [0.71–3.65][b] | SMR with local rates as the referent, 1.43 [95% CI, 0.57–2.95] |
| | | | Leukaemia | NR | NR | |
| | | | Buccal cavity/pharynx | NR | NR | |
| | | | Lung | 24 deaths | 1.56 [1.00–2.32] | |
| | | | Brain | NR | NR | |
| Edling *et al.* (1987a), Sweden, 1955–83 | Abrasives industry Standardized mortality, standardized incidence (521 male blue-collar workers) | None (area measurements) | All cancers | 24 inc. cases | 0.84 [0.54–1.25][c] | All cancer mortality SMR, 0.93 [95% CI, 0.54–1.49] |
| | | | Nasopharynx | 1 inc. case | NR | |
| | | | Nasal cavity | 0 inc. cases | NA | |
| | | | Lymphohaematopoietic | 4 inc. cases | NR | |
| | | | Leukaemia | 0 inc. cases | NA | |
| | | | Buccal cavity | 0 inc. cases | NA | |
| | | | Lung | 2 inc. cases | 0.57 [0.07–2.06] | |
| | | | Brain and central nervous system | 1 inc. case | NR | |
| Pinkerton *et al.* (2004), USA, 1955–98 (update of Stayner *et al.*, 1988) | Garment industry Standardized mortality (11 039 workers; 2015 men, 9024 women) | Duration, time since first exposure, year of first exposure | All cancers | 608 deaths | 0.89 (0.82–0.97) | |
| | | | Nasopharynx | 0 deaths | NA | 0.96 expected |
| | | | Nasal cavity | 0 deaths | NA | 0.16 expected |
| | | | Lymphohaematopoietic | 59 deaths | 0.97 (0.74–1.26) | |
| | | | Leukaemia | 24 deaths | 1.09 (0.70–1.62) | |
| | | | Myeloid leukaemia | 15 deaths | 1.44 (0.80–2.37) | Statistically significant excess among workers with both ≥ 10 years of exposure and ≥ 20 years since first exposure (SMR, 2.43; 95% CI, 0.98–5.01) |
| | | | Buccal cavity/pharynx | 4 deaths | 1.33 (0.36–3.41) | |
| | | | Lung | 147 deaths | 0.98 (0.82–1.15) | |
| | | | Brain and central nervous system | 19 deaths | 1.09 (0.66–1.71) | |

**Table 16 (contd)**

| Reference, location, years of study | Cohort description Type of analysis (cohort size) | Exposure assessment | Organ site (ICD code)[a] | No. of cases/ deaths | SMR (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Andjelkovich *et al.* (1995), USA, 1960–89 | Foundry workers Standardized mortality (3929 men with potential exposure) | Exposed/ unexposed; none, low, medium and high exposure | All cancers | 127 deaths | 0.99 (0.82–1.17) | |
| | | | Nasopharynx | 0 deaths | NA | |
| | | | Nasal cavity | 0 deaths | NA | |
| | | | Lymphohaematopoietic | 7 deaths | 0.59 (0.23–1.21) | |
| | | | Leukaemia | 2 deaths | 0.43 (0.05–1.57) | |
| | | | Buccal cavity/pharynx | 6 deaths | 1.31 (0.48–2.86) 1.16 (0.20–6.51)[d] | |
| | | | Lung | 51 deaths | 1.20 (0.89–1.58) 0.59 (0.28–1.20)[d] | |
| | | | Brain and central nervous system | 2 deaths | 0.62 (0.07–2.23) | |
| Hansen & Olsen (1995, 1996), Denmark | Workers from companies with a history of use or manufacture of formaldehyde Standardized proportionate incidence (eligible cancer cases: 2041 men, 1263 women diagnosed in 1970–84) | Low (white-collar) and above baseline (blue-collar) | ICD-7 | *Men* | | |
| | | | Nasopharynx | 4 cases | 1.3 (0.3–3.2) | |
| | | | Nasal cavity | 13 cases | 2.3 (1.3–4.0) | Risk increased among more highly exposed workers with (SPIR, 5.0; 95% CI, 0.5–13.4) or without (SPIR, 3.0; 95% CI, 1.4–5.7) exposure to wood dust |
| | | | Lymphohaematopoietic | NR | NR | |
| | | | Leukaemia (204) | 39 cases | 0.8 (0.6–1.6) | Risk not increased among more highly exposed |
| | | | Buccal cavity/pharynx | 23 cases | 1.1 (0.7–1.7) | |
| | | | Lung | 410 cases | 1.0 (0.9–1.1) | Risk not increased among more highly exposed |
| | | | Brain and nervous system (193) | 54 cases | 1.1 (0.9–1.5) | Risk not increased among more highly exposed |
| | | | | *Women* | | |
| | | | Nasal cavity | 4 cases | 2.4 (0.6–6.0) | |
| | | | Lymphohaematopoietic | NR | NR | |
| | | | Leukaemia | 21 cases | 1.2 (0.7–1.8) | |
| | | | Lung | 108 cases | 1.2 (0.96–1.4) | |
| | | | Brain and nervous system (193) | 39 cases | 1.2 (0.8–1.6) | |

**Table 16 (contd)**

| Reference, location, years of study | Cohort description Type of analysis (cohort size) | Exposure assessment | Organ site (ICD code)[a] | No. of cases/ deaths | SMR (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Chiazze *et al.* (1997), USA, 1951–91 | Fibreglass manufacturing plant workers Standardized mortality and nested case–control (4631 men and women) | Cumulative exposure | All cancers | 96 deaths | 0.94 (0.77–1.15)[b] | Analysis restricted to 2933 white men |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | NR | NR | |
| | | | Lymphohaematopoietic | 5 deaths | 0.46 (0.15–1.08) | |
| | | | Leukaemia | 1 death | 0.24 (0.006–1.36) | |
| | | | Buccal cavity/pharynx | 2 deaths | 0.70 (0.08–2.52) | |
| | | | Lung | 47 deaths | 1.26 (0.93–1.68) | Excess risk for lung cancer reduced when local rates were used (SMR, 1.17; 95% CI, 0.86–1.55); positive trend in case–control study with cumulative exposure to formaldehyde among smokers |
| | | | Brain and nervous system | 6 deaths | 1.48 (0.54–3.23) | |
| Stellman *et al.* (1998), USA, 1982–88 | Workers in the American Cancer Society CPS-II study employed in wood-related occupations or who reported exposure to wood dust Retrospective cohort mortality (45 399 men, of whom 387 reported exposure to formaldehyde) | Dichotomous (yes/no) with and without employment in a wood occupation | All cancers | | | |
| | | | Formaldehyde alone | 367 deaths | 0.98 (0.86–1.12) | |
| | | | Formaldehyde + wood | 14 deaths | 1.61 (0.95–2.72) | |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | NR | NR | |
| | | | Lymphohaematopoietic | | | |
| | | | Formaldehyde alone | 28 deaths | 1.22 (0.84–1.77) | |
| | | | Formaldehyde + wood | 3 deaths | 3.44 (1.11–10.68) | |
| | | | Leukaemia | | | |
| | | | Formaldehyde alone | 12 deaths | 0.96 (0.54–1.71) | |
| | | | Formaldehyde + wood | 2 deaths | 5.79 (1.44–23.25) | |
| | | | Buccal cavity/pharynx | NR | NR | |
| | | | Lung | | | |
| | | | Formaldehyde alone | 104 deaths | 0.93 (0.73–1.18) | |
| | | | Formaldehyde + wood | 7 deaths | 2.63 (1.25–5.51) | |
| | | | Brain (ICD-9, 191) | NR | NR | |

**Table 16 (contd)**

| Reference, location, years of study | Cohort description Type of analysis (cohort size) | Exposure assessment | Organ site (ICD code)[a] | No. of cases/ deaths | SMR (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Marsh *et al.* (2001); Youk *et al.* (2001), USA, 1945–92 | Fibreglass workers Standardized mortality and nested case–control (32 000 men and women, 22% of person–years exposed to formaldehyde) | Duration of, cumulative and average exposure | All cancers Nasopharynx Nasal cavity Lymphohaematopoietic   Leukaemia | 2243 deaths NR NR 199 deaths NR | 0.98 (0.94–1.02)[b] NR NR 0.92 (0.80–1.06) NR | |
| | | | Buccal cavity/pharynx Lung | 63 deaths 838 deaths | 1.07 (0.82–1.37) 1.17 (1.09–1.25) | SMR was reduced and no longer significant when local rates were used (SMR, 1.06; 95% CI, 1.00–1.14); a statistically significant excess among formaldehyde-exposed workers observed in the case–control study (smoking-adjusted odds ratio, 1.61; 95% CI, 1.02–2.56); no significant trend with duration of or cumulative exposure; some evidence for a trend with average exposure |
| | | | Brain and central nervous system | 50 deaths | 0.78 (0.58–1.03) | |

**Nested case–control studies**

| Reference, location, years of study | Characteristics of cases and controls | Exposure assessment | Organ site/exposure category | No. of cases (exposed) | Odds ratio (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Bond *et al.* (1986), USA, 1944–80 | 308 male incident cases of lung cancer from a cohort of 19 608 employees at a chemical company; two controls per case matched on race, year of birth (5 years) and year of first employment | Exposure profile developed based on work history at the company | Lung   No lag period   Lag period ≥ 15 years | (9) (4) | 0.62 (0.29–1.34) 0.31 (0.11–0.86) | Formaldehyde was not assessed in great detail. |

**Table 16 (contd)**

| Reference, location, years of study | Characteristics of cases and controls | Exposure assessment | Organ site/exposure category | No. of cases (exposed) | Odds ratio (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Ott *et al.* (1989), USA, 1940–78 | Deaths identified within a cohort of 29 139 male workers at two chemical manufacturing facilities and a research and development centre; five controls per case selected from cohort and frequency-matched by decade of first employment | Use of formaldehyde in department where subjects worked | *Ever exposed*<br>Non-Hodgkin lymphoma<br>Multiple myeloma<br>Non-lymphocytic leukaemia<br>Lymphocytic leukaemia | 52 (2)<br>20 (1)<br>39 (2)<br>18 (1) | 2.0<br>1.0<br>2.6<br>2.6 | Number of controls overall by exposure status and confidence intervals not given; adjustment for age was evaluated but dropped due to substantial change in risk estimates. |
| Partanen *et al.* (1990), Finland, 1957–80 (updated from Partanen *et al.*, 1985) | 136 male incident cases* from a cohort of 7307 workers in 35 particle-board, plywood and formaldehyde glue factories and sawmills who entered the factories in 1944–66; three controls per case selected randomly among the same cohort, matched by year of birth, alive at the time of diagnosis of the corresponding case | Plant- and time-specific job–exposure matrices; work history based on factory registers, interviews of factory personnel and questionnaires to study subjects or relatives | All cancers combined*<br>  Ever exposed<br>  Peak exposure<br>  Dustborne formaldehyde<br>Lung<br>  Ever exposed<br>  Peak exposure<br>  Dustborne formaldehyde | 136<br>(20)<br>(7)<br>(14)<br>118<br>(18)<br>(7)<br>(12) | <br>1.40 (0.72–2.74)[e]<br>0.95 (0.30–3.05)[e]<br>1.37 (0.66–2.82)[e]<br><br>1.25 (0.60–2.60)[e]<br>1.10 (0.31–3.85)[e]<br>1.13 (0.51–2.52)[e] | Adjusted for vital status; adjustment for cigarette smoking did not affect the results.<br>*Tongue, mouth, pharynx, nose and nasal sinuses, larynx and lung/trachea (ICD-7 141, 143–8, 160–1, 162,0–1) |

CI, confidence interval; ICD, international classification of diseases; inc., incident; NA, not applicable; NR, not reported; SMR, standardized mortality ratio; SPIR, standardized proportionate incidence ratio

[a] The ICD code is only mentioned when the organ site studied is different from that in the other studies.

[b] The authors presented results using either the national population or the local population as the referent. The results presented here are based on the national population.

[c] Data on cancer incidence and mortality were presented. The results in this column are for cancer incidence.

[d] Relative risk of medium- plus high-exposed groups versus unexposed, adjusted for race, smoking and exposure to silica

[e] 90% confidence interval

*et al*. (1983). For the purposes of this review, the results from these earlier studies were considered to be subsumed by the NCI study. In the earlier follow-up (Blair *et al*., 1986), the NCI study had found an excess of lung cancer in white men in comparison with the national population of the USA, but the excess did not appear to increase with increasing cumulative exposure to formaldehyde. Several investigators performed re-analyses of the results on lung cancer (Robins *et al*., 1988; Sterling & Weinkam, 1988, 1989a,b; Marsh *et al*., 1992a,b, 1994; Sterling & Weinkam 1994, 1995; Callas *et al*., 1996). The re-analyses by Sterling and Weinkam (1988, 1989a,b, 1994, 1995) did suggest a relationship between cumulative exposure and mortality from lung cancer, although their first two reports were found to have errors (Blair & Stewart, 1989; Sterling & Weinkam, 1989b). A positive exposure–response relationship between cumulative exposure to formaldehyde and lung cancer was not suggested in the re-analyses by Robins *et al*. (1988), Marsh *et al*. (1992a,b, 1994) or Callas *et al*. (1996). The results from these re-analyses are superseded by the most recent findings in the NCI cohort, which are described below.

The cohort that was originally followed for vital status through to 1980 was recently updated by Hauptmann *et al*. (2003, 2004) through to 1994. This study included a comprehensive evaluation of historical levels of exposure to formaldehyde and of other potentially confounding exposures (Stewart *et al*., 1986; Blair & Stewart, 1990). Time-dependent estimates were developed for duration of exposure (years), average exposure (parts per million [ppm]), cumulative exposure (ppm–years) and highest peak exposure (ppm) to formaldehyde. Concomitant exposure to particulates that contained formaldehyde was also assessed. Expected numbers of deaths were estimated using the person–years method and age-, race- and sex-specific rates for the general population in the USA; log-linear Poisson regression models were used to analyse the relationship between the various measures of exposure to formaldehyde and cancer mortality. In the analyses, exposures to formaldehyde were lagged by 2 years for lymphatic and haematopoetic neoplasms and by 15 years for solid cancers. Potential confounding by age, calendar time, sex, race and pay category (Poisson regression only) was controlled for in the analyses. In addition, potential confounding was evaluated for duration of exposure to each of 11 other substances (i.e. antioxidants, asbestos, carbon black, dyes and pigments, hexamethylenetetramine, melamine, phenol, plasticizers, urea, wood dust and benzene) and for duration of work as a chemist or laboratory technician.

Based on comparisons with the national population, mortality from all cancers was lower than expected in the unexposed (376 deaths; standardized mortality ratio [SMR], 0.76; 95% confidence interval [CI], 0.69–0.84) and, but to a lesser extent, in the population exposed to formaldehyde (1723 deaths; SMR, 0.90; 95% CI, 0.86–0.95) (Hauptmann *et al*., 2004). Decreased mortality was observed in both groups for lymphohaematopoietic neoplasms (exposed: 161 deaths; SMR, 0.80; 95% CI, 0.69–0.94; unexposed: 17 deaths; SMR, 0.62; 95% CI, 0.39–1.00) (Hauptmann *et al*., 2003) and solid tumours (exposed: 1580 deaths; SMR, 0.91; 95% CI, 0.87–0.96; unexposed: 341 deaths; SMR, 0.78; 95% CI, 0.70–0.86) (Hauptmann *et al*., 2004).

A statistically significant exposure–response relationship was observed between peak exposure to formaldehyde and all lymphatic and haematopoietic neoplasms ($p_{trend}$ = 0.002) in the Poisson regression analysis. (The trend tests presented here and subsequently were based on analyses that were restricted to the exposed workers.) This relationship was largely due to a strong exposure–response relationship for leukaemia ($p_{trend}$ = 0.004) and, to a lesser extent, for Hodgkin disease ($p_{trend}$ = 0.04). The relationship was stronger for myeloid leukaemia ($p_{trend}$ = 0.009) than for the other histological subtypes of leukaemia. The relative risk for the highest category of peak exposure (≥ 4.0 ppm) was 2.46 (29 deaths; 95% CI, 1.31–4.62) for all leukaemia and 3.46 (14 deaths; 95% CI, 1.27–9.43) for myeloid leukaemia. Weaker and statistically non-significant exposure–response relationships were observed with average intensity of exposure for leukaemia ($p_{trend}$ = 0.24) and myeloid leukaemia ($p_{trend}$ = 0.09). There was little evidence for a relationship between cumulative exposure or duration of exposure and risk for either leukaemia or myeloid leukaemia (Hauptmann *et al*., 2003). [The Working Group noted the contrast between the findings from the person–years analysis, which did not reveal an excess of leukaemia, and the Poisson regression analysis which demonstrated a significant exposure–response relationship between peak exposure and leukaemia. The Working Group also noted that Poisson regression, which uses internal analysis, is less prone to confounding by socioeconomic status and other factors.]

Based on eight cases, a significant excess mortality from nasopharyngeal cancer was observed among formaldehyde-exposed workers in comparison with the national population (SMR, 2.10; 95% CI, 1.05–4.21). A highly statistically significant ($p_{trend}$ < 0.001) exposure–response relationship was observed between peak exposure to formaldehyde and risk for nasopharyngeal cancer in the Poisson regression analysis. All exposed cases were in the highest category of peak exposure, and the relative risk was 1.83. This analysis excluded one case which, according to cancer registry data, had been misclassified as nasopharyngeal cancer. Weaker exposure–response relationships were observed between naso-pharyngeal cancer and average, cumulative and duration of exposure ($p_{trend}$ = 0.07, 0.03 and 0.15, respectively).

Three cases of cancer of the nose and nasal cavity were observed in the exposed group, which were slightly in excess of the expected (SMR, 1.19; 95% CI, 0.38–3.68). A total of 49 deaths from cancer of the buccal cavity occurred among exposed subjects, which was as expected with respect to mortality in the national population in the USA. Relative risks for the highest exposure categories of average intensity, peak and cumulative exposure were elevated (relative risks, 1.89, 1.83 and 1.74, respectively), but trends were not significant or only of borderline significance ($p_{trend}$ = 0.50, 0.07 and 0.37, respectively). No consistent positive association was observed for cancer of the larynx for any of the exposure metrics and the number of deaths (23) was as expected with respect to mortality in the national population. Combination of cancers of the nasopharynx, mouth, salivary gland, nasal cavity and larynx (upper respiratory tract) resulted in increasing relative risks with increasing average intensity (a twofold significantly elevated relative risk in the highest exposure category compared with the low exposure category; $p_{trend}$ = 0.12 among the

exposed only) and with peak exposure, but not with cumulative exposure or duration of exposure. Mortality from lung cancer was slightly lower than expected among the formaldehyde-exposed group (641 deaths; SMR, 0.97; 95% CI, 0.90–1.05). No evidence of a positive relationship between mortality from lung cancer and any of the exposure measures was observed. In fact, mortality from lung cancer appeared to decrease with duration of exposure ($p_{trend}$ = 0.03) and with cumulative exposure ($p_{trend}$ = 0.14) to formaldehyde (Hauptmann *et al*., 2004). [The Working Group noted that the strengths of this study included its relatively large number of workers, long period of follow-up and the high quality of the exposure assessment.]

Marsh and Youk (2004) re-analysed the updated data from the NCI cohort (Hauptmann *et al*., 2003). In addition to reproducing the results presented by Hauptmann *et al*. (2003), three further analyses were performed in relation to risk for mortality from leukaemia. Using the cut-off points for exposure categories defined in Hauptmann *et al*. (2003), exposure category-specific SMRs, based on mortality rates for the national population, increased with increasing peak and average intensity of exposure for all leukaemias combined and for myeloid leukaemia; the SMRs for myeloid leukaemia ranged from 0.43 and 0.71 in the lowest exposed category of peak and average intensity, respectively, to 1.42 and 1.45 in the highest category of these metrics. Findings were similar when regional mortality rates were used. The use of alternative cut-off points for average intensity of exposure, in order to achieve similar numbers of deaths from all leukaemias combined in each exposed category, resulted in relative risk estimates similar to those observed by Hauptmann *et al*. (2003). Analyses of duration of time worked in the highest peak category did not generally indicate higher risks among those who had experienced high peaks for a longer time.

Marsh *et al.* (1996) studied one plant (in Wallingford, CT) that was also included in the NCI cohort study (Hauptmann *et al*., 2003). They enumerated the cohort independently and conducted their own exposure assessment, but their general approach was similar. More recently, Marsh *et al*. (2002) analysed mortality through to 1998 and exposure through to 1995 for the 7328 workers (82% white men) who were employed during 1941–84. Overall, vital status was determined for 98% of the cohort and cause of death for 95% of 2872 deaths. The majority of subjects (54%) had worked for less than 1 year at the plant. More than 1300 workers (18%) had been employed for more than 10 years. The updated exposure assessment used the same methods as the earlier study (Marsh *et al*., 1996), and included an examination of data on sporadic measurements from the period 1965–87 and the use of protective equipment. The analysis evaluated malignancies of the upper and lower respiratory tract. Compared with local county mortality rates, SMRs were elevated for cancers of the nasopharynx (seven deaths; SMR, 5.00; 95% CI, 2.01–10.30), all pharynx (22 deaths; SMR, 2.23; 95% CI, 1.40–3.38), all buccal cavity and pharynx (31 deaths; SMR, 1.52; 95% CI, 1.03–2.15), nasal sinus (three deaths; SMR, 3.06; 95% CI, 0.63–8.93), larynx (13 deaths; SMR, 1.59; 95% CI, 0.84–2.71) and lung (262 deaths; SMR, 1.21; 95% CI, 1.06–1.36). SMRs for nasopharyngeal cancer based on local county rates increased monotonically with cumulative exposure to formaldehyde (no death; SMR, 0; 95% CI, 0–15.41 for unexposed; one death; SMR, 3.97; 95% CI, 0.10–22.10 for

> 0–< 0.004 ppm–years; three deaths; SMR, 5.89; 95% CI, 1.22–17.22 for 0.004–0.219 ppm–years; and three deaths; SMR, 7.51; 95% CI, 1.55–21.93 for ≥ 0.22 ppm–years). In a case–control study of pharyngeal cancer nested in the cohort, deaths from cancer of the oropharynx (five), nasopharynx (seven), hypopharynx (three) and unspecified pharynx (seven) were compared with 67 controls matched on race, sex, age and year of birth (within 2 years) with respect to occupational exposure to formaldehyde, and additional information on occupational and non-occupational exposures was obtained by telephone interviews, partly with next of kin [proportion of next-of-kin interviews not reported]. Based on exact conditional logistic regression, relative risks for the combined group of pharyngeal cancers, adjusted for tobacco smoking and years of employment in the factory, increased with increasing duration of exposure to formaldehyde and particularly with increasing duration of exposure to levels of formaldehyde > 0.2 ppm, but not with average intensity of exposure or cumulative exposure. Separate analyses for nasopharyngeal cancer were not presented due to small numbers.

[The earliest year of entry into this cohort was earlier than that in the NCI cohort, the cohort was enumerated independently from the NCI cohort and exposures were assessed separately using measurements and other information provided by the company but not those made by an industrial hygienist for the NCI study. The exposure estimates were generally about 10 times lower than those reported in Hauptmann *et al*. (2003, 2004). Marsh *et al.* (2002) suggested that this difference was because Hauptmann *et al*. (2003, 2004) used data from several plants to estimate exposure in each plant, whereas Marsh *et al*. (2002) based the assessment only on the plant under study. However, this suggestion is incorrect (Blair & Stewart, 1990). All data considered in the exposure estimates in a given plant in the Hauptmann *et al*. (2003, 2004) study were only from that plant.]

### (b)   *Garment workers: The National Institute for Occupational Safety and Health (NIOSH) Cohort*

Stayner *et al*. (1985, 1988) at NIOSH, USA, conducted a proportionate mortality study and a retrospective cohort study of mortality of garment workers exposed to formaldehyde. The cohort study included approximately 11 000 predominantly female (82%) workers from three facilities that manufactured shirts from fabrics that were treated with formaldehyde resins to impart permanent press characteristics. Workers who were included in the cohort study had worked for at least 3 months after the time that formaldehyde-treated fabrics were introduced into the process, which was 1959 in two of the facilities and 1955 in the third. Time-weighted 8-h geometric mean exposure levels in different departments in the three plants were found to range from 0.09 to 0.20 ppm at the time the study was initiated. Continuous air monitoring suggested no substantial peaks. Historical exposure levels were not available; however, exposure levels are believed to have been substantially higher in the earlier years of the study because the methods of treatment with formaldehyde resin have been steadily improved over time to reduce the amount of free formaldehyde in the fabrics. Exposure measurements reported at other facilities before 1970 ranged from 0.3 to 10 ppm (Stayner *et al*., 1988) (see Section 1.3.2(*f*)). The investigators reported

finding no evidence that other potentially carcinogenic exposures were present at the study facilities. Follow-up of the cohort for vital status, which was originally through to 1982, was recently extended to 1998 (Pinkerton *et al*., 2004). Life-table methods that applied national and state rates were used. The results from analyses were similar for the cancer sites of a-priori interest when both national and state rates were used. Life-table analyses that used a multiple cause-of-death approach (Steenland *et al*., 1992) were also conducted. Poisson regression models were used to analyse the relationship between duration of exposure and risk for cancer.

Mortality from all cancers (608 deaths; SMR, 0.89; 95% CI, 0.82–0.97) was shown to be significantly lower than that expected based upon comparisons with the national population. The observed numbers of cases of respiratory cancer (152 deaths; SMR, 0.98; 95% CI, 0.83–1.14) and of cancer of the brain and central nervous system (19 deaths; SMR, 1.09; 95% CI, 0.66–1.71) were found to be close to expectation. Mortality from buccal cancer, which was found to be elevated (four deaths; SMR, 3.53; 95% CI, 0.96–9.02) in the original study (Stayner *et al*., 1988), was only slightly elevated (four deaths; SMR, 1.33; 95% CI, 0.36–3.41) in the updated study (Pinkerton *et al*., 2004). No cases of nasopharyngeal (0.96 expected) or nasal (0.16 expected) cancer were observed. A slight excess of mortality from leukaemia (24 deaths; SMR, 1.09; 95% CI, 0.70–1.62) was observed, which was a certain degree higher for myeloid leukaemia (15 deaths; SMR, 1.44; 95% CI, 0.80–2.37). The excess mortality from myeloid leukaemia was greatest among workers who were first exposed during the earliest years of the study (before 1963) when exposures to formaldehyde were presumably higher (11 deaths; SMR, 1.61 [95% CI, 0.80–2.88]), among workers with 10 or more years of exposure (eight deaths; SMR, 2.19 [95% CI, 0.95–4.32]) and among workers with 20 or more years since first exposure (13 deaths; SMR, 1.91 [95% CI, 1.02–3.27]). A greater than twofold excess in mortality from myeloid leukaemia was observed among workers with both more than 10 years of exposure and 20 or more years since first exposure to formaldehyde (seven deaths; SMR, 2.43; 95% CI, 0.98–5.01). In contrast to leukaemia, the risk for respiratory cancer decreased with duration of employment and time since first exposure. [The Working Group noted that strengths of this study were the apparent absence of other potentially confounding carcinogenic exposures in the workplace and the long follow-up.]

### (c) Chemical industry workers

Acheson *et al*. (1984a) assembled a large cohort of workers from six chemical facilities in the United Kingdom, and Coggon *et al*. (2003) reported the findings from an update of the vital status of the cohort to 2000. The cohort included approximately 14 000 workers who had been employed after 1937 and before 1965, at a time when formaldehyde was used or produced, and personnel records at the plants were believed to be complete. Jobs were classified into one of five categories of exposure to formaldehyde, i.e. background, low, moderate, high or unknown. No exposure measurements were available before 1970. Based on the later measurements and workers' recall of irritant symptoms, it was estimated that the TWA exposure concentrations corresponded to: background, < 0.1 ppm; low

exposure, 0.1–0.5 ppm; moderate exposure, 0.6–2.0 ppm; and high exposure, > 2.0 ppm. Person–years and Poisson regression analyses were conducted. An adjustment for local geographical variations in mortality was made in some analyses, which entailed multiplying the expected deaths by SMRs for the area in which the plant was located.

Mortality was elevated to some extent for all cancers (1511 deaths; SMR, 1.10; 95% CI, 1.04–1.16), and this was more pronounced among workers who had ever worked in a job that was classified as entailing high exposure to formaldehyde (621 deaths; SMR, 1.31; 95% CI, 1.21–1.42). This excess mortality was largely attributable to a statistically significant excess of mortality from cancers of the stomach (150 deaths; SMR, 1.31; 95% CI, 1.11–1.54) and lung (594 deaths; SMR, 1.22; 95% CI, 1.12–1.32). The excess of mortality from lung cancer was greatest among men who had high exposure (272 deaths; SMR, 1.58; 95% CI, 1.40–1.78). The excess incidence of lung cancer among the highly exposed decreased with adjustment for local rates, although it remained statistically significant (SMR, 1.28; 95% CI, 1.13–1.44). Mortality from lung cancer was higher among workers who were highly exposed before 1965 when levels of exposure to formaldehyde would be expected to be higher (243 deaths; SMR, 1.61; 95% CI, 1.41–1.82). Mortality from lung cancer demonstrated a non-significant inverse relationship with the number of years worked in high-exposure jobs ($p_{trend} = 0.13$) and showed no trend with time since first employment in a job that entailed high exposure ($p_{trend} = 0.93$).

A statistically non-significant excess mortality from pharyngeal cancer was observed (15 deaths; SMR, 1.55; 95% CI, 0.87–2.56), which was to some degree greater among highly exposed workers (six deaths; SMR, 1.91; 95% CI, 0.70–4.17). One death from nasopharyngeal cancer was observed where 2.0 were expected; two cases of sinonasal cancer were observed where 2.3 were expected, but neither individual was highly exposed. A review of tumour registry data identified two additional cases of sinonasal cancer, both in individuals who were highly exposed, but it was not possible to determine the expected number of incident cases because of limitations in the tumour registry system. Slight excess mortality, based on a small number of cases, was observed in men who had had high exposure for cancers of the tongue (three deaths; SMR, 1.91; 95% CI, 0.39–5.58) and mouth (two deaths; SMR, 1.32; 95% CI, 0.16–4.75). Mortality from cancer of the brain and central nervous system and from leukaemia was lower than expected among the entire cohort (SMRs, 0.85 and 0.91, respectively) and among the high-exposure group (SMRs, 0.63 and 0.71, respectively). [The Working Group noted that this study probably included a substantial number of workers who had relatively high exposures: 4000 workers had ever worked in jobs that were classified as entailing exposures greater than 2 ppm. The Working Group also noted the long follow-up. However, there was a lack of exposure measurements before 1970, and this may have led to some misclassification of exposures.]

Bond *et al*. (1986) conducted a case–control study in a cohort of 19 608 men who had been employed for 1 year or longer at a large chemical production facility in Texas, USA, between 1940 and 1980, which included 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 (± 5 years) and year of first employment,

were selected: one among men who were 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, not including formaldehyde, were assessed in greater detail. Only nine men who had 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 0.62 (95% CI, 0.29–1.34); incorporation into the analysis of a 15-year minimal latency gave an odds ratio of 0.31 (95% CI, 0.11–0.86).

### (*d*)    *Fibreglass workers*

Marsh *et al*. (2001) updated and expanded an earlier cohort study of mortality of workers who had been employed at any of 10 fibreglass manufacturing plants in the USA that had been previously studied by Enterline *et al*. (1987). The study included over 32 000 workers who had been employed for at least 1 year between 1945 and 1978 in one of the 10 study facilities. The cohort was expanded to include women, workers who had been employed after the original 1963 end date and workers from additional worksites; the vital status of the cohort was established until the end of 1992. In addition to expanding and updating the cohort, the study introduced new information on potential exposures to several known and potential carcinogens other than fibreglass (asbestos, arsenic, asphalt, epoxy, polycyclic aromatic hydrocarbons, phenolics, silica, styrene and urea), including formaldehyde. Exposure to formaldehyde was the most common exposure [22% of the person–years] after respirable fibres [28% of the person–years] in the study. The median exposure to formaldehyde for the cohort was 0.066 ppm and ranged from 0.03 to 0.13 ppm in the different plants. Person–years methods were used to analyse the mortality of the cohort in comparison with both national population and local death rates. Overall cancer mortality was slightly lower than expected in comparison with both national (2243 deaths; $SMR_{US}$, 0.98; 95% CI, 0.94–1.02) and local rates ($SMR_{local}$, 0.94; 95% CI, 0.90–0.98). A statistically significant excess of mortality from respiratory cancer was observed for the whole cohort when national rates were used (874 deaths; $SMR_{US}$, 1.16; 95% CI, 1.08–1.24), which was weaker and of borderline significance ($p = 0.05$) when local rates were used as a referent ($SMR_{local}$, 1.06; 95% CI, 1.00–1.14). This excess was largely attributable to an excess mortality from cancers of the trachea, bronchus and lung (838 deaths; $SMR_{US}$, 1.17; 95% CI, 1.09–1.25; $SMR_{local}$, 1.07; 95% CI, 1.00–1.14).

The association of respiratory cancer with specific exposures was examined in a nested case–control study in which the cases were male members of the cohort who had died from respiratory tumours during 1970–92 (Marsh *et al*., 2001; Stone *et al*., 2001; Youk *et al*., 2001). Each case was randomly matched with a control who had the same date of birth to within 1 year, who was at risk during 1970–92 and who was alive and at risk at the age when the case died. Smoking histories were ascertained through telephone interviews with the subjects themselves or a proxy. Complete data were available for 502 of 713 matched pairs,

and unmatched cases and controls were combined with the matched set nearest in age (at the time of death of the case). Thus, the analysis was based on 631 cases and 570 controls. Of the cases, 96% had been diagnosed with carcinoma of the trachea, bronchus or lung. Individual exposures in the matched set to formaldehyde, respirable fibres and silica before the age at which the case died were estimated from industrial hygiene data using a job–exposure matrix that took into account time period, plant and department. Analysis was performed using conditional logistic regression with adjustment for smoking. In a first analysis (Youk *et al*., 2001), nine different configurations of time lag and window of exposure were examined for average intensity of exposure and cumulative exposure. When exposure was not weighted in relation to the time of case death, the odds ratio for ever exposure to formaldehyde was 1.61 (95% CI, 1.02–2.56) and a similar risk estimate was obtained when a 5-year lag was applied (odds ratio, 1.62; 95% CI, 1.04–2.54). Otherwise, however, the risk estimates for ever exposure were lower, and there were no clear trends with cumulative or average intensity of exposure (which for most subjects were < 2 ppm–years and < 0.14 ppm, respectively).

This analysis was then extended by application of a conditional logistic regression model that adjusted for exposure to respirable fibres as well as tobacco smoking, and used piecewise linear functions (linear splines) with knots at the deciles of the distributions of exposure in the cases. Cumulative exposure to formaldehyde was not significantly associated with increased risk in any of the models examined, but there was a suggestion of increased risk (of borderline statistical significance) with average intensity of exposure at the upper end of the range (Stone *et al*., 2001). [The Working Group noted that exposures to formaldehyde in this cohort of fibreglass workers appeared to be lower than those in the studies of industrial and textile workers reviewed earlier in this section.]

Chiazze *et al*. (1997) conducted a retrospective cohort study of mortality of 4631 workers at a fibreglass manufacturing plant in Anderson, SC, USA. This included a nested case–control study for lung cancer (47 cases) which collected information from interviews on tobacco smoking, socioeconomic factors and a historical reconstruction of several exposures at the plant, including formaldehyde. Controls for this analysis were individuals in the cohort who had not died from lung cancer, or from suicide or homicide (for ethical reasons). The controls were matched to the cases based on year of birth (± 2 years) and survival to the end of follow-up or death (± 2 years). Person–years methods of analysis were used to analyse the cohort study, and conditional logistic regression was used to analyse the case–control study. Cumulative exposure to formaldehyde was the only exposure in the case–control analysis to exhibit a positive relationship with risk for lung cancer. Among smokers only, lung cancer was elevated in the highest (> 1000 ppm–days; odds ratio, 2.07; 95% CI, 0.17–25.5) and next to highest (100–999 ppm–days; odds ratio, 1.72; 95% CI, 0.57–5.23) cumulative exposure groups, but these excesses were based on a small number of cases and were statistically non-significant.

(*e*)     *Woodworkers*

Partanen *et al*. (1985) conducted a case–control study in a cohort of 3805 male production workers who had been employed for at least 1 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 men were declared to the Finnish Cancer Registry as having 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 were combined with the work histories of the subjects to yield several indicators of exposure; supplementary information on tobacco smoking was collected for 68% of cases and 76% of controls, by means of a postal questionnaire, from study subjects or their relatives. A slight, non-significant increase in risk for all cancers combined was seen among workers who had had any exposure to at least 0.1 ppm (0.12 mg/m$^3$) formaldehyde in contrast to workers who had had no exposure to formaldehyde, which yielded an odds ratio of 1.44 [95% CI, 0.6–3.5]; an odds ratio of 1.27 [95% CI, 0.5–3.5] was obtained 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 of and cumulative exposure, repeated peak exposures and 'formaldehyde in wood dust'). Adjustment for cigarette smoking did not change the overall results.

In an expansion of the study to include a total of 35 Finnish factories and 7307 woodworkers who had been employed during 1944–65, Partanen *et al.* (1990) identified 136 newly diagnosed cases of 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 Finnish Cancer Registry for 1957–82. The additional factories were mainly involved in construction carpentry and furniture manufacture. Three controls were provided for each new cancer case, 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 who had had any exposure to formaldehyde (odds ratio, 1.4 [95% CI, 0.6–3.1]), 18 were cancers of the lung (odds ratio, 1.3 [95% CI, 0.5–3.0]) and two were cancers at other sites (odds ratio, 2.4 [95% CI, 0.3–18]). Adjustment for tobacco smoking reduced the odds ratios to 1.1 for all cancers combined and to 0.7 for lung cancer separately and rendered the odds ratio for cancers at other sites unassessable. The unadjusted odds ratios for all cancer cases were 1.5 [95% CI, 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 [95% CI, 0.1–8.2] for > 1 ppm, in comparison with no exposure. Other indicators of exposure to formaldehyde, which included an estimate of cumulative exposure and duration of exposure to peak levels > 2 ppm [2.46 mg/m$^3$], showed similarly inconsistent 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 for the subgroups who had had the presumed highest exposures to odds ratios generally below 1.0.

[The Working Group noted that there were too few cancers at sites other than the lung to allow a meaningful analysis; consequently, this was essentially a study of lung cancer.]

Stellman *et al*. (1998) studied mortality among workers exposed to wood dust in the American Cancer Society's Cancer Prevention Study. From the original cohort of over half a million men, sufficient data were available for 362 823 who were included in the study. Of these, 45 399 reported either employment in a wood-related occupation or exposure to wood dust. As part of the investigation, data were also collected on self-reported exposure to formaldehyde, and incidence density ratios according to exposure were derived for death from each of several cancers during 6 years of follow-up. This analysis adjusted for age and for smoking habits. In comparison with men who had never been employed in a wood-working occupation and who did not report regular exposure to wood dust, those who had been wood-workers and who reported exposure to formaldehyde had elevated mortality from lung cancer (seven deaths; relative risk, 2.63; 95% CI, 1.25–5.51) and leukaemia (two deaths; relative risk, 5.79; 95% CI, 1.44–23.25). In men exposed to formaldehyde who had not worked in wood-related occupations, the corresponding risk estimates for lung cancer and leukaemia were 0.93 (95% CI, 0.73–1.18) based on 104 deaths and 0.96 (95% CI, 0.54–1.71) based on 12 deaths, respectively. Results for sinonasal and nasopharyngeal cancers were not reported. [The Working Group noted that this study should be given little weight in the evaluation because of the small number of formaldehyde-exposed workers and the limitations in the subjective exposure assessment for formaldehyde.]

### (*f*)    *Iron foundry workers*

Andjelkovich *et al*. (1990) studied a cohort of 8147 men who had been employed for 6 months or longer at an iron foundry in the USA. In a nested case–control study (Andjelkovich *et al*., 1994), the case group comprised all members of the cohort who died from primary lung cancer during 1950–89 and were ascertained from various sources. They included 200 men in whom lung cancer was certified as the underlying cause of death, 13 in whom it was a contributory cause and seven who died from carcinomatosis with a primary lung tumour that was confirmed from hospital records or through the local cancer registry. Ten controls were selected for each case by incidence density sampling; they were of the same race and had attained at least the same age as their matched case. Just over half of the controls (52.2%) were still alive at the end of the follow-up period. In total, 50.9% of cases and controls were white. Exposure to silica (high, medium or low) and formaldehyde (high, medium, low or none) was classified by means of a job–exposure matrix based on industrial hygiene data, walk-through surveys, job description, knowledge of the tasks performed in a job and reports in the scientific literature. [In the analysis reported, exposure to formaldehyde was dichotomized as some versus none; no data were provided on the probable levels of airborne concentrations.] Data on tobacco smoking (yes or no) were available for 75.5% of cases and 68.6% of a random subset of two controls per case and were obtained from various sources including the subject himself, his next of kin, plant medical records, hospital medical records and death certificates. Analysis was performed using conditional logistic regression with and without the inclusion of lag

periods. Overall, 25% each of cases and controls were classed as having been exposed to formaldehyde. After adjustment for tobacco smoking, birth cohort (< 1915 versus ≥ 1915) and cumulative exposure to silica (partitioned to four levels at the quartiles), the odds ratio for unlagged exposure to formaldehyde was 1.31 (95% CI, 0.83–2.07); with the incorporation of increasing lag periods, this risk estimate decreased progressively to 0.84 (95% CI, 0.44–1.60) for a 20-year lag. Risk estimates were little affected by the inclusion of tobacco smoking in the regression models, and there was no evidence of an interaction between formaldehyde and smoking. [The Working Group noted that data to support this statement were not shown.]

The relation of formaldehyde to risk for cancer was examined further in a subset of 3929 men from the full cohort who had worked in jobs that entailed potential exposure to formaldehyde for at least 6 months between January 1960 and May 1987 (Andjelkovich *et al.*, 1995). The mortality of this group was compared with that of the national population (by the person–years method), with that of an internal reference population of 2032 cohort members who had worked during the same period in jobs that did not entail exposure to formaldehyde and with that of an occupational referent population assembled by the NCI and NIOSH, using Poisson regression analysis. Cumulative exposure to formaldehyde and silica was estimated for each worker based on detailed occupational histories and evaluation of job-specific exposure levels by an occupational hygienist. Smoking status was ascertained for 65.4% of the exposed subcohort and 55.1% of the unexposed control subcohort. In the follow-up through to 1989 and in comparison with national death rates, mortality from all cancers was close to that expected in both the formaldehyde-exposed (127 deaths; SMR, 0.99; 95% CI, 0.82–1.17) and unexposed (95 deaths; SMR, 0.97; 95% CI, 0.79–1.19) populations. In both the exposed and unexposed subcohorts, a statistically non-significant excess of mortality from cancers of the buccal cavity and pharynx (exposed: six deaths; SMR, 1.31; 95% CI, 0.48–2.86; unexposed: five deaths; SMR, 1.69; 95% CI, 0.54–3.95) and lung cancer (exposed: 51 deaths; SMR, 1.20; 95% CI, 0.89–1.58; unexposed: 38 deaths; SMR, 1.19; 95% CI, 0.84–1.63) was observed. Mortality from cancers of the lung, buccal cavity and pharynx was not found to increase with cumulative exposure in the Poisson regression analysis. Mortality from laryngeal cancer (two deaths; SMR, 0.98; 95% CI, 0.11–3.53), cancer of the brain and central nervous system (two deaths; SMR, 0.62; 95% CI, 0.07–2.23) and leukaemia (two deaths; SMR, 0.43; 95% CI, 0.05–1.57) was lower than expected among the exposed.

(*g*)     *Other chemical workers and plastics manufacturers*

A study of mortality among workers at a formaldehyde resin plant in Italy (Bertazzi *et al.*, 1986) included 1332 male workers who had ever been employed for at least 30 days between the launch of the plant in 1959 and 1980. Follow-up for vital status was extended from 1980 to 1986 in a second study (Bertazzi *et al.*, 1989). Work histories of past employees were reconstructed from interviews with retired workers, current workers and foremen. Actual or reconstructed work histories were available for all but 16.5% 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 concentrations in fixed area samples that were taken between 1974 and 1979 were 0.2–3.8 mg/m³ [0.2–3.1 ppm]. SMRs were calculated using the person–years methods to estimate expected numbers based on national and local mortality rates, and were adjusted for age and calendar time. A deficit of lung cancer was observed among workers who had been exposed to formaldehyde; six cases of lung cancer were observed and 8.7 were expected. Excess mortality from lymphatic and haematopoietic neoplasms was observed among formaldehyde-exposed workers based on only three deaths (SMR, 1.73 [95% CI, 0.36–5.06]). During the first follow-up (Bertazzi *et al.*, 1986), no nasal cancer was recorded (0.03 expected).

Ott *et al.* (1989) evaluated data from a nested case–control study within a cohort of 29 139 men who had been employed in two chemical manufacturing facilities and a research and development centre. Cases were subjects who had died between 1940 and 1978 from non-Hodgkin lymphoma (52 cases), multiple myeloma (20 cases), non-lympho-cytic leukaemia (39 cases) and lymphocytic leukaemia (18 cases); information on death certificates was used to determine cause of death. Five controls per case were selected from the total employee cohort and were frequency-matched to cases by decade of first employ-ment and duration of survival after first employment. Potential exposure to several chemicals, including formaldehyde, was assessed based on use of the chemical in the work area or in an activity in which the subject was involved at a specific time. Because adjust-ment for age did not substantially change the risk estimates, crude odds ratios were presented. Odds ratios for ever versus never exposed to formaldehyde for non-Hodgkin lymphoma (two exposed cases), multiple myeloma (one exposed case), non-lymphocytic (two exposed cases) and lymphocytic (one exposed case) leukaemia were 2.0, 1.0, 2.6 and 2.6, respectively. [The Working Group noted that confidence intervals were not provided and could not be calculated because the number of exposed controls was not given.]

Dell and Teta (1995) conducted a retrospective cohort study of mortality of 5932 male employees at a plastics manufacturing and research and development facility in Bound Brook, NJ, USA. Workers who were included in the cohort had worked for at least 7 months between 1946 and 1967 at the facility where they had been exposed to a number of chemi-cals, including asbestos, polyvinyl chloride and formaldehyde. The cohort was followed for vital status through to 1988. Only 111 of the cohort members had held jobs that involved potential exposure to formaldehyde. Person–years methods were applied in which national and state mortality rates were used as the referent. The analysis was stratified by whether workers were paid hourly or were salaried, by duration of employment with lag intervals of 0, 10 and 15 years and by time since first employment. Mortality for all cancers was close to expected (using national rates) among hourly workers (334 deaths; SMR, 1.02; 95% CI, 0.92–1.14). Excess mortality was observed among hourly workers for cancers of the pancreas (25 deaths; SMR, 1.46; 95% CI, 0.95–2.16), lung (124 deaths; SMR, 1.10; 95% CI, 0.92–1.31) and other parts of the respiratory system (five deaths; SMR, 3.73; 95% CI, 1.21–8.70). The excess mortality from cancers of other parts of the respiratory system was

entirely due to an excess mortality from pleural mesothelioma, which was most probably attributable to exposure to asbestos. An excess of mortality from lung cancer (4 observed, 1.1 expected) was noted among 57 workers who had been exposed to formaldehyde in the hexamethylenetetramine process. No cases of nasal or nasopharyngeal cancer were observed. [The Working Group and the authors noted that, because of its small size, this study was relatively uninformative with regard to formaldehyde.]

### (h)    *Abrasives industry*

Cancer mortality and incidence among workers in the abrasives industry in Sweden was evaluated by Edling *et al.* (1987a) in plants that manufactured grinding wheels and employed abrasives bound with formaldehyde resins. The levels of formaldehyde were reported to be 0.1–1.0 mg/m$^3$. A cohort of 911 workers (211 women in administration and production and 700 men, of whom 521 were blue-collar workers) who had been employed for at least 5 years between 1955 and 1983 was followed for mortality through to 1983 and for cancer incidence through to 1981, yielding 79 deaths and 24 incident cancers. Deaths and morbidity that occurred at the age of 75 years or older were excluded because of concerns about diagnostic validity. Person–years methods were used to generate expected numbers based on rates for the general population, stratified for age, calendar year and sex. No significant excesses of mortality or morbidity were seen among male blue-collar workers, administrative personnel or among women. All cancer mortality (17 deaths; SMR, 0.93 [95% CI, 0.54–1.49]) and incidence (24 cases; standardized incidence ratio (SIR), 0.84 [95% CI, 0.54–1.25]) were slightly lower than expected. Lung cancer incidence was lower than expected (two cases; SIR, 0.57 [95% CI, 0.07–2.06]). No cases of leukaemia, or nasal or buccal cancer were observed. One case of nasopharyngeal cancer and one of cancer of the nervous system were reported.

### (i)    *Mixed industrial exposures*

Hansen and Olsen (1995) conducted a standardized proportionate cancer incidence study of workers in Denmark. Individuals who were born between 1897 and 1964 and had been diagnosed with cancer between 1970 and 1984 were identified from the Danish Cancer Registry. Employment histories were established through linkage to the Supplementary Pension Fund, which began in 1964. A total of 91 182 men who had cancer, who met the study criteria and who had records in the Supplementary Pension Fund were identified. The companies in which individuals worked were identified by the Fund and the use of formaldehyde by these companies was retrieved from the Danish Product Register. Cancer patients whose longest work experience after 1964 was at one of the companies that used formaldehyde and was at least 10 years before the date of diagnosis were regarded as being potentially exposed to formaldehyde. White-collar workers were assumed to have low exposure, blue-collar workers were assumed to have high exposure and workers with a missing job title were assumed to have unknown exposure to formaldehyde. [The Working Group noted that this may not be a very reliable means of classifying workers with regard to exposure.] Blue-collar cases who had worked in wood and

furniture companies and carpentry enterprises or had worked as a cabinet maker, joiner or carpenter were classified as having potential exposure to wood dust. A parallel study included 73 423 women with incident cancer and records of the Supplementary Pension Fund (Hansen & Olsen, 1996). Standardized proportionate incidence of cancer ratios (SPICR) were estimated using age-, sex- and calender period-specific proportions among all employees in Denmark as the reference. A statistically significant excess of mortality from cancer of the nasal cavity and paranasal sinuses (SPICR, 2.3; 95% CI, 1.3–4.0) was observed among male workers who were potentially exposed to formaldehyde, based on 13 cases. Among women, the SPICR was 2.4 (95% CI, 0.6–6.0), based on four cases. The excess mortality from nasal cancer observed in men was more pronounced among blue-collar workers who were exposed to formaldehyde only (nine cases; SPICR, 3.0; 95% CI, 1.4–5.7) or who had co-exposure to formaldehyde and wood dust (two cases; SPICR, 5.0; 95% CI, 0.5–13.4). The observed number of cases was close to expected for cancers of the buccal cavity and pharynx (23 cases; SPICR, 1.1; 95% CI, 0.7–1.7), nasopharynx (four cases; SPICR, 1.3; 95% CI, 0.3–3.2), brain and nervous system (54 cases; SPICR, 1.1; 95% CI, 0.9–1.5), larynx (32 cases; SPICR, 0.9; 95% CI, 0.6–1.2) and lung (410 cases; SPICR, 1.0; 95% CI, 0.9–1.1) and for leukaemia (39 cases; SPICR, 0.8; 95% CI, 0.6–1.6). No cancer site showed risk estimates that were significantly different from unity among women.

### 2.1.2 *Cohort and proportionate mortality studies of professional groups*

Pathologists, anatomists, embalmers and funeral directors have been studied because they use formaldehyde as a tissue preservative. Investigations of these occupations have several methodological problems. The use of national statistics to generate expected numbers may bias estimates of relative risks downwards for some cancers and upwards for others because some of these groups have a higher socioeconomic level than the general population; only a few investigations included a special referent population that was designed to diminish potential socioeconomic confounding. None of these studies presented the data necessary to adjust for tobacco use. Since anatomists and pathologists in the USA 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 tobacco smoking may be strong enough to preclude any possibility of detecting an 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 presented in the following text, they were not provided in the original study. Non-diffe-rential error in exposure assessment, which occurs when the measures of exposure are about equally inaccurate for study subjects who do and do not have the cancer of interest, diminishes the chances of uncovering an underlying association, as it biases estimates of

the relative risk towards the null. Key study features and findings from the cohort and pro-portionate mortality studies of professional groups are summarized in Table 17 by sub-groups of profession.

### (a)    *Cohort of British pathologists and medical technicians*

Harrington and Shannon (1975) evaluated the mortality of pathologists and medical laboratory technicians in Great Britain in 1975. A total of 2079 members of the Royal College of Pathologists and the Pathological Society who were alive in 1955 were enrolled and followed for vital status through to 1973. The Council for Professions Supplementary to Medicine enabled the identification of 12 944 technicians. 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-, 5-year calendar period- and 5-year age group-specific rates for England and Wales or Scotland. A deficit in mortality from cancer was observed in both pathologists (40 observed, 66.9 expected) and medical technicians (37 observed, 59.8 expected). The SMR for lymphatic and haematopoietic cancer was significantly elevated among pathologists (eight deaths [SMR, 2.00; 95% CI, 0.86–3.94]), but not among technicians (three deaths [SMR, 0.55; 95% CI, 0.11–1.59]). No excess incidence of leukaemia was observed in either group. The SMRs for cancers at other sites were all 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 to 1980. The population now included 2307 men and 413 women. SMRs were calculated using expected rates based on age-, sex- and calendar time-specific data from England and Wales. The SMR for all cancers among men was 0.61 (32 deaths [95% CI, 0.42–0.86] and that among women was 1.41 (seven deaths [95% CI, 0.57–2.90]). Mortality from brain cancer was significantly elevated among men (four deaths; SMR, 3.33 [95% CI, 0.91–8.53] $p < 0.05$), but not among women. No cases of nasal or nasal sinus cancer were observed, but the expected number was small (0.12). Mortality from lung cancer among men was significantly lower than expected (nine deaths; SMR, 0.41 [95% CI, 0.19–0.78]). Mortality from leukaemia and other lymphatic and hematopoetic neoplasms was close to that expected [men and women combined: three deaths; SMR, 0.92; 95% CI, 0.18–2.68].

This cohort was further evaluated by Hall *et al*. (1991), who extended follow-up of mortality from 1980 through to 1986 and added new members of the Pathological Society, which resulted in 4512 individuals available for study (3069 men and 803 women in England and Wales; 409 men in Scotland; and 231 members from Northern Ireland and women from Scotland for whom corresponding reference rates were not available). Sex-specific SMRs were based on expected rates for England and Wales or Scotland (for men only), as appropriate, and were adjusted for age (5-year groups) and calendar time. The SMRs for all causes of death were all considerably below 1.0: men from England and Wales, 0.43 (176 deaths; 95% CI, 0.37–0.50); women from England and Wales, 0.65 (18 deaths; 95% CI, 0.38–1.03); and men from Scotland, 0.50 (29 deaths; 95% CI, 0.34–0.72). The SMRs for cancers at all sites were 0.40 (44 deaths; 95% CI, 0.29–0.54) and 0.59 (nine

**Table 17. Cohort and proportionate mortality studies of cancer in professionals exposed to formaldehyde**

| Reference, country, years of study | Study population, design (study size) | Exposure assessment | Organ site | No. of cases/ deaths | SMR[a] (95% CI) | Comments |
|---|---|---|---|---|---|---|
| **British pathologists and medical technicians** | | | | | | |
| Hall *et al.* (1991), United Kingdom, 1974–87 (update of Harrington & Oakes, 1984, plus new members since 1973) | Pathologists, SMR (4512 men and women) [sex distribution not reported] | None | All cancers | 53 deaths | 0.45 (0.34–0.59) | Data presented for men and women from England and Wales (*n* = 3872) |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | NR | NR | |
| | | | Lymphohaematopoietic | 10 deaths | 1.44 (0.69–2.65) | |
| | | | Leukaemia | 4 deaths | 1.52 (0.41–3.89) | |
| | | | Lung | 9 deaths | 0.19 (0.09–0.36) | |
| | | | Brain and central nervous system | 6 deaths | 2.18 (0.80–4.75) | |
| **Anatomists and pathologists in the USA** | | | | | | |
| Stroup *et al.* (1986), USA, 1925–79 | Anatomists, SMR (2239 men) | Duration | All cancers | 118 deaths | 0.64 (0.53–0.76) | |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | 0 deaths | (0.0–7.2) | 0.5 expected |
| | | | Lymphohaematopoietic | 18 deaths | 1.2 (0.7–2.0) | |
| | | | Lymphoma | 2 deaths | 0.7 (0.1–2.5) | |
| | | | Leukaemia | 10 deaths | 1.5 (0.7–2.7) | |
| | | | Chronic myeloid leukaemia | 3 deaths | 8.8 (1.8–25.5) | Analysis limited to 1969–79 |
| | | | Other lymphatic tissue | 6 deaths | 2.0 (0.7–4.4) | |
| | | | Buccal cavity/pharynx | 1 death | 0.2 (0.0–0.8) | |
| | | | Lung | 12 deaths | 0.3 (0.1–0.5) | No trend with duration |
| | | | Brain and central nervous system | 10 deaths | 2.7 (1.3–5.0) | Trend with duration |
| Logue *et al.* (1986), USA, 1962–77 | Pathologists, SMR (5585 men) | None | Nasopharynx | NR | NR | Rate of buccal cavity/pharyngeal cancer was twice as high among pathologists than among radiologists. |
| | | | Nasal cavity | NR | NR | |
| | | | Lymphohaematopoietic | NR | 0.48 (NR) | |
| | | | Leukaemia | NR | 1.06 (NR) | |
| | | | Buccal cavity/pharynx | NR | 0.71 (NR) | |
| | | | Respiratory system | NR | 0.24 (*p* < 0.01) | |

**Table 17 (contd)**

| Reference, country, years of study | Study population, design (study size) | Exposure assessment | Organ site | No. of cases/ deaths | SMR[a] (95% CI) | Comments |
|---|---|---|---|---|---|---|
| **Embalmers and funeral directors** | | | | | | |
| Walrath & Fraumeni (1983), New York, USA, 1925–80 | Embalmers and embalmers/funeral directors, PMR/PCMR (1132 white men) | Time since first licence, age at first licence | All cancers | 243 deaths | 1.00 | PCMR |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | 0 deaths | NA | 0.5 expected |
| | | | Lymphohaematopoietic | 25 deaths | 1.21 | PMR |
| | | | Lympho- and reticulosarcoma | 5 deaths | 0.82 | PCMR |
| | | | Other lymphatic cancers | 6 deaths | 1.23 | PMR |
| | | | Leukaemia | 12 deaths | 1.19 | PCMR |
| | | | Myeloid leukaemia | 6 deaths | [1.5] | PMR |
| | | | Buccal cavity/pharynx | 8 deaths | 1.03 | PCMR; 0 deaths from nasopharyngeal cancer |
| | | | | 7 deaths | 2.01 | PMR, embalmers only |
| | | | | 1 death | 0.28 | PMR, funeral directors |
| | | | Lung | 70 deaths | 1.11 | PCMR (+ two deaths from pleural cancer) |
| | | | Brain and central nervous system | 9 deaths | 1.38 | PCMR |
| | | | | 6 deaths | 2.34 | PMR, embalmers only, $p < 0.05$ |
| | | | | 3 deaths | 0.93 | PMR, funeral directors |
| Walrath & Fraumeni (1984), California, USA, 1925–80 | Embalmers, PMR/PCMR (1007 white men) | Duration | All cancers | 205 deaths | 1.00 | PCMR; $p < 0.05$ for PMR |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | 0 deaths | NA | 0.6 expected |
| | | | Lymphohaematopoietic | 19 deaths | 1.22 | PMR |
| | | | Lympho- and reticulosarcoma | 3 deaths | [1.0] | PMR |
| | | | Leukaemia | 12 deaths | 1.40 | PCMR; $p < 0.05$ for PMR; trend with duration |
| | | | Myeloid leukaemia | 6 deaths | [1.50] | PMR |
| | | | Buccal cavity/pharynx | 8 deaths | 0.99 | PCMR, inverse trend with duration; |
| | | | Lung | 41 deaths | 0.87 | 0 deaths from nasopharyngeal cancer |
| | | | Brain | 9 deaths | 1.68 | PCMR, no trend with duration PCMR; $p < 0.05$ for PMR; no trend with duration |

**Table 17 (contd)**

| Reference, country, years of study | Study population, design (study size) | Exposure assessment | Organ site | No. of cases/ deaths | SMR[a] (95% CI) | Comments |
|---|---|---|---|---|---|---|
| Levine *et al.* (1984), Canada, 1950–77 | Embalmers, SMR (1413 men) | None | All cancers | 58 deaths | 0.87 [0.66–1.12] | |
| | | | Nasopharynx | NR | NR | |
| | | | Nasal cavity | 0 deaths | NA | 0.2 expected |
| | | | Lymphohaematopoietic | 8 deaths | 1.23 [0.53–2.43] | |
| | | | Leukaemia | 4 deaths | [1.60] [0.44–4.10] | Histological type not mentioned |
| | | | Buccal cavity/pharynx | 1 death | [0.48] [0.01–2.65] | |
| | | | Lung | 19 deaths | 0.94 [0.57–1.47] | |
| | | | Brain and central nervous system | 3 deaths | [1.15] [0.24–3.37] | |
| Hayes *et al.* (1990), USA, 1975–85 | Embalmers/funeral directors, PMR (3649 white men, 397 non-white men) | None | All cancers | 900 deaths | 1.07 (1.01–1.15) | White |
| | | | | 102 deaths | 1.08 (0.87–1.31) | Non-white |
| | | | Nasopharynx | 3 deaths | 1.89 (0.39–5.48) | White |
| | | | | 1 death | 4.00 (0.10–22.3) | Non-white |
| | | | Nasal cavity | 0 deaths | NA | White and non-white, 1.7 expected |
| | | | Lymphohaematopoietic | 100 deaths | 1.31 (1.06–1.59) | White |
| | | | | 15 deaths | 2.41 (1.35–3.97) | Non-white |
| | | | Lympho- and reticulosarcoma | 11 deaths | 1.08 (0.54–1.93) | White |
| | | | | 1 death | 1.89 (0.05–10.5) | Non-white |
| | | | Lymphatic leukaemia | 5 deaths | 0.57 (0.19–1.33) | White |
| | | | | 2 deaths | 2.99 (0.36–10.7) | Non-white |
| | | | Myeloid leukaemia | 23 deaths | 1.61 (1.02–2.41) | White |
| | | | | 1 death | 1.06 (0.02–5.93) | Non-white |
| | | | Other and unspecified leukaemia | 17 deaths | 2.08 (1.21–3.34) | White |
| | | | | 3 deaths | 4.92 (1.01–14.36) | Non-white |
| | | | Buccal cavity/pharynx | 26 deaths | 1.19 (0.78–1.74) | White |
| | | | | 4 deaths | 1.25 (0.34–3.20) | Non-white |
| | | | Lung | 285 deaths | 0.97 (0.86–1.09) | White |
| | | | | 23 deaths | 0.75 (0.47–1.13) | Non-white men |
| | | | Brain and central nervous system | 24 deaths | 1.23 (0.80–1.84) | White |
| | | | | 0 deaths | NA | Non-white, 0.8 expected |

CI, confidence interval; NA, not applicable; NR, not reported; PCMR, proportionate cancer mortality ratio; PMR, proportionate mortality ratio; SMR, standardized mortality ratio

[a] Unless otherwise stated

deaths; 95% CI, 0.27–1.12) among men from England and Wales and Scotland, respectively, and 0.95 (nine deaths; 95% CI, 0.43–1.80) among women from England and Wales. No significant excess was seen for cancer at any site. Non-significant excess mortality occurred for brain cancer (six deaths; SMR, 2.40; 95% CI, 0.88–5.22) and lymphatic and haematopoietic cancer (nine deaths; SMR, 1.42; 95% CI, 0.65–2.69) among men from England and Wales, breast cancer (four deaths; SMR, 1.61; 95% CI, 0.44–4.11) among women from England and Wales and prostatic cancer (two deaths; SMR, 3.30; 95% CI, 0.39–11.8) among men from Scotland.

### (b)    *Anatomists and pathologists in the USA*

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 period, they were not included. Ninety-eight of the men were excluded because they had died, moved or were lost to follow-up before 1925, which resulted in a final study size of 2239. Follow-up of the cohort for vital status was accomplished from the date the person joined the association until 1979. The expected numbers of deaths were calculated from age-, race-, sex- and calendar time-specific rates for the general population of the USA 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. In comparison with the general population, the cohort showed a very large 'healthy worker effect', with SMRs of 0.65 for all causes (738 deaths) and 0.64 (118 deaths; 95% CI, 0.53–0.76) for cancer at all sites. Excess mortality was observed for cancers of the brain and central nervous system (10 deaths; SMR, 2.7; 95% CI, 1.3–5.0), leukaemia (10 deaths; SMR, 1.5; 95% CI, 0.7–2.7) and lymphatic tissues other than lymphosarcoma, reticulosarcoma, Hodgkin disease and leukaemia (six deaths; SMR, 2.0; 95% CI, 0.7–4.4). 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; no such pattern was seen for lung cancer or leukaemia. Of the 10 deaths from leukaemia, five were myeloid and the SMR for chronic myeloid leukaemia was statistically significantly elevated (three deaths; SMR, 8.8; 95% CI, 1.8–25.5) in the period 1969–79 for which cell type-specific mortality rates were available. The SMRs were below 1.0 for lung cancer (12 deaths; SMR, 0.3; 95% CI, 0.1–0.5) and oral and pharyngeal cancer (one death; SMR, 0.2; 95% CI, 0.0–0.8). No death from nasal cancer occurred (0.5 expected). When compared with members of the American Psychiatric Association, anatomists had deficits in mortality from lung cancer (seven deaths; SMR, 0.5; 95% CI, 0.2–1.1) and leukaemia (three deaths; SMR, 0.8; 95% CI, 0.2–2.9), but they still had an excess mortality from brain cancer (nine deaths; SMR, 6.0; 95% CI, 2.3–15.6).

Logue *et al*. (1986) evaluated mortality among 5585 members of the College of American Pathologists listed in the Radiation Registry of Physicians. The cohort was established by enrolling members between 1962 and 1972 and following them up through to 1977. Direct comparisons were made between the mortality rates of pathologists and a cohort of 4418 radiologists and used the Mantel-Haenszel procedure with adjustment for

age and calendar time for large categories of death (e.g. all cancers). Indirect comparisons that used mortality rates for white men in the USA in 1970 as the referent were also performed to compute SMRs. The age-adjusted mortality rate for all cancers was found to be slightly lower in pathologists than in radiologists (1.37 versus 1.51 per 1000 person–years). Based on comparisons with the national population, a deficit in mortality was observed among pathologists for cancers of the buccal cavity and pharnyx (SMR, 0.71) and respiratory system (SMR, 0.24) and for lymphatic and haematopoietic neoplasms other than leukaemia (SMR, 0.48). Mortality from leukaemia was slightly elevated (SMR, 1.06) among pathologists. [The number of deaths for each cancer site was not reported.] However, the age-adjusted mortality rate for leukaemia was higher among radiologists than among pathologists (0.15 versus 0.10 per 1000 person–years). [Confidence intervals were not reported and could not be estimated since observed and expected numbers of deaths were not reported.]

### (c)    *Embalmers and funeral directors*

Walrath and Fraumeni (1983) used licensing records from the New York State (USA) Department of Health, Bureau of Funeral Directing and Embalming to identify 1678 embalmers who had been licensed between 1902 and 1980 and who had died between 1925 and 1980. Death certificates were obtained for 1263 (75%) decedents (1132 white men, 79 non-white men, 42 men of unknown race and 10 women); proportionate mortality ratios (PMRs) and proportionate cancer mortality ratios (PCMRs) were calculated for white men and non-white 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 non-white men, but it was indicated that there was a significant excess mortality from cancers of the larynx (two deaths) and lymphatic and haematopoietic system (three deaths) in this group. Among white men, the PCMR was 1.00 (243 deaths) for all cancers combined. PCMRs for specific cancers were 1.03 (eight deaths) for buccal cavity and pharynx, 1.11 (70 deaths) for lung, 1.38 (nine deaths) for brain, 1.21 (PMR; 25 deaths) for lymphatic and haematopoietic system, 0.82 (five deaths) for lymphosarcoma and reticulosarcoma (ICD-8 200) and 1.19 (12 deaths) for leukaemia. Six of the leukaemia deaths (4.1 expected) were from myeloid leukaemia [PMR, 1.5]. No deaths occurred from cancer of the nasal sinuses or nasopharynx. There was little difference in PMRs by time since first licence. The subjects who were recruited had been licensed as either embalmers or as both embalmers and funeral directors. Mortality patterns were analysed separately for the two groups because the authors assumed that persons who were licensed only as embalmers would have had more exposure to formaldehyde than embalmers who were also funeral directors. The PMR for cancer of the brain and central nervous system was significantly increased among people who were licensed only as embalmers (six deaths; PMR, 2.34; $p < 0.05$) but not among those who also were licensed as a funeral director (three deaths; PMR, 0.93). A difference was also observed for mortality from cancer of the buccal cavity and pharynx: the PMR for embalmers was 2.01 (seven deaths) and that for embalmers/funeral directors was 0.28 (one death). Neoplasms of the lymphatic and haematopoietic system were only

elevated among individuals who were licensed as both an embalmer and funeral director (16 deaths; PMR, 1.39).

Walrath and Fraumeni (1984) used the records of the California (USA) Bureau of Funeral Directing and Embalming to examine proportionate mortality among embalmers who had first been licensed in California between 1916 and 1978. They identified 1109 embalmers who died between 1925 and 1980, comprised of 1007 white men, 39 non-white men, 58 white women and five non-white women. Only mortality of white men was ana-lysed. PMRs and PCMRs were calculated using age-, race-, sex- and calendar year-specific proportions from the general population of the USA. Total cancer mortality was signi-ficantly greater than that expected (205 deaths; PMR, 1.21 for all cancers combined). Also, a statistically significant excess of proportionate mortality was observed for cancers of the colon (30 deaths; PMR, 1.87), prostate (23 deaths; PMR, 1.75), brain and central nervous system (nine deaths; PMR, 1.94) and leukaemia (12 deaths; PMR, 1.75). The magnitude of these excesses was reduced and no longer statistically significant in the PCMR analyses (Table 17). Mortality from cancers of the buccal cavity and pharynx was slightly elevated in the PMR analysis (eight deaths; PMR, 1.31) but not in the PCMR analysis (PCMR, 0.99). Mortality from lung and pleural cancers was close to expected in both the PMR (41 observed, 42.9 expected; PMR, 0.96) and PCMR (0.87) analyses. There was no death from cancer of the nasal passages (0.6 expected). Mortality from leukaemia was found to be increased predominantly among embalmers who had had a licence for 20 or more years (eight deaths; PMR, 2.21). Six of the 12 cases of leukaemia were of the myeloid type [PMR, 1.5].

Mortality among 1477 male embalmers who had been licensed by the Ontario (Canada) Board of Funeral Services between 1928 and 1957 was evaluated by Levine et al. (1984). The cohort was followed for mortality from the date of first licence through to 1977. Expected numbers of deaths 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, which left 1413 men known to be alive in 1950. Morta-lity from all cancers was observed to be slightly lower than expected (58 deaths; SMR, 0.87 [95% CI, 0.66–1.12]). A small and statistically non-significant excess in mortality was observed for cancers of the lymphatic and haematopoietic system (eight deaths; SMR, 1.23 [95% CI, 0.53–2.43]) and leukaemia (four deaths [SMR, 1.60; 95% CI, 0.44–4.10]). Mortality from cancers of the buccal cavity and pharynx (one death [SMR, 0.48; 95% CI, 0.01–2.65]), lung (19 deaths; SMR, 0.94 [95% CI, 0.57–1.47]) and brain (three deaths [SMR, 1.15; 95% CI, 0.24–3.37]) was close to or lower than expected. No death from cancer of the nose, middle ear or sinuses was observed (0.2 expected).

Hayes et al. (1990) 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 in the USA between 1975 and 1985. Death certificates were received for 5265. Exclusion of 449 decedents included in previous studies of embalmers in New York (Walrath &

Fraumeni, 1983) and California (Walrath & Fraumeni, 1984), 376 subjects who probably did not work in the funeral industry, eight subjects of unknown race or age at death and 386 women left 4046 male decedents available for analysis (3649 whites and 397 non-whites). PMRs and PCMRs were calculated on the basis of expected numbers from race- and sex-specific groups of the general population, adjusted for 5-year age and calendar-time categories. The PMR for all cancers was 1.07 (900 deaths; 95% CI, 1.01–1.15) for whites and 1.08 (102 deaths; 95% CI, 0.87–1.31) for non-whites. The PMRs for specific cancers were: buccal cavity and pharynx (whites: 26 deaths; PMR, 1.19; 95% CI, 0.78–1.74; non-whites: four deaths; PMR, 1.25; 95% CI, 0.34–3.20), nasopharynx (whites: three deaths; PMR, 1.89; 95% CI, 0.39–5.48; non-whites: one death; PMR, 4.00; 95% CI, 0.10–22.3), nasal sinuses (whites and non-whites: 0 observed, 1.7 expected), lung (whites: 285 deaths; PMR, 0.97; 95% CI, 0.86–1.09; non-whites: 23 deaths; PMR, 0.75; 95% CI, 0.47–1.13), brain and central nervous system (whites: 24 deaths; PMR, 1.23; 95% CI, 0.80–1.84; non-whites: 0 observed, 0.8 expected) and lymphatic and haematopoietic system (whites: 100 deaths; PMR, 1.31; 95% CI, 1.06–1.59; non-whites: 15 deaths; PMR, 2.41; 95% CI, 1.35–3.97). The risks for cancers of the lymphatic and haematopoietic system and brain and central nervous system did not vary substantially by licensing category (embalmer versus funeral director), by geographical 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 (both groups combined: 24 deaths; PMR, 1.57; 95% CI, 1.01–2.34) and other and unspecified leukaemia (both groups combined: 20 deaths; PMR, 2.28; 95% CI, 1.39–3.52); non-significant excesses of mortality were observed for several other histological types.

### 2.1.3    *Other cohort studies*

In a study of users of various medicinal drugs based on computer-stored hospitalization records of the outpatient pharmacy at the Kaiser–Permanente Medical Center in San Francisco (CA, USA), 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 (four cases; morbidity ratio, 5.7 [95% CI, 1.6–15]) for people who used formaldehyde. Information on tobacco smoking was not provided. [The Working Group noted the short period of follow-up, the small number of cases and the lack of detailed information on exposure that made this study largely uninformative.]

Several studies have evaluated risk for cancer in haemodialysis patients who may have been potentially exposed to formaldehyde (see Section 1.3.2). [The Working Group

considered these studies to be largely uninformative since some patients with chronic renal failure receive immunosuppressive drugs, which are known to increase their risk for cancer, and because these studies are generally small, have short follow-up and provide limited or no information on exposures to formaldehyde.]

## 2.2      Case–control studies

Case–control studies have been used to examine the association between exposure to formaldehyde and various cancers. For rare tumours such as sinonasal and nasopharyngeal cancer, they have the potential to provide greater statistical power than can normally be achieved in cohort studies. Against this advantage, however, must be set the difficulties in assessing exposure to formaldehyde retrospectively in community-based studies. This requirement is usually addressed through expert evaluation of job histories by an occupational hygienist, or through the use of a job–exposure matrix. For a chemical such as formaldehyde, however, these methods tend to lack specificity when applied to the general population. Thus, the subjects who are classed as having been exposed to formaldehyde in community-based case–control studies usually have lower exposures on average than those in occupational cohorts that are specially selected for investigation because they are known to experience high exposures. Exposures to formaldehyde were assessed in some studies by asking study subjects whether they had been exposed to formaldehyde. This use of self-reported exposures is of questionable validity and in particular may lead to recall bias.

### 2.2.1    *Cancers of the nasal cavity and paranasal sinuses*

The study design of and results from case–control studies on cancers of the nasal cavity, paranasal sinuses, nasopharynx and hypopharynx associated with exposure to formaldehyde are summarized in Table 18.

With the purpose of investigating the carcinogenic effects of exposure to wood dust, Hernberg *et al.* (1983a) 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 and 167 country-, age- and sex-matched controls who had been diagnosed with cancers of the colon and rectum. 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 tobacco smoking habits of the study subjects was obtained by standardized telephone interview. 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. No association was found between sinonasal cancer and other occupations in which exposure to formaldehyde was considered to be most probable. A total of 18 cases and six controls had worked in 'painting, lacquering and glueing', a category that the authors considered may have entailed minimal exposure to

**Table 18. Case–control studies of cancers of the nasal cavity, paranasal sinuses, nasopharynx and hypopharynx**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Hernberg *et al.* (1983a), Denmark, Finland, Sweden, 1977–80 | Nasal cavity and parasinuses (160.0–160.9; ICD revision not given) | 167 patients [sex distribution not reported] with primary malignant tumours | 167 patients with cancer of the colon and rectum, matched by country, sex and age | Employment in particle-board or plywood industry | Yes/no | 0 cases, 0 controls | | |
| | | | | Painting, lacquering and glazing | Yes/no | 18 cases, 6 controls | | Concomitant exposure of 15 cases to wood dust |
| Brinton *et al.* (1984), USA, 1970–80 | Nasal cavity and parasinuses (ICD-8 160.0, 160.2–160.5, 160.8–160.9) | 160 (93 men, 67 women), including 86 squamous-cell carcinomas and 24 adeno-carcinomas or adenoid cystic carcinomas; 61 in nasal cavity, 71 in maxillary sinus and 28 other sinus or overlapping sites | 290 (178 hospital controls, 112 death certificate controls); hospital controls were required to be alive for living cases; death certificate controls were identified for deceased cases; matched on age, sex, race and county of residence | Telephone interviews with subjects or next of kin included a checklist of industries and self-reported exposures including formaldehyde. | *Men and women combined*<br>Unexposed<br>Exposed | 1.0<br>0.35 (0.1–1.8) | Adjusted for sex; control for tobacco use did not change results. | Formaldehyde exposure assessment was self-reported; only 33% of cases and 39% of controls were interviewed directly; for the remainder, exposures relied on recall of next of kin. |
| Olsen *et al.* (1984), Denmark, 1970–82 | Nasal cavity, nasal sinuses (160.0, 160.2, 160.9) and nasopharynx (146) (ICD revision not given) | 754 incident patients [sex distribution not reported] selected from the Danish Cancer Registry including 488 carcinomas of the nasal cavity and sinuses and 266 carcinomas of the nasopharynx | 2465 patients with cancers of the colon, rectum, prostate and breast; frequency-matched by sex, age (± 5 years) and year of diagnosis (± 5 years); 4.2% of men and 0.1% of women exposed to formaldehyde | Record linkage with pension fund with compulsory membership; job title from Central Pension Registry; exposure assessed blindly as certain, probable, unlikely, unknown | *Industries and occupations with certain exposure to formaldehyde*<br>Ever exposed<br>  Unexposed to wood dust<br>  Exposed to wood dust<br>Exposure for > 10 years before diagnosis<br>  Unexposed to wood dust<br>  Exposed to wood dust<br>  Adjusted for wood dust<br>*Industries and occupations with certain or possible exposure*<br>Men<br>Women | *Sinonasal*<br><br>2.8 (1.8–4.3)<br>1.8 (0.7–4.9)<br>3.5 (2.2–5.6)<br>3.1 (1.8–5.4)<br><br>1.5 (0.4–5.3)<br>4.1 (2.3–7.3)<br>1.6 (0.7–3.6)<br>*Nasopharynx*<br><br>0.7 (0.3–1.7)<br>2.6 (0.3–21.9) | Unadjusted<br><br><br><br><br><br><br><br><br>Unadjusted | Data for sinonasal cancer reported for men only |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Hayes *et al.* (1986a), Netherlands, 1978–81 | Nasal cavity and accessory sinuses (ICD-9 160.0, 160.2–160.5) | 91 male patients histo-logically confirmed, alive or deceased | 195 age-stratified random sample of living men resident in the Netherlands in 1982 or deceased in the Netherlands in 1980 | Taking into account job history, time period and potential frequency of exposure, exposure was classified into 10 groups independently by two occupational hygienists (assessment A and B) | *Any exposure to formaldehyde*<br>Assessment A<br>Assessment B<br>*No or little exposure to wood dust*<br>Assessment A<br>Assessment B<br>*Moderate to high exposure to wood dust*<br>Assessment A<br>Assessment B<br>*Squamous-cell carcinoma only*<br>Assessment A<br>Assessment B | 2.5 (1.5–4.3)[a]<br>1.9 (1.2–3.0)[a]<br><br>2.5 [1.0–5.9]<br>1.6 [0.8–3.1]<br><br>1.9 [0.6–6.5]<br>NR<br><br>3.0 [1.2–7.8]<br>1.9 [0.9–4.1] | Standardized for age in 10-year groups; control for usual number of cigarettes smoked did not modify the results.<br><br>No or little exposure to wood dust | Relative risk for adeno-carcinoma for those ever employed in the wood and paper industry, 11.3 (90% CI, 4.0–35.1); moderate increase associated with increase in level of exposure to formaldehyde with no concomitant exposure to wood dust |
| Olsen & Asnaes (1986), Denmark, 1970–82 | Nasal cavity, paranasal sinuses (160.0, 160.2–160.9) and naso-pharynx (146) (ICD revision not given) | 759 (509 men, 250 women) histologically confirmed cancers of the nasal cavity and para-nasal sinuses (466 cases; 310 men, 156 women) and nasopharynx (293 cases; 199 men, 94 women) | 2465 patients with cancers of the colon, rectum, prostate and breast frequency-matched by sex, age (± 5 years) and year of diagnosis (± 5 years); 4.2% of men and 0.1% of women exposed to formaldehyde | Record linkage with pension fund with compulsory membership; job title from Central Pension Registry; exposure assessed blindly as certain, probable, unlikely, unknown | *Likely or possible exposure to formaldehyde ≥ 10 years before diagnosis*<br>Squamous-cell carcinoma (215)<br>Adenocarcinoma (39) | <br><br><br>2.4 (0.8–7.4)<br>1.8 (0.5–6.0) | Adjusted for exposure to wood dust | Data presented for men for cancer of the nasal cavity and paranasal sinuses; no association observed with naso-pharyngeal cancer |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Vaughan *et al.* (1986a), USA, 1979–83 | Nasal cavity (160) and pharynx (146–149) (ICD revision not given) | 285 incident cases [sex distribution not reported] identified by the local Cancer Surveillance System, aged 20–74 years, including oro- and hypopharynx (205), nasopharynx (27) and sinuses (53) | 552 identified by random-digit dialling | Job–exposure linkage system, resulting in four categories: high, medium, low and background | *Sinonasal*<br>Low exposure<br>Medium or high exposure<br>Highest exposure score<br><br>*Nasopharynx*<br>Low exposure<br>Medium or high exposure<br>Highest exposure score<br><br>*Oro-/hypopharynx*<br>Low exposure<br>Medium exposure<br>High exposure<br>Highest exposure score | <br>0.8 (0.4–1.7)<br>0.3 (0.0–1.3)<br>0.3 (0.0–2.3)<br><br><br>1.2 (0.5–3.3)<br>1.4 (0.4–4.7)<br>2.1 (0.6–7.8)<br><br><br>0.8 (0.5–1.4)<br>0.8 (0.4–1.7)<br>0.6 (0.1–2.7)<br>1.5 (0.7–3.0) | Age, sex, cigarette smoking and alcohol con-sumption | |
| Vaughan *et al.* (1986b), USA, 1979–83 | Nasal cavity (160) and pharynx, (146–149) (ICD revision not given) | 285 incident cases [sex distribution not reported] identified by the local Cancer Surveillance System, aged 20–74 years, including oro- and hypopharynx (205), nasopharynx (27) and sinuses (53) | 552 identified by random-digit dialling | Residential exposure: residential history since 1950 | *Sinonasal*<br>Mobile home<br>Particle-board at home<br>  1–9 years<br>  ≥ 10 years<br>*Nasopharynx*<br>Mobile home<br>  1–9 years<br>  ≥ 10 years<br>Particle-board at home<br>  1–9 years<br>  ≥ 10 years<br>*Oro-/hypopharynx*<br>Mobile home<br>  1–9 years<br>  ≥ 10 years<br>Particle-board at home<br>  1–9 years<br>  ≥ 10 years | 0.6 (0.2–1.7)<br><br>1.8 (0.9–3.8)<br>1.5 (0.7–3.2)<br><br><br>2.1 (0.7–6.6)<br>5.5 (1.6–19.4)<br><br>1.4 (0.5–3.4)<br>0.6 (0.2–2.3)<br><br><br>0.9 (0.5–1.8)<br>0.8 (0.2–2.7)<br><br>1.1 (0.7–1.9)<br>0.8 (0.5–1.4) | Sex, age, cigarette smoking and alcohol con-sumption<br><br>Cigarette smoking and race<br><br><br><br>Sex, age, cigarette smoking and alcohol con-sumption | |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Rousch *et al.* (1987), USA, 1935–75 | Nasal cavity and sinuses, and naso-pharynx (ICD code not given) | 198 men with sinonasal cancer and 173 with nasopharyngeal cancer registered at the Connecticut Tumor Registry | 605 men who died during the same period, selected by random sampling without matching or stratification | Job title, industry, specific employment, year of employment, obtained from death certificates and city directories | *Sinonasal* <br> Probably exposed for most of working life <br> Plus exposure ≥ 20 years before death <br> Plus exposure to high level for some years <br> Plus exposure to high level ≥ 20 years before death <br><br> *Nasopharynx* <br> Probably exposed for most of working life <br> Plus exposure ≥ 20 years before death <br> Plus exposure to high level for some years <br> Plus exposure to high level ≥ 20 years before death | 0.8 (0.5–1.3) <br><br> 1.0 (0.5–1.8) <br><br> 1.0 (0.5–2.2) <br><br> 1.5 (0.6–3.9) <br><br><br> 1.0 (0.6–1.7) <br><br> 1.3 (0.7–2.4) <br><br> 1.4 (0.6–3.1) <br><br> 2.3 (0.9–6.0) | Age and calendar period | |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Luce *et al.* (1993), France, 1986–88 | Nasal cavity and parasinuses (ICD-9 160.0, 160.2–160.9) | 207 cases (167 men, 40 women): 59 men and 18 women with squamous-cell carcinomas, 82 men and five women with adeno-carcinomas and 25 men and 17 women with other histology | 409 from two sources: 323 hospital cancer controls (15 sites) frequency-matched by age and sex; 86 proposed by cases, matched by age (± 10 years), sex and residence | Industrial hygienist review of structured job interview, classifying exposure by frequency, concentration and duration; computation of cumulative exposure level and lifetime average level | *Squamous-cell carcinoma* Possibly exposed Probably or definitely   Average level ≤ 2   Average level > 2   Duration ≤ 20 years   Duration > 20 years   Cumulative level     ≤ 30     > 30 | **Men** 0.96 (0.38–2.42) <br> 0.70 (0.28–1.73) 1.32 (0.54–3.24) 1.09 (0.48–2.50) 0.76 (0.29–2.01) <br> 1.26 (0.54–2.94) 0.68 (0.27–1.75) | Adjusted for age, exposure to wood dust and exposure to glues and adhesives | Adjustment for usual cigarette use or for smoking history did not change results. |
| | | | | | *Adenocarcinoma* Possibly exposed Probably or definitely   Average level ≤ 2   Average level > 2   Duration ≤ 20 years   Duration > 20 years   Cumulative level     ≤ 30     30–60     > 60 | 1.28 (0.16–10.42) <br> 4.15 (0.96–17.84) 5.33 (1.28–22.20) 1.03 (0.18–5.77) 6.86 (1.69–27.80) <br> 1.13 (0.19–6.90) 2.66 (0.38–18.70) 6.91 (1.69–28.23) | | Most cases of adeno-carcinomas exposed to both formaldehyde wood dust; very large odds ratio (288) for wood dust; therefore, there is concern about the possibility of incomplete adjustment for wood dust in these results. |
| | | | | | *Other histology* Possibly exposed Probably or definitely   Average level ≤ 2   Average level > 2   Duration ≤ 20 years   Duration > 20 years   Cumulative level     ≤ 30     > 30 | 0.81 (0.15–4.36) <br> 1.67 (0.51–5.42) 3.04 (0.95–9.70) 2.82 (0.94–8.43) 1.62 (0.48–5.51) <br> 2.18 (0.65–7.31) 2.21 (0.73–6.73) | | |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| West *et al.* (1993), Philippines [study years not reported] | Nasopharynx (ICD code not given) | 104 incident cases (76 men, 28 women) histologically confirmed | 104 hospital controls matched for sex, age and hospital ward type; 101 community controls matched for sex, age and neighbourhood | Occupation classified as likely or unlikely to involve exposure to formaldehyde; duration of exposure; 10-year lag period; years since first exposure; age at start of exposure | < 15 years<br>≥ 15 years<br>< 15 years (10-year lag)<br>≥ 15 years (10-year lag)<br>Age ≥ 25 years at first exposure<br>Age < 25 years at first exposure<br>First exposure < 25 years before diagnosis<br>First exposure ≥ 25 years before diagnosis | 2.7 (1.1–6.6)<br>1.2 (0.5–3.2)<br>1.6 (0.6–3.8)<br>2.1 (0.7–6.2)<br>1.2 (0.5–3.3)<br><br>2.7 (1.1–6.6)<br><br>1.3 (0.6–3.2)<br><br>2.9 (1.1–7.6) | Years since first exposure to dust and/or exhaust fumes | |
| Gustavsson *et al.* (1998), Sweden, 1988–91 | Oro- and hypopharynx (ICD-9 146, 148) | 545 incident male cases among residents of two regions, aged 40–79 years [including at least 124 cases of pharyngeal cancer] | 641 selected by stratified random sampling; frequency-matched to cases by age (10–15-year groups) and region | Work history reviewed by occupational hygienist; occupations coded by intensity and probability of exposure | Ever exposed | 1.01 (0.49–2.07) | Age, region, alcohol, consumption and smoking habits | |
| Armstrong *et al.* (2000), Malaysia, (Selagor and Federal Territory), 1987–92 | Nasopharyngeal squamous-cell carcinoma (ICD code not given) | 282 Chinese men and women from four centres (prevalent and incident cases) [no information on age distribution] | One Chinese control selected by multistage area sampling per case; matched by age and sex | Structured in-home interviews; occupational exposures assessed by a job–exposure matrix | Any (unadjusted)<br>Any (adjusted) | 1.24 (0.67–2.32)<br>0.71 (0.34–1.41) | Diet and tobacco use | Mixture of prevalent (42%) and incident (58%) cases |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Laforest *et al.* (2000), France, 1989–91 | Hypopharynx (squamous-cell) (ICD code not given) | 201 men with confirmed histology from 15 hospitals [no information on age] | 296 male patients with other (selected) primary tumours from the same or nearby hospitals; recruited 1987–91; matched by age | Structured in-person interviews; occupational exposures assessed with a job–exposure matrix earlier developed | Ever exposed | 1.35 (0.86–2.14) | Age, tobacco smoking, alcohol con-sumption, coal dust and asbestos | |
| | | | | | *Probability of exposure (%)* | | | |
| | | | | | < 10 | 1.08 (0.62–1.88) | | |
| | | | | | 10–50 | 1.01 (0.44–2.31) | | |
| | | | | | > 50 | 3.78 (1.50–9.49) | | |
| | | | | | *Duration (years)* | | | |
| | | | | | < 7 | 1.09 (0.50–2.38) | | |
| | | | | | 7–20 | 1.39 (0.74–2.62) | | |
| | | | | | > 20 | 1.51 (0.78–2.92) | | |
| | | | | | *Cumulative level* | | | |
| | | | | | Low | 1.03 (0.51–2.07) | | |
| | | | | | Medium | 1.57 (0.81–3.06) | | |
| | | | | | High | 1.51 (0.74–3.10) | | |
| | | | | | *Exclusion of subjects with exposure probability < 10%* | | | |
| | | | | | Ever exposed | 1.74 (0.91–3.34) | | |
| | | | | | *Duration (years)* | | | |
| | | | | | < 7 | 0.74 (0.20–2.68) | | |
| | | | | | 7–20 | 1.65 (0.67–4.08) | | |
| | | | | | > 20 | 2.70 (1.08–6.73) | | |
| | | | | | *Cumulative level* | | | |
| | | | | | Low | 0.78 (0.11–5.45) | | |
| | | | | | Medium | 1.77 (0.65–4.78) | | |
| | | | | | High | 1.92 (0.86–4.32) | | |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Vaughan *et al.* (2000), USA (Connecticut, metropolitan Detroit, Iowa, Utah, Washington), 1987–93 | Epithelial nasopharyngeal carcinoma: epithelial NOS (801x–804x), undifferentiated or non-keratinizing (8020–1, 8072–3, 8082) and squamous-cell (805x–808x, except 8072–3) | 196 men and women [sex distribution not reported] from five cancer registries, aged 18–74 years | 244 population-based selected by random digit dialling; frequency-matched by sex, cancer registry and age (5-year groups) | Structured telephone interviews; occupational exposures assessed by a job–exposure matrix | Ever exposed<br>*Max. exposure (ppm)*<br>  < 0.1<br>  0.1–0.5<br>  > 0.5<br>  *p* for trend<br>*Duration (years)*<br>  1–5<br>  6–17<br>  ≥ 18<br>  *p* for trend<br>*Differentiated squamous-cell and epithelial NOS only*<br>Ever exposed<br>*Duration (years)*<br>  1–5<br>  6–17<br>  ≥ 18<br>  *p* for trend<br>*Cumulative exposure (ppm–years)*<br>  0.05–0.4<br>  > 0.4–1.10<br>  > 1.10<br>  *p* for trend | 1.3 (0.8–2.1)<br><br>1.4 (0.8–2.4)<br>0.9 (0.4–2.3)<br>1.6 (0.3–7.1)<br>0.57<br><br>0.8 (0.4–1.6)<br>1.6 (0.7–3.4)<br>2.1 (1.0–4.5)<br>0.070<br><br><br>1.6 (1.0–2.8)<br><br>0.9 (0.4–2.1)<br>1.9 (0.9–4.4)<br>2.7 (1.2–6.0)<br>0.014<br><br><br>0.9 (0.4–2.0)<br>1.8 (0.8–4.1)<br>3.0 (1.3–6.6)<br>0.033 | Age, sex, race, centre, cigarette use, proxy status and education | Data presented for any potential exposure (possible, probable or definite); not influenced by a 10-year lag period or adding wood dust exposure to models |

**Table 18 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Hildesheim *et al.* (2001) Taiwan, China, 1991–94 | Nasopharynx; > 90% non-keratinizing and undifferentiated and remainder squamous-cell carcinomas (ICD code not given) | 375 histologically confirmed hospital cases (31% women), aged < 75 years | 325 community controls, individually matched on sex, age (5 years) and district of residence | Structured in-person interviews; occupational exposures assessed by an industrial hygienist; blood specimen was tested for anti-EBV antibodies. | Ever exposed<br>*Duration*<br>  1–10 years<br>  >10 years<br>  *p* for trend<br>*Cumulative exposure*<br>  < 25<br>  ≥ 25<br>  *p* for trend | 1.4 (0.93–2.2)<br><br>1.3 (0.69–2.3)<br>1.6 (0.91–2.9)<br>0.08<br><br>1.3 (0.70–2.4)<br>1.5 (0.88–2.7)<br>0.10 | Age, sex, education and ethnicity | Observations were not influenced by adding wood dust exposure to models; in a sub-analysis restricted to 360 cases and 94 controls seropositive for at least one type of antibody against EBV, the association between exposure to formalde-hyde and nasopharyn-geal cancer appeared somewhat stronger. |
| Berrino *et al.* (2003), France, Italy, Spain, Switzerland, 1979–82 | Hypopharynx and epilarynx (ICD code not given) | 100 men, incident cases histologically con-firmed from six centres, aged ≤ 55 years | 819 men from the general local population of each centre; age- and sex-stratified | Structured in-person interviews; occupational exposures assessed by an expert panel using a previously established job–exposure matrix | *Probability of exposure*<br>  Possible<br>  Probable and certain | 1.3 (0.6–2.6)<br>0.5 (0.1–1.8) | Age, centre, tobacco use, alcohol con-sumption, diet, socio-economic status, asbestos, PAHs, chromium, arsenic, wood dust, solvents, other dusts and gases | [The credibility of the negative finding is limited because formal-dehyde was the agent for which the validity of the job–exposure matrix was lowest.] |

CI, confidence interval; EBV, Epstein-Barr virus; ICD, international code of diseases; NOS, not otherwise specified; PAHs, polycyclic aromatic hydrocarbons
[a] 90% confidence interval

formaldehyde; when workers exposed to wood dust were excluded, more controls than cases had been exposed (three cases, six controls). [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).]

In a case–control study conducted in four hospitals in North Carolina and Virginia, USA, in 1970–80, 193 men and women who had 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 who was identified from records of the state vital statistics offices. Patients who had cancer of the buccal cavity and pharynx, nasal cavity, middle ear and accessory sinuses, larynx and oesophagus and patients who had various nasal disorders were excluded from the control group. Telephone interviews were completed for 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 interviewee's recall in response to a checklist of exposures, including formaldehyde. Exposure to formaldehyde was reported for two nasal cancer patients (one man and one woman), to yield an odds ratio of 0.35 (95% CI, 0.1–1.8). [The Working Group noted that the exposure assessment was limited as it relied on self-reports and, furthermore, that a high proportion of interviews were with next of kin. The informativeness of the study was further limited by the small number of exposed subjects.]

In a population-based study in Denmark (Olsen *et al.*, 1984), 488 men and women in whom cancer of the sinonasal cavities had been diagnosed during the period 1970–82 and reported to the national cancer registry were matched to 2465 controls for sex, age and year of diagnosis, who were selected from all patients in whom cancer of the colon, rectum, prostate or breast had been 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. The industrial hygienists classified subjects according to whether they had definitely or probably been exposed, had not been exposed or had undetermined exposure to individual compounds during 1964–82. Of the controls, 4.2% of men and 0.1% of women had held occupations that presumably entailed exposure to formaldehyde. 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 (95% CI, 1.8–4.3) for men and 2.8 (95% CI, 0.5–14) for women. Further results were not presented for women. Adjustment for exposure to wood dust reduced the risk estimate for men to 1.6, which was 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; 95% CI, 0.8–1.7). [The Working Group noted that the employment histories of study subjects were restricted to 1964 or later and that the study was limited by the fact that the industries that used formaldehyde in Denmark in this study seemed to be dominated by exposure to wood dust, which makes assessment of the separate effect of exposure to formaldehyde on the risk for sinonasal cancer difficult.]

A re-analysis was performed (Olsen & Asnaes, 1986) in which data on 215 men with squamous-cell carcinoma and 39 with adenocarcinoma 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 cases who had ever been exposed to formaldehyde; of these, four had not been exposed to wood dust, which gave an odds ratio of 2.0 (95% CI, 0.7–5.9). Introduction of a 10-year lag period into the analysis yielded odds ratios of 2.4 (95% CI, 0.8–7.4) and 1.4 (95% CI, 0.3–6.4), respectively. The analysis revealed an association between exposure to wood dust and adenocarcinoma (odds ratios for any exposure, 16.3; 95% CI, 5.2–50.9) but only a weak association with squamous-cell carcinoma (odds ratio, 1.3; 95% CI, 0.5–3.6). 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 (95% CI, 0.7–7.2), and that among men who had been exposed 10 or more years before diagnosis was 1.8 (95% CI, 0.5–6.0); however, only one man who had an adenocarcinoma had been exposed to formaldehyde alone. [The Working Group noted a concern that possibly incomplete adjustment for confounding from exposure to wood dust in the assessment of the risk for adenocarcinoma could explain the weak association observed with exposure to formaldehyde, but also noted that the assessment of risk for squamous-cell carcinoma was unlikely to have been affected because squamous-cell carcinoma was 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.* (1986a) identified 116 men, aged 35–79 years, in whom a histologically confirmed epithelial cancer of the nasal cavity or paranasal sinuses had been diagnosed during 1978–81. The cases were frequency-matched on age with 259 population controls who were chosen randomly from among living male residents of the Netherlands 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' tobacco smoking habits, were obtained by personal interview of study subjects or their next of kin, with a participation of 78% for 91 case patients and 75% for 195 controls. Independently of one another, two industrial hygienists (A and B) reviewed job histories and graded possible exposure to formaldehyde. 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 for 44% by assessment B; among 224 subjects with little or no exposure to wood dust, exposure to formaldehyde was considered by assessments A and B to have occurred in 15 and 30%, respectively. For 62 subjects who were classed as having moderate or high

exposure to wood dust, there was a weak association with exposure to formaldehyde as assessed by hygienist A (odds ratio, 1.9 [95% CI, 0.6–6.5]), but no odds ratio could be derived for exposure as assessed by hygienist B. For the 224 subjects who had little or no exposure to wood dust, the odds ratios for exposure to formaldehyde were 2.5 [95% CI, 1.0–5.9] (hygienist A) and 1.6 [95% CI, 0.8–3.1] (hygienist B). When the analysis was restricted to 45 cases of squamous-cell carcinoma of the paranasal sinuses who had little or no exposure to wood dust, the odds ratios for high exposure to formaldehyde were 3.1 [95% CI, 0.7–13.5] (hygienist A) and 2.4 [95% CI, 0.9–6.1] (hygienist B). [The Working Group noted that a greater proportion of case patients than controls were deceased (36% versus 14%) and variable numbers of next of kin were interviewed; furthermore, 10% of controls but none of the case patients were interviewed by telephone. The Group noted, however, that, although assessments A and B differed, both gave positive results.]

Vaughan *et al*. (1986a) conducted a population-based case–control study in a 13-county area in western Washington State, USA. The study included incident cases of sino-nasal and pharyngeal cancer that were identified from a cancer registry that was reported to identify 98–99% of the cancers in the study area. Cases eligible for study were between the ages of 20 and 74 years and had a date of diagnosis between 1979 and 1983 for sino-nasal cancer, and from 1980 to 1983 for pharyngeal cancer. Control subjects were identi-fied by random-digit dialling and were frequency-matched to be similar in age and sex as the cases. Medical, tobacco smoking, alcohol use, residential and occupational histories were collected in a telephone interview with study subjects or their next of kin. Of the 415 cases eligible for study, 59 could not be located or were deceased with no known next of kin and 61 were not interviewed due to physician or subject refusal. Of the 295 cases who were successfully interviewed, 10 did not meet the eligibility requirements of the study, resulting in 285 cases being included in the analysis (53 sinonasal, 27 nasopharyngeal and 205 oro- or hypopharyngeal cancers). Approximately half of the case interviews were with their next of kin. Of a total of 690 persons eligible as controls, 573 were interviewed; 21 of these were excluded because they did not meet the eligibility requirements of the study, which resulted in 552 controls being available for analysis. [Although not explicitly stated, it appears that none of the interviews of the controls were by proxy.] Occupational expo-sure to formaldehyde was assessed by means of a job–exposure linkage system in which each job within each industry was classified according to the likelihood of exposure (unlikely, possible or probable). Those jobs that were defined as probably exposed were further classified into high or low exposure intensity. These two measures of exposure were then combined into a summary variable that resulted in the following four levels: (1) high (probable exposure to high levels), (2) medium (probable exposure to low levels), (3) low (possible exposure at any level) and (4) background. For the analysis, an estimate of the duration of exposure and the maximum exposure level (low, medium or high) reached in any job was developed for each individual. A cumulative exposure score was also developed by combining the information on duration and level of exposure. Uncondi-tional logistic regression was used for the analysis in which age, sex and other potential confounders were controlled for when necessary. The odds ratios for sinonasal cancer,

adjusted for sex, age, cigarette smoking and alcohol consumption, decreased with increasing exposure by all of the measures. The odds ratios observed were: 0.8 (95% CI, 0.4–1.7) for low and 0.3 (95% CI, 0.0–1.3) for medium or high maximum exposure level attained; 0.7 (95% CI, 0.3–1.4) for 1–9 years and 0.4 (95% CI, 0.1–1.9) for ≥ 10 years of exposure; and 0.5 (95% CI, 0.1–1.6) for 5–19 and 0.3 (95% CI, 0.0–2.3) for ≥ 20 units of the exposure score. [The number of exposed cases could not be determined for these analyses.] An analysis was also performed in which the exposure score was estimated at 16 years before the date of diagnosis for the case and 16 years before the date of interview for the controls (i.e. lagged by 16 years). Lagging the exposures in this way resulted in no cases in the high exposure group, and did not produce interpretable findings. [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 tumour and residential exposure to formaldehyde. Living in a mobile home and the presence of urea–formaldehyde foam insulation, 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, which yielded odds ratios of 1.8 (95% CI, 0.9–3.8) for periods of < 10 years and 1.5 (95% CI, 0.7–3.2) for ≥ 10 years. The risks associated with exposure to formaldehyde foam insulation could not be estimated, because of low exposure frequencies.

Roush *et al.* (1987) reported on a population-based case–control study of 371 men registered at the Connecticut (USA) Tumor Registry with a diagnosis of sinonasal cancer (198 cases) or nasopharyngeal cancer (173 cases), who had died of any cause in Connecticut in 1935–75, and 605 male controls who had died during 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. Odds ratios for occupation–cancer relationships based on occupational information obtained from death certificates were similar to the corresponding odds ratios based on city directory information in two previous studies. Each occupation held by case patients and controls was assessed by an industrial hygienist (blinded to case–control status) with regard to the likelihood (none, possibly, probably, definitely) and level (0, < 1 ppm, ≥ 1 ppm) of workplace exposure to formaldehyde, and study subjects were subsequently categorized into one unexposed and four exposed groups according to degrees of probable exposure to formaldehyde. For sinonasal cancer, the odds ratio, adjusted for age at death, year of death and number of jobs reported, was 0.8 (95% CI, 0.5–1.3) for those who had probably been exposed to some level of formaldehyde for most of their working life compared with all others. In order to evaluate high short-term exposures, the odds ratio for those who fulfilled the more restricted exposure criteria of being probably exposed to some level for most of their working life and probably exposed to high levels for some years was 1.0 (95% CI, 0.5–2.2) and, for those who had probably been exposed to some level for most

of their working life and probably exposed to high levels at some point 20 or more years before death, the odds ratio was 1.5 (95% CI, 0.6–3.9).

Luce *et al.* (1993) conducted a case–control study of men and women who had primary malignancies of the nasal cavities and paranasal sinuses and were diagnosed in one of 27 hospitals in France between January 1986 and February 1988. Three hundred and three cases were identified; 57 had died and, of the remaining 246 cases, 32 could not be located or were too ill and seven refused to participate. Histological confirmation was available in the medical records of all but one of the remaining 207 case patients. Four hundred and forty-three control subjects were 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 subjects) or from a list of names of healthy individuals provided by the cases (103 subjects). Sixteen could not be located or were too ill and 18 declined to participate, which left 409 controls for analysis. Occupational exposures to formaldehyde and 14 other substances or groups of substances were assessed by an industrial hygienist on the basis of information that was 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 tobacco smoking habits. Study subjects were classified according to the likelihood of exposure to each of the suspected determinants of sinonasal cancer and were 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 three levels and calendar periods of exposure and combinations thereof. For formaldehyde, a cumulative index was calculated from the levels and duration of exposure, as well as lifetime occupational exposure. Among men, 36% of the controls and 55% of the cases were classified as potentially exposed to formaldehyde. The risks associated with exposure to formaldehyde were reported for men only. For the 59 cases who had squamous-cell carcinoma, odds ratios (adjusted for age and exposure to wood and glue) were 1.26 (95% CI, 0.54–2.94) and 0.68 (95% CI, 0.27–1.75) for the index categories of lower and higher cumulative exposure among the probable/definite exposure group. Similar patterns were evident by lifetime average level and duration of exposure. Among the 82 cases of adenocarcinoma, 67 were in the probable/definite exposure group. Odds ratios (adjusted for age and exposure to wood and glue) categorized into three levels of the cumulative exposure index were 1.13 (95% CI, 0.19–6.90), 2.66 (95% CI, 0.38–18.70) and 6.91 (95% CI, 1.69–28.23), respectively. However, most (71/82) of the formaldehyde-exposed cases of adenocarcinoma had also been exposed to wood dust, and the odds ratio for being exposed to wood dust and formaldehyde versus neither was very large (odds ratio, 692; 95% CI, 91.9–5210). Only four cases of adenocarcinoma were classified as exposed to formaldehyde but not wood dust (odds ratio, 8.1; 95% CI, 0.9–72.9). [The Working Group noted that residual confounding by exposure to wood dust may have occurred.]

2.2.2    *Nasopharyngeal carcinoma*

The study design of and results from case–control studies of the association of expo-sure to formaldehyde with cancer of the nasopharynx are summarized in Table 18.

The study by Olsen *et al*. (1984) (described in detail in Section 2.2.1) also evaluated the risk of exposure to formaldehyde among 266 men and women who had been diagnosed with nasopharyngeal cancer. The odds ratio, unadjusted for other occupational exposures, for exposure to formaldehyde was 0.7 (95% CI, 0.3–1.7) for men and 2.6 (95% CI, 0.3–21.9) for women.

The association between nasopharyngeal carcinoma and exposure to formaldehyde was also examined in the population-based case–control study in 13 counties of Washington State conducted by Vaughan *et al*. (1986a,b) (described in Section 2.2.1). The odds ratios increased slightly with all of the measures of occupational exposure examined in this study. The observed odds ratios in the analysis of the maximum exposure level achieved were: 1.2 (seven exposed cases; 95% CI, 0.5–3.3) for low exposure and 1.4 (four exposed cases; 95% CI, 0.4–4.7) for medium or high exposures; 1.2 (eight exposed cases; 95% CI, 0.5–3.1) for 1–9 years and 1.6 (three exposed cases; 95% CI, 0.4–5.8) for ≥ 10 years of exposure; and 0.9 (three exposed cases; 95% CI, 0.2–3.2) for 5–19 units and 2.1 (three exposed cases; 95% CI, 0.6–7.8) for ≥ 20 units of the cumulative exposure score. When a lag period of 15 years or more was introduced into the analysis, the odds ratio associated with the highest cumu-lative exposure score to formaldehyde was unchanged (two exposed cases; odds ratio, 2.1; 95% CI, 0.4–10). An association was found between living in a mobile home and risk for nasopharyngeal cancer, with odds ratios of 2.1 (four exposed cases; 95% CI, 0.7–6.6) for < 10 years and 5.5 (four exposed cases; 95% CI, 1.6–19.4) for ≥ 10 years of residence. An analysis was performed that considered the joint effect of occupational exposure and residence in a mobile home. Subjects were considered to be occupationally exposed in this analysis if they had a cumulative exposure score of 5 or more. A relatively strong association was observed among individuals who were exposed occupationally and had ever lived in a mobile home compared with those who had neither exposure (odds ratio, 6.7; 95% CI, 1.2–38.9), although this finding was based on only two cases and seven controls with joint exposure.

In the study by Roush *et al*. (1987) (described in Section 2.2.1), the odds ratios for men with nasopharyngeal cancer were presented in the following categories: those who had probably been exposed to some level for most of their working life; those who had probably been exposed to some level for most of their working life and probably been exposed to high levels for some years; and those who had probably been exposed to some level for most of their working life and probably been exposed to high levels at some point 20 or more years before death. The odds ratios were, respectively, 1.0 (95% CI, 0.6–1.7), 1.4 (95% CI, 0.6–3.1) and 2.3 (95% CI, 0.9–6.0).

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) were intermediate between those in China and those in western countries. The cases (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; 101 community controls (77% response rate), who were matched on sex, age and neighbourhood, were also available. Hospital controls were selected from the rosters of patients who were present on the same day that a suspected case was confirmed by biopsy; patients who had disorders that were possibly linked to dietary patterns were excluded (gastrointestinal cancer, peptic ulcer, chronic cirrhosis, gallbladder disease). Community controls were asked to participate on the basis of their living in a house close to that of their matched case. A personal interview included questions on tobacco smoking and areca nut habits, diet, sociodemographic 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 period and duration of employment in such occupations. Since the findings on occupational exposures did not differ when hospital and community controls were considered separately, only results from the comparison of cases versus all controls are shown. Four exposure indices were established for each subject: total duration, duration lagged by 10 years, number of years since first exposure and age at first exposure. The risk for nasopharyngeal carcinoma was associated with exposure to formaldehyde; the odds ratios, adjusted for the effects of dusts and exhaust fumes and other suspected risk factors, were 1.2 (12 exposed cases; 95% CI, 0.41–3.6) for subjects who were first exposed < 25 years before diagnosis and 4.0 (14 exposed cases; 95% CI, 1.3–12.3) for those who were 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 15.7 (95% CI, 2.7–91.2) was found relative to people who were not exposed to either factor [numbers exposed not given]. The odds ratio for an overall exposure of ≥ 15 years (eight exposed cases; odds ratio, 1.2; 95% CI, 0.48–3.2) was lower than that for a duration of < 15 years (19 exposed cases; odds ratio, 2.7; 95% CI, 1.1–6.6). However, when exposure was lagged by 10 years, those exposed for ≥ 15 years showed an odds ratio of 2.1 (eight exposed cases; 95% CI, 0.70–6.2). Subjects who were first exposed before the age of 25 years had an odds ratio of 2.7 (16 exposed cases; 95% CI, 1.1–6.6), while the odds ratio for those who were first exposed at age 25 or more years was 1.2 (11 exposed cases; 95% CI, 0.47–3.3). Subjects who reported daily use of anti-mosquito coils had a 5.9-fold (95% CI, 1.7–20.1) increase in risk compared with those who reported never using coils in a model that adjusted for potential confounders (West *et al.*, 1993). [The Working Group noted that formaldehyde has been reported to occur in the smoke released from anti-mosquito coils (see Section 1), and that the authors did not control for the presence of Epstein-Barr viral (EBV) antibodies, which showed a strong association with nasopharyngeal cancer (odds ratio, 21) in the study of Hildesheim *et al.* (1992).]

A study from Malaysia investigated nasopharyngeal cancer based on cases that were ascertained through records of histologically confirmed diagnoses at four centres that had a radiotherapy unit (Armstrong *et al*., 2000). In total, 530 Chinese cases of squamous-cell carcinomas of the nasopharynx who had resided in the study area for at least 5 years were diagnosed between 1 January 1987 and 30 June 1992. Among these, only 282 (53%) were included in the study (69% men), since 121 (23%) had died, 63 (12%) could not be located, four (1%) were too ill to participate and 60 (11%) refused to participate. One control with no history of cancer of the head, neck or the respiratory system was selected from the Chinese population who had resided for at least 5 years in the study area and matched to each case by sex and age (within 3 years). Information on exposures (complete residential and occupational history, alcohol and tobacco use and consumption of 55 food items at age 10 and 5 years before diagnosis) of cases and controls was obtained by structured in-home interviews by trained interviewers. Occupational history included job description, work performed, calendar time, machines, tools and substances used, size and type of workplace, and exposure to dusts, smoke, gases and chemicals. [It appears that additional questionnaires that collected more detailed information on some jobs were also used.] Exposure to 22 agents, which were selected for their ability to deposit on or be absorbed into the nasopharynx, was identified by job, calendar years, frequency (days per week) and duration (hours per day). Jobs were coded using the official Malaysian classification scheme. Four levels of exposure (none, low, medium and high) were established. [It was not clear whether the exposure assessment was made using a job–exposure matrix approach or on an individual level, because both approaches are referenced.] Dermal exposure was considered. The proportion of study participants with exposure to formaldehyde was 9.9% of cases and 8.2% of controls. For any versus no occupational exposure to formaldehyde, the odds ratio for both sexes combined was 1.24 (95% CI, 0.67–2.32) and 0.71 (95% CI, 0.34–1.43) after adjustment for diet and tobacco use. No dose–response relationship appeared with increasing duration of formaldehyde exposure.

In a multicentred, population-based case–control study from five cancer registries in the USA, associations between occupational exposure to formaldehyde and wood dust and nasopharyngeal cancer were investigated (Vaughan *et al*., 2000). At four of the five registries, the investigators identified cases diagnosed between 1 April 1987 and 30 June 1991, while case ascertainment at the fifth registry was extended for an additional 2 years. Eligible cases were men and women aged 18–74 years who had any histological type of nasopharyngeal cancer. Interviews were completed for 231 of the 294 eligible cases identified, and included 44 (19%) that were conducted with the next of kin (usually the spouse). The 196 cases who had epithelial cancers were further classified into three histological subgroups: differentiated squamous-cell (118 cases), undifferentiated or non-keratinizing (54 cases) or epithelial not otherwise specified (24 cases). Controls were identified by random-digit dialling and were frequency-matched by age (5-year age groups), sex and cancer registry. Among 324 eligible controls, 246 were interviewed (76%), two of whom were excluded because they had no telephone, which left 244 controls for analysis; for three controls, the interview was conducted with the next of kin. Experienced interviewers from

each of the five cancer registries conducted structured telephone interviews with the study subjects, which included questions on demographic background, previous medical conditions and use of medication, family history of cancer, use of alcohol and tobacco, and a lifetime history of occupational and chemical exposures, including those to formaldehyde and wood dust. For each job that had been held for at least 6 months, information was collected on job title, typical activities within the job, the type of industry and the dates at which employment began and ended. Industrial hygienists blindly assessed exposure to formaldehyde and wood dust on a job-by-job basis for each subject, based on all the available information. For each job held, both the probability (none or unlikely, possible, probable, definite) of exposure to formaldehyde and a related estimated concentration of exposure to formaldehyde (low, moderate, high) which represented an 8-h TWA were assigned. Cut-off points for analyses by duration and cumulative exposure were based on the 50th and 75th percentiles among exposed controls. The proportion of subjects who were potentially exposed to formaldehyde was 40.3% of cases compared with 32.4% of controls. For persons who were ever exposed occupationally to formaldehyde versus those who were unexposed, the odds ratio adjusted for age, sex, race, cancer registry, cigarette use, next-of-kin status and education for all epithelial nasopharyngeal cancer was 1.3 (95% CI, 0.8–2.1); for the histological subcategories of undifferentiated and non-keratinizing, differentiated squamous-cell and epithelial not otherwise specified, the odds ratios were 0.9 (95% CI, 0.4–2.0), 1.5 (95% CI, 0.8–2.7) and 3.1 (95% CI, 1.0–9.6), respectively. There was no consistent pattern of association or trend in risk with estimated maximum exposure concentration for all histological types combined. A trend of increasing risk was seen with increasing duration of exposure ($p_{trend} = 0.07$). The odds ratio for persons who had worked at least 18 years in jobs with potential exposure was 2.1 (95% CI, 1.0–4.5). Further analyses were conducted that excluded cancers of undifferentiated and non-keratinizing histology. The adjusted odds ratio by estimated probability of exposure to formaldehyde was 1.6 (95% CI, 1.0–2.8) for ever having held a job classified as 'possible, probable or definite', 2.1 (95% CI, 1.1–4.2) for 'probable or definite' and 13.3 (95% CI, 2.5–70) for 'definite'. Within the group classified with 'possible, probable or definite' exposure to formaldehyde, the subgroups with duration of exposure of 1–5 years, 6–17 years and over 18 years had odds ratios of 0.9 (95% CI, 0.4–2.1), 1.9 (95% CI, 0.9–4.4) and 2.7 (95% CI, 1.2–6.0), respectively, and the $p_{trend}$ value for a dose–response relationship was 0.014. A similar dose–response pattern within this group was seen for estimated cumulative exposure ($p_{trend} = 0.033$). When the group was restricted to subjects with probable or definite exposure, the significance of trends lessened with respect to duration of exposure ($p = 0.069$) and cumulative exposure ($p = 0.13$). When a 10-year lag period was included, the overall findings remained similar. Moreover, the odds ratios for exposure to formaldehyde were essentially unaffected by adding exposure to wood dust to the models.

Hildesheim *et al*. (2001) investigated the associations between occupational exposure to formaldehyde, wood dust and organic solvents and risk for nasopharyngeal cancer. Incident cases (< 75 years) with histologically confirmed diagnoses were identified from two hospitals in Taipei, China (Province of Taiwan). Of 378 eligible cases that were identified,

375 agreed to participate in the study. About one third (31%) of the cases were women. One control with no history of nasopharyngeal cancer was matched to each case with respect to age (5 years), sex and district of residence. In total, 87% of eligible controls agreed to participate, which left 325 controls for the analysis. All study participants were interviewed by trained interviewers (nurses). Cases were interviewed at the time of biopsy and before treatment. The interviews obtained information on sociodemographic characteristics, diet, cigarette smoking and betel-quid chewing, residential and medical history and a complete occupational history for all jobs that had been held for at least 1 year since the age of 16 years. Living mothers were interviewed about the childhood diet of study participants. Data on occupational history were reviewed blindly by an industrial hygienist. Standard industrial and occupational classification codes were assigned to each job. Each code was assigned a classification (10 levels) for probability and intensity of exposure to formaldehyde, wood dust and organic solvents. In total, 156 of 2034 jobs (7.7%) were classified as entailing exposure to formaldehyde. Blood specimens were collected from 369 cases and 320 controls, and serum was tested for various antibodies against EBV, which is known to be associated with nasopharyngeal cancer. After adjustment for age, sex, education and ethnicity, the odds ratio (both sexes combined) for ever exposure to formaldehyde was 1.4 (95% CI, 0.93–2.2). The odds ratios for ≤ 10 years and > 10 years of exposure to formaldehyde were 1.3 (95% CI, 0.69–2.3) and 1.6 (95% CI, 0.91–2.9), respectively. Those exposed for > 20 years had an odds ratio of 1.7 (95% CI, 0.77–3.5), but the trend for ≤ 10, 10–20, and > 20 years of exposure did not reach statistical significance. The odds ratios by estimated cumulative exposure (intensity × duration) gave a similar pattern. The observed associations were not substantially affected by additional adjustment for exposure to wood dust or organic solvent. In the sub-analyses that were restricted to 360 cases and 94 controls who were seropositive for at least one of five antibodies against EBV, the association between exposure to formaldehyde and nasopharyngeal cancer appeared to be stronger to some extent. Thus, the odds ratio of ever versus never having been exposed was 2.7 (95% CI, 1.2–6.2). However, no clear dose–response pattern was observed with increasing duration of exposure or estimated cumulative exposure.

### 2.2.3    *Cancers of the oro- and hypopharynx*

The study design of and results from case–control studies of the association of exposure to formaldehyde with cancer of the oro- and hypopharynx are summarized in Table 18.

The association between oro- and hypopharyngeal cancer and exposure to formaldehyde was examined in the population-based case–control study by Vaughan *et al.* (1986a,b) (described in detail in Section 2.2.1). Evidence for a weak trend in the odds ratios was observed with the number of years of occupational exposure to formaldehyde (odds ratio, 0.6; 95% CI, 0.3–1.0 for 1–9 years; odds ratio, 1.3; 95% CI, 0.7–2.5 for ≥ 10 years) and the exposure score (odds ratio, 0.6; 95% CI, 0.3–1.2 for 5–19 units; odds ratio, 1.5; 95% CI, 0.7–3.0 for ≥ 20 units), but not with the maximum exposure level

attained (odds ratio, 0.8; 95% CI, 0.5–1.4 for low; odds ratio, 0.8; 95% CI, 0.4–1.7 for medium; odds ratio, 0.6; 95% CI, 0.1–2.7 for high). No association was observed between risk for oro- and hypopharyngeal cancer and living in a mobile home (odds ratio, 0.9; 95% CI, 0.5–1.8 for 1–9 years; odds ratio, 0.8; 95% CI, 0.2–2.7 for ≥ 10 years), or duration of living in residences with internal construction or renovation using particle-board or plywood (odds ratio, 1.1; 95% CI, 0.7–1.9 for 1–9 years; odds ratio, 0.8; 95% CI, 0.5–1.4 for ≥ 10 years).

Gustavsson *et al*. (1998) carried out a case–control study of histologically verified squamous-cell carcinoma of the oral cavity, pharynx, larynx and oesophagus among men aged 40–79 years who were born in Sweden and were resident in two regions of the country. Between 1 January 1988 and 31 January 1991, the investigators sought to identify all incident cases of these tumours in the study population through weekly reports from departments of otorhinolaryngology, oncology and surgery, supplemented by information from regional cancer registries. Cases identified incidentally at autopsy were excluded. The referents were selected by stratified random sampling from population registers, and were frequency-matched to the cases for region and age in 10- or 15-year age groups. All subjects were interviewed by one of two nurses (the cases were mostly interviewed in hospital and the referents mainly at home), who used a structured questionnaire to obtain information on smoking, oral snuff use, alcohol consumption and lifetime history of jobs held for > 1 year. The work histories were reviewed by an occupational hygienist who was blind to the case or referent status of the subject, and were coded for intensity and probability of exposure to 17 agents, including formaldehyde; 9.4% of the referents were classed as exposed. An index of cumulative exposure was derived from the product of the probability, intensity and duration of exposure across the entire work history. Exposure histories were available for 90% of the 605 cases identified (including 138 who had pharyngeal cancer) and for 85% of the 756 referents. [The exact number of cases of pharyngeal cancer included in study was not reported.] Unconditional logistic regression was used to estimate incidence rate ratios adjusted for region, age (in 10- or 15-year bands), average alcohol intake over the past 5 years (four levels) and smoking status (current, former or never). The incidence rate ratio for pharyngeal cancer and formaldehyde was 1.01 (95% CI, 0.49–2.07) based on 13 exposed cases.

A case–control study of incident male cases of hypopharyngeal and laryngeal squamous-cell cancers was conducted at 15 hospitals in France between 1 January 1989 and 30 April 1991 (Laforest *et al*., 2000). Initially, 664 such patients were identified, but 21% of cases from the combined group were excluded due to health problems, death before interview, refusal, being non-alcohol drinkers or because they could not be contacted, which left 201 cases of hypopharyngeal cancer for analysis. Potential controls were male patients with primary cancers at other sites who were selected from the same or nearby hospitals as the cases, were recruited between 1987 and 1991 and were frequency-matched to the cases by age. Of the 355 controls who were initially identified, 59 [17%] were excluded for similar reasons as the cases. Specially trained occupational physicians interviewed the study subjects on demographic characteristics, alcohol consumption, use of tobacco and lifetime

occupational history. Each job was coded with respect to occupation and industry, and occupational exposures, including formaldehyde, were assessed using a previously developed job–exposure matrix to estimate the probability and level of exposure. An index of cumulative exposure was derived for each subject based on the product of probability, level and duration of exposure in each job. Altogether, [29%] of controls and [41%] of the cases of hypopharyngeal cancer were classified as ever having been exposed to formaldehyde. The age-, asbestos-, coal dust-, alcohol- and smoking-adjusted odds ratio for ever versus never exposure to formaldehyde was 1.35 (95% CI, 0.86–2.14). There was a trend of increasing odds ratios with increasing probability of exposure to formaldehyde ($p_{trend} < 0.005$); a probability of exposure of over 50% showed an odds ratio of 3.78 (95% CI, 1.50–9.49). No significant trends were noted by duration of exposure or estimated cumulative exposure. After exclusion of study subjects who had a probability of exposure to formaldehyde of less than 10%, the odds ratio increased with duration of exposure ($p_{trend} < 0.04$) and with cumulative level of exposure ($p_{trend} < 0.14$). [The Working Group noted that the controls were interviewed at a later date than cases and did not necessarily come from the same hospital, and that interviewers were not blind to the case–control status, although they were not aware of the study hypotheses.]

A case–control study of incident laryngeal and hypopharyngeal cancer was conducted during 1979–82 in six centres in four European countries (Berrino *et al.*, 2003). An attempt was made to include all incident cases from the centres, and 304 cases of hypopharyngeal cancer (including the epilarynx) were included. The participation rate varied by centre from 70 to 92%. Initially, the purpose of the study was to investigate the association between alcohol consumption, use of tobacco and diet and cancer at the two sites. An age- and sex-stratified random sample of controls was selected from the general population from each centre with an average participation rate of 74%. Information on alcohol consumption, tobacco smoking, diet and all jobs held for at least 1 year after 1944 was obtained by in-person interviews at the hospital before the treatment of cases; controls were interviewed at home. A panel of occupational physicians, industrial hygienists and chemical engineers assessed blindly the probability of exposure to 16 industrial chemicals, including formaldehyde. Among persons younger than 55 years [for whom a lifelong complete job history was available], the odds ratio for hypopharyngeal cancer (100 cases) adjusted for age, centre, tobacco use, alcohol consumption, socioeconomic status, diet and exposure to potential chemical confounders was 1.3 (95% CI, 0.6–2.6) in the group that was possibly exposed versus those who were never exposed and 0.5 (95% CI, 0.1–1.8) in the group that was probably and certainly exposed versus those who were never exposed to formaldehyde. [It is unclear whether controls were all from the catchment populations of the hospitals at which the cases were diagnosed. In research outside this study to evaluate the job–exposure matrix used, it was found that its performance for formaldehyde was poor. Any resultant misclassification of exposures would be expected to bias risk estimates towards unity.]

### 2.2.4   *Cancers of the lung and larynx*

The study design of and results from case–control studies of the association of cancers of the lung and larynx with exposure to formaldehyde are summarized in Table 19.

Andersen *et al*. (1982) conducted a case–control study in Denmark of doctors (79 men and five women) for whom a notification of lung cancer had been made in the files of the nationwide Danish Cancer Registry during the period 1943–77. Three control subjects per case, 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 who had 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, to give 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 USA where formaldehyde was manufactured or used. A total of 493 active or pensioned men were known to have died from cancer during 1957–79, but 12 were excluded from the study because their work histories were unavailable. The remaining 481 men were individually matched on age, pay class, sex and date of first employment to 481 controls selected from among employees who had been on the company's active pay rolls during the last year of employment of the corresponding case. The cases included 181 lung cancers and eight laryngeal cancers. The work histories of both case and control subjects were ascertained principally from personnel records, but also from medical records and interviews with colleagues; a job–exposure matrix was used to classify jobs according to the nature and level of exposure to formaldehyde that they entailed into three categories: 'continuous-direct', 'intermittent' or '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. The data were analysed by latency period, duration of exposure, exposure level and frequency, cumulative exposure index, age at and year of death and age at and year of first exposure. In none of the analyses was the relative risk for lung cancer significantly greater than 1.0 ($p > 0.05$). When a cancer induction period of 20 years was allowed for, 39 subjects with lung cancer and 39 controls had potentially been exposed to formaldehyde; the odds ratios were 1.20 [95% CI, 0.6–2.8] and 0.79 [95% CI, 0.4–1.6] for subgroups with < 5 years and ≥ 5 years of exposure, respectively.

In a population-based case–control study, Coggon *et al.* (1984) used death certificates to obtain information on the occupations of all men under the age of 40 years in England and Wales who had died from bronchial carcinoma during 1975–79. These were compared with controls who had died from any other cause, and who were matched for sex, year of death, local authority district of residence and date of birth (within 2 years). Of 598 cases

**Table 19. Case–control studies of cancers of the lung and larynx**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Andersen *et al.* (1982), Denmark, 1943–77 | Lung | 84 doctors (79 men, five women) registered in Denmark who died of lung cancer | 252 randomly selected from official list of Danish doctors, matched on sex and age | Information on postgraduate specialization and professional career employment | Ever employed in pathology, forensic medicine or anatomy | 1.0 (0.4–2.4) | | Both cases and controls were medical doctors. |
| Fayerweather *et al.* (1983), USA, 1957–79 | Lung and larynx | Active or pensioned employees (all men) who died of cancer (181 lung, eight larynx) | 189 employees matched on sex, age, pay class and date at first employment, selected from annual payroll roster among employees active during the case's last year of employment | Job–exposure matrix to classify exposure according to frequency and intensity (continuous/direct, intermittent, background) based on personnel and medical records and interviews with colleagues | Lung < 5 years ≥ 5 years | 1.20 [0.6–2.8] 0.79 [0.4–1.6] | Tobacco smoking | Analysis included a latency period of 20 years between exposure and disease. |
| Coggon *et al.* (1984), United Kingdom, 1975–79 | Lung (bronchial carcinoma) | 598 men ≤ 40 years old who died of bronchial carcinoma in England and Wales | 1180 men who had died from any other cause, matched by year of death, district of residence and date of birth (± 2 years) | Job–exposure matrix based on classification coding in three categories (none, low, high) of exposure | All exposed occupations Occupations with high exposure | 1.5 (1.2–1.8) 0.9 (0.6–1.4) | | *p* < 0.001 |

**Table 19 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Gérin *et al.* (1989), Canada, 1979–85 | Lung (oat-cell carcinoma; squamous-cell carcinoma; adeno-carcinoma; others including unspecified) | 857 men aged 35–70 years resident in the area of Montréal | 1523 men with cancer at other sites (cancer controls) and 533 men selected from electoral list (population controls), stratified by age | Semi-structured questionnaire on lifetime work history; exposure profile developed based on probability, frequency, concentration and duration of exposure and period of first exposure | Cancer controls<br>  Ever<br>  Short<br>  Long-low<br>  Long-medium<br>  Long-high<br>Population controls<br>  Ever<br>  Short<br>  Long-low<br>  Long-medium<br>  Long-high | <br>0.8 (0.6–1.0)<br>0.8 (0.6–1.2)<br>0.5 (0.3–0.8)<br>1.0 (0.7–1.4)<br>1.5 (0.8–2.8)<br><br>0.8 (0.6–1.1)<br>1.0 (0.6–1.8)<br>0.5 (0.3–0.8)<br>0.9 (0.5–1.6)<br>1.0 (0.4–2.4) | Age, ethnic group, socio-economic status, cigarette smoking, dirtiness of job and various other potential confounders | Increased relative risk for adeno-carcinoma of the lung with long exposure to high concentration |
| Wortley *et al.* (1992), United Kingdom, 1983–87 | Larynx (ICD-0 161.0–161.9) | 235 [sex distribution not given] identified through local cancer surveillance system | 547 identified by random-digit dialling selected to be similar in age and same sex | In-person interview; job–exposure matrix based on both likelihood and degree of exposure | Peak<br>  Low<br>  Medium<br>  High<br>Duration<br>  < 1 year<br>  1–9 years<br>  ≥ 10 years<br>Exposure scores<br>  < 5<br>  5–19<br>  ≥ 20 | <br>1.0 (0.6–1.7)<br>1.0 (0.4–2.1)<br>2.0 (0.2–19.5)<br><br>1.0<br>0.8 (0.4–1.3)<br>1.3 (0.6–3.1)<br><br>1.0<br>1.0 (0.5–2.0)<br>1.3 (0.5–3.3) | Age, tobacco smoking, alcohol drinking and education | |
| Brownson *et al.* (1993), USA, 1986–91 | Lung | 429 white women aged 30–84 years, former or never smokers | 1021 women selected from state driver's licence files (< 65 years old) or health care roaster (≥ 65 years old), group-matched for age | Telephone and in-person interview | Ever exposed | 0.9 (0.2–3.3) | Age and history of previous lung disease | All exposed cases and controls were lifelong non-smokers. |

**Table 19 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Gustavsson *et al.* (1998), Sweden, 1988–91 | Larynx (ICD-9 161) | 157 male incident cases aged 40–79 years | 641 selected by stratified random sampling; frequency-matched to cases by age (10–15-year groups) and region | Work history reviewed by occupational hygienist; occupations coded by intensity and probability of exposure | Ever exposed | 1.45 (0.83–2.51) | Region of incidence, age, alcohol intake and tobacco smoking status | |
| Laforest *et al.* (2000), France, 1989–91 | Larynx (ICD code not given) | 296 men with confirmed histology of cancer of the epi-larynx, glottis, supra-glottis, subglottis and larynx unspecified | 296 men with other (selected) primary tumours selected from the same or nearby hospitals, recruited in 1987–91, matched by age | Structured in-person interviews; occupational exposures were assessed with a job–exposure matrix developed earlier | Ever exposed<br>Exposure probability<br>  < 10%<br>  10–50%<br>  > 50%<br>*Excluding subjects with exposure probability < 10%*<br>  Ever exposed<br>  Duration of exposure<br>    < 7 years<br>    7–20 years<br>    > 20 years<br>  Cumulative exposure<br>    Low<br>    Medium<br>    High | 1.14 (0.76–1.70)<br><br>1.16 (0.73–1.86)<br>1.12 (0.55–2.30)<br>1.04 (0.44–2.47)<br><br><br><br>1.17 (0.63–2.17)<br><br>1.68 (0.60–4.72)<br>0.86 (0.33–2.24)<br>1.14 (0.47–2.74)<br><br>0.68 (0.12–3.90)<br>1.86 (0.76–4.55)<br>0.91 (0.42–1.99) | Age, tobacco smoking, alcohol drinking and exposure to coal dust | |

**Table 19 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Berrino *et al.* (2003), France, Italy, Spain, Switzerland, 1979–82 | Larynx (glottis, supraglottis) | 213 male incident cases aged ≤ 55 years | 819 men from general local population of each centre, stratified by age | Structured in-person interviews; occupational exposures assessed by an expert panel using a previously established job–exposure matrix | Probability of exposure<br>Possible<br>Probable or definite | <br>1.4 (0.8–2.7)<br>1.0 (0.4–2.3) | Age, centre, tobacco use, alcohol drinking, diet, socioeconomic status, asbestos, PAHs, chromium, arsenic, wood dust, solvents, other dusts and gases | [The credibility of the negative finding is limited because formaldehyde was the agent for which the validity of the job–exposure matrix was lowest.] |
| Elci *et al.* (2003), Turkey, 1979–84 | Larynx (ICD-0 161.0–2, –9) | 940 male incident cases at Oncology Treatment Center | 1519 male patients with malignant or benign pathology | Standardized questionnaire administered at hospital on occupational history; job–exposure matrix | Ever exposed<br>Intensity<br>Low<br>Medium<br>High<br>Probability<br>Low<br>Medium<br>High | 1.0 (0.8–1.3)<br><br>1.1 (0.8–1.5)<br>0.5 (0.2–1.3)<br>0.7 (0.1–7.1)<br><br>1.0 (0.7–1.4)<br>1.1 (0.6–2.2)<br>1.0 (0.1–11.2) | Age, tobacco use and alcohol drinking | Analysis by subtype of cancer (glottis, supraglottis, other) did not show any elevation of risk. No trend with intensity or probability of exposure |

CI, confidence interval; ICD, international code of diseases; PAHs, polycyclic aromatic hydrocarbons

who were identified, 582 were matched with two controls and the remainder with one control. 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. The group of occupations that were classed as entailing exposure to formaldehyde was associated with an elevated odds ratio for bronchial carcinoma of 1.5 (95% CI, 1.2–1.8); for those occupations in which exposure was presumed to be high, the odds ratio was 0.9 (95% CI, 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.]

In a population-based case–control study in the area of Montréal, Canada, 857 men who were diagnosed with histologically confirmed primary lung cancer during 1979–85 were identified (Gérin et al., 1989). Two groups of control subjects were established: one was composed of 1523 men who were diagnosed during the same years as cases with cancers of other organs (oesophagus, stomach, colorectum, liver, pancreas, prostate, bladder, kidney, melanoma and lymphoid tissue) and the other was composed of 533 men who were selected from electoral lists of the Montréal area. Interviews or completed questionnaires that yielded lifelong job history and information on potential non-occupational confounders were obtained from the cancer patients or their next of kin and from the population controls, with response rates of 82% and 72%, respectively. Each job was classified by a group of chemists and hygienists according to the probability, intensity and frequency of exposure to some 300 agents, including formaldehyde. Nearly one-quarter of all men had potentially 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/m³] formaldehyde in the ambient air. Odds ratios, adjusted for age, ethnic group, socio-economic status, cigarette smoking, the 'dirtiness' of the jobs held and various other potentially confounding workplace exposures, were 0.8 (95% CI, 0.6–1.2) for < 10 years of exposure to formaldehyde, 0.5 (95% CI, 0.3–0.8) for ≥ 10 years of presumed exposure to < 0.1 ppm [0.12 mg/m³], 1.0 (95% CI, 0.7–1.4) for ≥ 10 years of presumed exposure to 0.1–1.0 ppm [0.12–1.23 mg/m³] and 1.5 (95% CI, 0.8–2.8) for ≥ 10 years of presumed exposure to > 1.0 ppm formaldehyde compared with controls with other cancers. In comparison with the population controls, the equivalent odds ratios were 1.0 (95% CI, 0.6–1.8), 0.5 (95% CI, 0.3–0.8), 0.9 (95% CI, 0.5–1.6) and 1.0 (95% CI, 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 (95% CI, 0.9–6.0) and 2.2 (95% CI, 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 aged 20–74 years of a 13-county area of western Washington, USA, in whom laryngeal cancer was diagnosed in

1983–87 and notified to a population-based cancer registry in the area; 81% were successfully interviewed. Control subjects were identified by random-digit dialling and were selected when similar in age and of the same sex as cases; 80% of eligible subjects were interviewed, which left 547 for analysis. Lifetime histories of occupational, tobacco smoking and alcohol drinking were obtained by personal interview, and each job held for at least 6 months was coded according to the US census codes for industries and occupations. A job–exposure matrix was used to classify each job according to the probability and degree of exposure to formaldehyde and five other agents. Summary measures were derived for each subject's lifetime peak exposure, duration of exposure and a score based on both duration and level of exposure. 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 (95% CI, 0.4–2.1) for any 'medium' exposure and 2.0 (two exposed cases; 95% CI, 0.2–20) for any 'high' exposure. Odds ratios of 0.8 (95% CI, 0.4–1.3) and 1.3 (95% CI, 0.6–3.1) were seen for exposure for < 10 years and ≥ 10 years and of 1.0 (95% CI, 0.5–2.0) and 1.3 (95% CI, 0.5–3.3) for medium and high formaldehyde score, respectively. [The report suggests that the cases in fact came from only three of the 13 counties, whereas the controls came from the larger area. If this is the case, there may have been important potential for bias.]

A case–control study in Missouri, USA, focused on white women aged 30–84 years, who were lifelong nonsmokers or who had stopped smoking for at least 15 years (Brownson *et al.*, 1993). Incident cases of lung cancer during 1986 to mid-1991 were identified through the local cancer registry; information for inclusion in the study was successfully obtained for 429 (69%) of the 650 eligible subjects. This was achieved through two series of interviews completed either by the subject (42%) or her next of kin, during which questions were asked on demographic characteristics, non-occupational risk factors and 28 occupational risk factors, including formaldehyde. For cases under the age of 65 years, controls were obtained from state drivers' licence files, while controls for older cases were selected from Medicare files, group-matched to the cases for age, with a ratio of approximately 2.2:1. Of 1527 potentially eligible controls, 1021 (73%) completed two interviews similar to those for the cases. Analysis was performed using multiple logistic regression. Three cases and 10 controls, all of whom were lifelong nonsmokers, reported occupational exposure to formaldehyde which, with adjustment for age and history of previous lung disease, gave an odds ratio of 0.9 (95% CI, 0.2–3.3).

A case–control study in Sweden of squamous-cell carcinoma of the upper airways and upper digestive tract (Gustavsson *et al.*, 1998) (described in detail in Section 2.2.3) compared 157 men who had laryngeal cancer with 641 referents. After adjustment for region of incidence, age, average alcohol intake over the past 5 years and smoking status, the estimated incidence rate ratio for cancer of the larynx in men exposed to formaldehyde was 1.45 (95% CI, 0.83–2.51) based on 23 exposed cases. No dose–response trend was apparent for either cumulative exposure or duration of exposure.

A case–control study at 15 hospitals in France (Laforest *et al*., 2000) (described in detail in Section 2.2.3) included 296 patients with laryngeal cancer. For this disease, comparison with the 296 controls gave an odds ratio (adjusted for age, alcohol consumption, smoking and exposure to coal dust) of 1.14 (95% CI, 0.76–1.70) for exposure to formaldehyde overall. No clear pattern of risk estimates was observed in relation to probability, duration or cumulative levels of exposure.

A case–control study by Berrino *et al*. (2003) at six centres in France, Italy, Spain and Switzerland (described in detail in Section 2.2.3) included 213 cases of laryngeal cancer who were under 55 years of age. No association was found with probable or definite exposure to formaldehyde at levels above the background for the general population (odds ratio, 1.0; 95% CI, 0.4–2.3).

A case–control study of laryngeal cancer in Turkey (Elci *et al*., 2003) focused on patients who were admitted to the oncology centre of a hospital in Istanbul during 1979–84. Information on occupational history and consumption of alcohol and tobacco was elicited at the time of admission by a trained interviewer using a standardized questionnaire, and a job–exposure matrix was applied to the occupational history to assign probability and intensity of exposure to each of five substances including formaldehyde. After exclusion of women and patients with incomplete information on risk factors or tumour site, 940 of 958 cases were available for analysis (mean age, 52.9 years). These men were compared with 1308 controls who had various cancers that are not thought to have the same causes as carcinoma of the larynx and 211 who had benign pathologies. Analysis was performed using unconditional logistic regression with adjustment for age, use of tobacco (ever versus never) and consumption of alcohol (ever versus never). The odds ratio for any exposure to formaldehyde was 1.0 (95% CI, 0.8–1.3) based on 89 exposed cases. No significant elevation of risk was found for subsets of cases classified by anatomical location of the tumour (supraglottis, glottis, others), and there were no significant trends in risk by intensity or probability of exposure. [It is unclear how completely the occupational information in this study reflected lifetime histories of work.]

### 2.2.5   *Lymphohaematopoietic malignancies*

The study design of and results from the case–control studies of the association of lymphohaematopoietic malignancies and exposure to formaldehyde are summarized in Table 20.

In the study of Gérin *et al*. (1989) (described in detail in Section 2.2.4) in Montréal, Canada, levels of occupational exposure to formaldehyde of 53 cases of Hodgkin lymphoma and 206 cases of non-Hodgkin lymphoma were compared with those of 2599 cases of other cancers and 533 population controls. Using population controls and adjusting for age, ethnic group, self-reported income, tobacco smoking and dirtiness of jobs held, plus occupational and non-occupational factors that were identified as potential confounders, odds ratios for non-Hodgkin lymphoma were 0.7 (13 exposed cases; 95% CI, 0.3–1.6) for < 10 years of exposure compared with non-exposed and 1.1 (15 exposed cases; 95% CI,

**Table 20. Case–control studies of lymphohaematopoietic malignancies**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Gérin *et al.* (1989), Canada, 1979–85 | Hodgkin lymphoma<br>Non-Hodgkin lymphoma | 53 male incident cases<br>206 male incident cases | 533 population-based | Lifetime job histories obtained by inter-view and translated into level of expo-sure to formaldehyde | Ever<br>< 10 years duration<br>≥ 10 years duration<br>Low[a]<br>Medium[a]<br>High[a] | 0.5 (0.2–1.4)<br>0.7 (0.3–1.6)<br><br>1.1 (0.5–2.2)<br>1.0 (0.5–2.1)<br>0.5 (0.1–1.7) | Age, ethnic group, self-reported income, tobacco smoking, dirtiness of jobs held and potentially confounding occupational and non-occupational factors | Similar results were obtained when 2599 cases of other cancers were used as control group. |
| Linos *et al.* (1990), USA (years of study not given) | Leukaemia<br><br>Non-Hodgkin lymphoma | 578 male incident cases<br><br>622 male incident cases | 1245 population-based | Lifetime occupa-tional history obtained | Ever employed in funeral home or crematorium | 2.1 [0.4–10.0] based on four exposed cases<br>3.2 [0.8–13.4] based on six exposed cases | Adjusted for age and state of residence | Significantly elevated relative risks of 6.7 and 6.7 for acute myeloid leukaemia and follicular non-Hodgkin lymphoma, but based on small numbers |
| Partanen *et al.* (1993), Finland, 1957–1982 | Leukaemia<br><br><br>Hodgkin disease<br><br>Non-Hodgkin lymphoma | 12 male cases diagnosed among a cohort of 7307 production workers in wood industry<br>Four male cases<br><br>Eight male cases | 79 randomly selected from cohort and matched by year of birth and vital status in 1983<br>21<br><br>52 | Work history from company records complemented for cases only by interviews with plant personnel and ques-tionnaires completed by subjects or next of kin; plant- and period-specific job–exposure matrix | < 3 ppm–months<br>≥ 3 ppm–months<br><br>< 3 ppm–months<br>≥ 3 ppm–months<br><br>< 3 ppm–months<br>≥ 3 ppm–months | 1.00<br>1.40 (0.25–7.91) (two exposed cases)<br><br>1.00<br>NA (one exposed case)<br><br>1.00<br>4.24 (0.68–26.6) (four exposed cases) | Matching factors accounted for by conditional logistic regression | Data collection was more exhaustive for cases than for controls, which could have led to bias. Relative risk for all three outcomes combined did not substantially change when adjusted for wood dust or for solvents. |

**Table 20 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| West *et al.* (1995), United Kingdom (years of study not given) | Myelo-dysplastic syndrome | 400 (216 men, 184 women) newly diagnosed, resident in study area and aged > 15 years | 400 cancer-free patients from out-patient clinics and inpatient wards; matched 1:1 by age (± 3 years), sex, area of residence and hospital and year of diagnosis (± 2 years) | Personal interview on work history and for duration and intensity of exposure to formaldehyde; all questionnaires reviewed by team of experts | > 10 h lifetime exposure of any intensity<br><br>> 50 h lifetime exposure of medium or high intensity<br><br>> 2500 h lifetime exposure of medium or high intensity | 1.17 [0.51–2.68]<br><br>2.33 [0.55–11.35]<br><br>2.00 [0.32–15.67] | No adjustment for smoking or other factors | |
| Tatham *et al.* (1997), USA, 1984–88 | Non-Hodgkin lymphoma and sub-groups | 1048 men (185 small-cell diffuse lymphoma, 268 follicular lym-phoma and 526 large-cell diffuse lymphoma) from population-based cancer registries, born 1929–53 | 1659 selected by random-digit dialling, matched by area of registry and 5-year categories of date of birth | Telephone interview including questions on specific materials which participants may have worked with | Ever exposed<br>  All combined<br>  Small-cell diffuse<br>  Follicular<br>  Large-cell diffuse | 1.20 (0.86–1.50)<br>1.40 (0.87–2.40)<br>0.71 (0.41–1.20)<br>1.10 (0.79–1.70) | Matching factors, age at diagnosis, year entered the study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviours, use of seizure medication, service in or off the coast of Viet Nam and cigarette smoking | |

**Table 20 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Relative risk (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Blair *et al.* (2001), USA, 1980–83 | Leukaemia and myelo-dysplasia | 513 white men, 30 years or older, identified from the Cancer Registry of Iowa and among all men from a surveillance network of hospitals in Minnesota; 214 chronic lymphoid, 132 acute myeloid, 46 chronic myeloid, 13 acute lymphoid, 58 myelodysplasia and 50 others | 1087 selected by random-digit dialling from Health Care Financing Administration lists and from state death certificate files, frequency-matched by 5-year age group, vital status at time of interview and state of residence | Personal interviews including lifetime occupational history; formaldehyde assessed in a blinded fashion in terms of probability and intensity, each on a 4-point scale based on job title and industry | Acute myeloid Low-medium High — Chronic myeloid Low-medium High — Chronic lymphoid Low-medium High — Myelodysplasia Low-medium High — All combined Low-medium High | 0.9 (0.5–1.6) – (no case) — 1.3 (0.6–3.1) 2.9 (0.3–24.5) — 1.2 (0.7–1.8) 0.6 (0.1–5.3) — 0.8 (0.3–1.9) – (no cases) — 1.0 (0.7–1.4) 0.7 (0.2–2.6) | Matching factors, post-secondary education, hair dye use, tobacco smoking, first degree relative with hematolympho-poietic tumour and agricultural use of pesticides | None of the acute lymphocytic lymphoma cases was exposed. |

AIDS, acquired immunodeficiency syndrome; CI, confidence interval; ICD, international code of diseases; NA, not applicable

[a] Average exposure index

0.5–2.2), 1.0 (14 exposed cases; 95% CI, 0.5–2.1) and 0.5 (five exposed cases; 95% CI, 0.1–1.7) for > 10 years of exposure to low, medium and high cumulative levels, respectively. Because there were only eight exposed cases of Hodgkin lymphoma, the odds ratio for ever versus never exposed was calculated to be 0.5 (95% CI, 0.2–1.4). Odds ratios did not differ substantially when cases of other cancers were used as the control group.

In an analysis of the same multi-site case–control study of Gérin *et al.* (1989), Fritschi and Siemiatycki (1996) evaluated risk from occupational exposure to 294 substances, including formaldehyde, with slightly different numbers of cases of Hodgkin lymphoma (54) and non-Hodgkin lymphoma (215) and 23 cases of myeloma. Cases were compared with a pool of 1066 controls that comprised 533 population controls who were selected from electoral lists of the Montréal area and by random-digit dialling and a random sample of 533 of 2357 patients who had other cancers (excluding lung cancer). Results for exposure to formaldehyde were not presented for Hodgkin or non-Hodgkin lymphoma due to a lack of previous evidence of an association, or for myeloma due to the same lack of previous evidence and because fewer than four cases had been exposed.

In a study of 578 male cases of leukaemia, 622 male cases of non-Hodgkin lymphoma and 1245 population-based controls in Iowa and Minnesota (USA), Linos *et al.* (1990) observed elevated risks for both leukaemia (four exposed cases; odds ratio, 2.1 [95% CI, 0.4–10]) and non-Hodgkin lymphoma (six exposed cases; odds ratio, 3.2 [95% CI, 0.8–13.4]) among men who had been employed in funeral homes and crematoria, which indicated some degree of occupational exposure to formaldehyde and other compounds. The risks were particularly high for the acute myeloid subtype of leukaemia (odds ratio, 6.7 [95% CI, 1.2–36]) and the follicular subtype of non-Hodgkin lymphoma (odds ratio, 6.7 [95% CI, 1.2–37]). However, each of these estimates was based on only three exposed cases.

In Finland, Partanen *et al.* (1993) identified eight cases of non-Hodgkin lymphoma, four cases of Hodgkin disease and 12 cases of leukaemia that were diagnosed between 1957 and 1982 and reported to the Finnish Cancer Registry among a cohort of 7307 production workers who were first employed in the wood industry between 1945 and 1963. One to eight referents were matched to each case by year of birth and vital status in 1983 from among cancer-free cohort members, which resulted in a total of 152 referents. Exposure to a number of substances, including formaldehyde, was estimated based on company records and a job–exposure matrix. For cases, but not for controls, job histories were completed by interviews of selected persons at the plants and by questionnaires sent to the cases or their next of kin in 1982–83. Using a 10-year lag interval, subjects were classified as exposed to formaldehyde when their estimated cumulative exposure reached 3 ppm–months. For leukaemia and lymphomas combined, exposure to formaldehyde was associated with an odds ratio of 2.49 (seven exposed cases; 95% CI, 0.81–7.59) based on conditional logistic regression. Adjustment of the analysis for exposure to solvents or for wood dust or exclusion of subjects who were exposed to solvents did not substantially alter the result. Odds ratios for specific cancers were 4.24 (four exposed cases; 95% CI, 0.68–26.6) for non-Hodgkin lymphoma and 1.40 (two exposed cases; 95% CI, 0.25–7.91) for leukaemia. Only one case of Hodgkin disease was exposed and the odds ratio was not calculated. [The Working Group

as well as the authors noted the small number of cases and the possibility of bias due to the higher accuracy and completeness in the collection of exposure data for cases compared with controls that most probably resulted in an upward bias of odds ratios for all exposures evaluated. However, the odds ratio for all cancers combined was not elevated for wood dust, terpenes, chlorophenols or engine exhaust.]

West *et al*. (1995) evaluated lifetime exposures through occupation, environment and hobby among 400 patients over 15 years of age who had been newly diagnosed with myelodysplastic syndrome in South Wales, Wessex and West Yorkshire, United Kingdom. Of 635 eligible cases, 28% died before the interview, 3% were too ill, 2% had moved out of the study area and 5% refused to participate. Cancer-free controls were selected from outpatient clinics and inpatient wards of medicine, ear, nose and throat surgery, ortho-paedics and geriatrics and were individually matched to cases by age ($\pm$ 3 years), sex, area of residence and hospital, and year of diagnosis ($\pm$ 2 years). The personal interviews collected, among other information, data on work history and probed study subjects for duration and intensity (low, medium, high) of exposure to more than 70 hazards, including formaldehyde. Lifetime duration of exposure was estimated after consultation with indus-trial chemists and occupational hygienists. A minimal practical background level of expo-sure was set at 10 h in a lifetime, under which people were considered to be unexposed. Odds ratios were calculated as the ratio of discordant pairs and were 1.17 (15 exposed cases [95% CI, 0.51–2.68]) for $\geq$ 10 h lifetime exposure of any intensity versus no expo-sure, 2.33 ([95% CI, 0.55–11.35]) for > 50 h lifetime exposure of medium or high inten-sity versus no exposure and 2.00 ([95% CI, 0.32–15.67]) for > 2500 h lifetime exposure of medium or high intensity versus no exposure.

In a population-based case–control study, Tatham *et al*. (1997) evaluated the risks for subtypes of non-Hodgkin lymphoma with respect to exposure to formaldehyde among 1048 male cases that included 185 cases of small-cell diffuse lymphoma, 268 cases of follicular lymphoma and 526 cases of large-cell diffuse lymphoma who were born between 1929 and 1953, diagnosed between 1984 and 1988 and listed in the population-based cancer registries of the states or cities of Connecticut, Iowa, Kansas, Atlanta, Miami, San Francisco, Detroit or Seattle, USA. Diagnosis was confirmed by a panel of three pathologists. A total of 1659 controls were selected by random-digit dialling and were frequency-matched to cases on area of the registry and 5-year categories of date of birth. Of the 2354 and 2299 eligible cases and controls, respectively, 2073 [88%] and 1910 [83%] were alive and could be inter-viewed, while a further 1025 cases and 251 controls were excluded for various reasons, that included non-confirmation of diagnosis [562 cases], not being a resident in the USA before 1969, a history of acquired immunodeficiency syndrome (AIDS) or related illness, systemic lupus erythematosus, non-AIDS-related immunodeficiency, rheumatoid arthritis or a history of treatment with immunosuppressive drugs, chemotherapy or radiation. Cases and controls were interviewed by telephone on their background characteristics, lifestyle and medical, military and work history. The job history included questions on specific materials with or around which participants may have worked, including formaldehyde. Relative risks were based on conditional logistic regression, stratified for the matching factors (area of registry

and date of birth) and adjusted for age at diagnosis, year of entry into the study, ethnicity, education, Jewish religion, never having married, AIDS risk behaviours, use of seizure medication, service in or off the coast of Viet Nam and cigarette smoking. For ever versus never having been exposed to formaldehyde, relative risks were 1.40 (21 exposed cases; 95% CI, 0.87–2.40) for small-cell diffuse lymphoma, 0.71 (17 exposed cases; 95% CI, 0.41–1.20) for follicular lymphoma, 1.10 (46 exposed cases; 95% CI, 0.79–1.70) for large-cell diffuse lymphoma and 1.20 (93 exposed cases; 95% CI, 0.86–1.50) for all cases of non-Hodgkin lymphoma combined. Of all the controls, 130 (7.8%) reported having been exposed to formaldehyde.

Blair *et al*. (2000) evaluated occupational exposure to formaldehyde in a population-based case–control study of leukaemia and myelodysplasia. Cases were identified among white men who were 30 years or older from the Cancer Registry of Iowa (1981–83) and among all men from a surveillance network of hospitals in Minnesota which covered 97% of hospital beds in this area (1980–82). Controls were identified by random-digit dialling, from Health Care Financing Administration lists or from state death certificate files, depending on their age and vital status, and were frequency-matched to cases by 5-year age group, vital status at the time of interview and state of residence. A total of 669 eligible cases was identified, and interviews were conducted with 340 cases of leukaemia and 238 surrogates for deceased subjects and those who were too ill to interview. Cases and controls who lived in four large cities were excluded because the main purpose of the study was to evaluate agricultural risks; furthermore, subjects who had farming as their sole occupation were excluded from this analysis because the incidence of leukaemia has been shown to be elevated among farmers. This left 214 cases of chronic lymphocytic leukaemia, 132 of acute myeloid leukaemia, 46 of chronic myeloid leukaemia, 13 of acute lymphocytic leukaemia, 58 of myelodysplasia and 50 others and 1087 controls. Interviews were conducted in 1981–84 and included a lifetime occupational history with job titles and industries. Exposure to selected substances, including formaldehyde, was assigned by an industrial hygienist in terms of probability and intensity in a blinded fashion, each on a four-point scale (non-exposed, low, medium and high intensity). Odds ratios were based on unconditional logistic regression adjusted for the matching factors and agricultural use of pesticides, post-secondary education, use of hair dyes, tobacco smoking and having a first-degree relative who had a haematolymphopoietic tumour. Compared with no exposure to formaldehyde, odds ratios were 0.9 (14 exposed cases; 95% CI, 0.5–1.6) for low/medium intensity of exposure for acute myeloid leukaemia (no cases with high exposure); 1.3 (seven exposed cases; 95% CI, 0.6–3.1) for low/medium exposure and 2.9 (one exposed case; 95% CI, 0.3–24.5) for high exposure for chronic myeloid leukaemia; 1.2 (29 exposed cases; 95% CI, 0.7–1.8) for low/medium exposure and 0.6 (one exposed case; 95% CI, 0.1–5.3) for high exposure for chronic lymphocytic leukaemia; 0.8 (six exposed cases; 95% CI, 0.3–1.9) for low/medium exposure for myelodysplasia (no cases with high exposure); and 1.0 (61 exposed cases; 95% CI, 0.7–1.4) for low/medium exposure and 0.7 (three exposed cases; 95% CI, 0.2–2.6) for high exposure for all leukaemias and myelodysplasia combined. Of the 1087 controls, 128 [11.8%] were estimated to have low/

medium and nine [0.8%] to have high exposure to formaldehyde. None of the cases of acute lymphocytic leukaemia was exposed.

Nisse *et al.* (2001) evaluated the risk for myelodysplastic syndrome among 204 incident cases who were diagnosed during 1991–96 at the University Hospital of Lille (northern France) and 204 controls who were randomly selected from the electoral register and individually matched to cases by size of town of residence, sex and age (± 3 years). Cases who had secondary myelodysplastic syndrome after treatment for cancer and those who were unable to answer the questionnaire were excluded. The questionnaire was the same as that used in the study by West *et al.* (1995) and exposure evaluation was based on the method of Siemiatycki *et al.* (1981). Odds ratios for exposure to formaldehyde were not reported because the 95% CI for the univariate odds ratio for ever versus never having been exposed included 1, or because there were fewer than four exposed subjects.

### 2.2.6    *Cancers at other sites*

The study design of and results from the case–control studies of exposure to formaldehyde and cancer at sites other than those presented in the above sections are summarized in Table 21, in chronological order. The description of the studies below, in contrast, groups the reports by study population.

Within the Montréal multisite cancer study, the database that was analysed for lung cancer (see Section 2.2.4), Hodgkin disease, non-Hodgkin lymphoma and myeloma (see Section 2.2.5) was also used to study various other cancer sites in relation to exposure to formaldehyde. The results were published in separate reports and are presented below.

In addition to the sites cited above, Gérin *et al.* (1989) (see Section 2.2.4) analysed data for cancer of the oesophagus, stomach, colorectum, liver, pancreas, prostate, urinary bladder and kidney and for melanoma of the skin. Odds ratios were not elevated for any of these cancers.

Siemiatycki *et al.* (1994) conducted an analysis of urinary bladder cancer using a set of 484 pathologically confirmed cases of bladder cancer, 1879 controls who had cancers at other sites, excluding lung and kidney cancers, and 533 population controls. No evidence of an association was found between exposure to formaldehyde and the risk for bladder cancer: odds ratios, adjusted for non-occupational and occupational confounders, were 1.2 (67 exposed cases; 95% CI, 0.9–1.6) for non-substantial exposure and 0.9 (17 exposed cases; 95% CI, 0.5–1.7) for substantial exposure.

Dumas *et al.* (2000) analysed the association between occupational exposure to a large number of substances, occupations and industries and rectal cancer. A total of 257 men, who were aged 35–70 years and diagnosed with a rectal cancer between 1979 and 1985, were compared with 1295 controls who had cancers at sites other than the rectum, lung, colon, rectosigmoid junction, small intestine and peritoneum; adjustments were made for potential non-occupational (age, education, cigarette smoking, beer consumption, body mass index and respondent status) but not for occupational variables. Exposure to formaldehyde was associated with rectal cancer: the odds ratios were 1.2 (36 exposed

**Table 21. Case–control studies of cancers at other sites**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Odds ratio (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Gérin *et al.* (1989), Canada, 1979–85 | Oesophagus<br>Stomach<br>Colorectum<br>Liver<br>Pancreas<br>Prostate<br>Bladder<br>Kidney<br>Skin melanoma | Men aged 35–70 years resident in Montréal<br><br>107<br>250<br>787<br>50<br>117<br>452<br>486<br>181<br>121 | Pool of population selected from electoral list, and cancer controls; depending of the cancer site under study, the number of controls varied from 1733 to 2741. | Semi-structural probing interview, assessment of exposures by chemists and industrial hygienists | Short<br>Long-low<br>Long-medium<br>Long-high | No association for any of these sites (most odds ratios very close to 1.0) | Selection of data-based confounders (variables according to each specific cancer), plus age, ethnic group, socio-economic status, cigarette smoking and dirtiness of job | Short and long refer to the duration, and low, medium and high to the intensity of exposure. |
| Merletti *et al.* (1991), Italy, 1982–84 | Oral cavity or oropharynx | 86 male incident cases | Random sample of 385 men, stratified by age, from the files of residents | Full occupational history linked to a job–exposure matrix | Any exposure<br>Probable or definite | 1.6 (0.9–2.8)<br>1.8 (0.6–5.5) | Age, education, area of birth, tobacco smoking and alcohol drinking | Only six exposed cases in the probable or definite exposure group |
| Goldoft *et al.* (1993), USA, 1979–89 | Melanoma of the nasal cavity or nasopharynx | Nine cases [sex distribution not reported] | Random-digit dial-ling, frequency-matched on sex and age at diagnosis (controls from Vaughan *et al.*, 1986a,b) | Interview | Living in a residence with foam insulation<br><br>Occupational exposure<br>Employed in industries with potential exposure[a] | 3.57 (0.09–19.8)<br><br><br>Obs./exp. 0/0.27<br><br>Obs./exp. 0/0.8 | | |
| Siemiatycki *et al.* (1994), Canada, 1979–86 | Bladder | 484 men aged 35–70 years resident in Montréal | 533 population and 1879 cancer controls | See Gérin *et al.* (1989) | Non-substantial<br>Substantial | 1.2 (0.9–1.6)<br>0.9 (0.5–1.7) | Age, ethnicity, socioeconomic status, tobacco smoking, coffee consumption, status of respondent and other occupa-tional exposures | Results based on pooled controls |

**Table 21 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Odds ratio (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Cantor *et al.* (1995), USA, 1984–89 | Breast (female) | 33 509 women with breast cancer as the cause of death | 117 794 women who died from non-cancer causes; frequency-matched for age and race | Usual occupation on death certificate linked to a job–exposure matrix, with levels of probability and of intensity of exposure | Exposure levels<br><br>Low<br>Medium<br>High<br><br>Low<br>Medium<br>High | *Blacks*<br>1.14  $p < 0.05$<br>0.93<br>1.20  $p < 0.05$<br>*Whites*<br>1.38  $p < 0.05$<br>1.30  $p < 0.05$<br>1.36  $p < 0.05$ | Age at death, socioeconomic status and excluding women with lowest probability of exposure | No trend was observed. |
| Holly *et al.* (1996), USA, 1978–87 | Uveal melanoma | 221 white men aged 20–74 years | 447 white men selected by random-digit dialling; matched for area and age | Recall through telephone interviews | Ever | 2.9 (1.2–7.0) | Age, number of naevis, eye colour and skin response to exposure to midday summer sun | |
| Gustavsson *et al.* (1998), Sweden, 1988–91 | Oral cavity and oesophagus (ICD-9 141, 143-5, 150) | 250 incident cases among men aged 40–79 years resident in two regions (oral cavity, 128; oesophagus, 122) | 641 men selected by stratified random sampling; frequency-matched to cases by age (10–15-year groups) and region | Work history reviewed by occupational hygienist; occupations coded by intensity and probability of exposure | Ever<br>Oral cavity<br>Oesophagus | <br>1.28 (0.64–2.54)<br>1.90 (0.99–3.63) | Region, age, alcohol consumption and tobacco smoking habits | |
| Kernan *et al.* (1999), USA, 1984–93 | Pancreas | 63 097 persons with pancreatic cancer as the cause of death [sex and race distribution not reported] | 252 386 persons who died from non-cancer causes; frequency-matched by state, sex, race and age (5-year groups) | Usual occupation on death certificate linked to a job–exposure matrix, with levels of probability and of intensity of exposure | Exposure level<br>Low<br>Medium<br>High<br>Exposure probability<br>Low<br>Medium<br>High | <br>1.2 (1.1–1.3)<br>1.2 (1.1–1.3)<br>1.1 (1.0–1.3)<br><br>1.2 (1.1–1.3)<br>1.2 (1.1–1.3)<br>1.4 (1.2–1.6) | Age, marital status, residential status, sex and race | No trend was observed; analysis by race and sex also provided |

**Table 21 (contd)**

| Reference, study location, years of study | Organ site (ICD code) | Characteristics of cases | Characteristics of controls | Exposure assessment | Exposure categories | Odds ratio (95% CI) | Adjustment for potential confounders | Comments |
|---|---|---|---|---|---|---|---|---|
| Dumas *et al.* (2000), Canada, 1979–85 | Rectum | 257 men aged 35–70 years resident in Montréal | 533 population and 1295 cancer controls | See Gérin *et al.* (1989) | Any Substantial | 1.2 (0.8–1.9) 2.4 (1.2–4.7) | Age, education, cigarette smoking, beer drinking, body mass index and respondent status | Results based on cancer controls and not in accordance with those of Gérin *et al.* (1989) |
| Wilson *et al.* (2004), USA, 1984–89 | Salivary gland (ICD-9, 142.0–1, –9) | [2405] persons with cancer of the salivary gland as the cause of death (whites: 1347 men, 890 women; African–Americans: 93 men, 75 women) | [9420] persons who died from non-cancer causes, excluding infectious diseases; frequency-matched for age, race, sex and region | Usual occupation on death certificate linked to a job–exposure matrix, with levels of probability and of intensity of exposure | Mid–high probability and intensity | *White men and women* 1.6 (1.3–2.0) *Black women* 1.9 (0.8–5.1) | Age, marital status and socioeconomic status | High level of diagnosis misclassification suspected |

CI, confidence interval; ICD, international code of diseases
<sup>a</sup> Wood-work, furniture manufacture, pulp and paper mill, textile, foundry and smelter

cases; 95% CI, 0.8–1.9) for any exposure and 2.4 (13 exposed cases; 95% CI, 1.2–4.7) for substantial exposure, with an increase in risk by concentration and duration of exposure. [This result contrasts with the findings of Gérin *et al.* (1989), in which none of the odds ratios for colorectal cancer was greater than 1.0 in any of the exposure subgroups, including the highest. These odds ratios were for all colorectal cancers, but the authors stated that "the results for subsites of the colorectum — colon, rectosigmoid and rectum — were essentially similar to those of the entire category".]

A series of systematic case–control analyses of various cancers in relation to exposure to different occupational agents, including formaldehyde, were conducted using death certificates collected from 1984 to 1989 in 24 states of the USA (Cantor *et al.*, 1995; Kernan *et al.*, 1999; Wilson *et al.*, 2004). Death certificates were coded for usual occupation and industry according to the classification designed for the 1980 US census. Individual exposures were derived by linking the occupation–industry codes with a job–exposure matrix that assessed the probability and level of exposure to 31 occupational agents.

Cantor *et al.* (1995) conducted a case–control study of occupational exposure and female breast cancer mortality in the USA. After excluding homemakers, 33 509 cases and 117 794 controls remained. Estimates were adjusted for age at death and socioeconomic status and excluded women who had a low probability of exposure. Exposure to formaldehyde was associated with the risk for breast cancer among white and black women: for whites, odds ratios were 1.14 ($p < 0.05$), 0.93 and 1.2 ($p < 0.05$) for women who had low, medium and high intensity of exposure, respectively; among black women, significantly elevated ($p < 0.05$) odds ratios of 1.38, 1.30 and 1.36 were found for those who had low, medium and high intensity of exposure, respectively [confidence intervals not shown].

Kernan *et al.* (1999) conducted a case–control study of pancreatic cancer. Cases were 63 097 persons who had died from pancreatic cancer in 1984–93. Controls were 252 386 persons who had died from causes other than cancer during the same period. Occupational exposure to formaldehyde was associated with a moderately increased risk for pancreatic cancer for both men and women and for both racial groups (blacks and whites), with odds ratios of 1.2 (95% CI, 1.1–1.3), 1.2 (95% CI, 1.1–1.3), 1.1 (95% CI, 1.0–1.3) for subjects with low, medium and high intensity of exposure, respectively, and 1.2 (95% CI, 1.1–1.3), 1.2 (95% CI, 1.1–1.3) and 1.4 (95% CI, 1.2–1.6) for subjects with low, medium and high probabilities of exposure, respectively. There was no apparent exposure–response pattern with intensity, but the exposure–response relationships by probability of exposure were consistent across each level of exposure intensity.

Using the same database as Cantor *et al.* (1995), Wilson *et al.* (2004) conducted a study of salivary gland cancer. The cases were [2405] persons who had died from salivary gland cancer between 1984 and 1989. Four controls per case, frequency-matched for sex, age, race and region, were selected from among persons who had died during the same period from other causes, excluding infectious diseases (because of a suspected viral etiology of salivary gland cancer); a total of 9420 controls were included. Occupation as coded on the death certificate was available for 95.3% of white and 87.3% of black men and for 45% of white and 30.9% of black women. Among white men and women, an odds ratio, adjusted

for age, marital status and socioeconomic status, of 1.6 (95% CI, 1.3–2.0) was observed with 'mid–high' probability and 'mid–high' intensity of exposure to formaldehyde [categories not further defined]. The trend was significant ($p < 0.001$), but there was no dose–response pattern of monotonically increasing risk with increasing intensity and probability of exposure. No association between exposure to formaldehyde and salivary gland cancer was observed among African-American men and women combined. Among African-American women, the adjusted odds ratio for 'mid–high' intensity of exposure was 1.9 (95% CI, 0.8–5.1). No results were given separately for African-American men.

[The Working Group considered that this series of systematic analyses was limited by potential misclassification of some specific cancers when ascertained through death certificates, and by the use of occupation codes from death certificates to assess lifelong occupational exposure to formaldehyde.]

Merletti *et al.* (1991) reported a case–control study of 86 male residents of Turin, Italy, who had a diagnosis of cancer of the oral cavity or oropharynx that was notified to the population-based cancer registry of the city between 1 July 1982 and 31 December 1984, and a random sample of 385 men, stratified by age, who were chosen from files of residents of Turin. The cancers among the cases were: oropharynx (12), tongue (15), floor of the mouth (24), soft palate complex (14), other sites (11) and unspecified sites of the oral cavity (10). Detailed occupational history since 1945 and lifelong histories of tobacco smoking and alcohol drinking were obtained by personal interview. Each job that had been held for at least 6 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 carcinogens of the respiratory tract and three non-specific exposures (dust, gas and solvents) was applied to the occupation–industry code combination of study subjects; the matrix was developed at the IARC 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 (no, any, probable or definite exposure), with the 'no exposure' group (exposure not higher than that of the general population) as the reference level. Odds ratios were calculated using unconditional logistic regression adjusting for age, tobacco smoking, alcohol drinking, education and place of birth. 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 (95% CI, 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, with odds ratios of 1.7 for 1–15 years of exposure and 1.5 for ≥ 16 years within the 'any exposure' category, and of 2.1 and 1.4, respectively, within the 'probable or definite' exposure category. Separate results for an association with exposure to formaldehyde were not reported for the 12 men who had oropharyngeal cancer. [The Working Group noted that confounding by tobacco and alcohol could not be excluded from the interpretation of the observed association between exposure to formaldehyde and oral cancer.]

As part of the population-based case–control study of sinonasal cancer by Vaughan *et al.* (1986a,b) (see Section 2.2.1), Goldoft *et al.* (1993) interviewed nine of 14 patients who had been diagnosed with melanoma of the nose or nasopharynx between 1979 and 1989. The frequency of their exposure to formaldehyde was compared with that of the control subjects included in the study of Vaughan *et al.* (1986a,b). One subject had lived in a residence that was insulated with formaldehyde-based foam [0.3 expected]. None of the melanoma patients reported specific occupational exposure to formaldehyde (0.3 expected), and none reported having been employed in industries that would probably entail exposure to formaldehyde (0.8 expected). [The Working Group noted that it was unclear how the expected numbers were calculated.]

Holly *et al.* (1996) conducted a case–control study in the western USA to determine the relation of occupations and chemical exposures to the risk for uveal melanoma. Two hundred and twenty-one white men, aged 20–74 years and referred for treatment to a specialized unit in San Francisco between 1978 and 1987, were included and successfully interviewed. A group of 447 controls were selected by random-digit dialling (white men from the same geographical area and within the same 5-year age group), and 77% were successfully interviewed by telephone. Exposure to chemicals, including formaldehyde, was determined by asking the subjects whether they thought they were ever regularly exposed (at least 3 h per week for at least 6 months) in their jobs, hobbies, leisure or home maintenance. When ever to never having been exposed to formaldehyde was compared, an elevated odds ratio of 2.9 (13 exposed cases; 95% CI, 1.2–7.0), adjusted for potential non-occupational confounders, was found. [The Working Group and the authors noted the potential for recall bias when chemical exposures are ascertained from the subject's memory.]

A case–control study by Gustavsson *et al.* (1998) (see Section 2.2.3) included 128 cases of oral cancer and 122 cases of oesophageal cancer (in addition to cancers of the pharynx and larynx). There was no significant association between exposure to formaldehyde and the risk for oral cancer (14 exposed cases; odds ratio, 1.28; 95% CI, 0.64–2.54), but the risk for cancer of the oesophagus was elevated and bordered on statistical significance (19 exposed cases; odds ratio, 1.90; 95% CI, 0.99–3.63).

## 2.3    Pooled analysis and meta-analyses

### 2.3.1    *Pooled analysis*

Luce *et al.* (2002) performed a pooled analysis of data from 12 case–control studies on sinonasal cancer [cancer of the nasal cavity and paranasal sinuses, ICD-9 code 160] that were conducted in China (Zheng *et al.*, 1992), France (Luce *et al.*, 1992, 1993; Leclerc *et al.*, 1994), Germany (Bolm-Audorff *et al.*, 1990), Italy (Merler *et al.*, 1986; Comba *et al.*, 1992a,b; Magnani *et al.*, 1993), the Netherlands (Hayes *et al.*, 1986a,b), Sweden (Hardell *et al.*, 1982) and the USA (Brinton *et al.*, 1984, 1985; Vaughan *et al.*, 1986a; Vaughan, 1989; Vaughan & Davis, 1991). An earlier pooled analysis ('t Mannetje *et al.*, 1999) used data

from eight of these 12 studies. As the earlier study is subsumed by the more extensive analysis of Luce *et al*. (2002), results from 't Mannetje *et al*. (1999) are not presented.

The analysis by Luce *et al.* (2002) included data from four (Brinton *et al*., 1984; Vaughan *et al*., 1986a; Hayes *et al*., 1986a; Luce *et al*., 1993) of the six case–control studies that primarily focused on exposure to formaldehyde that are described in Section 2.2.1, but not those by Olsen *et al*. (1989) or Roush *et al*. (1987). In addition, data were obtained from a further seven studies that were originally designed to address exposures to substances other than formaldehyde (particularly wood dust) and one unpublished study. A total of 195 cases of adenocarcinoma (169 men, 26 women) and 432 cases of squamous-cell carcinoma (330 men, 102 women) were compared with 3136 controls (2349 men, 787 women). The study by Luce *et al.* (1993) in France contributed approximately half of the cases of adenocarcinoma. Cases were diagnosed between 1968 and 1990 and were ascertained from different sources; study subjects were interviewed between 1979 and 1990 using different methods. Studies also varied with respect to the mode of selection of controls and the vital status of subjects at recruitment. Lifetime occupational histories collected in the individual studies were recoded with the occupation and industry codes from International Standard Classifications. These codes and industrial hygiene data were the basis for the development of a job–exposure matrix that provided estimates of the probability (unexposed, 1–10%, 10–50%, 50–90%, > 90%) and intensity (< 0.25 ppm, 0.25–1 ppm, > 1 ppm) of exposure to formaldehyde. Numerical values were assigned to each exposure category, and the job-specific products of the assigned value and duration of employment were summed over each individual's total work history (using 0-, 10- and 20-year lag intervals) to estimate cumulative exposure. For the analysis, the cumulative exposure index was categorized into one of four classes (unexposed and tertiles among controls) that were denoted as no, low, medium and high exposure. Odds ratios were derived by unconditional logistic regression and were stratified by sex and histology with adjustment for age (three categories) and study. In analyses of adenocarcinoma in men, adjustment was also made for wood and leather dust. Tobacco smoking was evaluated as a potential confounder, but was not included in the final models because effect estimates did not change substantially after adjustment. Among subjects exposed to low, medium or high levels of formaldehyde compared with unexposed subjects, estimated odds ratios were 1.2 (43 exposed cases; 95% CI, 0.8–1.8), 1.1 (40 exposed cases; 95% CI, 0.8–1.6) and 1.2 (30 exposed cases; 95% CI, 0.8–1.8) for squamous-cell carcinoma among men; 0.7 (six exposed cases; 95% CI, 0.3–1.9), 2.4 (31 exposed cases; 95% CI, 1.3–4.5) and 3.0 (91 exposed cases; 95% CI, 1.5–5.7) for adenocarcinoma among men; 0.6 (six exposed cases; 95% CI, 0.2–1.4), 1.3 (seven exposed cases; 95% CI, 0.6–3.2) and 1.5 (six exposed cases; 95% CI, 0.6–3.8) for squamous-cell carcinoma among women; and 0.9 (two exposed cases; 95% CI, 0.2–4.1), 0.0 (no cases) and 6.2 (five exposed cases; 95% CI, 2.0–19.7) for adenocarcinoma among women, respectively. Slight increases in these odds ratios were observed with 10- and 20-year lag intervals. Among men, studies were heterogeneous with respect to the effects of exposure to formaldehyde on adenocarcinoma, with a significantly better fit of a model that included interaction terms between exposure effects and study compared with a model with

no such interaction terms ($p < 0.01$). [The Working Group noted that this heterogeneity may have led to inappropriately narrow confidence intervals since the analytical model did not account for random effects.] Among men with little or no exposure to wood dust, the odds ratios for adenocarcinoma with high level exposure to formaldehyde was 2.2 (95% CI, 0.8–6.3). [The Working Group considered that, for adenocarcinoma, residual confounding by exposure to wood dust was possible despite the attempts to control for it. This is because of the high degree of correlation between exposure to wood dust and exposure to formaldehyde, and the very strong association between adenocarcinoma and exposure to wood dust. Only 11 male cases of adenocarcinoma who had low, medium or high exposure to formaldehyde were categorized as never having been exposed to wood dust.]

### 2.3.2 Meta-analyses

#### (a) Respiratory cancers (Table 22)

In a meta-analysis on the relationship between exposure to formaldehyde and cancer, Blair *et al*. (1990b) added up the observed and expected numbers of various cancers across 32 cohort and case–control studies. They found no substantially elevated mortality from cancer of the lung or of the nasal nasal cavity for persons who were ever exposed or for those who had a higher level or duration of exposure. For cancer of the nasopharynx, mortality in persons who had a higher level or duration of exposure was elevated 2.1-fold [95% CI, 1.1–3.5] with 13 observed deaths. Among professionals, mortality from leukaemia (SMR, 1.6 [95% CI, 1.3–1.9]) and that from brain cancer (SMR, 1.5 [95% CI, 1.1–1.9]) were elevated. No significant associations were observed for other cancers.

In addition to the studies evaluated by Blair *et al*. (1990b), a meta-analysis of respiratory cancers by Partanen (1993) included two additional studies (Brinton *et al.*, 1984; Merletti *et al.*, 1991) and two updates (Gallagher *et al.*, 1989; Partanen *et al.*, 1990). The analysis used lagged and confounder-adjusted inputs, whenever available, and derived summary relative risks using a log-Gaussian, fixed effects model. For nasopharyngeal cancer, risk ratios were 1.59 (23 deaths; 95% CI, 0.95–2.65) and 2.74 (11 deaths; 95% CI, 1.36–5.55) for low/medium and substantial level or duration of exposure, respectively. Partanen (1993) found a relative risk for cancer of the nasal cavities and paranasal sinuses of 1.68 (95% CI, 1.00–2.82) for the highest category of exposure, while the corresponding risk calculated by Blair *et al*. (1990b) was 1.1 [95% CI, 0.7–1.5]. [This discrepancy may be explained by differences in the selection of studies for inclusion in the two meta-analyses or by differences in the way in which exposure categories were defined]. For the combined category of cancers of the oropharynx, lip, tongue, salivary glands and mouth, the aggregated data did not suggest associations with exposure to formaldehyde. Overall, Blair *et al*. (1990b) and Partanen (1993) were in good agreement with regard to the risks for lung cancer, nasopharyngeal carcinoma and miscellaneous cancers of the upper respiratory tract.

Collins *et al*. (1997) calculated meta-relative risks for cancers of the lung, nose or nasopharynx based on results from 11 cohort studies, three proportionate mortality studies

**Table 22. Summary of results from three meta-analyses on respiratory cancers and exposure to formaldehyde**

| Level or duration of exposure to formaldehyde | Site | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Lung | | Nose and nasal sinuses | | Nasopharynx | | Other respiratory | |
| | O/E | mRR (95% CI) | O/E | mRR (95% CI) | O/E | mRR (95% CI) | O/E | mRR (95% CI) |
| **Any** | | | | | | | | |
| Blair *et al.* (1990b)[a] | [1692/1681] | [1.0 (0.95–1.06)] | [61/58] | [1.0 (0.8–1.3)] | [35/27] | [1.3 (0.9–1.8)] | NR | NR |
| Partanen (1993)[b,c] | 833/752 | 1.11 (1.03–1.19) | 93/78 | 1.11 (0.81–1.53) | 36/21 | 2.00 (1.36–2.90) | 69/57 | 1.18 (0.87–1.59) |
| Collins *et al.* (1997)[d] | 2080/2506 | 1.0 (0.9–1.0) | 936/808 | 1.0 (1.0–1.1) | 455/412 | 1.3 (1.2–1.5) | NR | NR |
| **Low/medium** | | | | | | | | |
| Blair *et al.* (1990b)[a] | 514/422 | 1.2 [1.1–1.3] | 38/46 | 0.8 [0.6–1.1] | 30/27 | 1.1 [0.7–1.6] | NR | NR |
| Partanen (1993)[b,c] | 518/425 | 1.2 (1.1–1.3) | 33/30 | 1.10 (0.67–1.79) | 23/16 | 1.59 (0.95–2.65) | 52/48 | 1.05 (0.74–1.51) |
| **Substantial** | | | | | | | | |
| Blair *et al.* (1990b)[a] | 250/240 | 1.0 [0.9–1.2] | 30/28 | 1.1 [0.7–1.5] | 13/6 | 2.1 [1.1–3.5] | NR | NR |
| Partanen (1993)[b,c] | 233/216 | 1.1 (0.95–1.2) | 36/21 | 1.68 (1.00–2.82) | 11/4 | 2.74 (1.36–5.55) | 23/20 | 1.15 (0.64–2.09) |

CI, confidence interval; mRR, meta-relative risk; NR, not reported; O/E, observed/expected

[a] Blair *et al.* (1990b) 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,b), 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), Partanen *et al.* (1985), Stayner *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.* (1986a,b), 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.* (1990a) and Hayes *et al.* (1990).

[b] The analysis for lung cancer was performed for industrial workers only, as at least some of the data for professionals were confounded by social class.

[c] Partanen (1993) included in his analysis the above studies and: Brinton *et al.* (1984), Merletti *et al.* (1991); in addition, Partanen *et al.* (1985) was updated with Partanen *et al.* (1990), and Gallagher *et al.* (1986) was updated with Gallagher *et al.* (1989).

[d] Collins *et al.* (1997) included in their analysis the above studies (except for Petersen & Milham (1980), Friedman & Ury (1983), Marsh (1983), Milham (1983), Wong (1983), Acheson *et al.* (1984a,b), Harrington & Oakes (1984), Liebling *et al.* (1984), Malker & Weiner (1984), Stayner *et al.* (1985), Walrath *et al.* (1985), Gallagher *et al.* (1986), Logue *et al.* (1986), Blair *et al.* (1987, 1990a) and Merletti *et al.* (1991)) and added the following studies: Hernberg *et al.* (1983a,b), Olsen & Asnaes (1986), Hall *et al.* (1991), Matanoski (1991), Chiazze *et al.* (1993), Gardner *et al.* (1993), Luce *et al.* (1993), West *et al.* (1993), Marsh *et al.* (1994) and Andjelkovich *et al.* (1995).

and 15 case–control studies that were published between 1975 and 1995. The analysis did not include all of the studies from the meta-analyses by Blair *et al.* (1990b) and Partanen (1993), but added several studies, most of which were published after 1992. Using a fixed effects model, an overall meta-relative risk for lung cancer of 1.0 (95% CI, 0.9–1.0) was calculated based on 24 studies with 2080 observed cases, but there was substantial hetero-geneity across studies ($p < 0.00001$) which was mainly due to the difference between industrial cohort studies (meta-relative risk, 1.1; 95% CI, 1.0–1.2) and case–control studies (meta-relative risk, 0.8; 95% CI, 0.7–0.9). For nasal cancer, the overall meta-relative risk was 1.0 (95% CI, 1.0–1.1) based on 20 studies with 936 observed cases. Separate analyses by study type gave a meta-relative risk of 0.3 (95% CI, 0.1–0.9) for cohort studies and 1.8 (95% CI, 1.4–2.3) for case–control studies. Meta-relative risks for nasopharyngeal cancer were 1.3 (95% CI, 1.2–1.5) overall based on 12 studies with 455 cases, and 1.6 (95% CI, 0.8–3.0) for cohort studies with reported expected deaths. To address a potential publica-tion bias, all cohort studies were combined and missing expected numbers were estimated based on an approximation of the ratio of deaths from nasopharyngeal and lung cancer from the corresponding ratio observed in another study; this gave a meta-relative risk of 1.0 (95% CI, 0.5–1.8).

(*b*)     *Pancreatic cancer* (Table 23)

Ojajärvi *et al*. (2000) evaluated occupational exposures in relation to pancreatic cancer in a meta-analysis based on 92 studies that represented 161 different exposed populations. Eligible studies had to fulfil certain criteria and had to be agent-specific with direct risk estimates for one or several of 23 agents or for job titles with verified exposures to the agents. Proportionate mortality and incidence studies were excluded. For exposure to formaldehyde, five eligible populations were identified with a meta-relative risk of 0.8 (95% CI, 0.5–1.0), and point estimates of the meta-relative risks for different subsets of the meta-analysis by gender, type of diagnosis and study design ranged from 0.5 to 1.0. There was no evidence of heterogeneity of point estimates between populations. [The studies or populations included in the evaluation of formaldehyde were not clearly identified. The NCI cohort study by Blair *et al*. (1986) (see Section 2.1.1(*a*)) was apparently not included.]

Collins *et al*. (2001a) calculated a meta-relative risk for pancreatic cancer based on results from 14 studies, including eight cohort studies, four proportionate cancer mortality or incidence studies and two case–control studies that were published between 1983 and 1999. Based on a fixed effects model, an overall meta-relative risk of 1.1 (95% CI, 1.0–1.2) was calculated with no substantial heterogeneity across studies ($p = 0.12$). Meta-relative risks by type of job were 0.9 (95% CI, 0.8–1.1) for industrial workers (five studies that included 137 pancreatic cancers), 1.3 (95% CI, 1.0–1.6) for embalmers (four studies that included 88 pancreatic cancers) and 1.3 (95% CI, 1.0–1.7) for pathologists and ana-tomists (three studies that included 60 pancreatic cancers). There was no indication of publication bias. It was mentioned that the two studies that evaluated risk for pancreatic cancer at various exposure levels (Blair *et al.*, 1986; Kernan *et al.*, 1999) did not find monotonically increasing risks with increasing exposure levels. [Four (three cohort

**Table 23. Summary of results from meta-analyses of pancreatic cancer and exposure to formaldehyde**

|  | Ojajärvi et al. (2000)[a] | | Collins et al. (2001a)[b] | | |
| --- | --- | --- | --- | --- | --- |
|  | Populations | mRR (95% CI) | Studies | No. of cases | mRR (95% CI) |
| All studies | 5 | 0.8 (0.5–1.0) | 14 | 364 | 1.1 (1.0–1.2) |
| *Sex* | | | | | |
|   Men | 3 | 0.8 (0.5–1.3) | | | |
|   Unspecified or both | 2 | 0.6 (0.3–1.1) | | | |
| *Histological diagnosis* | | | | | |
|   Yes | 2 | 0.5 (0.3–0.9) | | | |
|   No | 3 | 0.9 (0.7–1.3) | | | |
| *Study type* | | | | | |
|   Case–control and cohort with internal reference | 2 | 0.5 (0.3–1.6) | | | |
|   SMR/SIR | 3 | 0.9 (0.7–1.3) | | | |
|   Cohort | | | 8 | 132 | 1.0 (0.8–1.2) |
|   Case–control | | | 2 | 79 | 1.0 (0.5–2.0) |
|   PMR/PIR | | | 4 | 153 | 1.2 (1.0–1.4) |
| *Type of job* | | | | | |
|   Industrial | | | 5 | 137 | 0.9 (0.8–1.1) |
|   Embalmer | | | 4 | 88 | 1.3 (1.0–1.6) |
|   Pathologist and anatomist | | | 3 | 60 | 1.3 (1.0–1.7) |

CI, confidence interval; mRR, meta-relative risk; PMR/PIR, proportionate mortality ratio/proportionate incidence ratio; SMR/SIR, standardized mortality ratio/standardized incidence ratio
[a] Ojajärvi et al. (2000) studied occupational exposures and pancreatic cancer in 92 studies and 161 different exposed populations. The studies used for their evaluation of formaldehyde are not listed specifically. However, the study by Blair et al. (1986) was apparently not included.
[b] Collins et al. (2001a) included the following studies in their analyses: Walrath & Fraumeni (1983), Levine et al. (1984), Walrath & Fraumeni (1984), Blair et al. (1986), Stroup et al. (1986), Stayner et al. (1988), Gérin et al. (1989), Hayes et al. (1990), Matanoski (1991), Hall et al. (1991), Gardner et al. (1993), Andjelkovich et al. (1995), Hansen & Olsen (1995) and Kernan et al. (1999).

studies and one proportionate incidence study) of the 14 studies included were also referenced in the meta-analysis by Ojajärvi et al. (2000).]

(c)    *Leukaemia*

Collins and Lineker (2004) calculated meta-relative risks for leukaemia based on the results from 12 cohort studies, four proportionate mortality or incidence studies and two case–control studies that were published between 1975 and 2004. Using a fixed effects model, an overall meta-relative risk for leukaemia of 1.1 (95% CI, 1.0–1.2) was calculated

based on 287 observed cases with borderline heterogeneity across studies ($p = 0.07$). Separate analyses by study type showed heterogeneity among proportionate mortality or incidence studies (meta-relative risk, 1.2; 95% CI, 1.0–1.5; $p$-heterogeneity = 0.02), but not among cohort studies (meta-relative risk, 1.0; 95% CI, 0.9–1.2) or among the two case–control studies (meta-relative risk, 2.4; 95% CI, 0.9–6.5). Increased risk was observed in studies of embalmers (meta-relative risk, 1.6; 95% CI, 1.2–2.0) and pathologists and anatomists (meta-relative risk, 1.4; 95% CI, 1.0–1.9), but not among industrial workers (meta-relative risk, 0.9; 95% CI, 0.8–1.0). There was no indication of substantial publication bias. [This meta-analysis did not include the studies by Logue *et al*. (1986), Partanen *et al*. (1993), Stellman *et al*. (1998) or Blair *et al*. (2001). Results from Harrington and Shannon (1975) and Harrington and Oakes (1984) were both included despite overlapping study populations. The Working Group noted that the findings of the meta-analysis would be sensitive to the choice of effect measures based on external rather than internal comparisons from some studies. Also, the analysis did not take into account risk estimates for higher-exposure subgroups or information on exposure–response relationships in the industrial cohort studies.]

# 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 exposed to concentrations of 0, 50, 100 or 200 mg/m³ formaldehyde (US Pharmacopeia grade) vapour for 1 h per day, three times a week, ostensibly for 35 weeks. Treatment of mice with the highest concentration was discontinued after the 11th exposure because of severe toxicity, and 36 of the mice exposed to 50 mg/m³ for 35 weeks were subsequently exposed to 150 mg/m³ 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 B6C3F$_1$ mice, 6 weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm [0, 2.5, 6.9 or 17.6 mg/m³] formaldehyde (> 97.5% pure) vapour by whole-body exposure for 6 h per day on 5 days per week for up to 24 months, followed by a 6-month observation period with no further exposure. Ten males and 10 females from each group were killed at 6 and 12 months, no or one male and 19–20

females at 18 months, 17–41 of each sex at 24 months and 9–16 females at 27 months. Between 0 and 24 months, 78 male and 30 female controls, 77 males and 34 females exposed to 2 ppm formaldehyde vapour, 81 males and 19 females exposed to 5.6 ppm and 82 males and 34 females 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 that were identified grossly in the other two groups. Squamous-cell carcinomas occurred in the nasal cavities of 2/17 male mice in the high-dose group that were killed at 24 months. No nasal cavity tumours developed in male mice treated with 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, 7 weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm [0, 2.5, 6.9 or 17.6 mg/m³] formaldehyde (> 97.5% pure) vapour by whole-body exposure for 6 h per day on 5 days per week for up to 24 months and were then observed for 6 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, six males and 13 females in the control group, 10 males and 16 females exposed to 2 ppm, 19 of each sex exposed to 5.6 ppm and 57 males and 67 females 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 that were identified grossly and on all major tissues of each organ system (approximately 40 per animal) from control and high-dose rats. The findings for the nasal cavity are summarized in Table 24. While no nasal cavity malignancies were found in rats exposed to 0 or 2.0 ppm formaldehyde, two squa-mous-cell carcinomas (1/119 males and 1/116 females examined) occurred in the group exposed to 5.6 ppm and 107 (51/117 males and 52/115 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 ($p = 0.07$, Fisher's exact test) and in males at the middle dose ($p = 0.06$, Fisher's exact test) (see also Table 24). A variety of non-neo-plastic lesions were commonly found in the nasal cavities of rats exposed to formaldehyde, particularly at 14.3 ppm (Swenberg *et al*., 1980; Kerns *et al*., 1983a,b; Gibson, 1984). More

**Table 24. 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 |
| Polyoid adenoma | 1 | 0 | { 4 | 4[c] | 6[d] | 0 | 4 | 1 }[e] |

From Kerns *et al.* (1983a)

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

[b] One animal in this group 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]

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, 25% 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).

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 its formation, 99 male Sprague–Dawley rats, 8 weeks of age, were exposed to a mixture of 14.7 ppm [18.1 mg/m$^3$] formaldehyde [purity unspecified] vapour and 10.6 ppm [15.8 mg/m$^3$] hydrogen chloride gas for 6 h per day on 5 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 and examined microscopically. 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 a follow-up study, groups of 99–100 male Sprague-Dawley rats, 9 weeks of age, were exposed for 6 h per day on 5 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 25. At the end of the experiment, 38 squamous-cell carcinomas of the nasal cavities and 10 papillomas or polyps were observed in rats exposed to formaldehyde alone; none were seen in the controls $(p \leq 0.001$, 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 25. Neoplastic lesions in the nasal cavities of male Sprague-Dawley 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 |
| Papillomas or polyps | 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$^3$] formaldehyde [purity unspecified] vapour beginning 1 week after acclimatization. Whole-body exposures for 6 h per day on 5 days per week were continued for 4, 8 or 13 weeks; thereafter, the rats were observed during recovery periods of 126, 122 or 117 weeks, respectively, after which 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 26. In control rats, the only nasal tumours reported were two squamous-cell carcinomas among 45 rats that were exposed to air for 8 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

**Table 26. Nasal tumours in male Wistar rats exposed to formaldehyde for 4, 8 or 13 weeks 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 related to exposure to formaldehyde

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 4 weeks and killed at 100 weeks and in another rat exposed for 8 weeks and killed at 110 weeks; six were 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 and at an incidence of 4.5% (six tumours/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.]

A total of 720 male specific pathogen-free Wistar rats [age unspecified], initially weighing 30–50 g, were acclimatized for 1 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/m³] formaldehyde [purity unspecified] vapour by whole-body exposure for 6 h per day on 5 days per week. Half of the animals (30 undamaged and 60 damaged rats) were exposed for 28 months, and the other half (30 undamaged and 60 damaged rats) were exposed for only 3 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 27. A high incidence of nasal tumours (17/58) was found in rats that had damaged noses and were 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 that had undamaged noses and 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 27. Nasal tumours in male Wistar rats that had damaged or undamaged noses and were exposed to formaldehyde vapour for 28 months or 3 months followed by a 25-month recovery period**

| Exposure time; no. of rats | Tumour | Exposure (ppm [mg/m³]) | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | 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 nose; D, damaged nose

In a study to explore the interaction between formaldehyde and 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/m³]. Exposures were for 6 h per day for 5 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. Neither the frequency nor the latent periods of induction of tumours outside the nasal cavity differed from those in controls (Holmström *et al.*, 1989b). [The Working Group noted the small numbers of animals used in the study.]

To study the correlation of indices of regional cell proliferation with the sites of formaldehyde-induced nasal squamous-cell carcinomas, five groups of 90 and one (high-dose) group of 147 male Fischer 344 (CDF(F344)CrlBr) rats, 8–9 weeks of age, were exposed to 0, 0.69, 2.05, 6.01, 9.93 or 14.96 ppm [0, 0.84, 2.4, 7.2, 12 or 18 mg/m$^3$] formaldehyde vapour (produced by thermal depolymerization of paraformaldehyde) by whole-body exposure for 6 h per day on 5 days per week for up to 24 months; six rats per group were killed at 3, 6, 12 and 18 months for interim observation. Histopathological examination of the nasal cavities was performed on all rats. The distribution of the nasal tumours was recorded on diagrams of the nasal passages at 30 selected levels that were designed to permit accurate localization of nasal lesions. In the high-dose group, survival was significantly decreased relative to that in the control group (18.8% versus 35.7%; $p < 0.001$, life-table analysis using the product-limit procedure of Kaplan and Meier; Cox's method for pairwise comparisons). Survival in the other exposure groups was similar to that in controls. According to the authors, formaldehyde induced nasal squamous-cell carcinomas in a highly non-linear fashion: no such tumours were observed after exposure to 2 ppm or lower or in controls; the incidences in the groups exposed to 6.01, 9.93 and 14.96 ppm were 1/90 [1%], 20/90 (22%) and 69/147 (45%) [47% according to the Working Group], respectively. The single nasal tumour found in the 6.01-ppm group was located in the anterior lateral meatus, a region that was predicted to receive a relatively high dose of formaldehyde. The time-to-tumour appearance of nasal squamous-cell carcinomas was 622, 555 and 350 days in the 6.01-, 9.93- and 14.96-ppm groups, respectively. No other type of nasal tumour was found among controls or among animals exposed to the two lowest concentrations. Polypoid adenomas (5/90 (5.6%) and 14/147 (9.5%)), rhabdomyosarcomas (1/90 [1%] and 1/47 [1%]) and adenocarcinomas (1/90 [1%] and 1/147 [1%]) were observed in the nasal cavities of rats exposed to 9.93 and 14.96 ppm, respectively. Formaldehyde-induced non-neoplastic nasal lesions were primarily confined to the transitional and respiratory epithelium of the anterior passages, were only found in the groups exposed to the three highest concentrations and were most severe in the groups exposed to 9.93 and 14.96 ppm. These lesions mainly comprised epithelial hypertrophy, hyperplasia and metaplasia, mixed inflammatory cell infiltrates, turbinate adhesions and, in many high-dose animals, significant distortion and destruction of the nasoturbinate architecture. In rats exposed to 6.01 ppm, non-neoplastic lesions were minimal or absent, and were limited to focal squamous metaplasia in the anterior regions (Monticello *et al.*, 1996).

Four groups of 32 male Fisher 344 rats (F-344/DuCrj), 5 weeks of age, were exposed to 0, 0.3, 2.17 and 14.85 ppm [0, 0.36, 2.6 and 17.8 mg/m$^3$] formaldehyde [purity unspecified] vapour by whole-body exposure for 6 h per day on 5 days per week for up to 28 months. A group of 32 rats served as unexposed room controls. The formaldehyde vapour was produced from a 37% aqueous formaldehyde solution containing 10%

methanol as an anti-polymerization agent. Rats in the 0-ppm control group were exposed to the same concentration of methanol (4.2 ppm) as those of the high-dose group. At 12, 18 and 24 months, five (randomly selected) animals per group (in the high-dose group, only two animals were alive at 24 months) were killed and examined grossly. At 28 months, all survivors were killed and necropsied. Animals that were found dead or killed *in extremis* also underwent necropsy. Histopathological examinations were performed on five anatomically specified cross-sections of the nose from all animals, on all lesions identified grossly and on other major organs (approximately 23 per animal) [probably all control and all exposed animals, although this was not mentioned specifically]. The total number of animals that died or were killed in moribund condition were 11 room controls and eight, six, 10 and 20 0-ppm control, low-, mid- and high-dose rats, respectively. Mortality rates (calculated by the life-table technique) at 28 months were 59.6% of room controls, 45.5% of 0-ppm controls, 31.8% of the 0.3-ppm group, 55.9% of the 2.17-ppm group and 88.3% of the 14.85-ppm group ($p \leq 0.01$ compared with the 0-ppm group; Fisher's exact test). Gross and microscopic pathological changes attributable to exposure to formaldehyde were found only in the nose. Except for an unclassified sarcoma found in one room control, nasal tumours were seen only in the high-dose group, and included three squamous-cell papillomas, 13 squamous-cell carcinomas ($p \leq 0.01$; Fisher's exact test) and one sarcoma. Grossly, the first nasal tumour was observed in the high-dose group after 13 weeks of exposure. Most of the nasal tumours were located in the incisor teeth and maxillary turbinate regions. Large tumours invaded the subcutis through the nasal bones. Hyperplasia with squamous-cell metaplasia of the nasal epithelium [not further specified] was found only in rats exposed to formaldehyde, the incidences (combined for all animals examined at interim and terminal sacrifices and found dead or killed *in extremis*) of which were 0/32, 0/32, 4/32, 7/32 ($p \leq 0.01$; Fisher's exact test) and 29/32 ($p \leq 0.01$; Fisher's exact test) for the room-control, 0-, 0.3-, 2.17- and 14.96-ppm groups, respectively. Hyperkeratosis of the nasal epithelium was found in 1/32 rats exposed to 2.17 ppm and in 26/32 rats exposed to 14.96 ppm ($p \leq 0.01$; Fisher's exact test); papillary hyperplasia of the nasal epithelium was seen in 2/32 rats in the high-dose group (Kamata *et al.*, 1997).

### 3.1.3   *Hamster*

A group of 88 male Syrian golden hamsters [age unspecified] was exposed to 10 ppm [12.3 mg/m$^3$] formaldehyde [purity unspecified] for 5 h a day on 5 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 controls or animals exposed to formaldehyde.

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 a 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 study to evaluate the effects of formaldehyde on gastric carcinogenesis induced by oral administration of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) (see Section 3.4.2), two groups of 10 male Wistar rats, 7 weeks of age, received tap-water for the first 8 weeks of the study. During weeks 8–40, one group was continued on tap-water and the other group received 0.5% formaldehyde [purity unspecified] in the drinking-water. Animals that were still alive at 40 weeks were killed; rats that survived beyond 30 weeks were 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 the drinking-water and none of the controls developed forestomach papillomas ($p < 0.01$, Fisher's exact test) (Takahashi *et al.*, 1986).

Wistar rats, obtained at 5 weeks of age and acclimatized for 9 days, were divided into four groups of 70 males and 70 females and were treated for up to 24 months with drinking-water that contained 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 105 weeks. Thorough necropsies were performed 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 that received the low and middle doses, but the liver, lung, stomach and nose were examined in each case. Treatment-related atrophy, ulceration and hyperplastic lesions were found in the forestomachs and glandular 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 tumour response (Til *et al.*, 1989).

Two groups of male and female Sprague-Dawley breeder rats, 25 weeks of age, were given 0 (20 males and 20 females) or 2500 (18 males and 18 females) ppm formaldehyde [purity unspecified] in the drinking-water for life. The offspring of these breeders were initially exposed transplacentally to 0 (59 males and 49 females) or 2500 ppm (36 males and 37 females) formaldehyde via their mothers beginning on day 13 of gestation and then received the same levels in the drinking-water for life. [The Working Group noted the lack

of information on selection of the offspring.] All animals were necropsied and subjected to histopathological examination. The survival rates in the treated groups were similar to those of controls. According to the authors, the preliminary results of this study showed a slight, statistically non-significant increase in the incidence of leukaemias (including haemolymphoreticular lymphomas) in male and female breeders exposed to formaldehyde. A statistically non-significant increase in the incidence of leukaemias was also reported in the exposed male, but not in the exposed female, offspring (see Table 28). The authors also reported a variety of malignant and benign tumours of the stomach and intestines in the treated animals (see Table 28). Leiomyosarcoma was the most frequent malignant tumour. [The incidence of leiomysarcomas in the intestines was statistically significantly increased in the exposed offspring, both in females and in males and females combined; $p \leq 0.01$, $\chi^2$ test.] This gastrointestinal tumour was exceptionally rare in the historical controls of this laboratory (Soffritti *et al.*, 1989). Concerns about the results by Soffritti *et al.* (1989) and their interpretation were published by Feron *et al*. (1990). One concern was that incidences of leukaemia in untreated Sprague-Dawley rats vary widely and that incidences similar to those seen in the group that received formaldehyde have been reported previously among controls in the same laboratory and in others.

Seven groups of 50 male and 50 female Sprague-Dawley rats, 7 weeks of age, received 10, 50, 100, 500, 1000 or 1500 mg/L formaldehyde (purity > 99.0%; 0.3% methanol as stabilizer; impurities: 0.6 mg/L iron, 0.1 mg/L lead, < 5.0 mg/L sulfur and < 5.0 mg/L chlorine) or 15 mg/L methanol in the drinking-water for 104 weeks. A control group of 100 males and 100 females received tap-water alone. By week 163, all animals had died. The consumption of treated drinking-water decreased in males of the high-dose group and in females of the three highest-dose groups (approximately 30% according to Soffritti *et al.*, 1989). No differences between treated and control animals were observed in food consumption, body weight or survival. Moreover, no treatment-related non-neoplastic changes were detected by gross or histopathological examination. Percentages of animals that had malignant tumours and incidences of major tumours are presented in Table 29. Tumour incidences in the treated groups were compared with those in the untreated control group and statistically significantly increases were found in the number of males that had malignant tumours in the high-dose group, and in the incidences of malignant mammary gland tumours in females in the 1500-mg/L group, of testicular interstitial-cell adenomas in the 1000-mg/L group and of haemolymphoreticular tumours in males in the four highest- and in females in the two highest-dose groups. According to the authors, there was a dose–response relationship [no statistics given] for the increased incidences of haemo-lymphoreticular tumours. Gastrointestinal leiomyomas and leiomyosarcomas, which are very rare tumours in the strain of rats used, occurred sporadically in some formaldehyde-treated animals but not in controls (Soffritti *et al.*, 2002). [The Working Group performed statistical analyses for trend and incidence in comparison with the methanol-treated group and found that the only statistically significant increases were in the total number of animals that had malignant tumours ($p < 0.01$) and in the incidences of haemolymphoreticular tumours ($p < 0.01$) in high-dose males and of testicular interstitial-cell adenomas ($p < 0.01$)

**Table 28. Incidences (%) of leukaemia and tumours (benign and malignant) of the gastrointestinal tract after administration of formaldehyde in the drinking-water to Sprague-Dawley breeder rats and their offspring**

| Treatment | No. of rats | Leukaemias | | | | Stomach | | | Intestine | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Lymphoblastic leukaemias and lymphosarcomas | Immunoblastic lymphosarcomas | Others | Total | Papilloma/ acanthoma/ adenoma | Adeno-carcinoma/ squamous-cell carcinoma | Leiomyo-sarcoma | Adenoma | Adeno-carcinoma | Leiomyo-sarcoma |
| Breeders (25 weeks old) | | | | | | | | | | | |
| 0 ppm | | | | | | | | | | | |
| Male | 20 | – | – | – | – | – | – | – | – | – | – |
| Female | 20 | 5.0 | – | – | 5.0 | – | – | – | – | – | – |
| Male + female | 40 | 2.5 | – | – | 2.5 | – | – | – | – | – | – |
| 2500 ppm | | | | | | | | | | | |
| Male | 18 | – | 5.6 | 5.6 | 11.1 | – | 5.6 | – | – | – | – |
| Female | 18 | 5.6 | 5.6 | – | 11.1 | 5.6 | – | – | – | – | – |
| Male + female | 36 | 2.8 | 5.6 | 2.8 | 11.1 | 2.8 | 2.8 | – | – | – | – |
| Offspring | | | | | | | | | | | |
| 0 ppm | | | | | | | | | | | |
| Male | 59 | – | 3.4 | 1.7 | 5.1 | – | – | – | – | – | – |
| Female | 49 | – | 4.1 | 2.0 | 6.1 | – | – | – | – | – | – |
| Male + female | 108 | – | 3.7 | 1.8 | 5.5 | – | – | – | – | – | – |
| 2500 ppm | | | | | | | | | | | |
| Male | 36 | 2.8 | 8.2 | – | 11.1 | 2.8 | 2.8 | 2.8 | 2.8 | 2.8 | – |
| Female | 37 | – | – | – | – | – | 2.7 | 2.7 | – | 2.7 | 13.5[a] |
| Male + female | 73 | 1.4 | 4.1 | – | 5.5 | 1.4 | 2.8 | 2.7 | 1.4 | 2.7 | 6.8[a] |

From Soffritti *et al.* (1989)

[a] [$p \leq 0.01$; $\chi^2$ test, calculated by the Working Group]

**Table 29. Percentage of animals that had malignant tumours and incidence of selected types of tumour in a number of organs of Sprague-Dawley rats after administration of formaldehyde in the drinking-water for up to 24 months**

| Site and type of tumour | Formaldehyde dose (mg/L) | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Males | | | | | | | | Females | | | | | | | |
| | 0 | 0[a] | 10 | 50 | 100 | 500 | 1000 | 1500 | 0 | 0[a] | 10 | 50 | 100 | 500 | 1000 | 1500 |
| No. of animals | 100 | 50 | 50 | 50 | 50 | 50 | 50 | 50 | 100 | 50 | 50 | 50 | 50 | 50 | 50 | 50 |
| Animals bearing malignant tumours (%) | 38 | 42 | 28 | 24 | 44 | 48 | 46 | 72[b,c] | 43 | 46 | 40 | 40 | 50 | 38 | 58 | 54 |
| **Mammary gland** | | | | | | | | | | | | | | | | |
|   Adenocarcinoma | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 11 | 14 | 4 | 8 | 16 | 6 | 18 | 22 |
|   Fibrosarcoma | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 4 | 2 | 2 | 0 |
|   Liposarcoma | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 2 | 0 | 2 | 0 | 4 | 0 | 2 |
|   Angiosarcoma | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
|   Total | 1 | 2 | 0 | 0 | 2 | 2 | 0 | 2 | 11 | 16 | 6 | 10 | 20 | 12 | 20 | 24[d] |
| **Forestomach** | | | | | | | | | | | | | | | | |
|   Leiomyosarcoma | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Glandular stomach** | | | | | | | | | | | | | | | | |
|   Leiomyosarcoma | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| **Intestine** | | | | | | | | | | | | | | | | |
|   Leiomyoma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 2 | 0 | 0 | 0 | 6 |
|   Leiomyosarcoma | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 | 0 | 0 | 0 | 2 | 0 | 0 | 0 | 0 |
| **Testes** | | | | | | | | | | | | | | | | |
|   Interstitial-cell adenoma | 10 | 6 | 6 | 12 | 12 | 20 | 24[d,e] | 18 | | | | | | | | |
| **Haemolymphoreticular tissues[f]** | | | | | | | | | | | | | | | | |
|   Lymphomas and leukaemias | 8 | 20 | 8 | 20 | 26[b] | 24[d] | 22[d] | 46[b,c,g] | 7 | 10 | 10 | 14 | 16 | 14 | 22[d] | 20[d] |

From Soffritti *et al.* (2002)

[a] 15 mg/L methanol

[b] $p < 0.01$, $\chi^2$ test, versus untreated controls

[c] [$p < 0.01$, $\chi^2$ test, versus methanol group; calculated by the Working Group]

[d] $p < 0.05$, $\chi^2$ test, versus untreated controls [the Working Group noted that this category is an aggregate of tumours of different cellular origin]

[e] [$p < 0.01$, 2-tail Fisher exact test, versus methanol group; calculated by the Working Group]

[f] Including thymus, spleen and subcutaneous, mesenteric and pancreatic lymph nodes

[g] [$p < 0.01$ for trend, Cochran Armitage; calculated by the Working Group]

in the 1000-mg/L group. There was a statistically significant dose–response relationship for the increased incidences of haemolymphoreticular tumours ($p < 0.01$) in males. The Working Group noted the 'pooling' of lymphomas and leukaemias (designated as haemo-lymphoreticular neoplasias), the lack of reporting of non-neoplastic lesions and the absence of information on incidences of haemolymphoreticular tumours in historical controls.] Preliminary results of this study were published by Soffritti *et al*. (1989). [The Working Group noted that, in spite of the extensive histopathological examinations on which the preliminary data on tumours presented by Soffritti *et al*. (1989) were stated to be based, the reported total number of animals that had haemolymphoreticular neoplasias increased from 79 (Soffritti *et al*., 1989) to 150 (Soffritti *et al*., 2002).]

## 3.3       Dermal application

*Mouse*

In a study to evaluate the effects of formaldehyde on skin carcinogenesis induced by 7,12-dimethylbenz[*a*]anthracene (DMBA) (see Section 3.4.1), two groups of 16 male and 16 female Oslo hairless mice [age unspecified] received topical applications of 200 µL aqueous solution of 1 or 10% formaldehyde on the skin of the back twice a week for 60 weeks. Animals were observed weekly for skin tumours. 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 10% dose induced slight epi-dermal hyperplasia and a few skin ulcers. No benign or malignant skin tumours or tumours in other organs were observed in either group (Iversen, 1986). [The Working Group noted that no group treated with water only was included.]

## 3.4       Administration with known carcinogens and other modifying factors

### 3.4.1     *Mouse*

Oslo hairless mice [initial number and age unspecified] received a single topical application of 51.2 µg DMBA in 100 µL reagent-grade acetone on the skin of the back. Nine days later, a group of 16 male and 16 female mice received twice-weekly applications of 200 µL 10% formaldehyde in water (technical-grade formalin) on the skin of the back. Another group of 176 mice [sex unspecified] was given no further treatment. Animals were observed weekly for skin tumours for 60 weeks (first group) or 80 weeks (second group). 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 the first group, 3/32 mice had lung adenomas and 11/32 (34%) had 25 skin tumours, including three squamous-cell carcinomas and 22 papillomas. In mice that received 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

showed that formaldehyde significantly enhanced the rate of skin tumour induction ($p = 0.01$, Peto's test), and reduced the latency period for the tumours (Iversen, 1986). [The Working Group noted the incomplete reporting of the tumours in the group of rats treated with DMBA alone.]

### 3.4.2    *Rat*

Two groups of 30 and 21 male Wistar rats, 7 weeks of age, received 100 mg/L MNNG in the drinking-water and a standard diet that contained 10% sodium chloride for 8 weeks. Thereafter, the rats received the standard diet and 0 or 0.5% formaldehyde in the drinking-water for a further 32 weeks. Animals still alive at 40 weeks were killed, and rats that survived 30 weeks or more were considered as effective animals for the study. Necropsies were performed on most animals that died and on all animals that were killed at week 40. Malignant tumours of the stomach and duodenum were found in 4/30 (13%) rats that received MNNG and in 5/17 (29%) rats that received both MNNG and formaldehyde [not significant]. Adenocarcinomas of the glandular stomach were found in 4/17 (23.5%) rats that received the combined treatment and in 1/30 rats that received MNNG alone ($p < 0.05$, Fisher's exact test). Papillomas of the forestomach were found in 15/17 rats that received the combined treatment and in 0/30 that received MNNG alone ($p < 0.01$, Fisher's exact test). The incidence of adenomatous hyperplasia of the fundus of the glandular stomach was significantly greater in the group that received the combined treatment (15/17) than in those that received MNNG alone (0/30) ($p < 0.01$, Fisher's exact test) (Takahashi *et al.*, 1986).

Groups of 50 female white non-inbred rats [strain and age not specified] received intra-tracheal injections of one of three doses of benzo[*a*]pyrene as a suspension in 5% albumin in saline once every 2 weeks for 20 weeks (total doses, 0, 0.02, 0.1 or 5.0 mg/animal). One group of 50 female rats served as an untreated control. All benzo[*a*]pyrene-treated groups were then exposed by inhalation to 0, 0.003, 0.03 or 0.3 mg/m³ formaldehyde for 7 h per day on 5 days per week for 12 months. All animals were maintained until natural death, and organs and tissues that were suspected to have developed a tumour were subjected to histological examination. Tumours developed in rats of all 16 groups. Two of 39 effective (survived to the time of the first tumour development) rats in the control group developed reticulosarcomas of the lung and two developed fibroadenomas of the mammary gland. Similar tumours were observed at almost the same incidence in rats exposed to the three doses of formaldehyde alone. The incidence of total tumours in benzo[*a*]pyrene-treated rats was dose-dependent and varied from 13 to 28%. The incidence of lung tumours varied from 9 to 19%. In the mid- and high-dose groups, squamous-cell cysts and carcinomas of the lung were observed as well as lymphatic leukaemia. The tumour response to the combined treatment with benzo[*a*]pyrene and formaldehyde was also dose-dependent. The most prominent and statistically significant increase in the incidence of lung tumours (43%) and all tumours (69%) occurred in rats that were treated with the highest doses of benzo[*a*]pyrene and formaldehyde (5.0 mg and 0.3 mg/m³, respectively). In addition,

tumours developed earlier in this group and had greater multiplicity than those in animals that were exposed to benzo[*a*]pyrene or formaldehyde alone. The authors concluded that the combined treatment of rats with benzo[*a*]pyrene and formaldehyde leads to an increase in tumour response which is manifested as an increased incidence of tumours, a reduction in the latency period of tumour development and a broader spectrum of tumours (Yanysheva *et al.*, 1998). [The Working Group noted the very low level of exposure to formaldehyde compared with levels used in other experiments in rats.]

### 3.4.3    *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 2 weeks after the last injection of NDEA. A group of 50 animals served as untreated controls. 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 that received formaldehyde concurrently with and subsequent to injections of NDEA compared with that in animals that received 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    *Toxicokinetics*

#### (*a*)    *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 (Neuberger, 1981).

The endogenous concentration of formaldehyde, determined by GC–MS (Heck *et al.*, 1982), in the blood of human subjects not exposed to formaldehyde was $2.61 \pm 0.14 \, \mu g/g$ blood (mean $\pm$ standard error [SE]; range, $2.05$–$3.09 \, \mu g/g$) (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 both free and reversibly bound endogenous formaldehyde in the blood.

The concentration of formaldehyde 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 was $2.77 \pm 0.28 \, \mu g/g$, which did not differ from the pre-exposure concentration due to metabolically formed formaldehyde (see above). The absence of an increase is explained by the fact that formaldehyde reacts rapidly at the site of contact and is swiftly metabolized by human erythrocytes (Malorny *et al.*, 1965), which contain formaldehyde dehydrogenase (FDH) (Uotila & Koivusalo, 1987) and aldehyde dehydrogenase (ALDH) (Inoue *et al.*, 1979).

Overton *et al.* (2001) developed a mathematical model to predict interactions of formaldehyde in the respiratory tract, based on a one-dimensional equation of mass transport to each generation of an adult human, symmetric, bifurcating Weibel-type respiratory tract anatomical model, augmented by an upper respiratory tract. This predicted that over 95% of inhaled formaldehyde would be retained by the respiratory tract and that the flux is over 1000 times higher in the first tracheobronchial region compared with the first pulmonary region with no flux in the alveolar sacs.

A GC method was used to examine the urinary excretion of formate by veterinary medical students who were 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 this varied considerably both within and

among subjects (range, 2.4–28.4 mg/L). No significant changes in concentration were detected over a 3-week period of exposure to formaldehyde at a concentration in air of less than 0.5 ppm [0.61 mg/m³]. 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.

### (b) Experimental systems

#### (i) In vivo

The steady-state concentrations of endogenous formaldehyde have been determined by GC–MS (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(*a*)). The blood concentrations of formaldehyde immediately after a single exposure of rats to 14.4 ppm [17.6 mg/m³] (for 2 h) or subacute exposure of monkeys to 6 ppm [7.3 mg/m³] (for 6 h per day on 5 days per week for 4 weeks) were indistinguishable from those before exposure.

More than 93% of a dose of inhaled formaldehyde was absorbed readily by the tissues of the respiratory tract (Kimbell *et al.*, 2001a). 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).

The mucocilliary apparatus is an important defence system in the respiratory tract and may provide protection of the underlying epithelium from gases and vapours. Schlosser (1999) performed limiting-case calculations to determine the significance of convective mucus transport and chemical reaction to formaldehyde in rat nasal epithelial mucus. Less than 4.6% of absorbed formaldehyde can be bound to amino groups (serum albumin) after 20 min of exposure; therefore, at the slowest mucus flow rates measured in rats (~1 mm/min), a fluid element of mucus could travel more than 2 cm before binding 5% of the absorbed formaldehyde by which time the element would probably have left the nose (site of toxic response). Given the solubility of formaldehyde in mucus (water) and estimates of total mucus flow, as much as 22–42% of inhaled formaldehyde may be removed by mucus flow.

After exposure by inhalation, absorbed formaldehyde can be oxidized to formate and carbon dioxide or can be incorporated into biological macromolecules via tetrahydro-folate-dependent one-carbon biosynthetic pathways (see Fig. 1). The fate of inhaled formaldehyde was studied in Fischer 344 rats exposed to [¹⁴C]formaldehyde (at 0.63 or 13.1 ppm [0.8 or 16.0 mg/m³]) for 6 h. About 40% of the inhaled ¹⁴C was eliminated as

**Figure 1. Biological reactions and metabolism of formaldehyde**
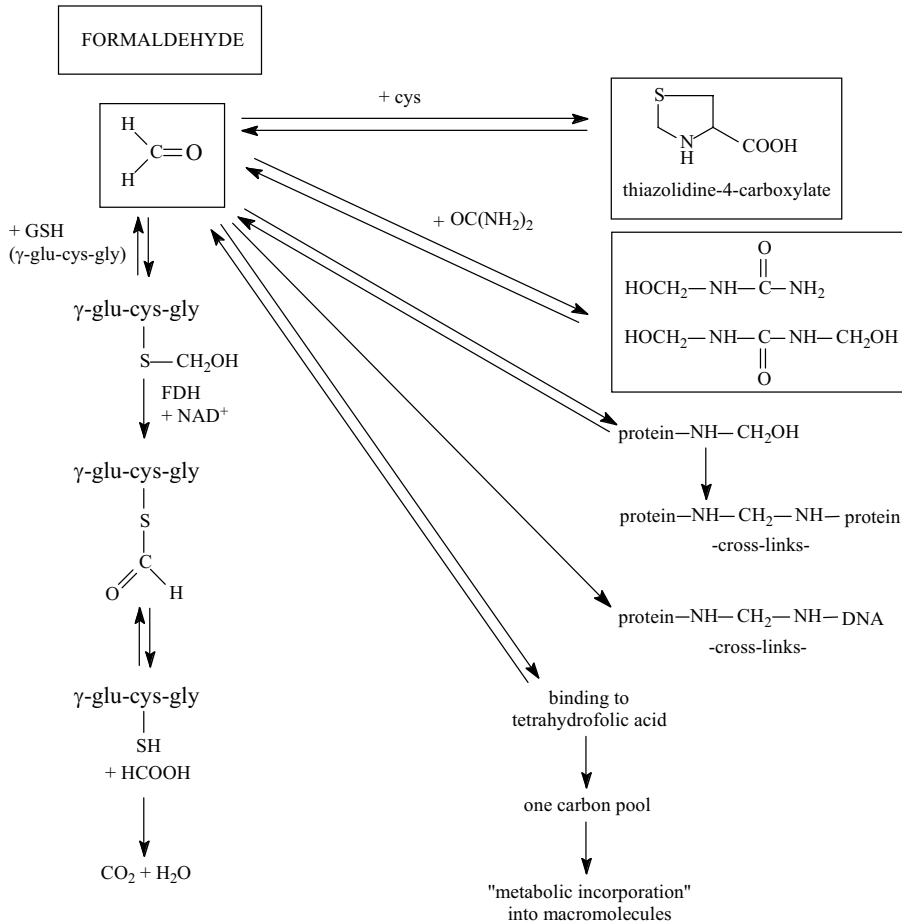


Adapted from Bolt (1987)

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. After inhalation, the terminal half-time of the radioactivity in the plasma was approximately 55 h (Heck *et al.*, 1983). 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 half-time of formaldehyde in rat plasma after intravenous administration is reported to be approximately 1 min (Rietbrock, 1965).

The fate of [$^{14}$C]formaldehyde after dermal 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 the 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. In another study in which Sprague-Dawley rats were injected intraperitoneally with 4 or 40 mg/kg bw [$^{14}$C]formaldehyde, a portion of the injected material (about 3–5% of a dose of 40 mg/kg bw) was excreted unchanged in the urine within 12 h (Mashford & Jones, 1982).

### (ii)    In vitro

Since formaldehyde can induce allergic contact dermatitis in humans (see Section 4.2.1), it can be concluded that formaldehyde or its metabolites penetrate human skin (Maibach, 1983). The kinetics of this penetration was determined *in vitro* using an excised full-thickness human 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, that flowed unidirectionally beneath the sample) was 16.7 $\mu$g/cm$^2$/h when a 3.7% solution of formaldehyde was used, and increased to 319 $\mu$g/cm$^2$/h when a 37% solution was used. The presence of methanol in both of these solutions (at 1–1.5% and 10–15%, respectively) may have affected the rate of uptake, and it is unclear whether the resorbed $^{14}$C was due only to formaldehyde. Skin retention of formaldehyde-derived radioactivity represented a significant fraction of the total amount of formaldehyde absorbed.

> (iii)   *Predictive models to analyse the effects of formaldehyde*
> *in the respiratory tract*

**Computational fluid dynamic models**

Anatomically accurate, three-dimensional computational fluid dynamics (CFD) models of formaldehyde in the nasal passages of rat, monkeys and humans have been developed to aid the understanding of absorption and mechanisms of action and risk assessment (Conolly *et al.*, 2000; Kimbell *et al.*, 2001a,b; Georgieva *et al.*, 2003). Conolly *et al.* (2000) sought to increase confidence in predictions of human DNA–protein cross-links (see Fig. 1) by refining earlier models of formaldehyde deposition and DNA–protein cross-links in nasal mucosa. Anatomically accurate CFD models of nasal airways of Fischer 344 rats, rhesus monkeys and humans that were designed to predict the regional flux of formaldehyde were linked to a model of tissue disposition of formaldehyde and kinetics of DNA–protein cross-links. Statistical optimization was used to identify parametric values, and good simulations were obtained. The parametric values obtained for rats and monkeys were used to extrapolate mathematically to the human situation. The results showed that the levels of nasal mucosal DNA–protein cross-links in rats, rhesus monkeys and humans varied with the concentration of formaldehyde inhaled and the predicted DNA–protein cross-link dose–response curves for the three species were similar, in spite of the significant interspecies differences in nasal anatomy and breathing rates.

Kimbell *et al.* (2001a) used anatomically accurate three-dimensional CFD models of nasal air flow and transport of formaldehyde gas in Fischer 344 rats, rhesus monkeys and humans to predict local patterns of wall mass flux ($pmol/(mm^2\,h–ppm)$). The nasal surface of each species was partitioned by flux into smaller regions (flux bins), each of which was characterized by surface area and an average flux value. Flux values higher than half the maximum flux value were predicted for nearly 20% of human, 5% of rat and less than 1% of monkey nasal surfaces at resting inspiratory flow rates. Human nasal flux patterns shifted distally and the percentage of uptake decreased as inspiratory flow rate increased.

Kimbell *et al.* (2001b) used anatomically accurate three-dimensional CFD models of nasal passages in Fischer 344 rats, rhesus monkeys and humans to estimate and compare the regional patterns of uptake of inhaled formaldehyde that were predicted among these species. Maximum flux values, averaged over one breath, in non-squamous epithelium were estimated to be 2620, 4492 and 2082 $pmol/(mm^2\,h–ppm)$ in rats, monkeys and humans, respectively. At sites where cell proliferation rates had been measured and found to be similar in rats and monkeys, predicted flux values were also similar, as were predicted fluxes in a region of high tumour incidence in the rat nose and anterior portion of the human nose.

**Thermodynamic model: exposure to particle-adsorbed formaldehyde**

The possibility that gaseous formaldehyde may be adsorbed to respirable particles, inhaled and subsequently released into the lung has been examined in a thermodynamic model based on measurable physicochemical properties of particles and volatile pollutants. In this model, analysis of the adsorption of formaldehyde to and its release from respirable

carbon black particles showed that only 2 ppb [0.0025 mg/m$^3$] of an airborne formaldehyde concentration of 6 ppm [7.4 mg/m$^3$] would be adsorbed to carbon black (Risby *et al.*, 1990).

### 4.1.2    *Biomonitoring and metabolism of formaldehyde*

#### (*a*)    *Humans*

##### (i)    *Biological monitoring*

A quantitative method that was developed for the determination of formaldehyde in biological tissues used stable-isotope dilution combined with GC–MS. Multilabelled form-aldehyde that contained 90 atom-% $^{13}$C and 98 atom-% deuterium ($^2$H) was used as the iso-topic diluent, which was added to homogenized tissue. Derivatization was conducted *in situ* with pentafluorophenylhydrazine, followed by extraction and analysis of the penta-fluorophenylhydrazone by selected ion monitoring. With this method, endogenous formal-dehyde could be analysed quantitatively in tissue samples as small as 20 mg wet wt (Heck *et al.*, 1982).

**Blood**

Concentrations of formaldehyde were determined by the method described above in samples of venous blood that were collected before and after exposure of six human volun-teers to 1.9 ppm [2.3 mg/m$^3$] formaldehyde by inhalation for 40 min. Average concentra-tions of formaldehyde were $2.61 \pm 0.14$ µg/g blood before and $2.77 \pm 0.28$ µg/g blood after exposure. These values were not significantly different. However, the subjects exhibited significant inter-individual variation with respect to their blood concentrations of formal-dehyde, and some showed significant differences — either an increase or a decrease — before and after exposure, which suggests that individual blood concentrations of formal-dehyde vary with time. The results are consistent with the assumption that toxicity due to exposure to formaldehyde is unlikely to occur at sites that are distant from the portal of entry (Heck *et al.*, 1985). The absence of an exposure-related increase in blood concentration of formaldehyde in this study can be explained by the fact this chemical is rapidly metabolized by human erythrocytes (Malorny *et al.*, 1965), which contain FDH (Uotila & Koivusalo, 1987) and ALDH (Inoue *et al.*, 1979) (see also Section 4.1.1(*a*)).

DNA–protein cross-links in blood leukocytes were used as a marker for exposure to formaldehyde in a study that involved 12 workers (Anatomy Department and Pathology Institute; duration of exposure, 2–31 years) and eight controls. Protein-bound DNA was separated from protein-free DNA by precipitation with sodium dodecylsulfate (Zhitkovich & Costa, 1992). A significantly higher ($p = 0.03$) level of cross-links was measured among exposed workers (mean $\pm$ SD, $28 \pm 5\%$; min., 21%; max., 38%) than among the unexposed controls (mean $\pm$ SD, $22 \pm 6\%$; min., 16%; max., 32%). Of the 12 exposed workers, four (33%) showed cross-link values above the upper range of the controls. The level of cross-links was generally higher in workers exposed for longer periods, and was reported not to be influenced by tobacco smoking. The data suggest that

DNA–protein cross-links can be used as a method for the biological monitoring of exposure to formaldehyde (Shaham *et al.*, 1996a).

**Urine**

Exposure to formaldehyde was monitored in a group of 35 students of veterinary medicine who were enrolled for 3 consecutive weeks in a functional anatomy class, where they worked extensively with animal tissue preserved in formalin. The biological monitoring was based on the known metabolism of formaldehyde to formic acid, which may then be excreted in the urine. Urinary formic acid was converted to methyl formate and measured by GC. The average concentration of formate in the urine of the subjects before the class was 12.5 mg/L, and considerable variation was observed both within and among subjects (range, 2.4–28.4 mg/L). No significant changes in concentration were detected over the 3-week period of exposure to formaldehyde at a concentration in air of < 0.4 ppm [0.5 mg/m³]. Biological monitoring of exposure to formaldehyde by measurement of urinary formic acid does not appear to be a suitable method at these levels of exposure (Gottschling *et al.*, 1984) (see also Section 4.1.1(*a*)).

**Respiratory tract: animal models and extrapolation to humans**

The pharmacokinetics of formaldehyde-induced formation of DNA–protein cross-links in the nose was investigated by use of a model in which the rate of formation is proportional to the tissue concentration of this chemical. The model includes both saturable and non-saturable elimination pathways and regional differences in DNA binding are attributed to anatomical rather than biochemical factors. Using this model, the concentration of DNA–protein cross-links formed in corresponding tissues of different species can be predicted by scaling the pharmacokinetic parameter that depends on minute volume and quantity of nasal mucosal DNA. The concentration–response curve for the average rate of formation of cross-links in the turbinates, lateral wall and septum of rhesus monkeys was predicted from that of Fischer 344 rats that were exposed under similar conditions. A significant overlap was observed between predicted and fitted curves, which implies that minute volume and nasal mucosal DNA are major determinants of the rate of formation of DNA–protein cross-links in the nasal mucosa of different species. Concentrations of DNA–protein cross-links that may be produced in the nasal mucosa of adult humans were predicted on the basis of experimental data in rats and monkeys. The authors suggested from their results that formaldehyde would generate lower concentrations of DNA–protein cross-links in the nasal mucosa of humans than that of monkeys, and much lower concentrations in humans than in rats. The rate of formation of DNA–protein cross-links can be regarded as a surrogate for the delivered concentration of formaldehyde (Casanova *et al.*, 1991).

(ii)    *Metabolism of formaldehyde*

Formaldehyde is an endogenous metabolic product of *N*-, *O*- and *S*-demethylation reactions in the cell (Neuberger, 1981). During exogenous exposure, gaseous formaldehyde — which is highly soluble in water — is virtually completely removed by the nose during

nasal respiration (Ballenger, 1984). In recent years, the metabolic capacities of nasal cavity tissues have been investigated extensively in mammals, including humans. ALDHs, cyto-chrome P450 (CYP)-dependent monooxygenases, glutathione (GSH) transferases (GSTs), epoxide hydrolases, flavin-containing monooxygenases and carboxyl esterases have all been reported to occur in substantial quantities in the nasal cavity. The contributions of some of these enzyme activities to the induction of toxic effects from volatile chemicals have been the subject of numerous studies (see reviews by Dahl & Hadley, 1991; Thornton-Manning & Dahl, 1997). The two main enzymes involved in the metabolism of formaldehyde in humans — a dehydrogenase and a hydrolase — are discussed in detail below.

Formaldehyde is detoxified by oxidation to formate by different enzyme systems (Fig. 2; from Hedberg *et al*., 2002). The primary and generally most important system ini-tially involves GSH-dependent FDH (Uotila & Koivusalo, 1974), which is identical to alcohol dehydrogenase 3 (ADH3; Koivusalo *et al*., 1989), that oxidizes *S*-hydroxymethyl-glutathione (the thiohemiacetal that is formed spontaneously from formaldehyde and GSH) to *S*-formylglutathione. The systematic name for the enzyme is formaldehyde:NAD+ oxidoreductase (glutathione-formylating) (CAS Registry No. 9028-84-6, IUBMB code EC1.2.1.1). (Other names for this enzyme are formaldehyde dehydrogenase, formaldehyde dehydrogenase (glutathione), NAD-linked formaldehyde dehydrogenase and formic de-hydrogenase.) This intermediate is then further metabolized by *S*-formylglutathione

**Figure 2. Fate and metabolism of formaldehyde**
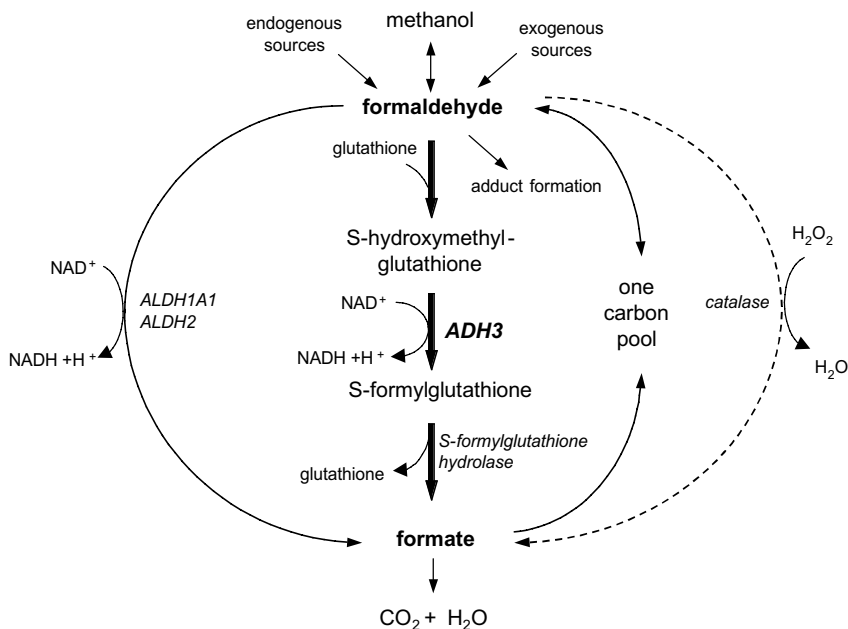


Adapted from Hedberg *et al*. (2002)

hydrolase to yield formate and reduced GSH (Uotila & Koivusalo, 1997). Analyses across species and among various mammalian tissues and cell types imply that ADH3 represents a ubiquitous enzyme, and that it is the ancestral form of ADH from which other types of vertebrate ADH have evolved (Estonius *et al*., 1996; Hedberg *et al*., 2000; Jörnvall *et al*., 2000; Hedberg *et al*., 2001; Höög *et al*., 2001, 2003). The activities of ADH3 are two to three orders of magnitude lower than those of *S*-formylglutathione hydrolase and thus the ADH3-catalysed step is rate-limiting (Uotila & Koivusalo, 1997). Formation of *S*-hydroxymethylglutathione efficiently counteracts the existence of free formaldehyde, a reaction that is determined by the fact that cellular GSH is an abundant molecule and is often present in millimolar concentration levels (Meister & Anderson, 1983). The equili-brium constant ($K_{eq}$) for the formation of this adduct — under conditions of excess GSH — was determined to be $1.77 \pm 0.13$ mM (Naylor *et al.*, 1988; Sanghani *et al.*, 2000). Furthermore, when formaldehyde is reacted with the thiols, cysteine and cysteinylglycine, it can function as an alternative substrate to *S*-hydroxymethylglutathione for ADH3, but at a far lower turnover (Holmquist & Vallee, 1991). The mechanism for the ADH3-dependent step is identical to any alcohol oxidation by ADH enzymes; it requires catalysis by zinc and uses NAD+/NADH as the electron acceptor and donor, respectively (Höög *et al.*, 2001). The second enzyme system is the ALDHs — class 1 (cytosolic ALDH; ALDH1A1) and class 2 (mitochondrial ALDH; ALDH2) — which have an affinity for free formaldehyde. Because the Michaelis-Menten constant ($K_m$) is less than micromolar for aldehyde sub-strates, they are called low-$K_m$ ALDHs (Petersen & Lindahl, 1997), except for free formaldehyde for which the $K_m$ values are high (in the range of 0.6 mM; Mukerjee & Pietruszko, 1992). This value is about 100-fold higher than the $K_m$ displayed by ADH3 for *S*-hydroxymethylglutathione (4 µM) (Holmquist & Vallee, 1991; Uotila & Koivusalo, 1997; Hedberg *et al*., 1998). Therefore, ADH3 is probably the predominant enzyme res-ponsible for the oxidation of formaldehyde at physiologically relevant concentrations, while low-$K_m$ ALDHs contribute increasingly when the concentrations of formaldehyde increase (Dicker & Cederbaum, 1986). Catalase may also contribute to the oxidation of formaldehyde to formate, but only under circumstances in which hydrogen peroxide is formed (Jones *et al*., 1978; Uotila & Koivusalo, 1989). Formaldehyde may also be reduced to methanol and then be re-converted to formaldehyde, when ADH1 is involved (Pocker & Li, 1991). Many endogenous and exogenous factors can contribute to the gene-ration of formaldehyde in cells (Grafström, 1990). Both formaldehyde and formate contri-bute to the 'one-carbon pool', which involves the folic acid metabolic pathway for synthesis of certain nucleic acids and amino acids, and, eventually, cellular macro-molecules (Neuberger, 1981). *S*-Hydroxymethylglutathione and *S*-formylglutathione are among the most notable components of this pool, which also includes the tetrahydrofolate adducts, $N^5$-hydroxymethyl-, $N^5,N^{10}$-methylene, and $N^5$- and $N^{10}$-formyl-tetrahydrofolate, serine, methionine, histamine and methylamine, other reversible amine adducts and hydrated formaldehyde.

ADH3 is the only ADH that can participate in the cellular detoxification of formal-dehyde. The nomenclature recommended by Duester *et al*. (1999) defines the protein as

ADH3 and the gene as *ADH3*, whereas previous nomenclature used χ (chi) for the protein and *ADH5* for the gene (Jörnvall & Höög, 1995). The older nomenclature used *ADH3* to define the gene that codes for *ADH1C*, which is important for the oxidation of ethanol, and studies of the latter protein, including the role of polymorphisms in the causation of cancer (Schwartz *et al*., 2001; Yokoyama *et al*., 2002), should not be confused with the enzyme that is involved in the oxidation of formaldehyde. *S*-Nitrosoglutathione constitutes an excellent substrate for reductive cleavage by ADH3, and, accordingly, ADH3 is also termed *S*-nitrosoglutathione reductase (Jensen *et al*., 1998; Liu *et al*., 2001). Comparative analysis indicates that ADH3 oxidizes GSH-conjugated formaldehyde (i.e. *S*-hydroxymethylglutathione) and reduces *S*-nitrosoglutathione with catalytic efficiencies of 58 000 min$^{-1}$.mM$^{-1}$ and 90 000 min$^{-1}$.mM$^{-1}$, respectively (Hedberg *et al*., 2003). Considering both reactions, exposure to formaldehyde would naturally favour the oxidant activity of ADH3, whereas nitrosative stress leading to the formation of *S*-nitrosoglutathione would favour reductive activity (Liu *et al*., 2001; Hedberg *et al*., 2003). The cellular levels of NAD$^+$ are normally two orders of magnitude higher than those of NADH and thus, under physiological conditions, the oxidation of *S*-hydroxymethylglutathione would be favoured rather than the reduction of *S*-nitrosoglutathione (Svensson *et al*., 1999; Molotkov *et al*., 2002; Höög *et al*., 2003). Although it has a lower efficiency than other ADH enzymes, ADH3 also mediates oxidation of all-*trans*-retinol to retinal, and may also oxidize ethanol to acetaldehyde at levels of exposure that are reached during alcohol intoxication (Svensson *et al*., 1999; Molotkov *et al*., 2003). ADH3 also shows oxidizing activity towards longer-chain primary alcohols, methylglyoxal, ketoxal, hydroxypyruvaldehyde, 20-hydroxy-leukotriene B$_4$ and ω-hydroxy fatty acids, e.g. 12-hydroxydodecanoic acid (Wagner *et al*., 1984; Gotoh *et al*., 1990; Jörnvall *et al*., 2000).

The physiological relevance of these activities remains unclear, since the catalytic efficiencies for these substrates are considerably lower than those of *S*-hydroxymethylglutathione and *S*-nitrosoglutathione. However, all of these substrates compete with *S*-hydroxymethylglutathione and *S*-nitrosoglutathione for the active site of ADH3, and thereby influence the catalytic activity for formaldehyde scavenging. The *ADH3* gene promoter sequence shows several polymorphisms that might influence *ADH3* transcription, but such polymorphisms were not observed in exons that code for the *ADH3* gene (Hedberg *et al*., 2001). In contrast, polymorphisms in *ALDH*, including *ALDH2*, may reduce the capacity for the oxidation of formaldehyde to less than half of that of the wild-type activity (Wang *et al*., 2002). Transcription of *ADH3* is coupled to proliferative states in human oral keratinocytes where *ADH3* mRNA exhibits a short half-life (7 h); when the protein is formed, it remains highly stable and metabolically active during cellular life expectancy (Hedberg *et al*., 2000; Nilsson *et al*., 2004). Formaldehyde and *S*-hydroxymethylglutathione regulate *ADH3* transcription in the bacterium *Rhodobacter sphaeriodes*, and wounding and growth hormones regulate ADH3 in the plant *Arabidopsis*, which provides examples of ADH3 regulation through feed-back control and from both external and internal signals (Barber & Donohue, 1998; Diaz *et al*., 2003). [The Working Group did not find evidence of such regulation in humans.] The biochemistry that underlies the metabolism of formaldehyde

indicates that changes in glutathione levels, $NAD^+$:NADH ratios, other redox changes and oxidant stress in general, including from nitric oxide and *S*-nitrosoglutathione, protein S-nitrosothiols and intermediates of the folic acid metabolic pathway should be considered in the assessment of the consequences of exposure to formaldehyde.

### (b)    Experimental systems

The distribution of selected metabolizing enzymes in the respiratory tract was compared with that in the liver of beagle dogs. Four beagle dogs (two males, two females; 13–18 kg, 13–130 months of age) were euthanized, the liver and respiratory tract were removed and tissues were prepared for isolation of metabolizing enzymes, including infusion of cold agarose into a lung lobe. The respiratory tract was separated into respiratory nasal epithelium, olfactory nasal epithelium, tracheal epithelium, epithelium from proximal middle and distal bronchus and lung parenchyma. The cytosolic fraction was isolated and the activity of sulfite oxidase, ADH, ALDH, FDH, GST and protein contents were quantified. Sulfite oxidase with sulfite as the substrate had greatest activity in the liver (9.95 nkat/mg protein); in the respiratory tract, the greatest activity was in the lung parenchyma (4.62 nkat/mg protein) and activity in the rest of the respiratory tract was below 4 nkat/mg protein. FDH with formaldehyde as the substrate had greatest activity in the nose (10.5 nkat/mg protein) while the liver (2.28 nkat/mg protein) had less activity than any site in the respiratory tract. ALDH with formaldehyde as the substrate had greatest activity in the trachea (1.28 nkat/mg protein), and the rest of the respiratory tract and liver had levels of activity below 1 nkat/mg protein. ADH with ethanol as the substrate had greatest activity in the liver (4.40 nkat/mg protein), and the respiratory tract had levels below 1 nkat/mg protein. All but one of the 1-chloro-2,4-dinitrobenzene-related GSTs had greatest activity in the liver parenchyma, which ranged from 50 to 300% greater than that in the respiratory tract. The cytosolic fraction of the epoxy-3-(*para*-nitrophenoxy)-propane-related GST had greatest activity in the trachea (3.94 nkat/mg protein); activity in the liver (0.24 nkat/mg protein) was less than 20% of that in any part of the respiratory tract on average. In general, metabolizing enzymes are spread throughout the respiratory tract and can have a metabolic capacity the same as or greater than the liver (Maier *et al*., 1999).

## 4.2    Toxic effects

### 4.2.1    *Humans*

#### (a)    *Irritation*

There is extensive literature on domestic exposures to products that contain formaldehyde, such as plywood, and to urea–formaldehyde foam (see Section 1). Irritative effects have consistently been reported after exposure to formaldehyde; these have also been observed in children and a wide variation in susceptibility has been reported. Because these domestic exposures also involve exposure to other agents, this literature is not reviewed in

detail here because the findings do not generally add any information on the specific mode of action of formaldehyde as a potential carcinogen.

(i)     *Experimental studies of acute effects*

Airborne formaldehyde irritates the eyes, nose and throat in healthy humans who had clinical disease. Chamber studies and the symptoms reported therein are summarized in Table 30.

Dose–response irritative effects were investigated (Kulle *et al.*, 1987; Kulle, 1993) in nonsmokers who received 3-h exposures to 0, 0.5, 1, 2 and 3 ppm [0, 0.61, 1.22, 2.44 and 3.66 mg/m$^3$] formaldehyde. The results are shown in Figure 3. Eye irritation increased linearly at doses of 0.5–3 ppm and was the dominant symptom; no effect was observed with 0.5 ppm; 21% of the volunteers had mild eye irritation with 1 ppm and 35% with 2 ppm. Of the volunteers, 40% could smell formaldehyde at 0.5 ppm (5% when no formaldehyde was present). Nose and/or throat irritation was the least sensitive response with an estimated threshold of 1 ppm.

**Adult asthmatics**

Green *et al.* (1987) exposed 22 healthy subjects and 16 asthmatics to 3 ppm formaldehyde for 1 h during exercise. In the healthy group, 32% of the subjects reported moderate-to-severe nose and throat irritation and 27% moderate-to-severe eye irritation. In the asthmatics, these percentages were 31% and 19%, respectively.

**Unsensitized adult asthmatics**

The effects of inhaled formaldehyde on the airways of healthy people and unsensitized asthmatics have been reviewed (Smedley, 1996; Krieger *et al.*, 1998; Suh *et al.*, 2000; Bender, 2002; Liteplo & Meek, 2003).

Bender (2002) reviewed nine controlled chamber studies of exposure to formaldehyde of asthmatic subjects (Reed & Frigas 1984; Sauder *et al.*, 1986; Green *et al.*, 1987; Kulle *et al.*, 1987; Schachter *et al.*, 1987; Witek *et al.*, 1987; Harving *et al.*, 1990; Pazdrak *et al.*, 1993; Krakowiak *et al.*, 1998). Exposure to 2–3 ppm formaldehyde for up to 3 h did not provoke asthma in unsensitized asthmatics. There was no asthmatic response to 0.1–3 ppm formaldehyde in 11 women and two men who reported chest tightness, cough and wheeze attributed to exposure to formaldehyde at home or at work (Reed & Frigas, 1984). Similar conclusions were reached in the review of Liteplo and Meek (2003) who included three further studies (Day *et al.*, 1984; Schachter *et al.*, 1986; Sauder *et al.*, 1987).

**Studies on nasal lavage**

Two studies have investigated the effect of exposure to formaldehyde on nasal lavage. Krakowiak *et al.* (1998) reported on 10 healthy subjects and 10 asthmatics who reported nasal or respiratory symptoms from formaldehyde at work (nurses, textile and shoe workers), who received a single, blind exposure to clean air or 0.5 mg/m$^3$ formaldehyde (range, 0.2–0.7 mg/m$^3$) for 2 h. Nasal washings were performed before and 0, 0.5, 4 and 24 h after exposure. During exposure to formaldehyde, all subjects developed sneezing,

**Table 30. Studies of acute exposure to formaldehyde that reported irritant-type symptoms**

| Subjects (no.) | Exposure to formaldehyde | Effect | Reference |
|---|---|---|---|
| Normal (22)<br>Asthmatics (16) | 3 ppm [3.7 mg/m$^3$] for 60 min | Moderate/severe symptoms<br>Eye, 27%; nose/throat, 32%<br>Eye, 19%; nose/throat, 31% | Green *et al.* (1987) |
| Normal with no exposure (10)<br>Asthmatics with allergic symptoms due to exposure to formaldehyde (10) | 0.5 mg/m$^3$ for 2 h | Scored on 0–7 point scale<br>Nasal itching and congestion in all<br>Score 4.3/7 in normal subjects<br>Score 4.6/7 in asthmatics | Krakowiak *et al.* (1998) |
| Healthy nonsmokers (19) | 3 ppm for 3 h | See Figure 3 | Kulle *et al.* (1987); Kulle (1993) |
| Healthy (11)<br>Formaldehyde con-tact dermatitis (9) | 0.5 mg/m$^3$ [0.41 ppm] for 2 h | Scored on 0–7 point scale (sneezes, nasal itching and congestion)<br>Mean nasal score 4/7 at 10 min for allergic and healthy subjects | Pazdrak *et al.* (1993) |
| Healthy nonsmokers (9) | 3 ppm for 3 h | Mean symptom scores (air/formaldehyde)<br>Throat/nose, 0.22/1.33<br>Eye irritation, 0/0.78 | Sauder *et al.* (1986) |
| Asthmatic non-smokers (9) | 3 ppm for 3 h | Eye and nose irritation started after 2 min | Sauder *et al.* (1987) |
| Normal formal-dehyde-exposed (15) | 2 ppm [2.5 mg/m$^3$] for 40 min | Odour, 12/15 (80%)<br>Sore throat, 0/15 (0%)<br>Nasal irritation, 0/15 (0%)<br>Eye irritation, 7/15 (47%) | Schachter *et al.* (1987) |
| Asthmatics (15) | 2 ppm for 40 min | Odour, 15/15 (100%)<br>Sore throat, 5/15 (33%)<br>Nasal irritation, 7/15 (47%)<br>Eye irritation, 11/15 (73%) | Witek *et al.* (1987) |
| Normal (9), asthmatics with UFFI symptoms (9) | 3 ppm for 2 h (1 ppm for 90 min and 2 ppm UFFI for 30 min) | Eye irritation, 15/18<br>Nasal congestion, 7/18<br>Throat irritation, 5/18<br>Same in UFFI symptomatic and normal groups | Day *et al.* (1984) |

UFFI, urea–formaldehyde foam insulation

**Figure 3. Symptoms reported by 19 nonsmoking healthy adults exposed to formaldehyde for 3 h**
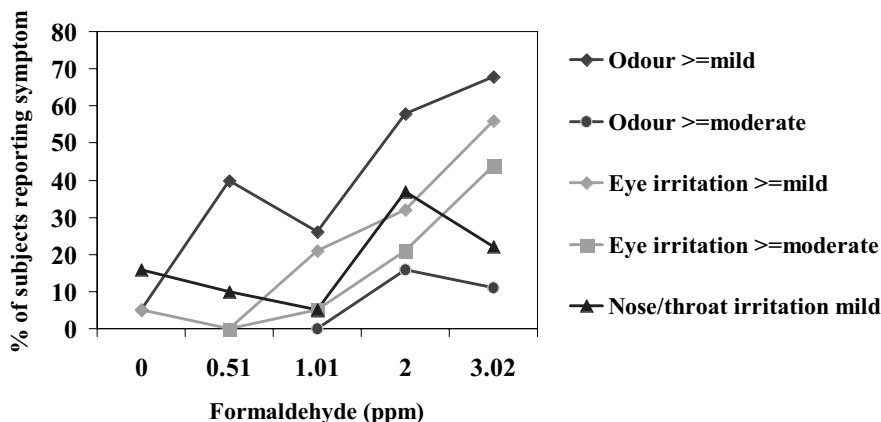


Adapted from Kulle (1993)

itching and congestion, with substantial resolution by 4 h. An increase in total leukocytes and eosinophils was observed immediately after exposure to formaldehyde that was similar in both groups of subjects, with resolution after 4 h. An increase was also observed in the albumin:total protein ratio with a similar time course that was interpreted as an increase in nasal mucosal permeability. No significant increases in tryptase or eosinophil cationic protein were found in either group. An earlier study by the same group (Pazdrak *et al.*, 1993) that used a similar methodology investigated nine workers who had skin hypersensitivity (positive patch test) to formaldehyde and 11 healthy men who had negative formaldehyde patch tests. Nasal lavage was performed at 0, 10 min, 3 (or 4) and 18 h after exposure. Eosinophils increased in the nasal lavage and were maximal immediately after exposure, but were still increased at 4 and 18 h; the percentage of epithelial cells was reduced. Albumin levels were increased in the lavage and albumin:total protein ratios were increased only immediately after exposure. The group that had dermatitis and the normal group had similar responses. The authors concluded that the irritative effects of formaldehyde were confirmed, and also suggested a non-specific, non-allergic pro-inflammatory effect when formaldehyde was inhaled at a low dose (0.5 mg/m$^3$).

An in-vitro study of human nasal ciliated epithelial cells showed reduced frequency of ciliary beat after exposure to 5000 µg/m$^3$ formaldehyde for 2 h, but no effect after exposure to 5000 µg/m$^3$ for 1 h or 500 µg/m$^3$ for 2 h (Schäfer *et al.*, 1999).

(ii)    *Residential exposure*

Studies have been conducted among residents who were exposed to formaldehyde in the home and school children who were exposed to formaldehyde in classrooms (Broder *et al.*, 1991; Wantke *et al.*, 1996a). These studies are difficult to interpret because they did

not control for confounding factors, particularly lack of ventilation and other allergens. It is possible that co-exposures to irritants and allergens increases the risk for allergen sensitization, but this has not been shown reliably for exposures to formaldehyde. Some studies looked for IgG and/or IgE antibodies to formaldehyde/human serum albumin conjugates, but the results were inconsistent (Patterson *et al.*, 1989; Wantke *et al.*, 1996a; Kim *et al.*, 2001; Doi *et al.*, 2003).

###### (b)    *Pulmonary function: effect of chronic occupational exposure*

Kriebel *et al.* (1993) noted that epidemiological studies of irritants are difficult to perform using standard epidemiological methods because of the reversible nature of the health outcomes, the selection of sensitive individuals from the study population and the wide heterogeneity of normal responses to irritants. Twenty-four physical therapy students, who were exposed to formaldehyde during dissection for 3 h per week over 10 weeks with breathing zone exposures to formaldehyde of 0.49–0.93 ppm, were included in the study. Peak expiratory flow and a symptom questionnaire were completed before and after each exposure, and again before and after 3-h laboratory sessions after several months with no exposure to formaldehyde. Symptoms increased following exposure (eyes, +43%; nose, +21%; throat, +15%; breathing, +20%; and cough, +5%). The intensity of symptoms tended to decrease over time [this might be due to a repeated questionnaire effect with weekly questionnaires]. The peak expiratory flow declined by an average of 4.8 L/min during the morning (pre-dissection to midday) and by 10 L/min before exposure over the 10 weeks of exposure (2% of baseline) with recovery after 12 weeks with no exposure (daily measurements before exposure). The study group included five asthmatics whose peak expiratory flow after exposure fell by 37 L/min (non-asthmatics, 3.9 L/min). [The Working Group noted the lack of controls in this study, to adjust for any seasonal effects over time. The Working Group also noted that this is a difficult study to interpret. The time of day of the dissection sessions is not given, and the peak expiratory flow would be expected to increase for the first 4–10 h after waking, so that the time of day may have affected the outcome of the measurements.]

Akbar-Khanzadeh and Mlynek (1997) compared 50 nonsmoking first-year medical students exposed to breathing zone levels of 1.36–2.58 ppm [1.66–3.2 mg/m$^3$] formaldehyde with 36 second-year physiotherapy students who had no exposure to formaldehyde. Lung function was measured before exposure, 1 h after exposure and at midday. An increase in lung function was observed in both exposed and unexposed groups during the morning (exposed forced expiry volume in 1 sec (FEV$_1$), +1.2%; control, +2.1% at 1 h; exposed FEV$_1$, + 2.4%; control, +6.2% at 3 h). In the exposed group, 82% reported nose irritation, 76% reported eye irritation (18% wore goggles), 36% reported throat irritation and 14% reported airway irritation. The authors concluded that the reduced increase in lung function during the morning in the exposed group was probably due to the exposure to formaldehyde.

The same group reported a similar study of 34 medical students and instructors who were exposed to 0.07–2.94 ppm (mean, 1.24 ppm) [0.08–3.6 mg/m$^3$ (mean, 1.22 mg/m$^3$)]

formaldehyde and 12 control students and instructors who had no exposure to formaldehyde (Akbar-Khanzadeh *et al.*, 1994). Pre- and post-morning sessions showed a 0.03% fall in $FEV_1$ in the formaldehyde-exposed group compared with a 1% increase in the controls.

### (c)    *Effect of chronic exposure on nasal mucosa*

#### (i)    *Occupational exposure*

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.

Cell smears were collected by a swab that was inserted 6–8 cm into the nose of 42 workers who were employed in two phenol–formaldehyde plants and 38 controls who had no known exposure to formaldehyde. The concentrations of formaldehyde 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 years, but no association was found 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 age. The concentrations of formaldehyde in the three plants were 0.1–1.1 mg/m$^3$, with peak concentrations of 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 number of years of employment. No difference was detected in the nasal histology of workers exposed to formaldehyde alone or 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 who were engaged in the manufacture of resins for laminate production, 89 workers who were employed in furniture factories and who were exposed to particle-board and glue and 32 controls who were mainly clerks in a local government office. The concentrations of formaldehyde in the resin manufacturing plant were 0.05–0.5 mg/m$^3$, with frequent peaks of over 1 mg/m$^3$, and those in the furniture factories were 0.2–0.3 mg/m$^3$, with rare peaks up to to 0.5 mg/m$^3$; the latter workers were also exposed to wood dust (1–2 mg/m$^3$). The control group was exposed to concentrations of 0.09–0.17 mg/m$^3$ formaldehyde. The average length of employment was about 10 years. The histological scores of workers who were exposed to formaldehyde alone were slightly but significantly higher than those of controls, but the histological scores of workers who were 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.* (1989a). [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 of 37 workers who were exposed at a chemical company where formaldehyde resins were produced and 37 age-matched controls. The concentrations of formaldehyde 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 more common among the exposed workers than among the controls, but the difference was not significant. The histological scores increased with age and with concentration and duration of exposure, 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 that was released from a urea–formaldehyde glue in a plywood factory. Each subject was paired with a control who was matched for age and sex. The mean age of the controls was $30.6 \pm 8.7$ years and that of exposed workers was $31.0 \pm 8.0$ years. The mean levels of exposure to formaldehyde (8-h TWA) 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. 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 and 0.41 mg/m$^3$ in shearing-press) occurred. 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, $2.3 \pm 0.5$ in the exposed group; $1.6 \pm 0.5$ in the control group; $p < 0.01$, Mann–Whitney U test) (Ballarin *et al.*, 1992).

### (ii)   *Residential exposure*

Samples of cells were collected by a swab that was inserted 2–3 cm into the nostrils of subjects who lived in urea–formaldehyde foam-insulated homes and of subjects who lived 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 1 year later (Broder *et al.*, 1991) showed a decrease in nasal symptoms that was unrelated to any decrease in levels of formaldehyde.

The effects of formaldehyde, other than cancer, on the nasal mucosa are summarized in Table 31.

### (*d*)   *Sensitization to formaldehyde*

Formaldehyde is a well recognized cause of allergic contact dermatitis and an occasional cause of occupational asthma. Provided that suitable control exposures for the affected patient are performed and that similar exposures of unsensitized asthmatics do not provoke asthma, cause and effect can reasonably be implied. The studies on asthma are summarized in Table 32.

Hendrick and Lane (1975) found a late asthmatic reaction following exposure to formaldehyde in a nurse who had no reaction after a control exposure. An asthmatic patho-

**Table 31. Findings in the nasal mucosa of people who had occupational exposure to formaldehyde**

| Industry | Concentration of formaldehyde $(mg/m^3)$ | No. of exposed | No. of controls | Method | Findings | Reference |
|---|---|---|---|---|---|---|
| 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.* (1987b) |
| Formaldehyde<br><br>Wood dust (laminated particle-board) | 0.1–1.1 (peaks to 5)<br><br>0.6–1.1 | 75 | 25 | Nasal biopsy | Histological score: exposed, 2.9; controls, 1.8 ($p < 0.05$). Six men had mild dysplasia. | Edling *et al.* (1988) |
| 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 | Berke (1987) |
| | | | | Clinical examination | More mucosal abnormalities in non-smoking exposed workers ($p = 0.04$) | |
| Formaldehyde (production of formaldehyde and formaldehyde resins) | 0.6–> 2.4 | 37 | 37 | Nasal biopsy | Histological score: exposed, 1.9; controls, 1.4 ($p > 0.05$). Three exposed and no controls had dysplasia. | Boysen *et al.* (1990) |
| 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 | Holmström *et al.* (1989a) |
| Formaldehyde<br>Wood dust (plywood factory) | 0.1–0.39<br>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. | Ballarin *et al.* (1992) |

**Table 32. Studies of occupational asthma/dermatitis**

| Sex | Route | Concentration of formaldehyde | Duration | Effects | Reference |
|---|---|---|---|---|---|
| Men (aged 39 years) | Inhalation | 0.06 ppm, max. 0.13 ppm | 6 months | Asthma | Kim *et al.* (2001) |
| | | 0.01 ppm | 20 min | None | |
| | | 0.5 ppm | 20 min | Late asthmatic reaction, IgE negative | |
| Men and women | Skin (patch test) | 1% in water | Unspecified | Case series of 280 health care workers; 13.9% positive patch test to formaldehyde, little cross reaction with glutaraldehyde (12.4%) and glyoxal (1.9%) | Kiec-Swierczynska *et al.* (1998) |
| Men and women | Inhalation | 2.3 mg/m$^3$ | 30 min | Late asthmatic reaction | Burge *et al.* (1985) |
| | | 4.8 mg/m$^3$ | 30 min | Dual immediate and late asthmatic reaction | |
| | | 31 mg/m$^3$ | 7 min | Irritant asthmatic reaction | |
| | | 4.8 mg/m$^3$ | 30 min | No reaction in unsensitized asthmatics | |
| Women | Inhalation | 5 ppm | 15 min | Late asthmatic reaction | Hendrick & Lane (1975, 1977); Hendrick *et al.* (1982) |
| | | 3 ppm | 5 min | Late asthmatic reaction No reaction in controls | |
| Unspecified | Inhalation | | | Immediate and late reactions in 2 workers | Popa *et al.* (1969) [few details] |
| Men and women | Inhalation | 1.2 mg/m$^3$ | 30 min | 1 worker, early response | Nordman *et al.* (1985) |
| | | 2.5 mg/m$^3$ | 30 min | 11 workers, 6 late response 12/230 exposed symptomatic workers + specific challenge to formaldehyde negative in 218, 71 with NSBR | |
| Men | Inhalation (cutting and preparing brain specimens) | | 2 h | Acute pneumonitis; breath smelled of formaldehyde; resolved | Porter (1975) |

NSBR, non-specific bronchial hyper-reactivity

logist had no reaction following a similar 60-min exposure to 5 ppm [6 mg/m$^3$] formaldehyde. A later study (Hendrick *et al*., 1982) repeated the original exposures, which were reported to be 5 ppm. A second report (Hendrick & Lane, 1977) mentioned a second case who reacted to exposure to 3 ppm [3.6 mg/m$^3$] formaldehyde for 5 min.

Burge *et al.* (1985) reported the results of challenge tests in 15 workers who were exposed to formaldehyde. Three had late asthmatic reactions that suggested sensitization; one reacted following exposure to 2.3 mg/m$^3$ and two after exposure to 4.8 mg/m$^3$. Control asthmatics had no asthma attack provoked by exposures to 4.8 mg/m$^3$; one asthmatic exposed to a sheep dip that contained formaldehyde had an irritant reaction following a 7-min exposure to 31 mg/m$^3$.

Nordman *et al.* (1985) reported the results of inhalation challenges in 230 workers who were investigated at the Finnish Institute of Occupational Medicine. One worker reacted to 1.2 mg/m$^3$ formaldehyde and 11 reacted to 2.5 mg/m$^3$ formaldehyde. No reaction was observed at 2.5 µg/m$^3$ among the remaining 218 workers, 71 of whom had non-specific hyper-responsiveness.

Kim *et al.* (2001) reported on a worker who made crease-resistant trousers and who had a late asthmatic reaction 5 h after exposure to 0.5 ppm [0.6 mg/m$^3$], but not to 0.01 ppm [0.01 mg/m$^3$] formaldehyde (20-min exposures). His IgE to formaldehyde conjugates was negative.

One patient developed anaphylaxis during dialysis with a dialyser that had been sterilized with formaldehyde and contained 5–10 µg/mL residual formaldehyde. She had previously been sensitized to formaldehyde on the skin through contact dermatitis. IgE antibodies to formaldehyde/human serum albumin were strongly positive (Maurice *et al.* (1986).

One case of toxic pneumonitis following a 2-h exposure to a concentration of formaldehyde that was sufficient to be smelled on the breath has been reported (Porter, 1975).

### (*e*)    *Oral poisoning*

Two reports have been made of three patients who were poisoned following ingestion of formaldehyde solution. All three patients died (Eells *et al.*, 1981; Köppel *et al.*, 1990). Two patients had ingested unknown amounts of formalin that had not been contaminated with methanol. Both developed acidosis with raised plasma formic acid levels (6.09 and 4.57 mmol/L) and additional lactic acidosis. Both survived the initial necrosis of the gut mucosa and renal failure, but died from late acute respiratory distress syndrome and cardiac failure at 3 weeks and 8 weeks after ingestion, respectively (Köppel *et al.*, 1990). The third patient had ingested 120 mL (37% w/v) formaldehyde that contained 12.5% v/v methanol. Initial blood levels 30 min after ingestion were 0.48 µg/dL formaldehyde, 44 mg/dL formate and 42 mg/dL methanol. She died after 28 h (Eells *et al.*, 1981).

4.2.2    *Experimental systems*

(*a*)    *In-vitro studies*

(i)    *Cytotoxicity*

The toxicity of formaldehyde was assessed in cultured human bronchial epithelial cells under defined serum- and thiol-free exposure conditions (Grafström *et al.,* 1996). Results obtained from studies of 1-h exposures showed that 0.2 mM and 0.6 mM formaldehyde inhibited cell growth by 50% as measured by loss of clonal growth rate and colony-forming efficiency, respectively. Membrane integrity, i.e. exclusion of trypan blue and cellular uptake of neutral red, an energy-dependent lysosomal accumulation of the dye, was decreased by 50% at concentrations of 2 mM and 6 mM formaldehyde, respectively. Inhibition of growth was also associated with significant decreases in GSH, which occurred without concomitant formation of oxidized GSH and with no alteration of the levels of protein thiols. This result indicated that exposure to formaldehyde was associated with the expected formation of thiohemiacetal, but not with overt oxidative stress as assessed by thiol status, in bronchial cells. Extensive loss of intracellular GSH coincided with loss of membrane integrity, which implies that plasma membrane leakage may have contributed to the effect. Moreover, active re-reduction of oxidized GSH to GSH by GSH reductase could potentially have masked an oxidant effect. Formaldehyde-dependent decreases in thiols provide a mechanism for formaldehyde-induced inhibition of growth, since minor decreases in GSH levels are known to inhibit cell growth efficiently (Atzori *et al.*, 1989, 1994). The steady-state concentration of intracellular $Ca^{2+}$ was increased by 50% within a few minutes after treatment with 0.5 mM formaldehyde, and transient increases were recorded at lower concentrations (Grafström *et al.*, 1996). The toxicity of formaldehyde to keratinocytes is manifested as aberrant induction of terminal differentiation, i.e. increases in involucrin expression and formation of cross-linked envelopes. This cellular response is probably linked to the noted increases in cellular $Ca^{2+}$, which activates transglutaminase-dependent cross-linking of various proteins, including involucrin, into the cross-linked envelope (Rice & Green, 1979). Various types of genetic damage and mutation are caused by formaldehyde at levels as low as 0.1 mM (see Section 4.4), and may also underlie some of the cytotoxic actions of formaldehyde. Inhibition of DNA repair was shown in bronchial cells following treatment with 0.1–0.3 mM formaldehyde, which implies that inhibition of enzyme function might be an essential aspect of the toxicity of formaldehyde. In this respect, enzymes that carry a thiol moiety in their active site may be particularly sensitive (Grafström *et al.*, 1996).

The toxicity of formaldehyde was evaluated in isolated rat hepatocytes (Teng *et al*., 2001); exposure to 4 mM for 2 h caused 50% cell lysis. Toxicity was associated with a dose-dependent loss of GSH and mitochondrial membrane potential and, moreover, was associated with inhibition of mitochondrial respiration and the formation of reactive oxygen species. Higher doses were associated with lipid peroxidation. Depletion of GSH and inhibition of ADH and ALDH activities increased the toxicity of formaldehyde, whereas anti-oxidants such as butylated hydroxytoluene and iron chelators such as desferoxamine

protected against toxicity. Prevention of toxicity by cyclosporine or carnitine, agents that prevent the opening of the mitochondrial transition pore, provided evidence that formaldehyde targets mitochondria.

### (ii)    *Proliferation and apoptosis*

The toxicity of formaldehyde and the influences of exogenous and endogenous thiols were studied in cultured human oral fibroblasts and epithelial cells (Nilsson *et al*., 1998). The presence of serum and cysteine counteracted the toxicity of formaldehyde, and lower levels of intracellular thiols, including GSH, in fibroblasts (relative to epithelial cells) were associated with greater toxicity. The results emphasize the high thiol-reactivity of formaldehyde and the central role of cellular thiols in the scavenging of formaldehyde. The toxicity of formaldehyde was compared in human dental pulp fibroblasts, buccal epithelial cells and HeLa cervical carcinoma cells (Lovschall *et al*., 2002). In assessments of proliferation (bromodeoxyuridine incorporation), methylthiazole tetrazolium conversion and neutral red uptake, both of the normal cell types were shown to be more sensitive than the carcinoma cells to the toxicity of formaldehyde. Formaldehyde, applied at concentrations of 0.1–10 mM to HT-29 colon carcinoma and normal endothelial cell cultures, stimulated proliferation at 0.1 mM, inhibited proliferation and induced apoptosis at 1 mM and induced cell lysis at 10 mM (Tyihák *et al*., 2001). The authors concluded that formaldehyde may either stimulate or inhibit proliferation or induce overt toxicity, depending on the dose. Apoptosis was also induced in rat thymocytes by concentrations of 0.1 mM formaldehyde or more after a 24-h exposure (Nakao *et al*., 2003). The proliferation-enhancing effects of formaldehyde are supported by studies of gene expression in mouse fibroblast C3H/10T1/2 cells (Parfett, 2003). Formaldehyde at 0.05–0.1 mM, concentrations that are known to induce cell transformation in this system, increased the transcription of proliferin, a response that is also shared by other transformation-promoting agents.

Formaldehyde at doses of 1 ng/mL to 1 µg/mL induced expression of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in human microvascular endothelial cells of the nasal mucosa (Kim *et al*., 2002). Exposures to formaldehyde were also associated with increased adhesiveness of the endothelial cells to eosinophils. The authors concluded that the noted effects and changes in gene expression of intercellular and vascular cell adhesion molecules might underlie the irritant effects of formaldehyde in the nasal mucosa.

### (iii)    *Effect on the mucociliary apparatus of the respiratory mucosa*

In an ex-vivo study, dose-dependent changes in the mucociliary apparatus of frog respiratory mucosa during exposure to formaldehyde in aqueous solutions were examined. Frog palates (10 per group) were removed and were refridgerated for 2 days to allow the mucous to clear. The palates were then immersed in Ringer solution alone or with 1.25, 2.5 or 5.0 ppm formaldehyde solution. The frequency of ciliary beat, as a measure of the fluctuation of light patterns during the ciliary wave over time, and mucociliary clearance, as a function of the time it took a mucous plug to travel 6 mm of palate,

were quantitated. Measurements were taken at time 0, before immersion in formaldehyde solution, and then every 15 min for a total of four measurements over 60 min of exposure at 20 °C and 100% humidity. The later time-points were all compared with their respective 0-time measurement to give a percentage of the baseline measurement. A dose- and time-dependent decrease was observed in both mucociliary clearance and frequency of ciliary beat (Flo-Neyret *et al.*, 2001).

(b)    *In-vivo studies*

(i)    *Acute effects*

**Irritation**

A quantitative measure of sensory irritation in rodents is provided by the reflex decrease in respiratory rate of mice or rats that is 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, and elicits a 50% decrease in respiratory frequency in B6C3F$_1$ mice at 4.9 ppm [6.0 mg/m$^3$] and in Fischer 344 rats at 31.7 ppm [38.7 mg/m$^3$] (Chang *et al.*, 1981). Swiss-Webster mice exposed for 5 days (6 h per day) to formaldehyde at a concentration that elicits a 50% decrease in respiratory frequency (3.1 ppm [3.8 mg/m$^3$]) 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, which results 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 in 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 4 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/F$_1$ mice and CD rats (Jaeger & Gearhart, 1982).

Rats exposed to 28 ppm [34.2 mg/m$^3$] formaldehyde for 4 days developed tolerance to its sensory irritancy, but those exposed to 15 ppm [18.3 mg/m$^3$] for 1, 4 or 10 days did not (Chang & Barrow, 1984).

Sensory irritation to formaldehyde, acrolein and acetaldehyde vapours and their mixture was studied in groups of male Wistar rats weighing 240–300 g (four per group) that were exposed to concentrations of the aldehyde vapours up to a level that decreased respiratory frequency by 50%. Formaldehyde vapours were produced by thermal depolymerization of paraformaldehyde in water and evaporation into the in-flow airstream. The maximal decrease in breathing frequency was observed within 3 min of exposure; desensitization occurred within a few minutes after maximal decrease in breathing frequency and only partial recovery was achieved within 10 min after exposure. The authors proposed that the decreased breathing frequency within the first few minutes of exposure is due to trigeminal nerve stimulation from the irritant effect of formaldehyde. The level of exposure to formaldehyde that resulted in a 50% respiratory depression was 10 ppm

**Figure 4. Time–response curves for respiratory rate, tidal and minute volume from naive and formaldehyde-pretreated mice and rats (6 ppm, 6 h/day, 4 days) during a 6-h exposure to 6 ppm formaldehyde**
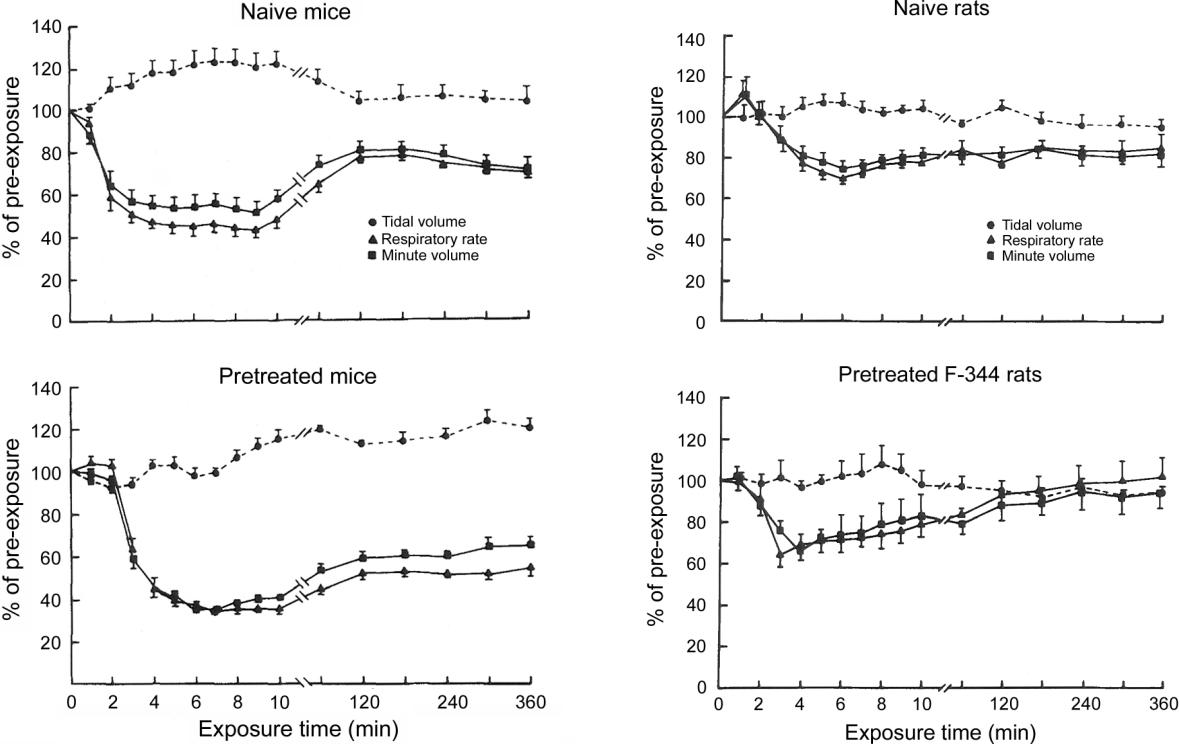


Adapted from Chang *et al.* (1983)

Data shown are $\bar{x} \pm$ SE for each time point; $n = 6$ for each group

[12.3 mg/m$^3$]. Since this was a study of the mixture, the authors also found that the reduction in breathing frequency after exposure to the mixture was always greater than after exposure to the same concentration of any of the components alone (Cassee *et al.*, 1996a).

The retinal toxicity of a single dose of formaldehyde, methanol and formate was investigated in male albino rabbits weighing 2.1–2.3 kg (four per group) by injection into the vitreous cavity of 100 µL of a buffered (pH 7.4) phosphate-saline solution that contained 1% methanol, 0.1% or 1.0% formaldehyde or 1% formate. The final vitreous concentrations were 700 µg/mL methanol, 70 µg/mL formaldehyde, 700 µg/mL formaldehyde and 700 µg/mL formate. The eyeballs were examined with a biomicroscope and ophthalmoscope before treatment and 1, 2, 7, 14 and 30 days after treatment. After 30 days, the rabbits were euthanized and the eyeballs were fixed in formalin for microscopic examination of the retina, choroid, sclera, optic disc and optic nerve. No lesions were observed in the methanol- or formate-treated eyes at any time-point. The eyes treated with formaldehyde had ophthalmoscopic alterations at all time-points and at both doses; the higher dose induced more severe alterations including subcapsular cataract, retinal vessel dilatation and juxtapapillary retinal haemorrhages. Histologically, the eyes treated with 0.1% formaldehyde had disorganization of the ganglion cell and outer nuclear layers of the retina; these symptoms were more severe in eyes treated with 1.0% formaldehyde. The optic nerves had vacuolization after treatment with either dose of formaldehyde (Hayasaka *et al.*, 2001).

**Pulmonary hyper-reactivity**

Formaldehyde induced pulmonary hyper-reactivity in guinea-pigs: exposure to 0.3 ppm [0.37 mg/m$^3$] for 8 h caused transient bronchoconstriction and hyper-reactivity to infused acetylcholine; exposure to higher concentrations (> 9 ppm [> 11 mg/m$^3$]) for 2 h induced bronchoconstriction. No evidence of tracheal epithelial damage was observed after exposure to 3.4 ppm [4.2 mg/m$^3$] for 8 h. However, the mechanism by which these effects occur is unknown (Swiecichowski *et al.*, 1993).

The effects of formaldehyde (vaporized formalin) on pulmonary flow were determined in cynomolgus monkeys that were tranquilized before exposure and received an endotracheal tube transorally. Pulmonary flow resistance was increased after exposure to formaldehyde at a concentration of 2.5 ppm [3.0 mg/m$^3$] for 2, 5 and 10 min. Narrowing of the airways by formaldehyde 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.]

Male Sprague-Dawley rats, 6 weeks of age, were exposed to formaldehyde (10 ppm [12.2 mg/m$^3$]), ozone (0.6 ppm [1 mg/m$^3$]) (with coefficients of variation of less than 12% and 5%, respectively) or a combination of the two during exercise on a treadmill that was modified to deliver a stream of control air or air that contained formaldehyde. The rats were exercised at a moderately fast-walking gait of 15 m/min on a 20% gradient for 3 h, which raised metabolic gas exchange over the resting rate by a factor of at least two. Resting exposure was conducted in a nose-only inhalation tube. Histology, including labelling indices, was examined quantitatively for the nose and lung. Formaldehyde increased labelling in the

transitional epithelium in the nose after individual or mixed exposure at rest or after exercise but ozone alone did not. Formaldehyde and ozone after exercice either individually or as a mixture produced injury in the trachea; the mixture caused greater (approximately additive) injury than either of the chemicals alone. The pulmonary parenchyma was unaffected by exposure to formaldehyde. Functional changes included decreased breathing frequency during exposure to formaldehyde; the response to the mixture was lower. Tidal volume decreased after treatment with ozone or formaldehyde but was increased after exposure to the mixture. Formaldehyde produced slow and shallow breathing which resulted in depressed minute ventilation (Mautz, 2003).

### Sensitizing effect and inflammatory response

In order to investigate the induction of sensitization to formaldehyde, undiluted formalin was painted on shaven and epilated dorsal sites of guinea-pigs; a second application was administered 2 days later at naive sites, to give a total dose of 74 mg/animal. Other animals received diluted formalin at doses of 0.012–9.3 mg/animal. All animals that received 74 mg formalin developed skin sensitivity when tested 7 days after exposure. A significant dose–response relationship was observed for the degree of sensitization and for the percentage of animals that were sensitized; however, pulmonary sensitization was not induced when formaldehyde was administered dermally, by injection or by inhalation, and no cytophilic antibodies were detected in the blood (Lee *et al.*, 1984).

In the guinea-pig maximization test, 10 guinea-pigs (five per exposure group) received six intradermal injections of saline or 0.25% [2.5 mg/mL] formaldehyde solution followed 6–8 days later by an occlusive dressing of a patch soaked in 10% [100 mg/mL] formaldehyde for 48 h. After an additional 12–14 days, another occlusive dressing was applied for 24 h; 24 h after removal, the size of the area of the erythema was measured. A similar study was conducted in guinea-pigs but only occlusive dressings were used. Both studies resulted in a positive response (Hilton *et al.*, 1996).

The local lymph node assay was conducted in BALB/c mice that received daily applications of 25 µL of 10%, 25% or 50% w/v solutions of formaldehyde on the pinna of both ears for 3 consecutive days. Five days after the initiation of exposure, all mice were injected with tritiated methyl thymidine and were killed 5 h later. The lymph nodes adjacent to the ear were removed and labelled cells were counted to measure the rate of cell proliferation. Formalin induced a strong proliferative response that was considered to be positive for a contact allergen (Hilton *et al.*, 1996).

The mouse IgE test is thought to identify allergens that have the potential to cause sensitivity in the respiratory tract by stimulating a significant increase in serum IgE concentration. This test was conducted in groups of six BALB/c mice that received 50 µL of a 10%, 25% or 50% formalin solution (37% formaldehyde dissolved in dimethylformamide) on an occlusive dressing applied to the shaved flank. Seven days later, 25 µL of the solution of formaldehyde at half the concentration used previously was applied to the dorsum of both ears. Fourteen days after the initial exposure, the mice were exsanguinated and blood was

collected for analysis of IgE. There was no significant change in levels of circulating IgE after treatment with formaldehyde (Hilton *et al.*, 1996).

Production of the cytokines interferon-γ (IFN-γ) and interleukin (IL)-10 was measured in draining lymph nodes of the skin of the flanks and the ears of 10 BALB/c mice that had received skin applications of 10%, 25% or 50% formalin solutions (37% formaldehyde in dimethylformamide) on the shaved flank twice a day for 5 days followed by 3 days on the dorsum of the ears. Thirteen days after the initiation of exposure, draining auricular lymph nodes were removed. Lymphocytes were isolated and cultured for up to 120 h, and the supernatant was collected and analysed for IFN-γ and IL-10. The levels of IFN-γ were significantly increased after all concentrations of formaldehyde but not those of IL-10. The authors suggested that formaldehyde causes a contact sensitization reaction in the skin (mediated by Th1-type lymphocytes that secrete IFN-γ) but not sensitization of the respiratory tract (Hilton *et al.*, 1996).

Eighteen 8-week-old male BN/Crj and Fischer 344/DuCrj rats were exposed to an aerosol of 1% formaldehyde solution (equivalent to 15–20 ppm) for 3 h per day for 5 days in a whole-body inhalation exposure system; another nine animals were exposed to an aerosol of ion-exchanged water only. After death by exsanguination, the nose was examined histologically or the nasal epithelium was removed by scraping and used to isolate RNA. Measurements of cDNA were made by reverse-transcriptase polymerase chain reaction (RT-PCR) for quantitative real-time analysis of *IFN-γ*, *IL-2*, *IL-4* and *IL-5* mRNA levels. All samples were examined for levels of glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*) mRNA and quantities of gene were presented as the ratio to *GAPDH*. The histological lesions were consistent with those reported previously and were of greater severity in Fischer 344 than in BN rats (Ohtsuka *et al.*, 1997). Compared with *GAPDH*, *IFN-γ* and *IL-2* (Th1-related cytokines involved in non-allergic inflammation) were expressed at significantly lower levels in BN rats treated with formaldehyde. None of the other mRNA levels were statistically significant, although the expression of *IL-4* and *IL-5* (Th2-related cytokines) in BN rats and that of *IL-2* and *IL-5* in Fischer 344 rats were lower than the levels observed in controls (Ohtsuka *et al*., 2003).

**Cytotoxicity and cell proliferation in the respiratory tract**

The acute and subacute effects of formaldehyde in experimental animals are summarized in Table 33. A critical issue for the mechanism of carcinogenesis is whether low concentrations of formaldehyde increase or decrease 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 per day for 3 days) has been reported to induce a small, transient increase in nasal epithelial cell turnover in Wistar rats (Zwart *et al.*, 1988), but this statistically significant increase 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 per day for 1, 4 or 9 days) (Monticello *et al.*, 1991) or to 0.5 or 2 ppm [0.6 or 2.4 mg/m$^3$] (6 h per day for 3 days) (Swenberg *et al.*, 1983). Low concentrations of formaldehyde (0.5 or 2 ppm; 6 h per day for 1, 2, 4, 9 or 14 days) also did not

**Table 33. Cytotoxicity and cell proliferation induced by acute and subacute exposure to formaldehyde**

| Strain, species, sex | Exposure | Effects | Reference |
|---|---|---|---|
| Fischer 344 rat, male; B6C3F$_1$ 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; B6C3F$_1$ 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 those of mice. | Chang *et al.* (1983) |
| Fischer 344 rat, male | 3.7 mg/m$^3$ × 12 h/day, 7.4 mg/m$^3$ × 6 h/day, 14.8 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; less proliferation 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.* (1986b) |
| 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.* (1986c) |
| 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, non-keratinized 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); 12.3 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 | Significant, transient increase in cell turnover at 1.2 and 3.7 mg/m$^3$ but not confirmed in later studies at concentration of 1.2 ppm (Reuzel *et al.*, 1990) | Zwart *et al.* (1988) |

**Table 33 (contd)**

| Strain, species, sex | 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 in 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, 5 days/week, 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) |
| Wistar rat, male | 0, 4.43 mg/m$^3$; 8 h followed by 4 h no exposure for 6 consecutive 12-h cycles Also investigated effect of simultaneous exposure to 0.4 ppm ozone. | 4.43 mg/m$^3$ resulted in increased GSH peroxidase in nasal respiratory tissue and increased PCNA expression by immunohistochemistry. | Cassee & Feron (1994) |
| Wistar rat, male | 0, 1.23, 3.94, 7.87 mg/m$^3$, 6 h/day, 1 or 3 days Also investigated effect of simultaneous exposure to acetaldehyde (750, 1500 ppm) and acrolein (0.25, 0.67 ppm). | The mixture resulted in more extensive and severe histopathology of the nose than the individual exposure. | Cassee *et al.* (1996b) |
| BN/Crj rat, male; Fischer 344/DuCrj rat, male | 0 or 18.45–24.6 mg/m$^3$ (estimate), 3 h/day, 5 days | Nasal respiratory degeneration and necrosis more severe in Fischer 344 rats | Ohtsuka *et al.* (1997) |

*C*, concentration; *t*, time; PCNA, proliferating cell nuclear antigen

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 per day for 1 or 4 days) (Monteiro-Riviere & Popp, 1986).

Wistar rats exposed to 3 ppm [3.7 mg/m$^3$] (6 h per day for 3 days (Zwart *et al.*, 1988) or 22 h per day for 3 days (Reuzel *et al.*, 1990)) had a transient increase in cell replication. Higher concentrations of formaldehyde ($\geq$ 6 ppm [7.3 mg/m$^3$]) induced erosion, epithelial hyperplasia, squamous metaplasia and inflammation in a site-specific manner in the nasal mucosa of Wistar rats (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 per day for 1, 4 or 9 days, or 6 h per day on 5 days per week for 6 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 that at 6 ppm (Monteiro-Riviere & Popp, 1986). Rhesus monkeys exposed to 6 ppm (6 h per day for 5 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 3 or 10 days (Swenberg *et al.*, 1983) or 4 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).

Ten 8-week-old male BN/Crj or Fischer 344/DuCrj rats were exposed to 100 L/min (2 mg 1% formaldehyde solution/L air, equivalent to 15–20 ppm) aerosol or water for 3 h per day on 5 days per week for 2 weeks. Clinical signs were monitored and light and scanning electron microscopy were performed. Both strains of rat had abnormal respiration, nasal discharge and sneezing following treatment with formaldehyde; the Fischer 344 rats had a more severe response. Lesions were present only in the nose and trachea from Fischer 344 rats and nose from BN rats; again, Fischer 344 rats were more severely affected. The typical lesions of squamous metaplasia, respiratory hyperplasia and degeneration and necrosis in the nose that were described with Fischer 344 rats affected all sections of the nose examined, whereas BN rats only had squamous metaplasia in the ventral portion of level II. Epithelial hyperplasia was present in the trachea of Fischer 344 rats. By scanning electron microscopy, squamous epithelial-like changes were seen in the anterior nose after treatment with formaldehyde in both rat strains. BN rats were less sensitive to exposure to formaldehyde than Fischer 344 rats (Ohtsuka *et al*., 1997).

**Co-exposure with other agents**

*Ozone*

The effects of simultaneous exposure to formaldehyde and ozone were investigated in Wistar rats exposed to 0.3, 1 or 3 ppm [0.37, 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 per day for 3 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 (non-irritating) concentrations of these irritants but a 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).

The pathophysiology of nasal alterations was investigated in 80 8-week-old male Wistar rats (20 per group) after nose-only exposure to formaldehyde or ozone, or their mixture for 8 h followed by 4 h of no exposure for six consecutive 12-h cycles. The formaldehyde was generated from paraformaldehyde by thermal depolymerization in water and evaporation into the air stream at a concentration of 3.6 ± 0.1 ppm or 3.5 ± 0.1 ppm [4.3 mg/m$^3$] in the individual or ozone mixture exposure groups, respectively (concentration of ozone, 0.4 ppm [0.8 mg/m$^3$]). After euthanasia, the respiratory portion of the nasal epithelium was collected on ice from a subset of the rats and another subset [numbers not specified] was used for microscopic examination of the nose with haematoxylin and eosin, periodic acid Schiff and proliferating cell nuclear antigen immunohistochemistry. The nasal respiratory epithelial samples were pooled (six rats), homogenized and centrifuged for extraction of the supernatant. The enzyme activities of GST, GSH peroxidase, glucose-6-phosphate dehydrogenase, GSH reductase, ADH and FDH were measured. In addition, GSH and protein levels were quantified. All animals lost weight during the exposure period and weight loss was significantly greater in the treated animals compared with controls. Ozone alone resulted in degenerative changes in the respiratory epithelium but formaldehyde alone or in combination with ozone induced necrosis in the respiratory epithelium. Rhinitis was induced by all three treatments but was more severe in rats treated with formaldehyde than in those treated with ozone and was most severe after exposure to the mixture. Cell proliferation was increased after all treatments compared with controls and a uniformly greater increase was observed in rats exposed to formaldehyde combined with ozone compared with those exposed to ozone alone. Rats treated with formaldehyde alone had proliferative rates in most

of the measured areas equivalent to those of the ozone–formaldehyde-exposed rats. However, rats that received formaldehyde only had greater proliferation indices in the septum and lateral wall of the posterior section than rats exposed to the mixture. Only GSH peroxidase activity was increased after exposure to formaldehyde and only GST activity was decreased after exposure to the mixture. Ozone alone did not alter any enzyme activities significantly. The authors suggested that there appeared to be no major role for GSH or GSH-dependent enzymes in the pathogenesis of toxicity induced by formaldehyde and/or ozone (Cassee & Feron, 1994).

*Other aldehydes*

The histological and biochemical effects of exposure to formaldehyde, acetaldehyde and acrolein individually or as mixtures were examined in rats. Groups of male Wistar rats, 8 weeks of age, were exposed to formaldehyde at 0, 1.0, 3.2 or 6.4 ppm [0, 1.23, 3.94 or 7.87 mg/m$^3$] for 6 h per day for 1 or 3 days in nose-only inhalation chambers. Additional rats were exposed to mixtures of 1.0 ppm formaldehyde and 0.25 ppm acrolein, 1.0 ppm formaldehyde, 0.25 ppm acrolein and 750 ppm acetaldehyde, or 3.2 ppm formaldehyde, 0.67 ppm acrolein and 1500 ppm acetaldehyde. After euthanasia, five or six treated animals per exposure group and a total of 19 control animals from all substudies were used for histology (haematoxylin and eosin and proliferating cell nuclear antigen immunohisto-chemistry) and nine animals from each exposure group were used for biochemical studies. Respiratory and olfactory epithelium were removed separately and homogenized on ice for extraction of the cytosolic fraction and analysis of GSH peroxidase, GST, GSH reductase, ADH, FDH and total amount of protein and non-protein sulfhydryl groups. No histological or biochemical alterations were observed after 1 day of exposure to formaldehyde at any concentration. Only acrolein or the high-dose mixture of all three chemicals induced a biochemical change after 1 day (a decrease in GSH reductase activity). Acetaldyde induced a dose-dependent increase in non-protein sulfhydryls. After 3 days of exposure to 1.0 ppm formaldehyde, no histological alterations were present. Only the group exposed to 3.2 ppm formaldehyde had histopathology that was characterized by degeneration and necrosis of the respiratory epithelium with basal-cell hyperplasia. The lesions were most pronounced along the lateral walls of the naso- and maxilloturbinates. An associated significant increase in cell proliferation was also observed after exposure to 3.2 ppm formaldehyde for 3 days. After 3 days of exposure to 3.2 or 6.4 ppm formaldehyde, only GSH peroxidase activity had increased statistically significantly. Three days of exposure to 1.4 ppm acrolein resulted in a decrease in GST and ADH and an increase in FDH activities while the groups of rats exposed to the mixtures of all three compounds had increased GST and GSH peroxi-dase activities. Histological alterations of the nasal epithelium were more severe after exposure to the mixture than after exposure to any of the components alone at comparable concentrations and duration of exposure. The distribution of the lesions induced by formal-dehyde was different from that produced by acetaldehyde or acrolein, in that lesions pro-duced by formaldehyde were concentrated in the respiratory epithelium (Cassee *et al.*, 1996b).

**Enzyme induction**

No increase in the activities of FDH or ALDH was seen in the nasal mucosa of Fischer 344 rats exposed to 15 ppm [18.3 mg/m$^3$] formaldehyde (6 h per day on 5 days per week for 2 weeks) (Casanova-Schmitz *et al.*, 1984a). A large increase in the concentration of rat pulmonary CYP 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 per day for 4 days) (Dallas *et al.*, 1989), although Dinsdale *et al.* (1993) could not confirm these results in the same strain of rat and found no increase in pulmonary concentration of CYP after exposure to 10 ppm [12.3 mg/m$^3$] formaldehyde (6 h per day for 4 days).

The relative contribution of three isoforms of ADH to ethanol, formaldehyde and retinoic acid acute toxicity was examined in knockout mice that had induced deletions of *Adh1*, *Adh3* or *Adh4* genes, which make the enzymes non-functional. The comparison with formaldehyde was based on the LD$_{50}$ after intraperitoneal injection of a 10% forma-lin solution that resulted in a dose range of 0.09–0.22 g/kg bw formaldehyde. A lethal dose to wild-type mice resulted in death within 90 min. It was assumed in the interpretation of these studies that formaldehyde and not a metabolite was the ultimate toxicant. Mice that had *Adh3* knocked out required significantly lower levels of formaldehyde (0.135 g/kg) than the wild-type control (0.2 g/kg) to achieve an LD$_{50}$ whereas there was no difference between wild-type and mice that had *Adh1* and *Adh4* knocked out. These studies showed that *Adh3* is responsible for the clearance of formaldehyde but does not play a role in the clearance of ethanol or retinoic acid. *Adh1* and *Adh4* demonstrate overlapping functions in the metabolism of ethanol and retinol *in vivo*. *Adh3* is conserved across most levels of biological organization including all mammalian species, invertebrates and plants (Deltour *et al.*, 1999).

**Other effects**

The nephrotoxicity of formaldehyde after intravascular injection was studied in male Sprague-Dawley rats (eight animals per group) that weighed 200 g. The rats were injected through the tail vein with 7.6 or 38 μM of a saline solution of formaldehyde or normal saline. Blood samples were taken for determination of blood urea and creatinine levels 24 and 48 h after injection of the test solution. Urine was also collected 24 h after injection and analysed for lactate dehydrogenase (LDH) and protein. All rats were killed 48 h after the single injection and the kidneys were removed for histological examination. No histo-logical alterations were present in the kidney. No statistical change in urinary protein or LDH levels nor in blood creatinine was observed. A small but statistically significant increase in blood urea was reported at 24 h (5.23 ± 0.3 versus 4.13 ± 0.5 for control [units not reported]) after treatment which returned to normal levels at 48 h. These data suggested that renal toxicity does not occur after acute intravascular exposure to formaldehyde (Boj *et al.*, 2003).

Twenty-one male (weighing 250–280 g) and 19 female (weighing 180–200 g) 16-week-old Wistar rats were trained over 14 days to find food in a maze and were then tested in the maze after exposure to formaldehyde. The number of mistakes and the length of time to find

the food were counted daily for 11 days as a baseline. The animals were exposed to aqueous formaldehyde solutions of either 0.25% (equivalent to $3.06 \pm 0.77$ mg/m$^3$; 2.6 ppm) or 0.7% (equivalent to $5.55 \pm 1.27$ mg/m$^3$; 4.6 ppm) for 10 min per day on 7 days per week for 90 days. Every 7th day, the animals were tested in the maze prior to exposure. After 90 days of exposure, the animals were then allowed a 30-day recovery and were tested in the maze every 10th day. At the end of the study, the animals were killed and the liver, trachea, lungs, kidneys, heart, spleen, pancreas, testicles, brain and spinal cord were collected and fixed in formalin. Both formaldehyde-exposed groups made more mistakes and took longer to complete the maze than the controls but no difference was observed between the exposed groups. None of the groups differed from one another after the recovery period. There were no treatment-related histological lesions (Pitten *et al.*, 2000). [There is no evidence that the changes seen in this study are due to formaldehyde-induced neurotoxicity, and could have just as easily have been from loss of olfactory capacity and visual difficulties from irritant effects to the cornea which would have improved after the treatment was stopped.]

Lewis rats were exposed to formaldehyde vapours and placed in a water maze to test the effect of formaldehyde on learning. A total of 120 male and female LEW.1K rats, 110–130 days of age, were separated into four groups and exposed to distilled water or $0.1 \pm 0.02$, $0.5 \pm 0.1$, or $5.4 \pm 0.65$ ppm [0.12 mg/m$^3$, 0.62 mg/m$^3$ or 6.64 mg/m$^3$] volatilized formaldehyde for 2 h per day for 10 days. Two hours after exposure, the rats were subjected to the water maze test. The length of time taken to complete the maze and the number of errors while attempting this were measured. At the conclusion of the study, the animals were killed and the lungs, heart, thymus, kidneys, liver, pancreas, skeletal muscle and spleen were examined microscopically. All rats exposed to formaldehyde made more errors in completing the maze, but no difference was observed between exposure groups or sexes. After 10 days, only the 0.5- and 5.4-ppm groups took longer to complete the water maze; no difference was observed between sexes. No histological lesions were found in the tissues examined. The authors suggested that formaldehyde vapours had a central effect on learning and memory. However, none of the tissues sampled were target organs for formaldehyde toxicity in the rat except at very high and prolonged exposure concentrations. [The nose was not examined in this study. Formaldehyde is a surface irritant which would cause degeneration and necrosis of the olfactory epithelium as well as the surface epithelium lining the cornea. The complications of blurry vision and loss of olfactory cues was not controlled for in this study, which suggests that an effect on the central nervous system may not have resulted in the treatment-related response] (Malek *et al.*, 2003).

Forty-two male Wistar rats (weighing approximately 250 g) were divided into six groups (seven rats per group) and exposed by inhalation to 0, 6.1 mg/m$^3$ or 12.2 mg/m$^3$ formaldehyde for 8 h per day on 5 days per week for subacute (4 weeks) or subchronic (13 weeks) periods. At the end of the exposure period, the animals were killed and the brains were removed for analysis of zinc, copper and iron levels (mg metal/kg parietal cortex). Both zinc and copper increased in concentration with increasing dose whereas iron decreased in concentration. The increase in copper concentration and decrease in iron concentration were both time-dependent. Exposure to formaldehyde altered the trace

element level of copper, zinc and iron in the brain. The greatest change was a 54% increase in levels of zinc after 4 weeks of exposure to the high dose which fell to a 33% increase over controls after 13 weeks (Özen *et al.*, 2003).

Forty male albino Charles Foster rats, weighing 147–171 g, were given daily intraperitoneal injections of 0, 5, 10 or 15 mg/kg bw formaldehyde in saline for 30 days. On day 31, the animals were anaesthetized for blood collection then killed and the thyroid glands were collected, weighed and processed for histology. Thyroid weights were significantly decreased after treatment with 10 and 15 mg/kg per day and histological changes of follicular degeneration, atrophy and epithelial size were observed. Triiodothyronine and thyroxine were significantly decreased and thyroid-stimulating hormone was increased after doses of 10 and 15 mg/kg per day. After treatment with 5 mg/kg per day, triiodothyronine was decreased and thyroid-stimulating hormone was increased but thyroxine was unchanged and the thyroid glands did not differ histologically from those of controls (Patel *et al.*, 2003).

Levels of serum corticosterone were examined in Sprague-Dawley rats (weighing 260–280 g) exposed by inhalation to 0.7 or 2.4 ppm [0.86 or 2.95 mg/m$^3$] formaldehyde for 20 or 60 min per day on 5 days per week for 2 or 4 weeks. Treatment had no effect after short-term exposure; however, rats exposed to 0.7 ppm for 4 weeks had increased baseline serum corticosterone. Rats treated with 2.4 ppm formaldehyde for 2 or 4 weeks had increased levels of serum corticosterone after a formaldehyde challenge (Sorg *et al.*, 2001).

### (ii)    *Chronic effects*

**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 34. No increase in cell turnover or DNA synthesis was found in the nasal mucosa after subchronic or chronic exposure to concentrations of ≤ 2 ppm [≤ 2.4 mg/m$^3$] formaldehyde (Rusch *et al.*, 1983; Maronpot *et al.*, 1986; Zwart *et al.*, 1988; Monticello *et al.*, 1993; Casanova *et al.*, 1994). Small, site-specific increases in the rate of cell turnover were noted at 3 ppm [3.7 mg/m$^3$] (6 h per day on 5 days per week for 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 per day on 5 days per week for 12 weeks) in Fischer 344 rats (Casanova *et al.*, 1994). At these concentrations, however, an adaptive response occurred in rat nasal epithelium, as cell turnover rates after 6 weeks (Monticello *et al.*, 1991) or 13 weeks (Zwart *et al.*, 1988) were lower than those after 1–3 or 4 days of exposure. Monticello *et al.* (1996) 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 3 months (6 h per day on 5 days per week). However, as already noted, Casanova *et al.* (1994) detected a small increase in DNA synthesis under these conditions, but after 12 weeks of treatment. Large, sustained increases in cell turnover were observed at 10 and 15 ppm [12.2 and 18.3 mg/m$^3$] (6 h per day on 5 days per week for 3, 6, 12 or 18 months) (Monticello & Morgan, 1994; Monticello *et al.*, 1996). The effects of subchronic exposure to various concentrations of formaldehyde on DNA synthesis in the rat nose are illustrated in Figure 5.

**Table 34. Cytotoxicity and cell proliferation induced by subchronic and chronic exposures to formaldehyde**

| Strain, species, sex | 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 | Rat: squamous metaplasia in nasal turbinates at 3.7 mg/m$^3$ only; hamster: 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, 24.6, 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 of exposure | 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 in respiratory epithelium (both intact and damaged nose); degeneration with or without hyperplasia of olfactory epithelium (damaged nose only) | Appelman *et al.* (1988) |

**Table 34 (contd)**

| Strain, species, sex | Exposure | Effects | Reference |
|---|---|---|---|
| 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, determined 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, 6 weeks | 0.86, 2.5: no increase in cell replication detected; 7.4: increase in cell proliferation; 12.3, 18.5: sustained cell proliferation | Monticello *et al*. (1991) |
| 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*. (1994) |
| 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. Site-specific increase in cell replication corresponded to location of squamous-cell carcinomas. | Monticello *et al*. (1996) |

*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 (HCHO) 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$^3$] formaldehyde**
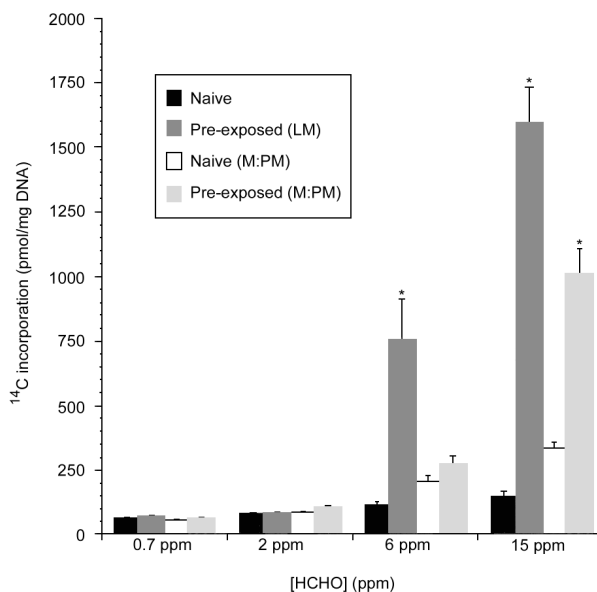


Reproduced, with permission, from Casanova *et al.* (1994)
Pre-exposed rats were exposed subchronically to the same concentrations of unlabelled formaldehyde (6 h per day on 5 days per week for 11 weeks and 4 days), while naive rats were exposed to room air. The exposure to [$^{14}$C]formaldehyde occurred on the 5th day of the 12th week. The asterisk denotes a significant difference between pre-exposed and naive rats.

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 nasal mucosa of Wistar rats was damaged by bilateral intranasal electrocoagulation and the susceptibility of the rats to inhalation of formaldehyde at concentrations of 0.1, 1 or 10 ppm [0.1, 1.2 or 12.2 mg/m$^3$] (for 6 h per day on 5 days per week for 13 or 52 weeks (Appelman *et al.*, 1988), 28 months or 3 months followed by a 25-month observation period (Woutersen *et al.*, 1989)) was evaluated. 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, and 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 mucosa was more susceptible to the cytotoxic effects of formaldehyde and that severe damage contributes to the induction of nasal tumours.

The time-dependent development of formaldehyde-induced lesions was examined in 180 male Fischer 344 rats (six per exposure group), 8–9 weeks of age, that were exposed by inhalation to nominal concentrations of 0, 0.7, 2, 6, 10 or 15 ppm [0, 0.86, 2.46, 7.38, 12.3 or 18.45 mg/m$^3$, respectively] formaldehyde [thermal depolymerization of para-formaldehyde, purity unspecified] for 6 h per day on 5 days per week for 3, 6, 12, 18 or 24 months. Five days before necropsy, the rats were anaesthetized and received an implant of an osmotic minipump that contained 2mCi [methyl-$^3$H]thymidine for incorporation of the thymidine into DNA during S-phase to allow subsequent quantitation of cell prolifera-tion. A detailed morphological analysis of the nasal cavity of each rat was made in order to collect information on the development and distribution of lesions in seven separate regions of the nose (anterior lateral meatus, posterior lateral meatus, anterior mid-septum, posterior mid-septum, anterior dorsal septum, anterior medial maxilloturbinate and maxil-lary sinus). The unit length labelling index method was used to establish the proliferation index in each area of the nose. The number of cells in each of the designated areas was also determined through a combination of actual cell counts and estimates of numbers using surface area measurements and a CFD model of the rat nose. A population-weighted unit length labelling index was calculated for direct comparison across time and dose. Survival was not different or greater in controls than in rats treated with 10 ppm formaldehyde or less. Survival was decreased in rats treated with 15 ppm formaldehyde. Formaldehyde-induced lesions were primarily confined to areas lined by respiratory and transitional epi-thelium and were more prevalent and severe in the anterior portion of the nose. The severity of the lesions was dose-dependent, with only minimal lesions present after expo-sure to 6 ppm and none after exposure to 2 ppm or 0.7 ppm. The predominant non-neoplastic formaldehyde-induced lesions were epithelial hypertrophy and hyperplasia, squamous metaplasia and inflammatory cell infiltration. The majority of formaldehyde-induced neoplasms were squamous-cell carcinomas with much lower incidences of poly-poid adenomas, adenocarcinomas and rhabdomyosarcomas. The 10- and 15-ppm groups had parallel cumulative incidence curves, although the 10-ppm group had a later time to onset of tumours. The squamous-cell carcinomas appeared to arise from regions lined by transitional and respiratory epithelium and were most common in the lateral meatus and mid-septum, the incidence was higher in the more anterior portions (Table 35). Significant increases in the unit length labelling index were only observed in the 10- and 15-ppm groups with the greatest increase in the more anterior portion of the nose where the tumour response was greatest. An elevated unit length labelling index developed in the anterior dorsal septum later in the course of the exposure. This belated elevation in the more posterior nose of animals exposed to the high dose may have been secondary to changes in airflow patterns and resultant local formaldehyde concentrations associated with growth of lesions and distortion of the airspace in the nose. The mapping of cell numbers per area showed significant differences in the total populations of nasal epithelium at risk in the different areas counted for this study. An additional method of examining the association between cells at risk and the labelling index used in this study was the population-weighted unit length labelling index which is the product of the total numbers of cells in the specified

**Table 35. Incidences of nasal squamous-cell carcinomas in male Fischer 344 rats exposed by inhalation to formaldehyde**

| Concentration of formaldehyde (ppm) | No. of nasal cavities examined | Nasal location | | | | | | | No. of animals with squamous-cell carcinoma[a] |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | | Anterior lateral meatus | Posterior lateral meatus | Anterior mid-septum | Posterior mid-septum | Anterior dorsal septum | Anterior medial maxillo-turbinate | Maxillary sinus | |
| 0 | 90 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 0.7 | 90 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 2 | 96 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 6 | 90 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| 10 | 90 | 12 | 2 | 0 | 0 | 0 | 0 | 0 | 20 |
| 15 | 147 | 17 | 9 | 8 | 1 | 3 | 4 | 0 | 69 |

From Monticello *et al*. (1996)
[a] Total number of animals with squamous-cell carcinoma, including those too large to allocate and those located in a site not listed in this table

area and the unit length labelling index. This product corresponded very closely with tumour development at all sites in the nose (Figs 6 and 7) (Monticello *et al*., 1996).

A rat CFD model was used to test whether the distribution of formaldehyde-induced squamous metaplasia was related to the location of high-flux regions posterior to the squamous epithelium. Histological sections of nose corresponding to level 6 (Mery *et al*., 1994) from male Fischer 344 rats exposed by whole-body inhalation to nominal concentrations of 0, 0.7, 2, 6, 10 and 15 ppm [0, 0.86, 2.46, 7.38, 12.3 and 18.45 mg/m³] formaldehyde were examined. Distribution of squamous epithelium within 20 subset areas within the section was mapped. Squamous metaplasia was considered to be present when ≥ 50% of the epithelium within a subsection was of the squamous type. The regions were then ranked by presence of squamous metaplasia by dose group. Inspiratory airflow and formaldehyde uptake were simulated based on a minute volume of 288 mL/min for a 315-g rat. Steady-state simulations were performed using air concentrations of 6, 10 or 15 ppm formaldehyde. Only these three concentrations were used because no squamous metaplasia was present in sections of nose from rats exposed to 2 ppm or less. Squamous metaplasia was present on the lateral and medial walls of the airway after exposure to 10 or 15 ppm; the highest incidence was on wells of the lateral meatus in all three groups (6, 10 and 15 ppm). The distribution of formaldehyde-induced squamous metaplasia was consistent with the location of high formaldehyde flux in rat noses after exposure to 10 or 15 ppm for 6 months. The data were inconclusive for the 6-ppm group, probably due to the insufficient number of rats examined (Kimbell *et al*., 1997).

A larger percentage of the nasal mucosal surface area of rhesus monkeys exposed to 6 ppm [7.3 mg/m³] formaldehyde (6 h per day on 5 days per week) was affected after 6 weeks of exposure than after 5 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/m³] (22 h per day on 7 days per week for 26 weeks) formaldehyde did not develop detectable nasal lesions (Rusch *et al*., 1983), but that rats exposed to 2 ppm [2.4 mg/m³] (6 h per day on 5 days per week for 24 months) developed mild squamous metaplasia in the nasal turbinates (Kerns *et al*., 1983b). Although the total dose received by the former group was 1.5 times higher than that received by the latter group, the incidence and severity of lesions was smaller, which demonstrates the greater importance of concentration than total dose (Rusch *et al*., 1983).

A computer simulation of the relationship between airflow and the development of formaldehyde-induced lesions was developed for rhesus monkeys. A three-dimensional computer model was developed using video image analysis of serial coronal sections from an 11.9-kg, 7-year-old male rhesus monkey. Coordinates were taken for every 0.1 mm over the 83 mm long nasal passage. Eighty cross sections were used for the final model and spanned 75 mm of airway. Values for airflow simulation were estimated by allometric scaling, using body weight and a calculated minute volume of 2.4 L/min and half maximum nasal airflow calculated to be 3.8 L/min. Simulations were performed using airflow parameters of 0.63–3.8 L/min. The nasal cavity of rhesus monkeys has two air-

**Figure 6. Calculated total proliferative population in areas of the nose of rats after exposure to formaldehyde for 3 months and T-site where tumours developed**
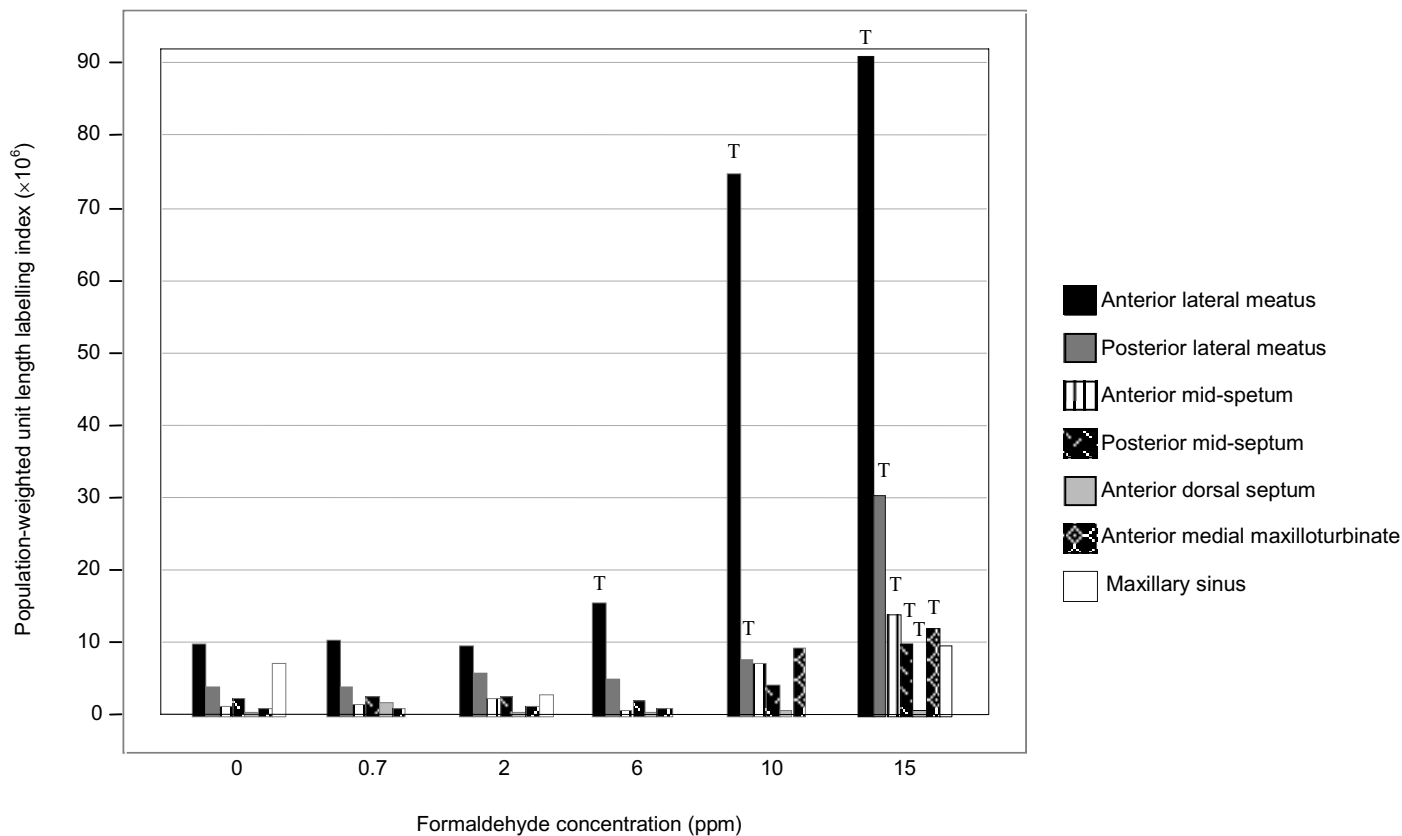


Adapted from Monticello *et al.* (1996)

**Figure 7. Sum of calculated total proliferative population in areas of the nose of rats after exposure to formaldehyde over time and T-site where tumours developed**
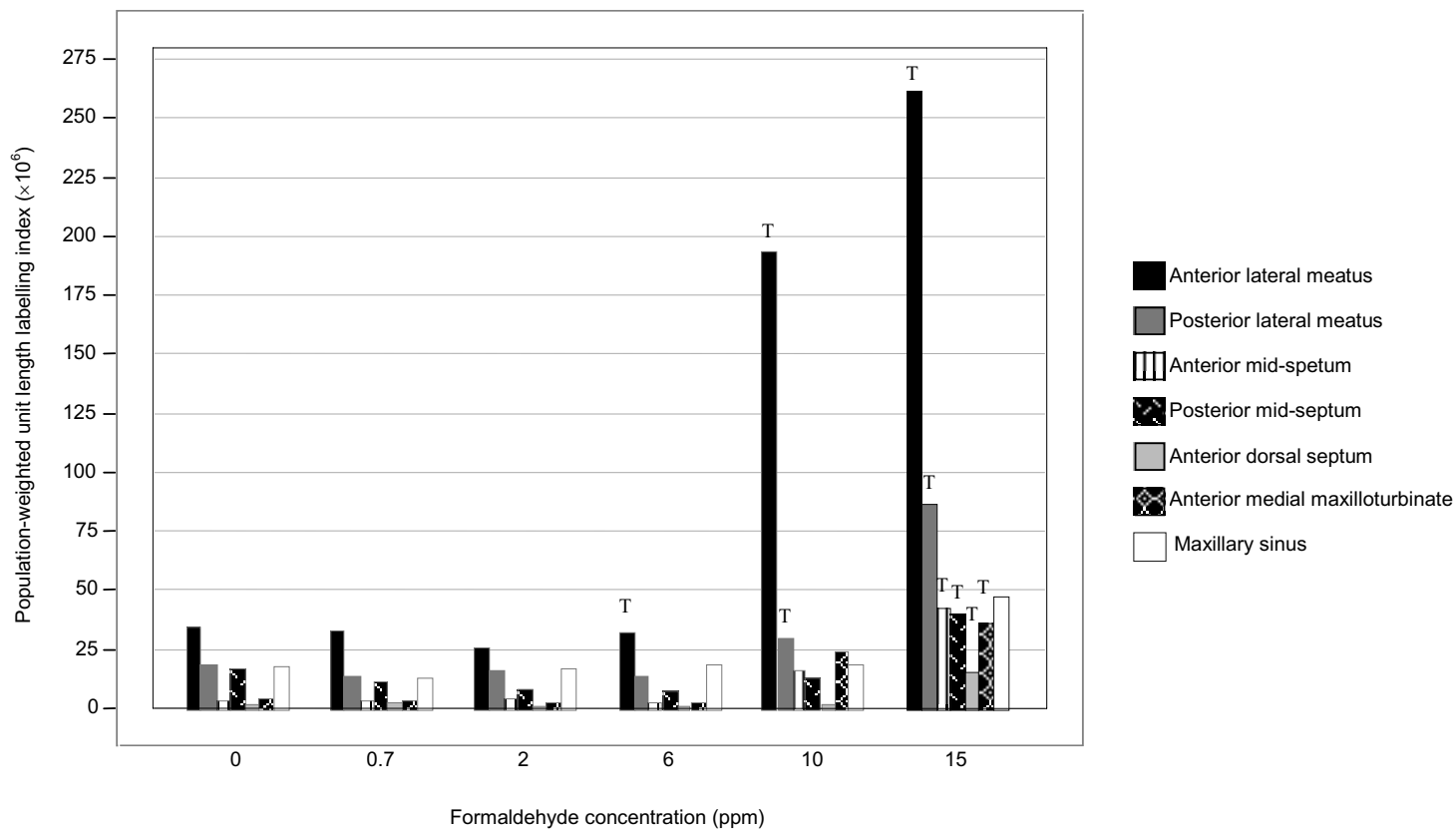


Adapted from Monticello *et al.* (1996)

ways that are separated by a septum that extends approximately 71.5 mm from the anterior tip of the nares to the nasopharynx. The nose has three distinct regions: the nasal vestibule, the central nasal passage and the nasopharynx. The nasal vestibule extends from the tip of the nostrils to the anterior margin of the middle turbinate. Airflow enters the nasal vestibule in an undeviated pattern and flows along the septal wall to the ventral medial, middle medial and dorsal airways in the central nasal passage. The central nasal passage begins at the anterior margin of the middle turbinate, extends to the middle and ventral turbinates and has a streamlined airflow in the middle portion of the nose which is slower than that of the nasal vestibule. The nasopharynx extends from the posterior nasal passage at the point where the middle turbinate attaches to the nasal wall dorsally to the soft palate and has streamlined airflow in the anterior portion which increases in velocity toward the posterior after the end of the dorsal meatus. The model predicted that 90% of gas uptake would be from the nostrils to the end of the septal wall. In general, the regions where mass flux was predicted to be high (nasal vestibule, mid-septum, floor of the anterior meatus, medial inferior turbinate and the middle turbinate) are also areas where formaldehyde-induced lesions occurred (Monticello *et al.*, 1989). Areas with low mass flux (dorsal meatus and the wall of the ventral lateral meatus) did not develop formaldehyde-induced lesions. An exception was the lateral wall where lesions occurred but mass flux was predicted to be low (Kepler *et al*., 1998).

## Toxicity in the gastrointestinal tract after oral administration

The toxic effects of formaldehyde administered orally 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 90 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 to be 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 2 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 2 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 15 mg/kg bw per day (males) or 21 mg/kg bw per day (females) (Til *et al.*, 1989). In a 4-week study, the effects of formaldehyde that were also observed only in the highest-dose group (125 mg/kg bw) were thickening of the limiting ridge and hyperkeratosis in the forestomach and focal gastritis in the glandular stomach (Til *et al.*, 1988).

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 2 years. Estimated from the water intake and body weight, 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 hyper-keratosis was observed in a small number of rats (2/14) that received 0.1% formaldehyde (50 mg/kg bw per day) (Tobe *et al.*, 1989).

<p align="center">(iii)   *Immunotoxicity*</p>

The possibility that formaldehyde may induce changes in the immune response was examined in B6C3F$_1$ mice exposed to 15 ppm [18.3 mg/m$^3$] formaldehyde (6 h per day on 5 days per week for 3 weeks). A variety of tests of immune function revealed no significant changes, except for an increase in host resistance to challenge with the bacterium, *Listeria monocytogenes*, which implied an increased resistance to infection. Exposure did not alter the number or impair the function of resident peritoneal macrophages, but increased their competence for release of hydrogen peroxide (Dean *et al.*, 1984; Adams *et al.*, 1987). Formaldehyde enhanced the anti-ovalbumin IgE titre after pre-exposure of BALB/c mice to 2 mg/m$^3$ formaldehyde for 6 h per day for 10 days (Tarkowski & Gorski, 1995) but did not enhance the IgG1 response of ICR mice to a mite allergen in the respiratory tract after exposure to an aerosol of 0.5% formaldehyde saline solution (Sadakane *et al*., 2002).

Sprague-Dawley rats were exposed to 12.6 ppm [15.5 mg/m$^3$] formaldehyde (6 h per day on 5 days per week for 22 months), then vaccinated with pneumococcal polysaccharide antigens and tetanus toxoid and were tested 3–4 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).

## 4.3      Reproductive and developmental effects

### 4.3.1   *Humans*

A variety of epidemiological studies are available that have evaluated the reproductive effects of occupational exposures to formaldehyde both directly and indirectly. The outcomes examined in these studies include spontaneous abortions, congenital malformations, birth weight and infertility.

The incidence of spontaneous abortion was studied among hospital staff in Finland who used ethylene oxide (see IARC, 1994b), glutaraldehyde and formaldehyde to sterilize 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. 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 tobacco smoking habits, intake of alcohol, reproductive history, including the number of pregnancies and their outcome, and occupation at the time of each pregnancy. Information on exposure to chemical sterilizing agents was obtained from the supervising nurses. The crude rates of spontaneous abortion 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 learned that they were pregnant (the difference being significant) and 10.6% for controls. When adjusted for age, parity, decade of pregnancy, tobacco 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 ($p < 0.05$), whereas that associated with formaldehyde, with or without other agents, was 8.4%, which was comparable with the reference level of 10.5% and was thus not significantly correlated with spontaneous abortions (Hemminki *et al.*, 1982).

In a nationwide record linkage study in Finland, all nurses who had been pregnant between 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 that was 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 5.3% of matched controls, to give an odds ratio of 1.74 [95% CI, 0.39–7.7]; the latter analysis was based on eight exposed subjects (Hemminki *et al.*, 1985). [The Working Group noted that these numbers appear to be recalculated from published reports.]

The occurrence of spontaneous abortions among women who worked in laboratories in Finland, and congenital malformations and birth weights of the children were investigated in a matched retrospective case–control study using a case–referent design. 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, tobacco smoking and alcohol consumption during the first trimester of the pregnancy was collected by postal questionnaire. The exposure to individual chemicals was estimated on the basis of a

reported frequency of chemical use. An occupational hygienic assessment was conducted and an exposure index was calculated. The odds ratio for spontaneous abortion was increased among women who had been exposed to formalin for at least 3 days per week (odds ratio, 3.5; 95% CI, 1.1–11.2). 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, 1989). The authors stated that the results for individual chemicals should be interpreted with caution 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).

Reduced fertility was investigated in a retrospective study of time to pregnancy that was conducted among female wood workers who were exposed to formaldehyde and who had given birth between 1985 and 1995 (Taskinen *et al.*, 1999). Time to pregnancy was analysed using a discrete proportional hazards regression approach. Study criteria included women who had worked in the wood-processing industry for at least 1 month and for whom employment in wood-related work had started at least 6 months before pregnancy. Exposure assessment was based on responses from a detailed questionnaire that asked women to describe their occupational title and their work tasks. Women estimated the number of hours they spent in various types of factories/enterprises in the industry and the number of hours they were exposed to various chemicals including formaldehyde, organic solvents, wood preservatives, glues or wood-protecting chemicals. The questionnaire also collected information on the use of personal protective equipment, and exposure to welding fumes, exhaust gases, pesticides and tobacco smoke. An occupational hygienist assessed the exposures and calculated a daily exposure index. The authors used workplace exposure measurements to support these exposure estimates. Among the 699 female wood workers, exposure to formaldehyde was significantly associated with delayed conception density, as assessed by an adjusted fecundability density ratio, which was 0.64 (95% CI, 0.43–0.92). When no gloves were used during high levels of exposure, the fecundability density ratio was 0.51 (95% CI, 0.28–0.92). Exposure to phenols, dusts, wood dusts or organic solvents was not related to the time to pregnancy. All women exposed to phenols were also exposed to formaldehyde but the opposite was not true.

Although the study focus was time to pregnancy, other analyses of these workers showed an increased odds ratio for spontaneous abortion (52 pregnancies) of 3.2 (95% CI, 1.2–8.3) in the high-exposure and 2.4 (95% CI, 1.2–4.8) in the low-exposure categories. Exposure to formaldehyde at high levels was also associated with an increased risk (odds ratio, 4.5; 95% CI, 1.0–20.0) for endometriosis (Taskinen *et al.*, 1999).

A meta-risk analysis conducted by Collins *et al.* (2001b) noted that, of the 11 epidemiological studies that they reviewed for their evaluation of reproductive effects among workers exposed to formaldehyde, nine evaluated spontaneous abortions. Four of these studies reported significantly higher rates of spontaneous abortion among women who were occupationally exposed to formaldehyde (Axelsson *et al.*, 1984; John *et al.*, 1994; Taskinen

*et al*., 1994, 1999). Four other studies did not find an increased association (Hemminki *et al*., 1982, 1985; Stücker *et al*., 1990; Lindbohm *et al*., 1991). One study did not report relative risks but showed no increased risk for spontaneous abortion (Shumilina, 1975). Collins *et al*. (2001b) suggested that there is a reporting bias against negative studies and described some of the difficulties in conducting studies of spontaneous abortions.

Collins *et al.* (2001b) discussed the four epidemiological studies that used a case–control design to evaluate congenital defects among children of women exposed to formaldehyde (Axelsson *et al*., 1984; Ericson *et al*., 1984; Hemminki *et al*., 1985; Taskinen *et al*., 1994).

Three epidemiological studies evaluated birth weights. Neither Taskinen *et al.* (1994) nor Axelsson *et al.* (1984) reported associations between exposure to formaldehyde and decreased birth weight among the 500 and 968 births examined, respectively. A study in Russia by Shumilina (1975) reported an elevated number of births of babies that weighed less than 3000 g among 81 newborns of women who were potentially exposed to formaldehyde; however, if the cut-point of below 2500 g is used (more traditional definition of low birth weight), then these increases disappear.

It is important to note that most of the epidemiological studies reported in this section were not designed to evaluate exposures to formaldehyde specifically. For example, the studies by Taskinen *et al.* (1994), Hemminki *et al.* (1982, 1985), Ericson *et al.* (1984) and Axelsson *et al.* (1984) were designed to investigate pregnancy outcomes in laboratory workers and that of John *et al.* (1994) to investigate pregnancy outcomes in cosmetologists. All of these studies are confounded by significant co-exposures and, in general, have directed research to examine specific exposures in follow-up studies.

Other studies of reproductive effects in humans have investigated sperm abnormality. 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 F-bodies. Subjects were matched for 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 2–3-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 [0.75–1.6 mg/m$^3$] (weekly exposure, 3–40 ppm·h [3.7–48.8 mg/m$^3$·h]). No significant difference was observed between the exposed and control groups with regard to sperm parameters (Ward *et al.*, 1984).

### 4.3.2   *Experimental systems*

The reproductive and developmental toxicity of formaldehyde has been reviewed (Feinman, 1988; WHO, 1989; Collins *et al*., 2001b).

Numerous studies have been performed to examine the potential effects of formaldehyde on pregnancy and fetal development in rats, mice, hamsters, rabbits and dogs.

Routes of exposure have included inhalation, oral gavage, administration in the drinking-water and dermal application. The inhalation studies (Gofmekler, 1968; Gofmekler *et al.*, 1968; Pushkina *et al.*, 1968; Gofmekler & Bonashevskaya, 1969; Shevelera, 1971; Kilburn & Moro, 1985; Saillenfait *et al.*, 1989; Martin, 1990) and studies of dermal exposure (Overman, 1985) use relevant routes of exposure for evaluation. Studies conducted before 1970 (Gofmekler, 1968; Gofmekler *et al.*, 1968; Pushkina *et al.*, 1968; Gofmekler & Bonashevskaya, 1969) reported a prolongation of pregnancy, changes in fetal organ weight and a variety of clinical and biochemical changes in the spleen, liver, kidney, thymus and lymphocytes in rats (Thrasher & Kilburn, 2001; Collins *et al.*, 2001b). Thrasher and Kilburn (2001) reviewed studies of embryotoxicity and teratogenicity (Katakura *et al.*, 1990, 1991, 1993) and reported that [$^{14}$C]-labelled formaldehyde crossed the placenta and entered fetal tissues at levels greater than those in the dam. Embryotoxic and teratogenic outcomes were a function of the exposure regimen. Rats exposed before mating had increased embryo mortality and those exposed during mating had increased fetal anomalies. [The Working Group agreed with the authors' suggestion that this [C$^{14}$]-labelling would be consistent with the entry of the [$^{14}$C]-label from formaldehyde into the one-carbon pool.]

Groups of 25 pregnant Sprague–Dawley rats were exposed by inhalation to formaldehyde (0, 5, 10, 20 or 40 ppm [0, 6.2, 12.3, 24.6 or 49.2 mg/m$^3$]) for 6 h per day on 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 administered 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 attributed to maternal toxicity. However, the authors stated that the significant reductions in fetal body weight observed at 20 ppm did not cause overt signs of maternal toxicity (Saillenfait *et al.*, 1989). [The Working Group noted that 20-ppm exposures in other studies would be considered to be 'toxic' doses.]

Groups of 25 mated female Sprague–Dawley rats were exposed by inhalation to formaldehyde (0, 2, 5 or 10 ppm [2.5, 6.2 or 12.3 mg/m$^3$]) for 6 h per 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. An increased incidence of reduced ossification was observed at 5 and 10 ppm in the absence of maternal toxicity (10 ppm) (Martin, 1990). The author of this study noted that the effects at both 5 and 10 ppm were attributed to larger litter sizes which could have reduced fetal body weights (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 treat-

ment. 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, as females were anaesthetized during formaldehyde exposures. No effect on maternal weight gain was observed (Overman, 1985).

In a study of post-implantation effects, 27 mature female Wistar rats were exposed by inhalation to 0.5 mg/m$^3$ or 1.5 mg/m$^3$ formaldehyde every day for 4 h for up to 4 months. On day 120, treated females were mated with untreated males. The effect of formaldehyde was evaluated in developing embryos at the 2nd and 3rd day after mating. The authors reported a significant increase in the number of degenerating embryos only from pregnant females who had been exposed to 1.5 mg/m$^3$. The impaired embryonic morphology was reported as structural impairment in blastomers. In a cytogenetic analysis, no increase was found in the number of embryos with chromosomal aberrations in comparison with the controls (Kitaeva *et al.*, 1990).

Reproductive effects were observed in a study of sperm head abnormalities and dominant lethal mutations. Male albino rats (six per group) received five daily intraperitoneal injections of 37% formaldehyde solution to provide 0.125, 0.25 or 0.5 mg/kg bw based on the $LD_{50}$ and a lethal dose of 2 mg/kg bw to examine sperm head abnormalities 3 weeks after the last injection. A separate group of 12 male albino rats was injected intraperitoneally with the same doses, then housed with two untreated virgin female rats that were replaced weekly for 3 weeks to provide 24 females for each treatment group. Mating was detected by the presence of vaginal plugs. All females were killed and necropsied 13 days after the midweek of housing with the males. Total implant scores per female were collected and a dominant lethal mutation index was calculated based on the formula [1–(live implants treated/live implants control)] × 100. Formaldehyde induced sperm head abnormalities at all doses tested, which included pinhead, short hook, long hook, hook at wrong angle, unusual head and wide acrosome; short and long hook were the most common. Only total numbers of abnormalities were compared statistically, and only the incidence of wide acrosome was much greater than that in controls at the lowest dose tested (46 versus 0). In general, there was a decrease in sperm count with increasing dose of formaldehyde. A lower frequency of fertile matings was observed in females within the first 2 weeks after treatment, and the severity of effect was greater when mating took place earlier after treatment. The highest dose with the shortest time between final treatment and mating had the most severe effect and showed a dose- and time-dependent response. By 3 weeks after the last treatment, there was no longer a difference from controls (Odeigah, 1997). Morphological changes in sperm from mice were also identified after five daily intraperitoneal injections of 4, 10 or 30 mg/kg bw formaldehyde. Sperm counts were decreased after 10 and 30 mg/kg bw and deformed sperm were present after all doses (Yi *et al.*, 2000). [The Working Group noted that, because of the reactivity of formaldehyde, the positive results seen after intraperitoneal injection are of questionable biological significance.]

## 4.4      Genetic and related effects

The genotoxicity of formaldehyde has been reviewed extensively (IARC, 1982, 1987a; Ma & Haris, 1988; WHO, 1989; Feron *et al*., 1991; Monticello & Morgan, 1994; IARC, 1995; Conaway *et al*., 1996; Mathison *et al*., 1997; Monticello & Morgan, 1997; Bolt, 2003; Liteplo & Meek, 2003).

### 4.4.1    *Humans*

#### (*a*)    *DNA–protein cross-links*

The induction of DNA–protein cross-links due to exposure to formaldehyde was studied in humans (Shaham *et al*., 1996a,b, 2003) (see Table 36). The number of DNA–protein cross-links and the amount of p53 protein, both pantropic (wild-type + mutant) and mutant, were measured in peripheral blood lymphocytes and serum, respectively, of 399 workers from 14 hospital pathology departments, 186 of whom were exposed to formal-dehyde (59 men and 127 women), and 213 control workers (127 men and 86 women) from the administrative section of the same hospitals. The mean period of exposure to formal-dehyde was 15.9 years (range, 1–51 years). The exposed group was divided into two sub-groups: (1) low-level exposure (mean, 0.4 ppm [0.5 mg/m³]; range, 0.04–0.7 ppm [0.5–0.62 mg/m³]); and (2) high-level exposure (mean, 2.24 ppm [2.75 mg/m³]; range, 0.72–5.6 ppm [0.88–6.9 mg/m³]). Before comparing the results obtained in the exposed and the unexposed group, adjustment was made for age, sex, origin and education. The amount of DNA–protein cross-links was expressed as a ratio to total DNA. The adjusted mean number of DNA–protein cross-links was significantly higher ($p < 0.01$) in all exposed subjects (adjusted mean, 0.21; SE, 0.006) compared with that in all unexposed subjects (adjusted mean, 0.14; SE, 0.006). It was also significantly higher ($p < 0.01$) in the sub-groups of exposed men (adjusted mean, 0.21; SE, 0.011) and women (adjusted mean, 0.20; SE, 0.008) compared with that of unexposed men and women (adjusted mean, 0.15 and 0.12; SE, 0.008 and 0.008, respectively). Age, tobacco smoking habits, years of education and origin were not significant confounders. The study population was divided into those who had levels of pantropic p53 protein above or below 150 pg/mL. High levels of p53 (> 150 pg/mL) were more prevalent in the exposed group than in the unexposed (44.1% and 36.3%, respectively). The difference between high and low p53 was significant among exposed men, and exposure to formaldehyde was associated with a higher level of pan-tropic p53 (> 150 pg/mL). In the exposed group, a significantly ($p < 0.05$) higher propor-tion of p53 > 150 pg/mL was found among workers with DNA–protein cross-links above the median (0.19). Studies have shown elevated serum levels of p53 protein years before the diagnosis of malignant tumours such as lung cancer (Luo *et al*., 1994; Hemminki *et al*., 1996). [The Working Group noted that the reported increases in p53 occurred in the serum and its relationship to the toxicity of formaldehyde is not known.]

**Table 36. Genetic effects of formaldehyde in humans**

| Target tissue | End-point | Response | Comments | Reference |
|---|---|---|---|---|
| Peripheral blood lymphocytes | Chromosomal aberrations<br>Micronuclei<br>Sister chromatid exchange | + ($p < 0.01$)<br>+ ($p < 0.01$)<br>+ ($p < 0.05$) | Exposed, 13; unexposed, 10; chromosomal aberrations included breaks and gaps, which renders interpretation difficult. | He *et al*. (1988) |
| Nasal mucosa | Micronuclei | + ($p < 0.01$) | Exposed, 15; unexposed (control), 15; concurrent exposure to wood dust; no dose–response | Ballarin *et al*. (1992) |
| Peripheral blood lymphocytes | Chromosomal aberrations | – | Exposed, 20; unexposed (control), 19; high frequency in controls | Vargova *et al*. (1992) |
| Peripheral blood lymphocytes | DNA–protein cross-links | + ($p = 0.03$) | Exposed, 12; unexposed, 8; pilot study | Shaham *et al*. (1996a) |
| Oral mucosa<br>Nasal mucosa | Micronuclei | + ($p = 0.007$)<br>+ (NS) | Exposed, 28; pre- versus post-exposure; no details on tobacco smoking habits | Titenko-Holland *et al*. (1996) |
| Peripheral blood lymphocytes | Sister chromatid exchange | + ($p = 0.05$) | Exposed, 13; unexposed, 20; linear relationship between years of exposure and mean number of sister chromatid exchanges | Shaham *et al*. (1997) |
| Nasal mucosa<br>Oral mucosa<br>Peripheral blood lymphocytes | Micronuclei | + ($p < 0.001$)<br>+ ($p < 0.01$)<br>+ (NS) | Exposed, 25; pre- versus post-exposure; control for age, sex and tobacco smoking habits questionable | Ying *et al*. (1997) |
| Peripheral blood lymphocytes | Sister chromatid exchange | – | Exposed, 23; pre- versus post-exposure | Ying *et al*. (1999) |
| Nasal mucosa | Micronuclei | + ($p < 0.01$) | Exposed, 23; unexposed, 25; no dose–response | Burgaz *et al*. (2001) |

**Table 36 (contd)**

| Target tissue | End-point | Response | Comments | Reference |
|---|---|---|---|---|
| Oral mucosa | Micronuclei | + ($p < 0.05$) | Exposed: 22 variable exposures, 28 exposed to formaldehyde; unexposed, 28; unexposed (control), 18; correlation with duration of exposure only in group with variable exposures (not exposed to formaldehyde) | Burgaz *et al.* (2002) |
| Peripheral blood lymphocytes | Sister chromatid exchange | + ($p < 0.01$) | Exposed, 90; unexposed, 52; no dose–response relationship | Shaham *et al.* (2002) |
| Peripheral blood lymphocytes Serum | DNA–protein cross-links p53 protein | + ($p < 0.01$) + ($p < 0.01$) | Exposed, 186; unexposed, 213; high levels of p53 protein | Shaham *et al.* (2003) |

NS, not significant

(*b*)    *Chromosomal effects*

The effects of formaldehyde on the frequencies of chromosomal aberrations and sister chromatid exchange in peripheral blood lymphocytes and micronuclei in nasal mucosa cells from workers exposed to formaldehyde have been reviewed previously (IARC, 1987a, 1995). Since that time, several further studies have assessed the induction of micronuclei, chromosomal aberrations and sister chromatid exchange in workers exposed to formaldehyde (see Table 36).

In a study of exposure to formaldehyde in a factory that manufactured wood-splinter materials, short-term cultures of peripheral lymphocytes were examined from a group of 20 workers (10 men and 10 women) aged 27–57 years (mean, 42.3 years) who were exposed to 8-h TWA concentrations of 0.55–10.36 mg/m$^3$ formaldehyde for periods of 5–≥ 16 years. The unexposed group consisted of 19 people [sex and age unspecified] who were employed in the same plant and whose habits and social status were similar to those of the exposed group. No significant difference was observed between control and exposed groups with respect to any chromosomal anomaly (including chromatid and chromosome gaps, breaks, exchanges, breaks per cell, percentage of cells with aberrations) scored in the study (controls: 3.6% aberrant cells, 0.03 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 tobacco smoking habits of the subjects.]

In the study of Ballarin *et al*. (1992), the frequency of micronuclei in respiratory nasal mucosa cells was investigated in 15 nonsmokers who were exposed to formaldehyde in a plywood factory. Mean exposure levels were 0.1–0.39 mg/m$^3$, with simultaneous exposure to wood dust at a very low level (about one tenth below the threshold limit value). At least 6000 cells from the nasal turbinate area from each individual were scored for micronuclei. A significant increase in the incidence of micronucleated cells was seen in the exposed group (mean percentage of micronucleated cells in the exposed group, 0.90 ± 0.47; range, 0.17–1.83; in controls, 0.25 ± 0.22; range, 0.0–0.66; Mann–Whitney U test, $p < 0.01$). No dose–response relationship between exposure to formaldehyde and the frequency of micronuclei was found. Concurrent exposure to wood dust could have contributed to the increased incidence of micronucleated cells seen in the exposed group.

Burgaz *et al*. (2001) studied the frequency of micronuclei in cells of the nasal mucosa of 23 individuals (11 women and 12 men) who were exposed to formaldehyde in pathology and anatomy laboratories and 25 healthy men who were not exposed to formaldehyde. The mean age of the exposed group was lower than that of the controls (mean ± SD, 30.56 ± 5.52 and 35.42 ± 9.63 years, respectively). More smokers were included in the control group ($n = 19$) than in the exposed group ($n = 9$). Mean duration of exposure to formaldehyde was 5.06 years (range, 1–13 years). From each individual, 3000 cells were scored for micronuclei. The mean frequency of micronuclei was significantly higher

($p < 0.01$) in the exposed group than in the control group (mean ± SD, 1.01 ± 0.62‰ and 0.61 ± 0.27‰, respectively). No significant difference in the mean frequency of micronuclei was observed between smokers and nonsmokers in the controls or in the exposed group ($p > 0.05$), but significantly higher ($p < 0.01$) mean frequencies of micronuclei were found in unexposed than in exposed smokers (1.18 ± 0.47‰ and 0.63 ± 0.29‰, respectively). No significant difference in the mean frequency of micronuclei was observed between men and women in the exposed group. The air concentration of formaldehyde was 2 ppm [2.4 mg/m³] in the breathing zone of the pathology laboratory workers and 4 ppm [4.9 mg/m³] in that of the anatomy laboratory workers. No dose–response was found between years of exposure and the frequency of micronuclei.

In another study, Burgaz *et al*. (2002) compared the frequency of micronuclei in buccal cells in three groups: group I, 22 workers (all men) from a shoe factory who were exposed to *n*-hexane, toluene and methyl ethyl ketone; group II, 28 workers (15 men and 13 women) who were pathologists or staff in pathology or anatomy laboratories and were exposed to formaldehyde; and group III, 18 unexposed workers (controls), none of whom had been occupationally exposed to potential genotoxic chemicals. The mean duration of exposure to formaldehyde was 4.7 ± 3.33 years (range, 1–13 years). Both exposed and control groups included smokers, most of whom were moderate smokers. There were no significant differences in mean age and smoking habits between the controls and the exposed groups. From each individual, 3000 cells were scored for micronuclei. The concentration of formaldehyde in the breathing zone of the laboratory workers was 2–4 ppm [2.4–4.9 mg/m³]. A significant increase in the frequency of micronucleated cells ($p < 0.05$) was seen in the exposed groups (mean ± SD for workers in group I, group II and controls, 0.62 ± 0.45%, 0.71 ± 0.56% and 0.33 ± 0.30%, respectively). Analysis of variance indicated that only occupational exposure, but not smoking habits or sex, was associated with an increased frequency of micronuclei in groups I and II ($p < 0.05$). Duration of exposure was significantly associated with the frequency of micronuclei only in group I who were not exposed to formaldehyde ($p < 0.05$).

Titenko-Holland *et al*. (1996) assessed the induction of micronuclei in exfoliated buccal and nasal cells from 28 mortality science students who were exposed to embalming fluid that contained formaldehyde. The original study population included 35 students (seven women and 24 men [specifications of the additional four subjects not given]). Seven were excluded. The students were mainly nonsmokers. Previously unstained and unanalysed slides from the participants in a study by Suruda *et al*. (1993) were used. Each student was sampled before and after the 90-day embalming class. Exposure to formaldehyde was estimated for the 7–10 days before the post-exposure sample in order to correct for the possibility of exposure misclassification. The mean exposure to formaldehyde for the 19 subjects who had data on buccal cell micronuclei was 14.8 ± 7.2 ppm–h [18.2 ± 8.8 mg/m³–h] for the entire 90-day period and 1.2 ± 2.1 ppm–h [1.5 ± 2.6 mg/m³–h] for the 7–10 days before the post-exposure sample. For the 13 subjects who had data on nasal cell micronuclei, the mean exposure to formaldehyde was 16.5 ± 5.8 ppm–h [20.3 ± 7.1 mg/m³–h] for the entire 90-day period and 1.9 ± 2.5 ppm–h [2.3 ± 3 mg/m³–h] during the 7–10 days before the post-exposure sampling. Air samples of glutaraldehyde, phenol, methanol and isopropanol

revealed undetectable or very low exposure below the Occupational Safety and Health Administration permissible exposure limits. Quantification of micronuclei was performed by fluorescent in-situ hybridization with a centromeric probe. The mean total frequency of micronuclei was significantly increased in the buccal mucosa (mean ± SD per 1000 epithelial cells, $0.6 \pm 0.5$ pre-exposure, $2.0 \pm 2.0$ post-exposure; Wilcoxon rank sum test two-tailed $p = 0.007$), whereas in nasal cells, it was almost the same ($2.0 \pm 1.3$ and $2.5 \pm 1.3$, respectively; Wilcoxon rank sum test two-tailed $p = 0.2$). Cells with multiple micronuclei were present only in buccal cell samples after exposure to embalming fluid, while in the nasal cell samples, nearly all cells with micronuclei had only one micronucleus per cell in both pre- and post-exposure samples. A weak statistical association (assessed by a Spearman rank order correlation) between cumulative exposure to embalming fluid (90 days) and the change in total micronucleus frequency was observed only in buccal cells ($r = 0.44$; $p = 0.06$). The authors suggested that the main mechanism of micronucleus induction by formaldehyde is due to chromosome breaks.

The frequency of micronuclei in cells of the nasal mucosa, oral mucosa and lymphocytes was evaluated for 25 students (13 men and 12 women; average age, $18.8 \pm 1.0$ years; all nonsmokers) from anatomy classes. The duration of the anatomy classes was 3 h, three times a week for a period of 8 weeks. The TWA concentrations (mean ± SD) of exposure during the anatomy classes and in the dormitories were $0.508 \pm 0.299$ mg/m$^3$ (range, $0.071–1.284$ mg/m$^3$) and $0.012 \pm 0.0025$ mg/m$^3$ (range, $0.011–0.016$ mg/m$^3$), respectively. Samples of nasal and oral mucosa cells and venous blood were taken before the beginning of the first class and after the end of the last class, so that every student served as his/her own control. A significant difference (paired t-test $p < 0.001$) was found in the mean frequency of micronuclei in the nasal and oral mucosa (mean ± SD per 1000 cells): $1.2 \pm 0.67$ versus $3.84 \pm 1.48$ (paired t-test, $p < 0.001$) and $0.568 \pm 0.317$ versus $0.857 \pm 0.558$ (paired t-test $p < 0.01$), respectively. The mean frequency of micronuclei in lymphocytes was higher after exposure ($1.11 \pm 0.543$) than before exposure ($0.913 \pm 0.389$), but this difference was not significant (Ying *et al.*, 1997). [The Working Group noted that there were no data related to the possible influence of factors such as age, sex and smoking on the results.]

He *et al.* (1998) studied the frequency of sister chromatid exchange, chromosomal aberrations and micronuclei in peripheral blood lymphocytes of 13 students from an anatomy class. The duration of the anatomy classes was 10 h per week for 12 weeks. Average exposure to formaldehyde (from breathing-zone air samples) during dissection procedures was 2.37 ppm [3.17 mg/m$^3$]. The unexposed group included 10 students. The sex and age of the two groups were similar and all were nonsmokers. The mean frequency of micronuclei and chromosomal aberrations in the exposed group was significantly higher ($p < 0.01$) than that in the control group ($6.38 \pm 2.50‰$ versus $3.15 \pm 1.46‰$ and $5.92 \pm 2.40\%$ versus $3.40 \pm 1.57\%$, respectively). The main types of chromosomal aberration in the exposed group were chromatid breakages and gaps. A significantly higher ($p < 0.05$) frequency of sister chromatid exchange was observed in the exposed students ($5.91 \pm 0.71$/cell) than in the controls ($5.26 \pm 0.51$/cell). A correlation between micronuclei and chromosomal aberrations was observed. [The Working Group noted that the

evaluation of chromosomal aberrations included chromosomal breaks and gaps together, which makes the results difficult to interpret. In addition, the baseline frequencies of sister chromatid exchange and micronuclei in the controls were unusually low.]

Ying *et al*. (1999) studied the frequency of sister chromatid exchange in peripheral blood lymphocytes of 23 students from an anatomy class (11 men and 12 women), all of whom were nonsmokers. The duration of the anatomy classes was 3 h, three times a week for 8 weeks. Peak exposure was during cadaver dissection. TWA (mean $\pm$ SD) concentrations of formaldehyde were $0.508 \pm 0.299$ mg/m$^3$ (range, 0.071–1.284 mg/m$^3$) in the laboratory rooms compared with $0.012 \pm 0.0025$ mg/m$^3$ (range, 0.011–0.016 mg/m$^3$) in the dormitories. Blood samples were taken at the beginning of the anatomy classes and again after 8 weeks. No significant difference was found in the mean frequency of sister chromatid exchange before and after exposure, either in the total population ($6.383 \pm 0.405$ versus $6.613 \pm 0.786$, respectively) or in the subgroups of men and women.

In a pilot study, Shaham *et al*. (1997) studied the frequency of sister chromatid exchange in the peripheral blood lymphocytes of 33 workers, including 13 from a pathology institute who were exposed to formaldehyde and 20 unexposed controls. The mean age of the exposed workers was $42 \pm 10$ years and that of the control group was $39 \pm 14$ years. The range of concentrations of formaldehyde was 1.38–1.6 ppm [1.7–2 mg/m$^3$] in the rooms and 6.9 ppm [8.5 mg/m$^3$] in the laminar flow. Personal samples showed a range of 2.8–3.1 ppm [3.5–3.7 mg/m$^3$] formaldehyde at the period when most of the work was in progress and 1.46 ppm [1.8 mg/m$^3$] at midday, when most of the work had already been carried out. In order to score sister chromatid exchange, cells that had 44–48 clearly visible chromosomes were examined and the sister chromatid exchange count was normalized to the frequency expected for 46 chromosomes. The mean numbers of cells scored per individual were 28 for the exposed group (range, 25–32; SD, 2.36) and 32 for the controls (range, 25–34; SD, 2.0). A significant difference ($p = 0.05$) was found between the mean number of sister chromatid exchanges per chromosome in the exposed workers (mean $\pm$ SD, $0.212 \pm 0.039$) and the controls (mean $\pm$ SD, $0.186 \pm 0.035$). A significant difference ($p < 0.05$) was found between the mean number of sister chromatid exchanges per chromosome of nine exposed and six unexposed nonsmokers and those of three exposed and two unexposed smokers. The group of smokers who were exposed to formaldehyde had the highest mean number of sister chromatid exchanges per chromosome, and a linear relationship was reported between years of exposure and the mean number of sister chromatid exchanges per chromosome.

In a second study, Shaham *et al*. (2002) evaluated the frequency of sister chromatid exchange in peripheral blood lymphocytes of pathology staff exposed to formaldehyde compared with that in unexposed workers. The study population included 90 workers (25 men and 65 women) from 14 hospital pathology departments who were exposed to formaldehyde (mean age, $44.2 \pm 8.5$ years) and 52 unexposed workers (44 men and eight women) from the administrative section of the same hospitals (mean age, $41.7 \pm 11.4$ years). Tobacco smoking habits did not differ significantly between the study groups. The exposed group was divided into two subgroups according to levels of exposure to

formaldehyde (low-level exposure: mean, 0.4 ppm [0.5 mg/m$^3$]; range, 0.04–0.7 ppm [0.05–0.86 mg/m$^3$]; high-level exposure: mean, 2.24 ppm [2.8 mg/m$^3$]; range, 0.72–5.6 ppm [0.9–6.9 mg/m$^3$]). The mean duration of exposure to formaldehyde was 15.4 years (range, 1–39 years). The results on the frequency of sister chromatid exchange were expressed in two variables: (*a*) mean number of sister chromatid exchanges per chromosome; and (*b*) proportion of high-frequency cells (namely, the proportion of cells with more than eight sister chromatid exchanges). A high correlation between these two variables ($rs = 0.94$; $p < 0.01$) was found in the study population and in each of the two subgroups (exposed $rs = 0.79$; $p < 0.01$; unexposed $rs = 0.92$; $p < 0.01$). Before the results obtained from the exposed and the unexposed groups were compared, adjustment was made for age, sex, origin, education and tobacco smoking. The adjusted mean number of sister chromatid exchanges per chromosome was significantly higher ($p < 0.01$) among the exposed group (0.27; SE, 0.003) than the unexposed group (0.19; SE, 0.004). The adjusted mean of the proportion of high-frequency cells was also significantly higher ($p < 0.01$) among the exposed group (0.88; SE, 0.01) than the controls (0.44; SE, 0.02). After adjustment for potential confounders, the adjusted mean of the two variables of sister chromatid exchange were similar for the two periods of exposure (up to 15 years and more than 15 years). Tobacco smoking was found to be a significant confounder. With regard to levels of exposure, both variables of sister chromatid exchange were similar in the low- and high-level exposure subgroups. However, among smokers, both variables of sister chromatid exchange were higher in the high-exposure subgroup than in the low-exposure subgroup.

(*c*)    *DNA repair*

Hayes *et al.* (1997) studied the effect of formaldehyde on DNA repair capacity by assessing the activity of $O^6$-alkylguanine–DNA alkyltransferase (AGT), which was found to be involved in the repair of DNA damage due to exposure to formaldehyde *in vitro*. AGT activity was measured in peripheral blood lymphocytes of 23 mortuary science students (seven women and 16 men), of whom 17 were nonsmokers and six were smokers. Blood samples were taken before the beginning of the course and after 9 weeks of practice. The number of embalmings that the students experienced varied, both before and during the course. The average air concentration of formaldehyde during embalming was about 1.5 ppm and, during some peak exposures, was three to nine times that of the corresponding TWA. Measurements of glutaraldehyde and phenol were below the limit of detection. Total exposure to formaldehyde during the study period, including embalming carried out outside the school, was within the range of 5.7–82.0 ppm–h [7–100 mg/m$^3$–h] (mean ± SD, 18.4 ± 15.6 ppm [22.5 ± 19.2 mg/m$^3$]). The total number of embalmings was correlated with the estimated total exposure to formaldehyde ($r = 0.59$; $p < 0.01$). Students who had had previous experience of embalming had greater estimated exposure to formaldehyde during the study period ($p < 0.05$), and their DNA repair capacity at baseline was reduced ($p = 0.08$). No exposure–response relationship was found between the number of embalmings during the 90 days before the course and the AGT activity ($r = –0.29$; $p = 0.19$). Sex,

age and tobacco smoking were not clearly related to pre-exposure DNA repair activity. Post-exposure and pre-exposure AGT activity were correlated ($r = 0.42$; $p < 0.05$). At the end of the course, a reduction in DNA repair capacity was found in 17 students and an increase in DNA repair capacity in six ($p < 0.05$). These findings were confirmed after analysis of variance, including adjustment for age, sex and tobacco smoking status. Among the eight students who had no embalming experience during the 90 days before the study, seven (88%) had decreased and only one had increased AGT activity during the study period ($p < 0.05$). Of the 15 students who had had previous embalming experience, 10 (67%) had decreased and five (33%) had increased AGT activity ($p > 0.05$). No relation was found between the extent of the decrease in AGT activity and the levels of exposure to formaldehyde throughout the 9-week study period or during the last 28 days. As was also noted by the authors, the limitation of the study was the small study population and the fact that many of the students had previous embalming experience.

Schlink *et al.* (1999) studied the activitity of the DNA repair enzyme, $O^6$-methyl-guanine–DNA methyltransferase (MGMT). The study population included 57 medical students from two universities who were exposed to formaldehyde during anatomy courses. Blood samples of 41 students from the first university were collected before (day 0, control group No. 1), during (day 50) and after (day 111) the course, which lasted 111 days; two 3-h courses were held per week. Additional blood samples from 16 students from the second university were taken at the end of their course, namely 98 days after the start, and an additional 10 blood samples were taken from unexposed students (control group No. 2). The first group of 41 students was exposed to levels of formaldehyde between 0.14 mg/m$^3$ and 0.3 mg/m$^3$ (mean ± SD, 0.2 ± 0.05 mg/m$^3$). The mean MGMT activity (± 95% CI) was 133.2 ± 14.9 fmol MGMT/10$^6$ cells. No significant difference was observed before and after 50 days of exposure or after 111 days of exposure. Age, sex, cigarette smoking, alcohol consumption and allergic disease had no influence on MGMT activities in either the exposed group or the controls. The exposure level of the second group of 16 students was 0.8 ± 0.6 mg/m$^3$. No significant difference in MGMT activity was observed between this exposed group and the controls (146.9 ± 22.3 fmol MGMT/10$^6$ cells and 138.9 ± 22.1 fmol MGMT/10$^6$ cells, respectively). In addition, the activity of MGMT of students at the second university who were exposed to a higher level of formaldehyde than those at the first university was not statistically significant from that of control group No. 1, and very similar results were obtained in both control groups.

### (d)    Urinary mutagenicity

Hospital autopsy service workers in Galveston, TX (USA) (15 men and four women), aged < 30–> 50 years, and a control group from the local medical school (15 men and five women), who were in the same age range and were 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 2-month intervals. The TWA 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 the livers of Aroclor-1254-induced rats. No increase in mutagenicity was seen in the autopsy workers compared with the control group.

### 4.4.2    *Experimental systems*

#### (*a*)    *DNA–protein cross-links*

##### (i)    *In-vitro studies*

Formaldehyde induces DNA–protein cross-links in animal and human cells *in vitro* (see Table 37). The precise nature of these cross-links is unknown.

##### (ii)    *In-vivo studies in animals*

Groups of four male Fischer 344 rats were exposed for 6 h to 0.3, 0.7, 2, 6 or 10 ppm [0.37, 0.9, 2.4, 7.4 or 12.3 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 head-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 concentrations of cross-links increased non-linearly with the airborne concentration in both species, but those 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 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).

In order to determine whether the yields of DNA–protein cross-links after chronic and acute exposures are equivalent and to locate the site of DNA–protein cross-links and of DNA replication in the rat nasal respiratory mucosa in relation to tumour incidence, groups of rats were exposed (whole body) to concentrations of 0.7, 2, 6 or 15 ppm [0.8, 2.4, 7.4 or 18.5 mg/m$^3$] unlabelled formaldehyde for 6 h per day on 5 days per week for 11 weeks and 4 days (pre-exposed rats) while other groups were exposed to room air (naive rats). On day 5 of week 12, the pre-exposed and naive rats were simultaneously exposed (nose only) for 3 h to [$^{14}$C]-labelled formaldehyde at the same concentrations as those used for pre-exposure to quantitate the acute yield of DNA–protein cross-links and to measure cell proliferation in specific sites of the nose. Alternatively, in order to determine the cumulative yield of DNA–protein cross-links in comparison with unexposed rats, rats that were pre-exposed to 6 or 10 ppm formaldehyde and naive rats that were exposed to room air were simultaneously exposed for 3 h to the same concentration of unlabelled formaldehyde on day 5 or at week 12. The cumulative yield of DNA–protein cross-links was measured immediately after exposure. Nasal mucosal DNA was extracted

from proteins, and the percentage of interfacial DNA (an indicator for the concentration of DNA–protein cross-links) was determined. The percentage of interfacial DNA was also determined in a group of unexposed rats. Increases in the percentage of interfacial DNA, namely, decreases in the extractability of DNA from proteins in the exposed rats, was found by the authors to correlate highly with the yield of DNA–protein cross-links (Casanova-Schmitz *et al.*, 1984b). The amount of [$^{14}$C] incorporation into DNA was an indicator of cell replication. Comparison of cell replication rates in the lateral meatus with those in the medial and posterior meatus showed no significant difference at 0.7 and 2 ppm formaldehyde, but this difference became significant at 6 and 15 ppm formaldehyde in pre-exposed rats ($p \leq 0.02$, Scheffé's test). At 6 and 15 ppm formaldehyde, a significantly ($p \leq 0.01$, Scheffé's test) greater amount of [$^{14}$C] was incorporated into the DNA in the lateral meatus of pre-exposed rats compared with naive rats and, at 15 ppm, into the DNA in the medial and posterior meatus of pre-exposed rats compared with naive rats. The acute yield of DNA–protein cross-links increased non-linearly with concentrations and, in naive rats, was approximately sixfold greater in the lateral than in the medial and posterior meatus at all concentrations. At 0.7 and 2 ppm, the acute yield was not significantly different between naive and pre-exposed rats. However, at both 6 and 15 ppm formaldehyde, a greater acute yield of DNA–protein cross-links was found in the lateral meatus of naive rats than in that of pre-exposed rats, a difference that was significant at 15 ppm formaldehyde ($p = 0.028$, paired *t* test). Based on histopathological evidence, this difference can be attributed to an increase in the quantity of DNA due to an increase in the number of cells in the nasal mucosa of the lateral meatus at high concentrations, which results in a dilution of the DNA–protein cross-links. No significant difference was found between naive and pre-exposed rats in relation to acute yield of DNA–protein cross-links in the medial and posterior meatus at any concentration of formaldehyde. Since measurement of the percentage of interfacial DNA does not require the use of [$^{14}$C]formaldehyde, this parameter was used to investigate whether DNA–protein cross-links accumulated during subchronic, whole-body exposure to formaldehyde. The percentage of interfacial DNA following acute exposure (3-h nose-only exposure) to formaldehyde increased significantly ($p < 0.02$, Scheffé's test) at 6 and 10 ppm. However, at these levels, the percentage of interfacial DNA was lower in pre-exposed rats than in naive rats, a difference that was significant at 10 ppm formaldehyde ($p = 0.01$, Scheffé's test). The authors suggested that the cumulative and acute yields of DNA–protein cross-links in rats exposed to formaldehyde are essentially identical (Casanova *et al.*, 1994). [The Working Group noted that there is doubt about the adequacy of the methods that use interfacial DNA to detect DNA–protein cross-links; the connection between DNA yield needs to be clarified.]

## Table 37. Genetic and related effects of formaldehyde in experimental systems and animals

| Test system | Result[a] Without exogenous metabolic system | Result[a] With exogenous metabolic system | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| Misincorporation of DNA bases into synthetic polynucleotides *in vitro* | + | NT | 30 | Snyder & Van Houten (1986) |
| pUC13 plasmid DNA bound to calf-thymus histones, DNA–protein cross-links | + | NT | 0.0075 | Kuykendall & Bogdanffy (1992) |
| *Escherichia coli* PQ37, SOS repair test, DNA strand breaks, cross-links or related damage | + | NT | 20 | Le Curieux *et al.* (1993) |
| *Escherichia coli* K12 (or *E. coli* DNA), DNA strand breaks, cross-links or related damage; DNA repair | + | NT | 60 | Poverenny *et al.* (1975) |
| *Escherichia coli* K12, DNA strand breaks, cross-links or related damage; DNA repair | + | NT | 600 | Wilkins & MacLeod (1976) |
| *Escherichia coli* K12 KS160-KS66 *pol*AI, differential toxicity | + | NT | 60 | Poverenny *et al.* (1975) |
| *Escherichia coli* $pol$A[+]/W3110 and $pol$A[−] p3478, differential toxicity (spot test) | + | NT | 10 µL of pure substance | Leifer *et al.* (1981) |
| *Salmonella typhimurium* TA100, TA1535, TA1537, TA1538, TA98, reverse mutation | – | – | 60 µg/plate | Gocke *et al.* (1981) |
| *Salmonella typhimurium* TA100, reverse mutation | – | + | 10 µg/plate | Haworth *et al.* (1983) |
| *Salmonella typhimurium* TA100, reverse mutation | (+) | + | 30 µg/plate (toxic above 125 µg/plate)[c] | Connor *et al.* (1983) |
| *Salmonella typhimurium* TA100, reverse mutation | + | +[d] | 9 µg/plate | Pool *et al.* (1984) |
| *Salmonella typhimurium* TA100, reverse mutation | (+) | NT | 51 µg/plate[c] | Marnett *et al.* (1985) |
| *Salmonella typhimurium* TA100, reverse mutation | + | NT | 6 µg/plate | Takahashi *et al.* (1985) |
| *Salmonella typhimurium* TA100, reverse mutation | (+) | + | 3 | Schmid *et al.* (1986) |
| *Salmonella typhimurium* TA100, reverse mutation | + | NT | 9.3 | O'Donovan & Mee (1993) |
| *Salmonella typhimurium* TA100, TA104, reverse mutation | + | + | 6.25–50 µg/plate | Dillon *et al.* (1998) |
| *Salmonella typhimurium* TA102, TA104, reverse mutation | + | NT | 21 µg/plate[c] | Marnett *et al.* (1985) |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| *Salmonella typhimurium* TA102, reverse mutation | + | NT | 10 | Le Curieux *et al.* (1993) |
| *Salmonella typhimurium* TA102, reverse mutation | + | NT | 25 µg/plate | O'Donovan & Mee (1993) |
| *Salmonella typhimurium* TA102, reverse mutation | + | NT | 0.1–0.25 µg/plate | Chang *et al.* (1997) |
| *Salmonella typhimurium* TA102, reverse mutation | + | ? | 6.25–50 µg/plate | Dillon *et al.* (1998) |
| *Salmonella typhimurium* TA1535, TA1537, reverse mutation | – | – | 100–200 µg/plate | Haworth *et al.* (1983) |
| *Salmonella typhimurium* TA1535, reverse mutation | NT | –[d] | 18 µg/plate | Pool *et al.* (1984) |
| *Salmonella typhimurium* TA1535, TA1537, TA1538, reverse mutation | – | NT | 100 µg/plate | O'Donovan & Mee (1993) |
| *Salmonella typhimurium* TA98, reverse mutation | + | NT | 12 µg/plate | Marnett *et al.* (1985) |
| *Salmonella typhimurium* TA98, reverse mutation | – | (+) | 10 µg/plate | Haworth *et al.* (1983) |
| *Salmonella typhimurium* TA98, reverse mutation | (+) | (+) | 30 µg/plate (toxic above 100 µg/plate) | Connor *et al.* (1983) |
| *Salmonella typhimurium* TA98, reverse mutation | NT | (+)[d] | 9 µg/plate | Pool *et al.* (1984) |
| *Salmonella typhimurium* TA98, reverse mutation | + | NT | 12.5 µg/plate | O'Donovan & Mee (1993) |
| *Salmonella typhimurium* (other miscellaneous strains), reverse mutation | – | – | 100 µg/plate (toxic at 250 µg/plate) | Connor *et al.* (1983) |
| *Salmonella typhimurium* TM677, forward mutation to 8-azaguanine | + | + | 5; 10[e] | Temcharoen & Thilly (1983) |
| *Salmonella typhimurium* TA97, reverse mutation | + | NT | 12 µg/plate[c] | Marnett *et al.* (1985) |
| *Salmonella typhimurium* TA7005 (*his*[+]), reverse mutation | + | NT | 1.5 µg/plate | Ohta *et al.* (2000) |
| *Escherichia coli* K12, forward or reverse mutation (*gpt* locus) | + | NT | 120 | Crosby *et al.* (1988) |
| *Escherichia coli* K12, forward or reverse mutation | + | NT | 60 | Zijlstra (1989) |
| *Escherichia coli* K12, forward or reverse mutation | + | NT | 18.8 | Graves *et al.* (1994) |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| *Escherichia coli* WP2 *uvr*A, reverse mutation | + | NT | 15 | Takahashi *et al.* (1985) |
| *Escherichia coli* WP2 *uvr*A (pKM101), reverse mutation | + | NT | 12.5 µg/plate | O'Donovan & Mee (1993) |
| *Escherichia coli* WP2, reverse mutation | + | NT | 1200 | Nishioka (1973) |
| *Escherichia coli* WP2, reverse mutation | + | NT | 60 | Takahashi *et al.* (1985) |
| *Escherichia coli* WP2 (pKM101), reverse mutation | + | NT | 25 µg/plate | O'Donovan & Mee (1993) |
| *Escherichia coli* (other miscellaneous strains), reverse mutation | + | NT | 100 | Demerec *et al.* (1951) |
| *Escherichia coli* (other miscellaneous strains), reverse mutation | + | NT | 900 | Panfilova *et al.* (1966) |
| *Escherichia coli* (other miscellaneous strains), reverse mutation | + | NT | 30 | Takahashi *et al.* (1985) |
| *Escherichia coli* WP3104P, reverse mutation | (+) | NT | 5 µg/plate | Ohta *et al.* (1999) |
| *Escherichia coli* WP3104P, reverse mutation | + | NT | ~2 µg/plate | Ohta *et al*. (2000) |
| *Saccharomyces* species, DNA strand breaks and DNA repair | + | NT | 990 | Magaña-Schwencke *et al.* (1978) |
| *Saccharomyces* species, DNA strand breaks, DNA–protein cross links or related damage | + | NT | 500 | Magaña-Schwencke & Ekert (1978); Magaña-Schwencke & Moustacchi (1980) |
| *Saccharomyces cerevisiae,* gene conversion | + | NT | 540 | Chanet *et al.* (1975) |
| *Saccharomyces cerevisiae,* homozygosis by mitotic recombination or gene conversion | + | NT | 18.5 | Zimmermann & Mohr (1992) |
| *Neurospora crassa* heterokaryons H-12 strain, forward mutation | (+) | NT | 250 | de Serres *et al.* (1988); de Serres & Brockman (1999) |

**Table 37 (contd)**

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| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| *Neurospora crassa* heterokaryons H-59 strain, forward mutation | + | NT | 100 | de Serres *et al.* (1988); de Serres & Brockman (1999) |
| *Neurospora crassa*, reverse mutation | – | NT | 732 | Dickey *et al.* (1949) |
| *Neurospora crassa*, reverse mutation | + | NT | 300 | Jensen *et al.* (1951) |
| *Neurospora crassa*, reverse mutation | – | NT | 300 | Kölmark & Westergaard (1953) |
| *Agaricus bisporus, Glycine max, Lycopersicon esculentum, P. americana, Pinus resinosa, Pisum sativum, Populus × eur-americana, Vicia faba, Zea mays*, DNA damage | + | NT | 3.7% solution, pH 3 and 7, 37 000 µg/mL | Douglas & Rogers (1998) |
| Plants (other), mutation | + | NT | NG | Auerbach *et al.* (1977) |
| *Tradescantia pallida*, micronucleus formation | + | NT | 250 ppm [250 µg/mL], 6 h | Batalha *et al.* (1999) |
| *Drosophila melanogaster*, genetic crossing over or recombination | + | | 1260 | Sobels & van Steenis (1957) |
| *Drosophila melanogaster*, genetic crossing over or recombination | + | | 420 | Alderson (1967) |
| *Drosophila melanogaster*, genetic crossing over or recombination | + | | 2500 | Ratnayake (1970) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 1000 | Kaplan (1948) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 1800 | Auerbach & Moser (1953) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 1260 | Sobels & van Steenis (1957) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 420 | Alderson (1967) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 420 | Khan (1967) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | (+) | | 2000 | Ratnayake (1968) |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 250 | Stumm-Tegethoff (1969) |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| *Drosophila melanogaster*, sex-linked recessive lethal mutations | + | | 2200 | Ratnayake (1970) |
| *Drosophila melanogaster*, heritable translocation | + | | 420 | Khan (1967) |
| *Drosophila melanogaster*, heritable translocation | + | | 2500 | Ratnayake (1970) |
| *Drosophila melanogaster*, dominant lethal mutation | + | | 1800 | Auerbach & Moser (1953) |
| *Drosophila melanogaster*, dominant lethal mutation | + | | 1300 | Šrám (1970) |
| *Caenorhabditis elegans,* recessive lethal mutations | + | | 700 | Johnsen & Baillie (1988) |
| DNA strand breaks, DNA–protein cross-links or related damage, mouse leukaemia L1210 cells *in vitro* | + | NT | 6 | Ross & Shipley (1980) |
| DNA–protein cross-links, mouse leukaemia L1210 cells *in vitro* | + | NT | 3.75 | Ross *et al.* (1981) |
| DNA single strand breaks, DNA–protein cross-links or related damage, sarcoma rat cell line *in vitro* | + | NT | 7.5 | O'Connor & Fox (1987) |
| DNA single strand breaks or related damage, rat hepatocytes *in vitro* | + | NT | 22.5 | Demkowicz-Dobrzanski & Castonguay (1992) |
| DNA–protein cross-links, Chinese hamster ovary cells *in vitro* | + | NT | 7.5 | Olin *et al.* (1996) |
| DNA–protein cross-links, male B6C3F$_1$ mouse hepatocytes *in vitro* | + | NT | 15 | Casanova *et al.* (1997) |
| DNA–protein cross-links, Chinese hamster V79 lung fibroblast cells *in vitro* | + | NT | 4 | Merk & Speit (1998, 1999) |
| Unscheduled DNA synthesis, Syrian hamster embryo cells *in vitro* | + | NT | 3 | Hamaguchi *et al.* (2000) |
| Gene mutation, Chinese hamster V79 cells, *Hprt* locus | + | NT | 9 | Grafström *et al.* (1993) |
| Gene mutation, Chinese hamster V79 cells, *Hprt* locus | − | NT | 15 | Merk & Speit (1998, 1999) |
| Gene mutation, mouse lymphoma L5178Y cells, *Tk*$^{+/−}$ locus *in vitro* | NT | + | 24 | Mackerer *et al.* (1996) |
| Gene mutation, mouse lymphoma L5178Y cells *in vitro* | + | NT | > 2 | Speit & Merk (2002) |
| Sister chromatid exchange, Chinese hamster cells *in vitro* | + | NT | 1 | Obe & Beek (1979) |
| Sister chromatid exchange, Chinese hamster cells *in vitro* | + | + | 3.2 | Natarajan *et al.* (1983) |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| Sister chromatid exchange, Chinese hamster cells *in vitro* | + | – | 2 | Basler *et al.* (1985) |
| Sister chromatid exchange, Chinese hamster V79 cells *in vitro* | + | NT | 4 | Merk & Speit (1998, 1999) |
| Micronucleus formation, Chinese hamster V79 cells *in vitro* | + | NT | 4 | Merk & Speit (1998, 1999) |
| Chromosomal aberrations, Chinese hamster cells *in vitro* | + | NT | 18 | Ishidate *et al.* (1981) |
| Chromosomal aberrations, Chinese hamster cells *in vitro* | + | + | 6.3 | Natarajan *et al.* (1983) |
| Cell transformation, C3H10T1/2 mouse cells | +[f] | NT | 0.5 | Ragan & Boreiko (1981) |
| DNA single strand breaks, DNA–protein cross-links, human bronchial cells *in vitro* | + | NT | 24 | Fornace *et al.* (1982) |
| DNA single strand breaks, DNA–protein cross-links or related damage, human bronchial and skin cells *in vitro* | + | NT | 3 | Grafström *et al.* (1984) |
| DNA single strand breaks, DNA–protein cross-links or related damage, human bronchial cells *in vitro* | + | NT | 3 | Saladino *et al.* (1985) |
| DNA single strand breaks, DNA–protein cross-links or related damage, human bronchial cells *in vitro* | + | NT | 3 | Grafström *et al.* (1986) |
| DNA strand breaks, cross-links or related damage, human fibroblast cells *in vitro* | + | NT | 3 | Snyder & Van Houten (1986) |
| DNA strand breaks, DNA–protein cross-links or related damage, human lymphoblast cells *in vitro* | + | NT | 1.5 | Craft *et al.* (1987) |
| DNA strand breaks, DNA–protein cross-links or related damage, human bronchial cells *in vitro* | + | NT | 12 | Grafström (1990) |
| DNA–protein cross-links, human fibroblasts *in vitro* | + | NT | 7.5 | Olin *et al.* (1996) |
| DNA–protein cross-links, human white blood cells *in vitro* | + | NT | 3 | Shaham *et al.* (1996) |
| DNA–protein cross-links, EBV-BL human lymphoma cells *in vitro* | + | NT | 37 × 18 h | Costa *et al.* (1997) |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| DNA double-strand breaks, human lung epithelial (A549) cells *in vitro* | + | NT | 30 (8, 24, 72 h) | Vock *et al*. (1999) |
| DNA–protein cross-links, Comet assay, human gastric mucosa cells *in vitro* | + | NT | 30 | Blasiak *et al*. (2000) |
| DNA–protein cross-links, human lymphocytes *in vitro* | + | – | 3 | Andersson *et al*. (2003) |
| DNA repair exclusive of unscheduled DNA synthesis, human bronchial and skin cells *in vitro* | + | NT | 6 | Grafström *et al*. (1984) |
| DNA repair, human MRC5CV1 normal cell line, XP12 ROSV cell line, GMO6914 FA cell line, *in vitro* | + | NT | 3.75 | Speit *et al*. (2000) |
| Unscheduled DNA synthesis, human bronchial epithelial cells *in vitro* | - | NT | 3 (> 3 was lethal) | Doolittle *et al*. (1985) |
| Gene mutation, human lymphoblasts TK6 line (*TK* locus) *in vitro* | + | NT | 3.9 | Goldmacher & Thilly (1983) |
| Gene mutation, human fibroblasts *in vitro* | + | NT | 3 | Grafström *et al*. (1985) |
| Gene mutation, human lymphoblasts TK6 line (*TK* locus) *in vitro* | + | NT | 0.9 | Craft *et al*. (1987) |
| Gene mutation, human lymphoblasts TK6 line (*HPRT* locus) *in vitro* | + | NT | 4.5, 2 h, × 8 times | Crosby *et al*. (1988) |
| Gene mutation, human lymphoblasts TK6 line (*HPRT* locus) *in vitro* | + | NT | 4.5, 2 h, × 8 times | Liber *et al*. (1989) |
| Gene mutation, human bronchial fibroblasts (*HPRT* locus) *in vitro* | + | NT | 3 | Grafström (1990) |
| Sister chromatid exchange, human lymphocytes *in vitro* | + | NT | 5 | Obe & Beek (1979) |
| Sister chromatid exchange, human lymphocytes *in vitro* | + | NT | 5 | Kreiger & Garry (1983) |
| Sister chromatid exchange, human lymphocytes *in vitro* | + | + | 3.75 | Schmid *et al*. (1986) |
| Micronucleus formation, human MRC5CV1 normal cell line, XP12 ROSV cell line, GMO6914 FA cell line, *in vitro* | + | NT | 3.75 | Speit *et al*. (2000) |
| Chromosomal aberrations, human fibroblasts *in vitro* | + | NT | 60 | Levy *et al*. (1983) |

Table 37 (contd)

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| Chromosomal aberrations, human lymphocytes *in vitro* | + | NT | 10 | Miretskaya & Shvartsman (1982) |
| Chromosomal aberrations, human lymphocytes *in vitro* | + | + | 7.5 | Schmid *et al.* (1986) |
| Chromosomal aberrations, premature chromosome condensation technique, human lymphocytes *in vitro* | + | NT | 3.75 | Dresp & Bauchinger (1988) |
| DNA–protein cross-links, rat respiratory and olfactory mucosa and bone marrow *in vivo* | + | | 2 ppm [2.5 mg/m$^3$], 6 h | Casanova-Schmitz *et al.* (1984b) |
| DNA–protein cross-links, rat nasal mucosa *in vivo* | + | | 6 ppm [7.4 mg/m$^3$], 6 h | Lam *et al.* (1985) |
| DNA–protein cross-links, rat respiratory mucosa *in vivo* | + | | 2 ppm [2.5 mg/m$^3$], 3 h | Heck *et al.* (1986) |
| DNA–protein cross-links, rat respiratory and olfactory mucosa and bone marrow *in vivo* | + | | 2 ppm [2.5 mg/m$^3$], 3 h | Casanova & Heck (1987) |
| DNA–protein cross-links, rat tracheal implant cells *in vivo* | + | | 50 ppm [50 μg/mL], instil. | Cosma *et al.* (1988) |
| DNA–protein cross-links, rat nasal respiratory mucosa *in vivo* | + | | 0.3 ppm [0.4 mg/m$^3$], inhal. 6 h | Casanova *et al.* (1989) |
| DNA–protein cross-links, rhesus monkey nasal turbinate cells *in vivo* | + | | 0.7 ppm [0.9 mg/m$^3$], inhal. 6 h | Heck *et al.* (1989) |
| DNA–protein cross-links, rhesus monkey nasal turbinate cells *in vivo* | + | | 0.7 ppm [0.9 mg/m$^3$], inhal. 6 h | Casanova *et al.* (1991) |
| Gene mutation, rat cells *in vivo* (*p53* point mutations in nasal squamous-cell carcinomas) | + | | 15 ppm [18.45 mg/m$^3$], inhal. 6 h/d, 5 d/wk, 2 y | Recio *et al.* (1992) |
| Mouse spot test | – | | 15 ppm [18 mg/m$^3$], inhal. 6 h/d × 3 | Jensen & Cohr (1983) [Abstract] |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| Sister chromatid exchange, rat cells *in vivo* | – | | 15 ppm [18.45 mg/m$^3$], inhal. 6 h/d × 5 | Kligerman *et al.* (1984) |
| Micronucleus formation, mouse bone-marrow cells *in vivo* | – | | 30 ip × 1 | Gocke *et al.* (1981) |
| Micronucleus formation, mouse bone-marrow cells *in vivo* | – | | 25 ip × 1 | Natarajan *et al.* (1983) |
| Micronucleus formation, rat gastrointestinal tract *in vivo* | + | | 200 po × 1 | Migliore *et al.* (1989) |
| Micronucleus formation, newt (*Pleurodeles waltl*) *in vivo* | – | | 5 µg/mL, 8 d | Siboulet *et al.* (1984) |
| Chromosomal aberrations, mouse bone-marrow cells *in vivo* | – | | 25 ip × 1 | Natarajan *et al.* (1983) |
| Chromosomal aberrations, rat bone-marrow cells *in vivo* | + | | 0.4 ppm [0.5 mg/m$^3$] inhal. 4 h/d, 4 mo | Kitaeva *et al.* (1990) |
| Chromosomal aberrations, rat bone-marrow cells *in vivo* | – | | 15 ppm [18.45 mg/m$^3$], inhal. 6 h/d × 5, 8 wk | Dallas *et al.* (1992) |
| Chromosomal aberrations, rat leukocytes *in vivo* | – | | 15 ppm [18.45 mg/m$^3$], inhal. 6 h/d × 5 | Kligerman *et al.* (1984) |
| Chromosomal aberrations, mouse spermatocytes treated *in vivo*, spermatocytes observed | – | | 50 ip × 1 | Fontignie-Houbrechts (1981) |
| Chromosomal aberrations, mouse spleen cells *in vivo* | – | | 25 ip × 1 | Natarajan *et al.* (1983) |
| Chromosomal aberrations, rat pulmonary lavage cells *in vivo* | + | | 15 ppm [18.45 mg/m$^3$] inhal. 6 h/d × 5 | Dallas *et al.* (1992) |

**Table 37 (contd)**

| Test system | Result[a] | | Dose[b] (LED/HID) | Reference |
|---|---|---|---|---|
| | Without exogenous metabolic system | With exogenous metabolic system | | |
| Dominant lethal mutation, mouse | – | | 20 ip × 1 | Epstein & Shafner (1968) |
| Dominant lethal mutation, mouse | – | | 20 ip × 1 | Epstein *et al.* (1972) |
| Dominant lethal mutation, mouse | (+) | | 50 ip × 1 | Fontignie-Houbrechts (1981) |
| Dominant lethal mutation, rat | (+) | | 1.2 ppm [1.5 mg/m$^3$] inhal. 4 h/d, 4 mo | Kitaeva *et al.* (1990) |

EBV, Epstein–Barr virus; BL, Burkitt lymphoma; XP, xeroderma pigmentosum; FA, Fanconi anaemia

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

[b] In-vitro tests, μg/mL; in-vivo tests, mg/kg bw; d, day; inhal., inhalation; instil., instillation; ip, intraperitoneal; mo, month; NG, not given; po, oral; wk, weeks; y, year

[c] Estimated from the graph in the paper

[d] Tested with exogenous metabolic system without co-factors

[e] LED with exogenous metabolic system is 0.33 mM [10 μg/mL].

[f] Positive only in presence of 12-*O*-tetradecanoylphorbol 13-acetate

(*b*)     *Mutation and allied effects* (see also Table 37)

(i)     *In-vitro studies*

Formaldehyde induced mutation and DNA damage in bacteria, mutation, gene conversion, DNA strand breaks and DNA–protein cross-links in fungi and DNA damage in plants. In *Drosophila 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, sister chromatid exchange and micronuclei in Chinese hamster V79 cells and transformation of mouse C3H10T1/2 cells *in vitro.* Formaldehyde 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, such as *N*-nitroso-*N*-methylurea or ionizing radiation (Grafström, 1990; Grafström *et al.*, 1993).

(ii)     *In-vivo studies in animals*

Formaldehyde induces cytogenetic damage in the cells of tissues of animals exposed either by gavage or by inhalation. 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 gastro-intestinal epithelium. The frequency of mitotic figures was used as an index of cell proliferation. Treated rats had significant (greater than fivefold) 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 was 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).

Male Sprague–Dawley rats were exposed by inhalation 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 5 days per week for 1 and 8 weeks. No significant increase in chromosomal abnormalities in the bone-marrow cells of formaldehyde-exposed rats was observed relative to controls, but the frequency of chromosomal aberrations was significantly increased in pulmonary lavage cells (lung alveolar macrophages) from rats that inhaled 15 ppm formaldehyde. Aberrations, which were predominantly chromatid breaks, were seen in 8.0 and 9.2% of the scored pulmonary lavage cells from treated animals and in 3.5 and 4.4% of cells from controls after 1 and 8 weeks, respectively (Dallas *et al.*, 1992).

In a second in-vivo study on bone-marrow cytogenetics, Wistar rats were exposed by inhalation to formaldehyde (0.5 or 1.5 mg/m$^3$) every day for 4 h (except for non-working days) for 4 months (Kitaeva *et* al., 1990). The concentration of 1.5 mg/m$^3$ formaldehyde caused diverse effects on germ cells that the authors correlated with their subsequent studies that showed impairment of early embryonic development (see Section 4.3.2). Both

concentrations (0.5 and 1.5 mg/m³) caused a significantly increased number of chromosomal aberrations in the bone marrow that were of the chromatid (at 0.5 mg/m³) and chromosomal (at 1.5 mg/m³) type. The number of hypoploidal and hyperploidal cells was increased. The increase in aneuploidy was due only to chromosomal loss, not to chromosomal gain. At the higher exposure, chromosomal type aberrations were observed. [The Working Group noted that this was the only study that evaluated bone-marrow cytogenetics. Since chromosomal loss can frequently occur as an artefact of sample preparation, these studies should be repeated.] The study showed that exposure to formaldehyde at the lower dose was cytotoxic and mutagenic to bone-marrow cells. In an in-vitro part of this study, exposure to 0.5 mg/m³ formaldehyde caused a decrease in the mitotic index in bone-marrow cells while, at 1.5 mg/m³, the mitotic index was increased (Kitaeva *et al.*, 1990). [The Working Group noted that this is the only in-vivo study that showed positive cytogenetic effects of formaldehyde in the bone marrow.]

### (c)    Mutational spectra

#### (i)    In-vitro studies (see also Table 37 and references therein)

The spectrum of mutations induced by formaldehyde was studied in human lymphoblasts *in vitro*, in *Escherichia coli* and in naked pSV2*gpt* plasmid DNA (Crosby *et al.*, 1988). Thirty mutant TK6 X-linked *HPRT⁻* human lymphoblast colonies induced by eight repetitive treatments with 150 µmol/L [4.5 µg/mL] 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.

Sixteen of the 30 formaldehyde-induced human lymphoblast TK6 X-linked *HPRT* mutants referred to above that 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, one had a smaller size of mRNA and three produced no detectable mRNA. Sequence analyses of cDNA prepared from *HPRT* mRNA were performed on one spontaneous and seven formaldehyde-induced mutants indicated 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.

In *E. coli*, the mutations induced by formaldehyde were characterized with the use of the xanthine guanine phosphoribosyl transferase gene as the target gene. Exposure of *E. coli* to 4 mmol/L [120 µg/mL] 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 pSV2*gpt* plasmid DNA was exposed to 3.3 or 10 mmol/L [99 or 300 µg/mL] formaldehyde and used to transform *E. coli*, most of the resulting mutations were frameshifts that resulted from the addition or deletion of one base, which again suggests a different mechanism of mutation.

The potential of formaldehyde to induce mutation was determined in mouse lymphoma L5178Y cells treated for 2 h with different concentrations (62.5–500 µM [1.9–15 µg/mL]). The mouse lymphoma assay detects gross alterations as large deletions and rearrangements. Treated cells showed a concentration-related increase in mutation frequency. While the frequency of small colonies was increased, only a marginal increase was observed in the frequency of large colonies. The extent of loss of heterozygosity was studied at five polymorphic markers — D11Agll, D11Mit67, D11Mit29, D11Mit21 and D11Mit63 — all of which are equally distributed along chromosome 11. The analysis showed increased loss of heterozygosity at the marker D11Agll, which is located in the tirosine kinase gene. The authors suggested that the main mechanism involved in the mutagenesis of formaldehyde in the mouse lymphoma assay is the production of small-scale chromosomal deletion or recombination (Speit & Merk, 2002).

Exposure of Chinese hamster V79 cells to formaldehyde did not induce gene mutation at the *Hprt* locus, while DNA–protein cross-links, sister chromatid exchange and micronuclei were induced (Merk & Speit, 1998). Formaldehyde induced G:C→T:A transversion in *E. coli* Lac[+] WP3104P and in *S. typhimurium* His[+] TA7005 (Ohta *et al.*, 1999, 2000).

Specific locus mutations at two closely linked loci in the *adenine-3* (*ad-3*) region were compared in two strains of *Neurospora crassa* (H-12, a DNA repair-proficient heterokaryon; and H-59, a DNA repair-deficient heterokaryon) exposed to formaldehyde. The majority (93.2%) of formaldehyde-induced *ad-3* mutations in H-12 resulted from gene/point mutations and only 6.8% resulted from multilocus deletion mutations. In contrast, a greater percentage of formaldehyde-induced *ad-3* mutations (62.8%) observed in H-59 resulted from multilocus deletion mutations. The distribution of *ad-3* mutation in this mutational spectra is highly significantly different ($p \ll 0.001$). While formaldehyde induced only a 12.8-fold increase in the frequency of *ad-3* mutations over that which occurs spontaneously in H-12, it induced a 412-fold increase in H-59. Formaldehyde induced a 3.4-fold higher ($p \ll 0.001$) *ad-3B*[R]/*ad-3A*[R] ratio in H-12 than in H-59. According to the authors, these results indicated that there was a quantitative and qualitative strain difference in formaldehyde-induced mutagenesis (de Serres *et al.*, 1988; de Serres & Brockman, 1999).

(ii)    *In-vivo studies in animals*

DNA sequence analysis of PCR-amplified cDNA fragments that contain 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 that had been exposed by inhalation to 15 ppm [18.5 mg/m^{3}] formaldehyde for up to 2 years. Point mutations at GC base-pairs in the *p53* complementary DNA sequence were found in five of the tumours

(Table 38). The authors pointed out that all five human counterparts of the mutated *p53* codons listed in Table 38 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 that occurs in many human cancers (Recio *et al.*, 1992).

**Table 38. DNA sequence analysis of *p53* cDNA (PCR 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 | TT<u>C</u>→TT<u>A</u> (132) | phe→leu | 134 | II |
| $_{398}$G→T | T<u>G</u>C→T<u>T</u>C (133) | cys→phe | 135 | II |
| $_{638}$G→T | A<u>G</u>C→A<u>T</u>C (213) | ser→ile | 215 | |
| $_{812}$G→A | C<u>G</u>T→C<u>A</u>T (271) | arg→his | 273 | V |
| $_{842}$G→C | C<u>G</u>G→C<u>C</u>G (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.

An immunohistochemical technique was used to assess the presence of p53 protein, a marker of cell proliferation (proliferating cell nuclear antigen) and tumour growth factor-α in the histopathological sections of the above tumours. In addition to the positive p53 immunostaining in squamous-cell carcinomas, especially in cells with keratization, p53-positive immunostaining was also observed in preneoplastic hyperkeratotic plaques while normal nasal mucosa immunostained negatively. A correlation was found between both the pattern and the distribution of immunostaining of proliferating cell nuclear antigen and p53 (Wolf *et al.*, 1995).

Cell lines were established from the above set of squamous-cell carcinomas and, when injected into nude mice, two of them that contained the *p53* mutation were tumorigenic while the two cell lines that contained wild-type *p53* were not. The author suggested that these findings indicate that *p53* mutation occurs in the development of certain rodent nasal squamous-cell carcinomas and that it is associated with tumorigenicity (Recio, 1997). All the mutated *p53* codons that were identified in formaldehyde-induced rat squamous-cell carcinomas have also been found to be mutated in a variety of human cancers (for example, rat codon 271, human codon 273). *P53* is mutated in various human squamous-cell carcinomas including those of the respiratory tract, skin and oesophagus. It was suggested that these data indicate that the development of certain human and rat squamous-cell carcinomas share a molecular change. The author proposed a possible mechanistic explanation, which is based on the fact that the induction of nasal squamous-cell carcinomas by formal-

dehyde is accompanied by cytotoxicity and inflammation followed by cell proliferation that may induce genetic alterations.

Formaldehyde is also known to be genotoxic; a number of lesions have been proposed to explain this genotoxic effect, including DNA–protein cross-links (reviewed in IARC, 1995). Studies on the *HPRT* mutation spectrum in formaldehyde-exposed human cells revealed that 50% of the mutations are deletions, while 50% are due to point mutation at the A:T base-pair (Liber *et al.*, 1989). The finding of deletions as part of the formaldehyde mutation spectrum may explain the homozygous nature of pair mutations observed in *p53* in formaldehyde-induced squamous-cell carcinomas. However, there is an inconsistency with regard to the base-pair that is found to be A:T in *HPRT* in human (Liber *et al.*, 1989) and mammalian cell lines (Graves *et al.*, 1996) and G:C in *p53* in formaldehyde-induced squamous-cell carcinomas. The author suggested that an indirect mechanism of genotoxicity and not a direct effect of formaldehyde on the genome is involved in the carcinogenic process of formaldehyde (Recio, 1997).

In order to evaluate transcriptional changes involved with acute exposure to formaldehyde, two groups of male Fischer 344 rats received either 40 µL distilled water or formaldehyde (400 mM [12 mg/mL]) instilled into each nostril. Twenty-four hours after this treatment, total RNA was extracted from the nasal epithelium to generate cDNA. Adjusted signal intensity was obtained from image analysis of 1185 genes from samples from four controls and three formaldehyde-treated rats. Significance analysis of microarray hybridization data using Clontech™ Rat Atlas 1.2 arrays revealed that 24/1185 genes studied were significantly up-regulated and 22 genes were significantly down-regulated. Ten of the most highly expressed genes for formaldehyde-treated animals included the *N*-methyl-D-aspartate receptor, inducible nitric oxide synthase, macrophage inflammatory protein 1 α and macrophage inflammatory protein 2, Wilms tumour protein homologue 1, tumour necrosis factor ligand, methyl-CpG-binding protein 2, GABA receptor, Fos-responsive gene 1 and presomatotrophin. Of the 24 significantly up-regulated genes, six were receptors, six were involved in extracellular cell signalling and four were oncogene/tumour-suppressor genes, all of which are pathways that could be affected by treatment with formaldehyde. Of the 22 significantly down-regulated genes, five were involved in ion channel regulation and four were involved in protein turnover which suggests that an early response to treatment with formaldehyde may be impaired ion channel function and interruption of protein processing. Many phase I and phase II genes that regulate xenobiotic metabolism and oxidative stress — the CYP and glutathione family, respectively — were altered in treated but not in controls rats. In order to validate the direction of gene expression observed on the microarray, results for 10 of the differentially expressed genes were confirmed by quantitative real-time PCR. Eight of the 10 gene expression values were in positive agreement. No significant difference was found between formaldehyde-treated and control groups in relation to the expression of apoptosis genes. However, in comparison with the control group, the formaldehyde-treated group had a general trend of lower levels of expression of nine apoptic genes that represent three of the major apoptosis regulation pathways, including receptor-mediated, caspase and the mitochondrial-

associated *bcl2* family of genes. The authors suggested that their results indicated that exposure to formaldehyde can cause alteration in the levels of expression of genes that are involved in several functional categories including xenobiotic metabolism, cell cycle regulation, DNA synthesis and repair, oncogenes and apoptosis (Hester *et al.*, 2003).

## 4.5     Mechanistic considerations

### 4.5.1     *Deposition (airway deposition models)*

Anatomically accurate CFD models have been applied to study the role of nasal airflow and formaldehyde flux in rats, monkeys and humans in order to achieve more accurate risk assessments (Kimbell & Subramaniam, 2001; Kimbell *et al.*, 2002). The use of DNA–protein cross-links as a measure of internal dose, as opposed to the use of air concentration, coupled with the use of monkey-based as opposed to rat-based predictions, resulted in a 50-fold reduction in risk for humans (McClellan, 1995).

Using the Fischer 344 rat CFD model, a sharp anterior to posterior gradient of formaldehyde deposition in the rat nose is predicted, which agrees with observed patterns of formation of DNA–protein cross-links and effects on cell replication (Monticello *et al.*, 1996; Cohen Hubal *et al.*, 1997). In another study, predictions of formaldehyde dosimetry in the non-squamous epithelium in the rat CFD model were used to analyse the role of local flux on the distribution of squamous metaplasia induced by 10 ppm and 15 ppm formaldehyde (Kimbell *et al.*, 1997). Squamous metaplasia is a useful indicator for formaldehyde-induced squamous-cell carcinoma in rodents due to its temporal relevance and consistency (McMillan *et al.*, 1994). Predictions obtained with the model illustrate how, as squamous metaplasia develops, the sites of maximum absorption of formaldehyde move further back in the nose.

In the rhesus monkey, a CFD model of the nasal passages was used to facilitate species-to-species extrapolation of data on the toxicity of formaldehyde (Kepler *et al.*, 1998). As with rats, an anterior to posterior gradient in formaldehyde deposition was predicted and a strong correlation was observed between patterns of airflow and the occurrence of nasal lesions.

In a comparison of Fischer 344 rats, rhesus monkeys and humans, the role of mucous- and non-mucous-coated tissue on formaldehyde uptake was analysed (Kimbell *et al.*, 2001b). Flux values for rats and monkeys were found to be very similar at sites where the effects of formaldehyde on cell proliferation had previously been observed. Similar flux values were predicted in a region of the nasal passage where a high incidence of tumours had been observed in rats and in an anterior region of the human nasal passage. It was suggested that a similar formaldehyde-induced response in rats might be expected in humans when regional fluxes are similar.

CFD models of Fischer 344 rat, rhesus monkey and human nasal passages were also used to predict patterns of wall mass flux in order to reduce the uncertainty in interspecies extrapolation of dose within the nasal passages (Kimbell *et al.*, 2001a). In all cases, steep

anterior-to-posterior gradients of formaldehyde deposition were predicted. The surface area and average flux were estimated for the flux bins at different airflow rates. At a minute volume of 15 L/min, approximately 20% of the surface area of the human nasal passages had a predicted flux value greater than the median flux value. Increasing airflow in humans was also associated with a distal shift in flux patterns and a reduced percentage of uptake in the nasal passages. Differences across species in nasal anatomy and associated differences in flux were also suggested to play a potentially large role in the occurrence of local adverse effects due to the non-linear relationships of flux with DNA–protein cross-links and with cell proliferation. The adsorption of formaldehyde on inhaled particles does not appreciably alter the patterns of formaldehyde deposition associated with the inhalation of formaldehyde vapour (Rothenberg *et al.*, 1989; Risby *et al.*, 1990).

### 4.5.2    *Metabolism*

Formaldehyde is an endogenous metabolite that is formed by demethylation reactions and used in the biosynthesis of macromolecules. Average concentrations, including bound and free forms, in cells and biological fluids are reported to be about 0.1 mM (Heck *et al.*, 1985). Formaldehyde readily combines with GSH to form hydroxymethylglutathione, which is converted to formate in a two-step enzymatic reaction that initially involves ADH3. The $K_m$ for the initial binding of hydroxymethylglutathione with ADH3 is in the order of 4 µM and the level of free formaldehyde is probably even lower (Holmquist & Vallee, 1991; Uotila & Koivusalo, 1997; Hedberg *et al.*, 1998). The half-life of formaldehyde in plasma is very short, and is approximately 1 min in rats exposed intravenously (Rietbrock, 1965).

### 4.5.3    *Genotoxicity*

Formaldehyde induced DNA–protein cross-links *in vitro* in human bronchial epithelial cells, fibroblasts and lymphocytes, in Chinese hamster ovary cells and in non-transformed human fibroblasts (Grafström *et al*., 1984; Olin *et al*., 1996; Shaham *et al*., 1996a,b). The formation of DNA–protein cross-links showed a consistent dose–effect relationship and was induced at concentrations of formaldehyde that allowed survival of up to 75% of the cells (Merk & Speit, 1998, 1999). A range of half-lives for the removal of DNA–protein cross-links from the cells has been reported (3–66 h), but most of the values are in the vicinity of 24 h (Gräfstrom *et al*., 1984; Merk & Speit, 1998, 1999; Quievryn & Zhitkovich, 2000).

Several studies that compared the kinetics of the formation and removal of DNA–protein cross-links in a variety of cell types reported no differences among normal and DNA repair-deficient cell types (Grafström *et al*., 1984; Speit *et al*., 2000). DNA single-strand breaks and/or alkali-labile sites are generated from the repair of formaldehyde damage in normal cells (Grafström *et al*., 1984). Formaldehyde is more toxic to Xeroderma Pigmentosum cells, which also show a higher percentage of micronuclei than normal cells. The data

suggested that neither defective nucleotide excision repair (Xeroderma Pigmentosum cells) nor defective cross-link repair (Fanconi anaemia cells) seem to delay the removal of formaldehyde-induced DNA–protein cross-links significantly and that more than one repair pathway may be involved in the removal of cross-links (Grafström *et al*., 1984; Speit *et al*., 2000). Human peripheral blood lymphocytes lost DNA–protein cross-links at a significantly slower rate than established cell lines (Quievryn & Zhitkovich, 2000). Repair of formaldehyde-induced DNA–protein cross-links was not changed significantly due to loss of GSH. Additional studies have indicated that the active removal of DNA–protein cross-links from cells may involve proteolytic degradation of cross-link proteins (Quievryn & Zhitkovich, 2000). Several studies indicate that formaldehyde may also interfere with the processes of repair of DNA by (*a*) inhibiting DNA repair enzymes, (*b*) inhibiting the removal of DNA lesions and (*c*) altering gene expression (Grafström *et al*., 1996).

Assessment of DNA–protein cross-links and sister chromatid exchange in peripheral lymphocytes from formaldehyde-exposed workers demonstrated an association with overall exposure (Shaham *et al*., 1996a,b, 2003). It remains unclear to what extent these endpoints contribute to the mutagenesis and carcinogenicity of formaldehyde (Recio *et al.*, 1992; Merk & Speit, 1998; Speit *et al*., 2000; Liteplo & Meek, 2003).

Studies in humans have reported both positive and negative results for the incidence of micronuclei in nasal and buccal mucosa in workers exposed to formaldehyde (see Table 36). In one study of both buccal and nasal mucosa, a greater increase was observed in centromere-negative micronuclei than centromere-positive micronuclei, which implicates chromosome breakage as the major mechanism responsible for these effects (Titenko-Holland *et al.*, 1996). Although micronuclei are correlated with risk for cancer in animals, the association between micronuclei and cancer in humans requires clarification because of the high degree of inter-individual variability within the human population (Fenech *et al*., 1999).

The formation of DNA–protein cross-links in the nasal respiratory mucosa of rats after inhalation exposure to 6 ppm [7.4 mg/m$^3$] formaldehyde and higher 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 by HPLC of formaldehyde released from cross-links after exposure to [$^{14}$C]formaldehyde (Casanova *et al.*, 1989, 1994). The formation of DNA–protein cross-links is a non-linear function of concentration (Casanova & Heck, 1987; Casanova *et al.*, 1989, 1994; Heck & Casanova, 1995; see Fig. 8) and correlates with the site-specificity of tumours (Casanova *et al*., 1994). Cross-links were not detected in the olfactory mucosa or in the bone marrow of rats (Casanova-Schmitz *et al.*, 1984b; Casanova & Heck, 1987).

DNA–protein cross-links were also measured in the respiratory tract 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 7.4 mg/m$^3$]) (Casanova *et al.*, 1991). The concentrations of cross-linked formaldehyde in the nose of monkeys decreased in the order: middle

**Figure 8. Average concentration of DNA–protein cross-links formed per unit time in the turbinates and lateral wall/septum of Fischer 344 rats and rhesus monkeys versus the airborne concentration of formaldehyde (CH$_2$O)**
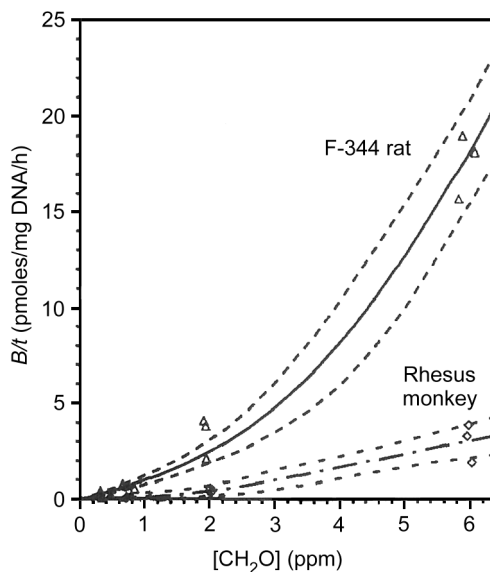
All animals were exposed to formaldehyde for 6 h. Data in rats are taken from Casanova *et al.* (1989). (Results obtained in rats at 10 ppm are omitted for clarity.) Dashed lines are the 95% confidence limits about the mean for each species.

turbinates > lateral wall–septum > nasopharynx, which 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. The yield of cross-links in the nose of monkeys was 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; Fig. 8). 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).

In order to determine whether DNA–protein cross-links accumulate with repeated exposure, the yield of formaldehyde from cross-links was investigated in rats that were exposed either once or subchronically to unlabelled formaldehyde (6 or 10 ppm [7.4 or 12.3 mg/m$^3$]) for 6 h per day on 5 days per week for 11 weeks and 4 days (Casanova *et al.*, 1994). The yield was not higher in pre-exposed than in naive rats, which suggests that no accumulation had occurred in the former. The results also suggest that DNA–protein cross-links in the rat nasal mucosa are removed rapidly.

Conolly *et al.* (2000) described a model of tissue disposition of formaldehyde, which included CFD and measurements of mucosal epithelial thickness in order to refine previous predictions of the occurrence of DNA–protein cross-links in rats, monkeys and humans. The thickness of the epithelial tissue is approximately 4.5 times greater in humans than in rats, which results in a lesser net dose of formaldehyde in humans at concentrations that saturate the metabolic capacity of rats (Schlosser *et al.*, 2003). Good correlations of model predictions and data of cross-links were obtained in association with the regions of high and low tumour response in the rat nose (Conolly *et al.*, 2000).

Merk and Speit (1998) evaluated the significance of DNA–protein cross-links for mutagenesis in V79 Chinese hamster cells. Formaldehyde was seen to induce DNA–protein cross-links, sister chromatid exchange and micronuclei in conjunction with a reduction in relative cloning efficiency. However, no gene mutations were observed in the *Hprt* test. It was concluded that DNA–protein cross-links were related to chromosomal effects, but not directly to gene mutations.

Shaham *et al.* (2003) reported that the formation of DNA–protein cross-links in peripheral lymphocytes in exposed workers was associated with increased serum p53 protein, including wild-type and mutant forms. Recio *et al.* (1992) found *p53* point mutations in 5/11 squamous-cell carcinomas in formaldehdye-exposed rats. Studies have shown (Luo *et al.*, 1994; Hemminki *et al.*, 1996) that higher levels of p53 protein are found in serum years before the diagnosis of malignant tumours such as lung cancer. [The Working Group felt that there may be an association, although further studies are needed to clarify the association between DNA–protein cross-links and effects on the state of p53.]

### 4.5.4    *Cytotoxicity and cell proliferation*

Formaldehyde is well established as a toxicant at the site of contact. Following inhalation exposure, cytotoxicity was evident in the nasal passages of rats and mice (Chang *et al.*, 1983). Toxicity was greatest in the respiratory epithelium of rats, and the median septum and nasoturbinates were the sites most affected. At 15 ppm [18.45 mg/m³], necrosis and sloughing of respiratory epithelium was evident immediately after a single 6-h exposure and early hyperplasia was present 18 h after a single exposure. Mice exhibited lower toxicity in the nasal epithelium associated with reduced exposure due to reduced minute volume. Severe ulcerative rhinitis, inflammation, epithelial hyperplasia and increased cell proliferation were observed in rats exposed to 15 ppm formaldehyde for 5 days (6 h per day). A second study examined cell proliferation and histopathology in rats exposed to 0, 0.7, 2, 6, 10 or 15 ppm [0, 0.86, 2.46, 7.38, 12.3, 18.45 mg/m³] formaldehyde. Increased cell proliferation was evident at 6 and 15 ppm, but not at 2 ppm or lower following 9 days or 6 weeks of exposure (Monticello *et al.*, 1991).

In a mechanistic 24-month carcinogenesis bioassay with interim sacrifices at 1, 4 and 9 days, 6 weeks, and 3, 6, 12 and 18 months, increased cell proliferation was demonstrated at all time-points in rats exposed to 6, 10 and 15 ppm (Monticello *et al.*, 1991, 1996).

Monticello *et al.* (1996) evaluated the relationship of regional increases in nasal epithelial cell proliferation with nasal cancer in rats. Sublinear increases in both cell proliferation and squamous-cell carcinoma were observed with increasing concentration of formaldehyde. A good correlation was observed between site-specific tumour occurrence and the population-weighted unit length labelling index, which incorporates information on both the rate of cell replication and the numbers of cells at specific sites. It was therefore suggested that not only the rate at which cells divided but also the size of the target cell population that underwent DNA replication were crucial factors in the development of formaldehyde-induced nasal squamous-cell carcinoma. Both the rate of cell division and the number of cells in the proliferative pool are thought to increase the chance for mutation at a given dose of formaldehyde. Monticello *et al.* (1996) stated that, although there is evidence to suggest that concentration is more important than duration of exposure in determining the extent of formaldehyde-induced nasal epithelial damage, the development of formaldehyde-induced nasal squamous-cell carcinoma probably requires repeated and prolonged damage to the nasal epithelium. Sustained cellular proliferation, which was seen at 6, 10 and 15 ppm, is thought to play a crucial role in carcinogenesis through the transformation of cells with damaged DNA to mutated cells and the clonal expansion of the mutated cell population (McClellan, 1995).

Studies of cell cultures provide some support that proliferation is stimulated after exposure to formaldehyde (Tyihák *et al.*, 2001). Transcription of *ADH3* was associated with proliferative states (Nilsson *et al.*, 2004), formaldehyde and formate were shown to serve as donors to the one-carbon pool synthesis of macromolecules and, in one study, exposure to formaldehyde was shown to increase cell proliferation (Tyihák *et al.*, 2001).

### 4.5.5    *Cancer*

Nasal squamous-cell carcinomas have been observed in toxicological studies of rats exposed to concentrations of at least 6 ppm formaldehyde (Swenberg *et al.*, 1980; Kerns *et al.*, 1983a,b). Epidemiological studies have also suggested increases in risk for sinonasal carcinomas and particularly for nasopharyngeal carcinoma in humans following exposure to formaldehyde. The exact biological mechanism by which exposure to formaldehyde may cause cancer is currently unknown (Conolly, 2002; Liteplo & Meek, 2003); however, formaldehyde causes formation of DNA–protein cross-links and increases cellular proliferation in the upper respiratory tracts of rats and monkeys.

However, most epidemiological studies of sinonasal cancer have not distinguished tumours that arise in the nose from those that develop in the nasal sinuses. Thus, any effect on the risk for nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk for cancer in the sinuses, and could easily be undetectable through the lack of statistical power.

### 4.5.6    *Computational dose–response modelling*

A theoretical model for DNA replication in the presence of DNA cross-links was developed by Heck and Casanova (1999). This model assumes that DNA–protein cross-links are formed randomly in the DNA and that replication can advance up to but not past a DNA–protein cross-link. This analysis is consistent with the experimental observation of decreased cell proliferation in the nasal epithelium of rats exposed to concentrations of 0.7 and 2.0 ppm [0.86 and 2.46 mg/m³] formaldehyde.

A biologically based model of carcinogenesis of formaldehyde was described by Conolly (2002), which included a two-stage clonal growth model and used the incorporation of both DNA–protein cross-links and cell proliferation, together with linked regional dosimetry predictions, into the model to predict tumour incidence. Through inclusion of this information, the author suggested that a smaller degree of uncertainty was associated with the model.

Since both squamous-cell carcinoma and preneoplastic lesions develop in a characteristic site-specific pattern, Conolly *et al*. (2003) used anatomically accurate three-dimensional CFD models to predict the site-specific flux of formaldehyde from inhaled air into the tissues in rats. Flux into tissues was used as a dose metric for two modes of action: direct mutagenicity and cytolethality–regenerative cellular proliferation (CRCP). The two modes were linked to key parameters of a two-stage model of clonal growth. The direct mutagenic mode of action was represented by a low linear dose–response model of DNA–protein cross-link formation. An empirical J-shaped dose–response model and a threshold model fit to experimental data were used to describe CRCP. The J-shaped dose–response for CRCP provided a better description of the data on squamous-cell carcinoma than the threshold model. Sensitivity analysis indicated that the rodent tumour response is primarily due to the CRCP mode of action and the direct mutagenic pathway has little or no influence. The study suggests a J-shaped dose–response for formaldehyde-mediated nasal squamous-cell carcinoma in Fischer 344 rats. [The Working Group felt that uncertainty remains on some components and parameters of this model, which can affect both predictions of risk and qualitative aspects of model behaviour, and warrants further developmental work.]

Gaylor *et al*. (2004) conducted an analysis of the concentration–response relationship for formaldehyde-induced cell proliferation in rats using statistical methods designed to identify J-shaped concentration–response curves. Such J-shaped curves demonstrate an initial decline in response, followed by a return to background response rates at the zero equivalent dose and then an increase above background response at concentrations above the zero equivalent dose. This analysis demonstrated a statistically significant reduction in cytotoxicity at concentrations below the zero equivalent dose. The authors suggested that, at low doses, the increased risk for nasal cancer due to DNA damage may be offset by a reduction in cell proliferation, a postulate that is consistent with the threshold-like behaviour of the concentration–response curve observed for nasal cancer in rats.

Schlosser *et al*. (2003) described a dose–response assessment of formaldehyde that used a combination of benchmark dose and pharmacokinetic methods. Following the identification of points of departure for both tumours and cell proliferation in rats by analysis of the benchmark dose, extrapolation to humans was performed using either a CFD model alone to predict formaldehyde flux or a CFD model in combination with a pharmacokinetic model to predict the tissue dose and the formaldehyde-induced DNA–protein cross-links as a dose metric. Risk predictions obtained with the benchmark dose model are similar to earlier risk predictions obtained with previous benchmark dose models. The benchmark dose risk predictions are substantially higher than those obtained from the clonal growth time-to-tumour model (Liteplo & Meek, 2003).

### 4.5.7    *Summary of experimental data*

Formaldehyde is an essential metabolic intermediate in all cells, and average concentrations in the blood of unexposed subjects has been reported to be about 0.1 mmol/L. It is a potent nasal irritant, is cytotoxic at high doses and induces nasal cancer in rats exposed to high airborne concentrations. Nasal squamous-cell carcinomas have been observed in toxicological studies of rats exposed to concentrations of at least 6 ppm; the incidence of these tumours increases sharply with further increases in concentration (Monticello *et al*., 1996). In addition, at concentrations of 2 ppm or less, no histological changes have been observed in rodents, although changes at these concentrations have been seen in humans (IARC, 1995; Liteplo & Meek, 2003).

Early assessments estimated the risk for cancer from exposure to low concentrations of formaldehyde using linear extrapolations from data on high concentrations in animals. However, linear low-dose extrapolation does not account for the sublinearities in the observed concentration–response relationship (Casanova *et al*., 1994; Monticello *et al*., 1996; Bolt, 2003). It was suggested that the risk for cancer in humans was probably overestimated by linear low-dose extrapolation from rats at concentrations that do not increase cell proliferation or the size of the cell population at risk (Monticello *et al*., 1996). Bolt (2003) recommended that predictions of risk at low ($\leq$ 2 ppm) versus high ($\geq$ 6 ppm) concentrations be made separately.

Formaldehyde demonstrates positive effects in a large number of in-vitro tests for genotoxicity, including bacterial mutation, DNA strand breaks, chromosomal aberrations and sister chromatid exchange. Studies in humans showed inconsistent results with regard to cytogenetic changes (micronuclei, chromosomal aberrations and sister chromatid exchange). The frequency of DNA–protein cross-links was found to be significantly higher in peripheral lymphocytes from exposed workers (Shaham *et al*., 1996, 2003).

In-vitro studies have shown that 0.1 mM [3 µg/mL] formaldehyde increases cell proliferation without detectable cytotoxicity (Tyihák *et al*., 2001). Formaldehyde also induces genetic damage at concentrations as low as 0.1 mM and inhibits DNA repair in bronchial cells at 0.1–0.3 mM [3–9 µg/mL], although it does not appear to be associated with oxidative stress. Formaldehyde inhibits cell growth at 0.2 mM [6 µg/mL] and 0.6 mM

[18 µg/mL], as expressed by loss of clonal growth rate and colony-forming efficiency, respectively. It alters membrane integrity, which leads to increases in cellular $Ca^{2+}$ and could affect cell death rates by accelerating terminal differentiation (Grafström *et al.*, 1996). Apoptosis has been demonstrated in rat thymocytes at concentrations at or above 0.1 mM (Nakao *et al.*, 2003). HeLa cervical carcinoma cells have been shown to be fairly resistant to the toxic effects of formaldehyde in comparison with untransformed human dental pulp fibroblasts and buccal epithelial cells (Lovschall *et al.*, 2002). In contrast, formaldehyde is only weakly genotoxic in in-vivo tests.

Using a variety of techniques, inhalation of formaldehyde has been shown to induce the formation of DNA–protein cross-links in nasal tissue from rats and monkeys, including decreased extractability of DNA from proteins, labelling studies and isolation of DNA by HPLC. The formation of DNA–protein cross-links is a non-linear function of formaldehyde concentration, described by an initial linear component with a shallow slope and a second linear component with a steeper slope that follows a significant decrease in survival of the cells and depletion of GSH at about 0.1 mM (Merk & Speit, 1998).

Species-specific differences in the rate of formation of DNA–protein cross-links, in the prevalence of squamous metaplasia (McMillan *et al.*, 1994) and in the occurrence of nasal cancer have also been observed at given concentrations of formaldehyde in rats, mice and monkeys (McMillan *et al.*, 1994; McClellan, 1995). Differences in nasal anatomy and regional airflow as well as differences in the absorptive properties of the nasal lining between species have been suggested to influence greatly the dose of formaldehyde that reaches different anatomical regions and subsequent formaldehyde-induced lesions at a given exposure concentration (Kimbell *et al*., 1997; Kepler *et al*., 1998; Zito, 1999; Kimbell *et al*,. 2001b; Conolly, 2002).

Anatomically accurate CFD models have been developed to describe the nasal uptake of formaldehyde in rats, monkeys and humans (Conolly, 2000). Interspecies differences in formaldehyde-induced DNA–protein cross-links and nasal lesions appear to be related to species-specific patterns in formaldehyde flux in different regions within the nasal passages (see Fig. 9; Kimbell *et al*., 2001a). CFD modelling predicts anterior-to-posterior gradients of formaldehyde deposition in the noses of rats, rhesus monkeys and humans (Kimbell *et al*., 2001a). This might suggest that formaldehyde is more likely to cause cancer of the nose than of the nasopharynx in humans.

Although formaldehyde is mainly deposited in the upper respiratory tract, the distribution of the deposition is expected to vary by species (Conaway *et al*., 1996; Liteplo & Meek, 2003). The lack of parallel data on the formation of nasal mucosal DNA–protein cross-links and on cell proliferation in humans complicates the extrapolation of the animal data, in particular rodent data, to humans (Conolly *et al*., 2000; Liteplo & Meek, 2003).

The current data indicate that both genotoxicty and cytoxicity play important roles in the carcinogenesis of formaldehyde in nasal tissues. DNA–protein cross-links provide a potentially useful marker of genotoxicity. The concentration–response curve for the formation of DNA–protein cross-links is bi-phasic, and the slope increases at concentrations of formaldehyde of about 2–3 ppm [2.5–3.7 mg/m³] in Fischer 344 rats. Similar results have been

**Figure 9. Allocation of nasal surface area to flux bins in rats, monkeys and humans**
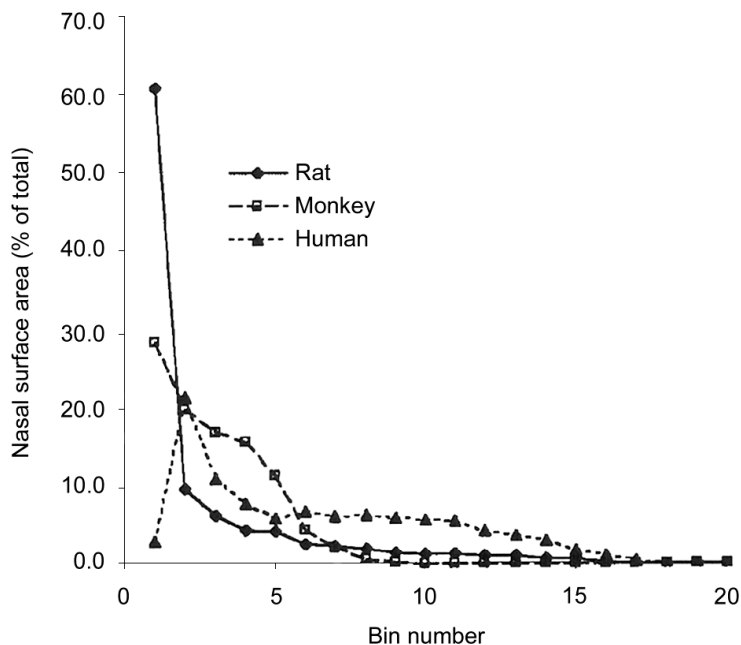


Adapted from Kimbell *et al.* (2001a)
Low bin numbers are associated with low flux values. Inspiratory airflow rates were 0.576 L/min in rats, 4.8 L/min in monkeys and 15 L/min in humans.

observed in rhesus monkeys, although the dose–response curve for DNA–protein cross-links is less well defined in this species. Cellular proliferation, which appears to amplify the genotoxic effects of formaldehyde greatly, increases considerably at concentrations of formaldehyde of about 6 ppm [7.4 mg/m³], and results in a marked increase in the occurrence of malignant lesions in the nasal passages of rats at concentrations of formaldehyde above this level (Monticello *et al.*, 1996). Recent evidence suggests that cytotoxicity may demonstrate a J-shaped concentration–response curve, with a significant reduction in cellular proliferation rates at concentrations of 0.7–2 ppm [0.86–2.5 mg/m³] (Conolly & Lutz, 2004; Gaylor *et al.*, 2004).

### 4.5.8    *Leukaemia*

The epidemiological evidence that formaldehyde may cause acute myelogenous leukaemia raises a number of mechanistic questions, including the processes by which inhaled formaldehyde may reach a myeloid progenitor (Heck & Casanova, 2004). The possibility that formaldehyde causes leukaemia is supported by the detection of cytogenetic abnormalities and an increase in the fraction of DNA–protein cross-links in circulating lymphocytes following occupational exposure to formaldehyde, as well as chromosomal aberrations in

bone marrow in a single inhalation study in rats (Kitaeva *et al.*, 1990, 1996; Shaham *et al.*, 1996a,b, 1997, 2003).

It is possible that formaldehyde itself can reach the bone marrow following inhalation, although the evidence is inconsistent (Kitaeva *et al.*, 1990; Dallas *et al*., 1992; Heck & Casanova, 2004). The relatively rapid rate of metabolism of formaldehyde by circulating red blood cells suggests that little if any inhaled formaldehyde could reach any tissue beyond the respiratory tract. [The Working Group noted that a clastogenic product of formaldehyde could conceivably be formed in the blood and circulate to the bone marrow, although this has not been suggested in the literature. Alternatively, it is possible that circulating myeloid progenitor stem cells could be the source of leukaemia. Such stem cells are known to be present in the blood and plausibly could be exposed to formaldehyde in the respiratory tract vasculature; however, there is currently no known prototype for such a mechanism of leukaemogenesis.]

Another mechanistic issue is the relation of cellular background levels of formaldehyde, as part of the one-carbon pool, to any risk from exogenous formaldehyde. Cellular background concentrations of formaldehyde are about 0.1 mM. In one study in humans, inhalation of 1.9 ppm [2.3 mg/m$^3$] formaldehyde for 40 min did not alter blood concentrations (Heck *et al.*, 1985). Elevated concentrations of formaldehyde were not observed in the blood of rats and rhesus monkeys exposed to formaldehyde at concentrations of up to 14.4 ppm [17.7 mg/m$^3$] (Heck *et al.*, 1985; Casanova *et al.*, 1988); nor were protein adducts or DNA–protein cross-links observed in the bone marrow of rats or rhesus monkeys exposed to formaldehyde at concentrations of up to 15 or 6 ppm [18.4 or 7.4 mg/m$^3$], respectively (Casanova-Schmitz *et al.*, 1984b; Heck *et al.*, 1989).

Known human myeloid leukaemogens include ionizing radiation, benzene and chemotherapeutic agents such as alkylators, DNA topoisomerase inhibitors and DNA-complexing agents. All of these agents produce overt bone marrow toxicity, including pancytopenia and aplastic anaemia in both laboratory animals and humans. Agents known to cause leukaemia in humans and animals are also known to induce chromosomal aberrations in peripheral lymphocytes. The absence of clear evidence of bone-marrow toxicity, even at high doses, indicates that, if formaldehyde is a human myeloid leukaemogen, its mechanism of action differs from those by which the known myeloid leukaemogens noted above operate. This is not inconceivable, because there is epidemiological evidence that butadiene and ethylene oxide are probably human leukaemogens, although neither is a classic bone-marrow toxicant.

Studies of workers exposed to benzene and of individuals who received cancer chemotherapy suggest that the induction period for acute myeloid leukaemia is less than 20 years, and is usually in the range of 2–15 years (Goldstein, 1990). This relatively short lag time for carcinogenesis reflects the intrinsic biology of the myeloid progenitor cell, irrespective of the mechanism that caused the initial cancer mutation. The epidemiological reports that suggest an association of formaldehyde with myeloid leukaemia have not clearly defined an induction period for the effect.

[The Working Group could not identify any rodent model for acute myeloid leukaemia. The lack of evidence of increased risk for leukaemia in long-term studies of formaldehyde in rodents is not informative with respect to myeloid leukaemogenesis in humans. The Working Group felt that, based on the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans by formaldehyde.]

# 5.   Summary of Data Reported and Evaluation

## 5.1      Exposure data

Formaldehyde is produced worldwide on a large scale by catalytic, vapour-phase oxidation of methanol. Annual world production is about 21 million tonnes. Formaldehyde is used mainly in the production of phenolic, urea, melamine and polyacetal resins. Phenolic, urea and melamine resins have wide uses as adhesives and binders in wood product, pulp and paper, and synthetic vitreous fibre industries, in the production of plastics and coatings and in textile finishing. Polyacetal resins are widely used in the production of plastics. Formaldehyde is also used extensively as an intermediate in the manufacture of industrial chemicals, such as 1,4-butanediol, 4,4′-methylenediphenyl diisocyanate, pentaerythritol and hexamethylenetetramine. Formaldehyde is used directly in aqueous solution (formalin) as a disinfectant and preservative in many applications.

Occupational exposure to formaldehyde occurs in a wide variety of occupations and industries. The highest continuous exposures (2–5 ppm) [2.5–6.1 mg/m³] were measured in the past during the varnishing of furniture and wooden floors, in the finishing of textiles, in the garment industry, in the treatment of fur and in certain jobs within manufactured board mills and foundries. Shorter-term exposures to high levels (3 ppm and higher) [3.7 mg/m³ and higher] have been reported for embalmers, pathologists and paper workers. Lower levels have usually been encountered during the manufacture of man-made vitreous fibres, abrasives and rubber, and in formaldehyde production industries. A very wide range of exposure levels has been observed in the production of resins and plastic products. The development of resins that release less formaldehyde and improved ventilation have resulted in decreased levels of exposure in many industrial settings in recent decades.

Formaldehyde occurs as a natural product in most living systems and in the environment. In addition to these natural sources, common non-occupational sources of exposure include vehicle emissions, particle boards and similar building materials, carpets, paints and varnishes, food and cooking, tobacco smoke and the use of formaldehyde as a disinfectant. Levels of formaldehyde in outdoor air are generally below 0.001 mg/m³ in remote areas and below 0.02 mg/m³ in urban settings. The levels of formaldehyde in the indoor air of houses are typically 0.02–0.06 mg/m³. Average levels of 0.5 mg/m³ or more have been measured in 'mobile homes', but these have declined since the late 1980s as a result of standards that require that building materials emit lower concentrations of formaldehyde.

## 5.2      Human data

*Nasopharyngeal cancer*

Since the last monograph on formaldehyde (in 1995), the follow-up of three major cohort studies has been extended and three new case–control studies have been published.

In the largest and most informative cohort study of industrial workers exposed to formaldehyde, a statistically significant excess of deaths from nasopharyngeal cancer was observed in comparison with the US national population, with statistically significant exposure–response relationships for peak and cumulative exposure. An excess of deaths from nasopharyngeal cancer was also observed in a proportionate mortality analysis of the largest US cohort of embalmers and in a Danish study of proportionate cancer incidence among workers at companies that used or manufactured formaldehyde. In three other cohort studies of US garment manufacturers, British chemical workers and US embalmers, cases of nasopharyngeal cancer were fewer than expected, but the power of these studies to detect an effect on nasopharyngeal cancer was low and the deficits were small.

The relationship between nasopharyngeal cancer and exposure to formaldehyde has also been investigated in seven case–control studies, five of which found elevated risks for overall exposure to formaldehyde or in higher exposure categories, including one in which the increase in risk was statistically significant; three studies (two of which have been published since the last monograph) found higher risks among subjects who had the highest probability, level or duration of exposure.

The most recent meta-analysis, which was published in 1997, included some but not all of the above studies and found an increased overall meta-relative risk for nasopharyngeal cancer.

The Working Group considered it improbable that all of the positive findings for naso-pharyngeal cancer that were reported from the epidemiological studies, and particularly from the large study of industrial workers in the USA, could be explained by bias or un-recognized confounding effects.

Overall, the Working Group concluded that the results of the study of industrial workers in the USA, supported by the largely positive findings from other studies, provided sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans.

*Leukaemia*

Excess mortality from leukaemia has been observed relatively consistently in six of seven studies of professional workers (i.e. embalmers, funeral parlour workers, patho-logists and anatomists). A recently published meta-analysis of exposure to formaldehyde among professionals and the risk for leukaemia reported increased overall summary rela-tive risk estimates for embalmers, and for pathologists and anatomists, which did not vary significantly between studies (i.e. the results were found to be homogeneous). The excess incidence of leukaemia seen in several studies appeared to be predominantly of a myeloid

type. There has been speculation in the past that these findings might be explained by exposures to viruses that are experienced by anatomists, pathologists and perhaps funeral workers. However, there is currently little direct evidence that these occupations have a higher incidence of viral infections than that of the general population or that viruses play a causal role in myeloid leukaemia. Professionals may also be exposed to other chemicals, but they have no material exposure to known leukaemogens. Furthermore, the exposure to other chemicals would differ between anatomists, pathologists and funeral workers, which reduces the likelihood that such exposures could explain the observed increases in risk.

Until recently, the findings for leukaemia in studies of professional workers appeared to be contradicted by the lack of such findings among industrial workers. However, some evidence for an excess of deaths from leukaemia has been reported in the recent updates of two of the three major cohort studies of industrial workers. A statistically significant exposure–response relationship was observed between peak exposures to formaldehyde and mortality from leukaemia in the study of industrial workers in the USA. This relationship was found to be particularly strong for myeloid leukaemia, a finding that was also observed in the study of anatomists and in several of the studies of embalmers. However, in the study of industrial workers in the USA, mortality from leukaemia was lower than expected when comparisons were made using the general population as the referent group. This raises concerns about whether these findings are robust with respect to the choice of a comparison group. Leukaemia has been found to be associated with socioeconomic status, and that of industrial workers tends to be low. Thus, the lack of an overall finding of an excess of deaths from leukaemia in the cohort of industrial workers in the USA might be explained by biases in the comparison between the study and referent populations. The study also failed to demonstrate an exposure–response relationship with cumulative exposure, although other metrics may sometimes be more relevant.

Mortality from leukaemia was also found to be in excess in the recent update of the study of garment workers exposed to formaldehyde in the USA. A small and statistically non-significant excess was observed for the entire cohort in comparison with rates among the general population. This excess was somewhat stronger for myeloid leukaemia, which is consistent with the findings from the study of industrial workers in the USA and several of the studies of medical professionals and embalmers. The excess was also stronger among workers who had a long duration of exposure and long follow-up, and who had been employed early in the study period when exposures to formaldehyde were believed to be highest. This pattern of findings is generally consistent with what might be expected if, in fact, exposure to formaldehyde were causally associated with a risk for leukaemia. The positive associations observed in many of the subgroup analyses presented in the study of garment workers in the USA were based on a relatively small number of deaths, and were thus not statistically stable.

The updated study of British industrial workers failed to demonstrate excess mortality among workers exposed to formaldehyde. The lack of positive findings in this study is difficult to reconcile with the findings from the studies of garment workers and industrial workers in the USA and studies of professionals. This was a high-quality study of adequate

size and with sufficiently long follow-up to have had a reasonable chance to detect an excess of deaths from leukaemia. The British study did not include an evaluation of peak exposures, but neither did the study of garments workers in the USA nor the studies of professionals. Also, the British study did not examine specifically the risk for myeloid leukaemia, which represented the strongest findings in the studies of garment workers and industrial workers in the USA and in several of the studies of medical professionals and funeral workers.

In summary, there is strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde. Increased risk for leukaemia has consistently been observed in studies of professional workers and in two of three of the most relevant studies of industrial workers. These findings fall slightly short of being fully persuasive because of some limitations in the findings from the cohorts of industrial and garment workers in the USA and because they conflict with the non-positive findings from the British cohort of industrial workers.

*Sinonasal cancer*

The association between exposure to formaldehyde and the risk for sinonasal cancer has been evaluated in six case–control studies that primarily focused on formaldehyde. Four of these studies also contributed to a pooled analysis that collated occupational data from 12 case–control investigations. After adjustment for known occupational confounders, this analysis showed an increased risk for adenocarcinoma in both men and women and also (although on the basis of only a small number of exposed cases) in the subset of subjects who were thought never to have been occupationally exposed to wood or leather dust. Moreover, a dose–response trend was observed in relation to an index of cumulative exposure. There was little evidence of an association with squamous-cell carcinoma, although in one of the two other case–control studies, a positive association was found particularly for squamous-cell carcinomas. An analysis of proportionate cancer incidence among industrial workers in Denmark also showed an increased risk for squamous-cell carcinomas.

Against these largely positive findings, no excess of mortality from sinonasal cancer was observed in other cohort studies of formaldehyde-exposed workers, including the three recently updated studies of industrial and garment workers in the USA and of chemical workers in the United Kingdom.

Most epidemiological studies of sinonasal cancer have not distinguished between tumours that arise in the nose and those that develop in the nasal sinuses. Thus, any effect on the risk for nasal cancer specifically would tend to be diluted if there were no corresponding effect on the risk for cancer in the sinuses, and would thus mask its detection, particularly in cohort studies that have relatively low statistical power. However, the apparent discrepancy between the results of the case–control as compared with the cohort studies might also reflect residual confounding by wood dust in the former. Almost all of the formaldehyde-exposed cases in the case–control studies were also exposed to wood dust, which

resulted in a high relative risk, particularly for adenocarcinomas. Thus, there is only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans.

*Cancer at other sites*

A number of studies have found associations between exposure to formaldehyde and cancer at other sites, including the oral cavity, oro- and hypopharynx, pancreas, larynx, lung and brain. However, the Working Group considered that the overall balance of epidemiological evidence did not support a causal role for formaldehyde in relation to these other cancers.

## 5.3      Animal carcinogenicity data

Several studies in which formaldehyde was administered to rats by inhalation showed evidence of carcinogenicity, particularly the induction of squamous-cell carcinomas of the nasal cavities. A similar study in hamsters showed no evidence of carcinogenicity, and one study in mice showed no effect.

In four studies, formaldehyde was administered in the drinking-water to rats. One study in male rats showed an increased incidence of forestomach papillomas. In a second study in male and female rats, the incidence of gastrointestinal leiomyosarcomas was increased in females and in males and females combined. In a third study in male and female rats, the number of males that developed malignant tumours and the incidences of haemolymphoreticular tumours (lymphomas and leukaemias) and testicular interstitial-cell adenomas in males were increased. A fourth study gave negative results.

Skin application of formaldehyde concomitantly with 7,12-dimethylbenz[*a*]anthracene reduced the latency of skin tumours in mice. In rats, concomitant administration of formaldehyde and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine in the drinking-water increased the incidence of adenocarcinomas of the glandular stomach. Exposure of hamsters by inhalation to formaldehyde increased the multiplicity of tracheal tumours induced by subcutaneous injections of *N*-nitrosodiethylamine.

## 5.4      Other relevant data

*Toxicokinetics and metabolism*

The concentration of endogenous formaldehyde in human blood is about 2–3 mg/L; similar concentrations are found in the blood of monkeys and rats. Exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter these concentrations. The average level of formate in the urine of people who are not occupationally exposed to formaldehyde is 12.5 mg/L and varies considerably both within and between individuals. No significant changes in urinary formate were detected in humans after exposure to 0.5 ppm [0.6 mg/m$^3$] formaldehyde for up to 3 weeks. More than 90% of inhaled

formaldehyde is absorbed in the upper respiratory tract. In rats, it is absorbed almost entirely in the nasal passages; in monkeys, it is also absorbed in the nasopharynx, trachea and proximal regions of the major bronchi. Absorbed formaldehyde can be oxidized to formate and carbon dioxide or may be incorporated into biological macromolecules via tetrahydrofolate-dependent one-carbon biosynthetic pathways. Formaldehyde has a half-life of about 1 min in rat plasma. Rats exposed to [$^{14}$C]formaldehyde eliminated about 40% of the $^{14}$C as exhaled carbon dioxide, 17% in the urine and 5% in the faeces; 35–39% remained in the tissues and carcass. After dermal application of aqueous [$^{14}$C]formaldehyde, approximately 7% of the dose was excreted in the urine by rodents and 0.2% by monkeys. After oral administration, about 40% of [$^{14}$C]formaldehyde was excreted as exhaled carbon dioxide, 10% in the urine and 1% in the faeces within 12 h.

*Toxic effects in humans*

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

Nasal lavage studies show increased numbers of eosinophils and protein exudation following exposures to 0.5 mg/m$^3$ formaldehyde. Bronchial provocation tests have confirmed the occurrence of occupational asthma due to formaldehyde in small numbers of workers from several centres. The mechanism is probably hypersensitivity, because the reactions are often delayed, there is a latent period of symptomless exposure and unexposed asthmatics do not react to the same concentrations. One case of pneumonitis was reported in a worker who was exposed for 2 h to a level that was sufficient for his breath to smell of formaldehyde. High levels of formaldehyde probably cause asthmatic reactions by an irritant mechanism. Formaldehyde is one of the commoner causes of contact dermatitis and is thought to act as a sensitizer on the skin.

*Toxic effects in animals*

Formaldehyde is a well documented irritant that causes mild inflammation to severe ulceration. It caused direct toxicity in the upper respiratory system in a concentration- and location-specific manner. There is evidence that formaldehyde can induce irritation to the forestomach after high-dose oral exposure. Formaldehyde is also a sensory irritant that induces a decrease in respiratory rate in rodents; mice are more sensitive than rats, as measured by respiratory depression. This respiratory depression is thought to be secondary to stimulation of the trigeminal nerve by the irritant effect of formaldehyde. Formaldehyde can also result in pulmonary hyperactivity through transient bronchoconstriction.

It can also act as a skin contact sensitizer via a type IV T-cell mediated hypersensitivity reaction. Formaldehyde does not induce haematological effects.

## In-vitro toxicity

Formaldehyde exerts dose-dependent toxicity in cell cultures. Cytotoxicity involves loss of glutathione, altered $Ca^{2+}$-homeostatis and impairment of mitochondrial function. Thiols, including glutathione, and metabolism through alcohol dehydrogenase 3, act in a protective manner.

## Reproductive and developmental effects

Eleven epidemiological studies have evaluated directly or indirectly the reproductive effects of occupational exposures to formaldehyde. The outcomes examined in these studies included spontaneous abortions, congenital malformations, birth weights, infertility and endometriosis. Inconsistent reports of higher rates of spontaneous abortion and lowered birth weights were reported among women occupationally exposed to formaldehyde. Studies of inhalation exposure to formaldehyde in animal models have evaluated the effects of formaldehyde on pregnancy and fetal development, which have not been clearly shown to occur at exposures below maternally toxic doses.

## Genetic and related effects

There is evidence that formaldehyde is genotoxic in multiple in-vitro models and in exposed humans and laboratory animals. Studies in humans revealed increased DNA–protein cross-links in workers exposed to formaldehyde. This is consistent with laboratory studies, in which inhaled formaldehyde reproducibly caused DNA–protein cross-links in rat and monkey nasal mucosa. A single study reported cytogenetic abnormalities in the bone marrow of rats that inhaled formaldehyde, while other studies did not report effects in bone marrow.

## Mechanistic considerations

The current data indicate that both genotoxicty and cytoxicity play important roles in the carcinogenesis of formaldehyde in nasal tissues. DNA–protein cross-links provide a potentially useful marker of genotoxicity. The concentration–response curve for the formation of DNA–protein cross-links is bi-phasic, and the slope increases at formaldehyde concentrations of about 2–3 ppm [2.4–3.7 mg/m$^3$] in Fischer 344 rats. Similar results are found in rhesus monkeys, although the dose–response curve is less well defined in this species. Cell proliferation, which appears to amplify greatly the genotoxic effects of formaldehyde, is increased considerably at concentrations of formaldehyde of about 6 ppm [7.4 mg/m$^3$], and results in a marked increase in the occurrence of malignant lesions in the nasal passages of rats at concentrations above this level.

Several possible mechanisms were considered for the induction of human leukaemia, such as clastogenic damage to circulatory stem cells. The Working Group was not aware of any good rodent models that simulate the occurrence of acute myeloid leukaemia in humans. Therefore, on the basis of the data available at this time, it was not possible to identify a mechanism for the induction of myeloid leukaemia in humans.

## 5.5      Evaluation

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

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

## Overall evaluation

Formaldehyde is *carcinogenic to humans (Group 1)*.

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