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# 3 Formaldehyde

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## General description

Formaldehyde (molecular formula $H_2$-C=O; CAS number 50-00-0) is a colourless gas, flammable and highly reactive at room temperature. Formaldehyde can also be obtained commercially as a 30–50% (by weight) aqueous solution, known as formalin.

In ambient air, formaldehyde is quickly photo-oxidized in carbon dioxide. It also reacts very quickly with the hydroxyl radicals to give formic acid. The half-life estimated for these reactions is about one hour depending on the environmental conditions.

The main chemical and physical properties (of the pure substance) are as follows (1,2): molecular mass 30.03 g/mol; relative vapour density 1.03–1.07 (air = 1); melting point −92 °C; and boiling point −19.1 °C. Formaldehyde is soluble in water (around 400 g/l at 20 °C), ethanol and chloroform and miscible with acetone, benzene and diethylether. The octanol/water partition coefficient (log $K_{ow}$) is 0.35, the vapour pressure is $5.19 \times 10^5$ Pa at 25 °C and the Henry's Law constant is $3.41 \times 10^{-2}$ Pa.m$^3$/mol at 25 °C.

Formaldehyde is ubiquitously found in the environment, because it is formed primarily by numerous natural sources and anthropogenic activities. In the environment, it is released through biomass combustion (forest and bush fires) or decomposition and through volcanoes, for example. Anthropogenic sources include direct ones such as on-site industrial emissions and fuel combustion from traffic. Other combustion processes (power plants, incineration, etc.) also represent sources of formaldehyde emissions in the atmosphere. However, formaldehyde is also extensively produced industrially worldwide for use in the manufacture of resins, as a disinfectant and fixative, or as a preservative in consumer products.

All these man-made products and uses are the major indirect sources of formaldehyde, in particular indoors. Finally, it should be noted that secondary formation of formaldehyde occurs in air through the oxidation of volatile organic compounds (VOCs) and reactions between ozone (mainly from outdoors) and alkenes (especially terpenes) have been widely described. The contribution of these secondary chemical processes to the ambient and indoor concentrations is still not fully quantified.

Common techniques to measure formaldehyde concentrations include both integrated active and passive methods. Formaldehyde is generally trapped on a sorbent impregnated with 2,4-dinitrophenylhydrazine (2,4-DNPH). Analysis is then conducted in the laboratory by high-performance liquid chromatography and ultraviolet detection at 350 nm. Detection and quantification limits around 1 µg/m$^3$ can be achieved. The use of an ozone scrubber is recommended to remove the latter from the sample stream to prevent interference during the analysis. Recent comparisons of formaldehyde measurement techniques have shown that, in the presence of low relative humidity, 2,4-DNPH-based methods could underestimate concentrations (3,4).

### Conversion factors

At 760 mmHg and 20 °C, 1 ppm = 1.249 mg/m$^3$ and 1 mg/m$^3$ = 0.801 ppm; at 25 °C, 1 ppm = 1.228 mg/m$^3$ and 1 mg/m$^3$ = 0.814 ppm.

## Sources and pathways of exposure

Indoor sources may be combustion processes such as smoking, heating, cooking, or candle or incense burning (1,5). However, major sources in non-smoking environments appear to be

building materials and consumer products that emit formaldehyde (5,6). This applies to new materials and products (7) but can last several months, particularly in conditions with high relative humidity and high indoor temperatures (8).

Formaldehyde sources in indoor environments include: furniture and wooden products containing formaldehyde-based resins such as particleboard, plywood and medium-density fibreboard; insulating materials (in the early 1980s, urea formaldehyde foam insulation was a major source of indoor pollution); textiles; do-it-yourself products such as paints, wallpapers, glues, adhesives, varnishes and lacquers; household cleaning products such as detergents, disinfectants, softeners, carpet cleaners and shoe products; cosmetics such as liquid soaps, shampoos, nail varnishes and nail hardeners; electronic equipment, including computers and photocopiers; and other consumer items such as insecticides and paper products.

As mentioned above, secondary formation of formaldehyde occurs indoors through chemical reactions between, for example, ozone and terpenes (9,10).

Taking all the indoor sources of formaldehyde into account, it is difficult to identify the major ones that contribute to indoor levels. During a large-scale indoor survey carried out between 1997 and 1999 in 876 homes in the United Kingdom, Raw et al. (11) found that, depending on the age of the building, the presence of particleboard flooring in the home was the second most important determinant of indoor concentration. Clarisse et al. (12) measured formaldehyde in the bedroom, the kitchen and the living room of 61 Parisian flats with no previous history of complaint for olfactory nuisance. They found that indoor levels depended on the age of wall or floor coverings (renovations less than one year old), smoking and ambient parameters (carbon dioxide levels and temperature). Using emission factors from the literature, the German Federal Institute for Risk Assessment found that pressed wood products were the major sources contributing to exposure through inhalation at home (13). Marchand et al. (14) carried out aldehyde measurements in 162 homes in the Strasbourg area in 2004–2005. Variance analyses showed that formaldehyde concentration was a function of the age of the ceiling coverings for both bedrooms and living rooms. Formaldehyde concentrations tended to decrease with increasing furniture age for both living rooms and bedrooms, but the analyses were not significant. In Canada, Gilbert et al. (15) measured formaldehyde levels in 96 homes in Quebec City in 2005. Formaldehyde concentrations were negatively correlated with air exchange rates. They were significantly elevated in homes heated by electricity, in those with new wooden or melamine furniture purchased in the previous 12 months, and in those where painting or varnishing had been done in the sampled room in the previous 12 months. Similarly, relative high levels that can be measured in schools are usually considered to be linked to the high density of furniture in the classrooms (and to poor ventilation).

The possible routes of exposure to formaldehyde are inhalation, ingestion and dermal absorption. Almost no data are available in the literature on dermal exposure (16). Concerning the oral pathway, exposure through food may not be negligible. Estimates of daily formaldehyde intake by six age groups of the general population in Canada were carried out to determine the relative contributions from different media (17). These calculations indicate that daily formaldehyde intake via inhalation is much lower than for intake from food. However, since critical effects associated with exposure to formaldehyde are directly linked to the site of contact, inhalation and ingestion are usually considered separately. Considering exclusively inhalation, indoor exposure contributes up to 98% to the integrated exposure (considering time–activity patterns and daily inhalation volume) (16).

## Indoor concentrations and relationship with outdoor levels

A large review of formaldehyde concentrations worldwide in all types of indoor environment, including mobile homes, has been summarized by Salthammer et al. (5). A second large review compiles information on indoor, outdoor and personal exposures to formaldehyde (18).

During a large indoor air survey carried out in homes by the Building Research Establishment (BRE) in the United Kingdom in 1997–1999, the geometric mean, 95th percentile and maximum

value of three-day samples of formaldehyde in bedrooms (n = 833) were, respectively, 22.2, 61.2 and 171 μg/m$^3$ (11).

During Phase IV of the German longitudinal environmental survey 2003–2006 (GerES IV), formaldehyde was measured through passive samplers for one week in bedrooms of a randomly selected population of children and teen agers. The geometric mean, 95th percentile and maximum concentration (n = 586) were, respectively, 23.3, 47.7 and 68.9 μg/m$^3$ (19). These levels were lower than the concentrations measured previously in the framework of the GerES.

In the EXPOLIS study in Helsinki, the average air concentration of formaldehyde in homes was 41.4 μg/m$^3$ (range 8.1–77.8 μg/m$^3$) and at the workplace 15 μg/m$^3$, whereas average personal exposure was 26.8 μg/m$^3$ (20).

Hutter et al. measured formaldehyde concentrations in 160 Austrian homes and found a median concentration of 25 μg/m$^3$ and a maximum value of 115 μg/m$^3$ (21).

The French Observatory on Indoor Air Quality carried out a large monitoring campaign in 567 randomly selected dwellings between 2003 and 2005. The median concentration, 95th percentile and maximum value of formaldehyde following seven days of passive sampling in bedrooms (n = 554) were, respectively, 19.6, 46.7 and 86.3 μg/m$^3$ (22).

In Canada, Gilbert et al. (15) measured formaldehyde levels in 96 homes in Quebec City between January and April 2005. The indoor concentrations ranged from 9.6 to 90 μg/m$^3$, with a geometric mean of 29.5 mg/m$^3$.

In the National Human Exposure Assessment Survey (NHEXAS) in Arizona, the median and 90th percentile indoor concentrations were, respectively, 21 and 46 μg/m$^3$, about the same levels as those measured in Europe (21).

Dingle & Franklin (23) observed, in a study carried out in 185 homes in Perth, Australia, indoor formaldehyde concentrations of between 2.5 and 133.7 μg/m$^3$, i.e. the same range of concentrations as measured in other countries.

Formaldehyde concentrations in Japanese dwellings have been regularly measured within large-scale monitoring campaigns since the 1090s (24,25). The National Institute of Health Sciences conducted a first national field survey in 230 houses in 1996 and found an arithmetic mean concentration of 78 μg/m$^3$ (range 5–600 μg/m$^3$). During the last survey conducted in 2005 (n = 1181 homes), the arithmetic mean decreased to 31 μg/m$^3$ (maximum concentration 300 μg/m$^3$). In between, the Japanese authorities amended the national building codes and instituted restrictions on the use of formaldehyde-emitting materials for interior finishing.

In China, a large number of monitoring results are available for new homes, since it is mandatory to check whether the maximum allowable formaldehyde concentration in residential buildings (100 μg/m$^3$) has been exceeded (26). The mean concentration in approximately 6000 recently refurbished dwellings in urban areas was 238 μg/m$^3$ (remodelled after one year or less; measurements conducted between 1999 and 2006; mean outdoor level around 12 μg/m$^3$).

Formaldehyde concentrations in dwellings vary according to:

- the age of the building, since the release of formaldehyde decreases with time (11);
- temperature and relative humidity (8);
- the air exchange rate (11,15); and
- the season (11).

Moreover, indoor concentrations can reach more than 200 μg/m$^3$ close to somebody who is smoking in a room (27). There are many fewer data on offices compared to the residential environment.

A large monitoring campaign carried out in Germany between 2001 and 2004 in 419 rooms found a median indoor formaldehyde concentration of 28 μg/m$^3$ (28).

Over the period 2004–2007, the EU's Joint Research Centre in Ispra, Italy monitored priority pollutants, including formaldehyde, in European public buildings and environments where children frequently stay, such as schools and kindergartens (29). Formaldehyde concentrations in offices in public buildings (n = 94) varied from 3 to 33 μg/m$^3$.

Formaldehyde concentrations were measured between 2001 and 2006 in office buildings in southern Finland (30). The occupants had complained of symptoms, but inspection by indoor air experts had not revealed any sources of pollutants. The mean formaldehyde concentration and maximum value were found to be 11 and 44 μg/m$^3$, respectively.

In the United States, within the framework of the Building Assessment Survey and Evaluation (BASE) study (31), 100 office buildings were investigated between 1994 and 1998. Formaldehyde was detected in all the buildings. The 50th and 95th percentiles were 15 and 32 μg/m$^3$, respectively.

In China, the mean formaldehyde concentration in 351 offices located all over the country (data from 1996–2005) was of the same order of magnitude as in recently refurbished dwellings, i.e. 256 μg/m$^3$ (26). In Hong Kong SAR, formaldehyde was measured in 422 air-conditioned offices; the geometric mean was found to be equal to 32 μg/m$^3$ (± 2.7 μg/m$^3$) (32).

In France, in the frame of the International Study on Asthma and Allergies in Childhood (ISAAC), formaldehyde was measured in 1999 in 401 classrooms in 108 schools located in 6 cities (Strasbourg, Créteil, Reims, Marseille, Bordeaux and Clermont-Ferrand) (33). Concentrations varied from 4 to 100 μg/m$^3$ with a mean value of 27 μg/m$^3$. In 50 Parisian kindergartens studied between 1999 and 2001, both in winter and in summer (n = 222), indoor formaldehyde concentrations ranged from 1.5 to 56 μg/m$^3$ with a median value of 14 μg/m$^3$ (34).

In Germany, the indoor air quality was evaluated in 92 classrooms in the winter of 2004/2005 and in 75 classrooms in the summer of 2005 in southern Bavaria. Indoor formaldehyde concentrations ranged from 3.1 to 46.1 μg/m$^3$ (35).

Formaldehyde concentrations measured in European kindergartens by the EU's Joint Research Centre between 2004 and 2007 (n = 57) varied from 1.5 to 50 μg/m$^3$, with an arithmetic mean of 17.4 μg/m$^3$ (29).

In Japan, formaldehyde concentrations measured in 50 schools in 2000 were around 14 μg/m$^3$ in winter and 30 μg/m$^3$ in summer (36).

Outdoor air does not contribute to indoor pollution (or the contribution is minor) since ambient levels are generally rather low. Mean ambient air background concentrations remain low compared to those indoors, typically around 1–4 μg/m$^3$. Data from the HEXPOC report (16), collected from Brazil, Canada, Germany, Italy, Mexico, the Netherlands and the United States, provide ambient concentrations of 1.5–16.4 μg/m$^3$ with a mean value of 7.2 μg/m$^3$ (SD = 5.1 μg/m$^3$). Consequently, the indoor : outdoor ratio is always far above 1. Formaldehyde can be qualified as a very specific indoor pollutant.

## Kinetics and metabolism

### Absorption

Owing to its solubility in water, formaldehyde is rapidly absorbed in the respiratory and gastrointestinal tracts and metabolized. More than 90% of inhaled formaldehyde gas is absorbed and rapidly metabolized to formate in the upper respiratory tract (37). In rats, it is absorbed in the nasal passages (38,39); in primates, some absorption takes place in the nasal cavity as well as in the nasopharynx, trachea and bronchi (40,41). The mucociliary apparatus is an important defence

system in the respiratory tract and may provide protection of the underlying epithelium from gases and vapours (42). 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 (37,43). It has been shown that when formaldehyde is mixed with particles, more of it is retained by the respiratory tract than when it is inhaled alone. This suggests that some particles can bind with gases and increase the retained dose of a gas (44). However, some estimates show that the deposited dose of formaldehyde in the particle phase is substantially smaller than the dose from the vapour phase (45).

Formaldehyde is absorbed rapidly and almost completely from the rodent intestinal tract (39,46). Although formaldehyde or its metabolites can penetrate human skin – it induces allergic contact dermatitis in humans – dermal absorption appears to be very slight (47,48).

### Endogenous sources of formaldehyde

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 (49).

Owing to its high reactivity at the site of contact and rapid metabolism, exposure of humans, monkeys or rats to formaldehyde by inhalation does not alter the concentration of formaldehyde in the blood from that endogenously present, which is about 2–3 mg/l for each of the three species. This concentration represents the total concentration of both free and reversibly bound endogenous formaldehyde in the blood. 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, as described below. From a mathematical model describing the absorption and removal of inhaled formaldehyde in the human nose, it was predicted that exposures in the range of 0.125–12.5 mg/m$^3$ only cause extremely small increases in formaldehyde concentrations compared to the pre-exposure concentrations (50). Intravenous administration of formaldehyde to dogs, cats and monkeys also does not result in accumulation of formaldehyde in the blood, largely owing to its rapid metabolism (1,39,46).

### Distribution

Following a 6-hour inhalation exposure of rats to formaldehyde, about 40% of the inhaled compound was eliminated as expired carbon dioxide over a 70-hour period; 17% was excreted in the urine, 5% was eliminated in the faeces and 35–39% remained in the tissues and carcass, indicating that absorbed formaldehyde and its metabolites are rapidly removed by the mucosal blood supply and distributed throughout the body (39). In dogs, orally administered formaldehyde results in a rapid increase in formate levels in the blood. In rats, oral exposure results in about 40% being eliminated as carbon dioxide within 12 hours, 10% being excreted in the urine and 1% being excreted in the faeces (51).

Rodents excreted about 6.6% of the dermally applied dose in the urine over 72 hours, while 21–28% was collected in air traps, likely due to the evaporation of formaldehyde from the skin (52). Approximately 22–28% of the compound or its metabolites remained in the body, including the blood and skin at the site of application. In monkeys, less than 1% of dermally 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 in monkeys than in rodents, the results suggest that the skin of monkeys may be less permeable to aqueous formaldehyde than that of rodents.

### Metabolism and elimination

Formaldehyde reacts rapidly at the site of contact and is swiftly metabolized in humans by erythrocytes, which contain the enzymes formaldehyde dehydrogenase and aldehyde dehydrogenase (53–56). Formaldehyde reacts virtually instantaneously with primary and

secondary amines, thiols, hydroxyls and amides to form methylol derivatives. Formaldehyde acts as an electrophile and can react with macromolecules such as DNA, RNA and protein to form reversible adducts or irreversible cross-links (1).

Formate, the metabolic product of formaldehyde, is incorporated in normal metabolic pathways or further oxidized to carbon dioxide. This becomes important when performing fate and transport studies with radio-labelled formaldehyde, as the label appears in all tissues due to the one-carbon pool. Formaldehyde disappears from the plasma with a half-time of about 1–1½ minutes, most of it being converted to carbon dioxide and exhaled via the lungs. Smaller amounts are excreted in the urine as formate salts and several other metabolites (47).

The primary metabolism system for formaldehyde involves an initial spontaneous reaction with glutathione to form S-hydroxymethylglutathione, followed by reaction facilitated by alcohol dehydrogenase to convert the intermediate to S-formylglutathione (57,58). This intermediate is then further metabolized by S-formylglutathione hydrolase to yield formate and reduced glutathione.

### Biomarkers of exposure

To determine whether formate is a useful biomarker for human exposure to formaldehyde, urine was examined in veterinary medical students exposed to low concentrations of formaldehyde (59). Exposed students (formaldehyde air concentration < 0.61 mg/m$^3$ over a 3-week period) were compared to control subjects. 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. Thus formate in urine does not appear to be a useful biomarker for human exposure, especially at low exposure concentrations.

Inhalation of formaldehyde leads to the formation of DNA–protein crosslinks in cells at the site of contact, particularly in the nasal respiratory mucosa of rats and monkeys. The formation of these cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m$^3$, and the yield of DNA–protein cross-links at a given inhaled concentration is approximately an order of magnitude lower in monkeys than in rats. There is no detectable accumulation of DNA–protein cross-links during repeated exposure. Application of a pharmacokinetic model to the data obtained in rats and monkeys indicates that the concentration of DNA–protein cross-links in the human nasal mucosa would be lower than those in rats and monkeys (1,41,60,61). No data are available on DNA–protein cross-links in humans (1). Carraro et al. (62) have suggested that an immunological assay that measures the humoral immune response of adducts of formaldehyde and human serum albumin could be used as a biomarker of environmental exposure to formaldehyde, but such a marker has not been developed.

## Health effects

### Identification of studies

The literature for the cancer part was indentified in PubMed with search terms that included “formaldehyde AND DNA-protein crosslink/crosslinks”, “formaldehyde AND genotoxic/genotoxicity AND blood AND lymphocyte”, “lymphatic AND tissue AND nose AND review”, “micronucleus AND test AND review”, “formaldehyde AND cancer AND meta-analysis”, “formaldehyde AND cancer AND humans”, “unit risk AND formaldehyde”, “Epstein-Barr AND nasopharyngeal cancer AND review”, “Hauptmann M AND nasopharyngeal carcinoma”, “Hauptmann M AND silver smithing”, “silver smithing AND nasopharyngeal carcinoma”, “silver smithing AND cancer”, “acid AND nasopharyngeal carcinoma AND review”, “nickel AND nasopharyngeal carcinoma”, “unit risk AND cancer AND review” and “Zhang L AND formaldehyde”. References were also obtained from IARC (1), Bosetti et al. (68) and the European Commission (64). Approximately 200 articles were deemed relevant and read. Of these, more than 120 were evaluated in detail; the relevance of these articles is discussed by

Nielsen & Wolkoff (65). However, articles were only included here if they were used directly in the derivation of the WHO indoor air guidelines.

For non-cancer effects, publications from the period 1997–2009 were searched with special emphasis on human effects. Except in special cases, animal and in vitro studies were excluded owing to the huge amount of human data. Formaldehyde was searched in combination with the following terms: allergy, asthma(tics), airway (irritation), bronchoconstriction, children, eye (irritation), inflammation, homes, IgE, (nasal) irritation, kindergartens, lung effects, lung function, offices, odour, schools, sensory irritation, sick-building syndrome, sensitization and trigeminal stimulation.

Eczema was not included except if retrieved in the above-mentioned searches. In addition to databases such as PubMed and Google Scholar, recent comprehensive reviews were considered (66–68), including Gilbert (69) and international reports (1,17,64).

Of the 170 papers identified (and listed by Wolkoff & Nielsen (70)), 90 were included in the discussion presented below addressing human exposure and epidemiological issues (65 studies), children (11 studies), animal studies (8 studies), cell studies (3 studies) and dust (4 studies).

## Respiratory effects of formaldehyde

Nasal retention of formaldehyde in the moist layers covering the nasal mucosa exceeds 90–95%. For example, a maximum of 5% formaldehyde reaches the lower airways in dogs (71). The high retention is also deduced from a mouse bioassay, because only sensory irritation of the upper airways has been observed below 5 mg/m$^3$ formaldehyde (72). Recent computational fluid dynamic calculations at boundary conditions of fast formaldehyde uptake indicate similar total nasal extraction in adults and children (on average 90%), and thus a limited amount of formaldehyde may traverse the nasal cavity (73).

Human exhaled air contains formaldehyde in concentrations in the order of 0.001–0.01 mg/m$^3$, with an average value of about 0.005 mg/m$^3$ (74–76).

### Effects after acute and short-term exposure to formaldehyde at indoor levels (non-cancer effects)

The effects include odour (which may cause discomfort), sensory irritation to the eyes and upper airways, lung effects (asthma and allergy) and finally eczema. These effects have been discussed in comprehensive reviews during the last decade (64,66–69,77), including international reports (1,17). Selected key studies from the last decade about exposure–response relationships are listed in Table 3.1. They represent controlled, usually double-blind exposure studies, including both sexes, of which some were tested with both questionnaires and objective methods. In addition, Table 3.1 lists a number of epidemiological studies with lung function testing.

**Table 3.1**

Effects on the airways in humans after acute and short-term exposure to formaldehyde.

***Odour.*** A large number of odour thresholds have been reported for formaldehyde, varying from 0.05 to 0.5 mg/m$^3$ (90), some of which are listed in Table 3.2. Two recent studies, carried out under controlled olfactometric conditions, indicate that the odour threshold lies between 0.2 and 0.4 mg/m$^3$ (79,91); this also agrees with the fact that 33 subjects (mean age 30 years) perceived formaldehyde at about 0.3 mg/m$^3$ (0.25 ppm) (92). Lower values down to about 0.1 mg/m$^3$, obtained under conditions of careful generation and monitoring of formaldehyde, have been reported for women (93). Olfactometric determination of odour thresholds depends on a number of experimental factors, such as air purity of the background, and possibly also personal factors such as smoking status and previous olfactory experience; generally, however, it is considered that lower values have higher validity than higher values (94). In addition, recent olfactometric

studies indicate less intra- and inter-variability of sensitivity among subjects than in previous studies (94). In view of the above-mentioned studies, it is considered that a significant fraction of the population may perceive formaldehyde at or below 0.1 mg/m$^3$.

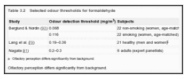

**Table 3.2**

Selected odour thresholds for formaldehyde.

Both eye and upper airway sensory symptoms may be over-reported by odour cues, which cause perceptual uncertainty because of the difficulty of separating the simultaneous and integrated input from odours and sensory irritants (95,96). The perceived odour intensity will depend on a number of psychological factors, such as information about the risk of the chemical (97).

***Sensory irritation.*** Generally, sensory irritation (nasal pungency) is perceived as an unpleasant sensation from the eyes and airways caused by stimulation of the trigeminal nerve endings by airborne sensory irritants (95). A number of reviews have assessed the threshold for self-reported sensory irritation. In general, the eyes are considered to be more sensitive to such irritants than the upper airways (95). Values have been suggested of from 0.15 up to 1.25 mg/m$^3$ (66,67,77). Raw data on exposure–response relationships obtained from reported human exposure studies about irritating effects were used in a regression model. A value below 0.94 mg/m$^3$ formaldehyde was considered safe against sensory irritation of the eyes for all workers; about 6% of workers may experience moderate irritation between 0.94 and 1.25 mg/m$^3$, while none would experience severe irritation (98).

One of the key experimental studies involved 21 healthy subjects exposed double-blind and randomly to formaldehyde for 4 hours (79). Questionnaires and objective methods were used to evaluate eye and airway irritation and lung function. Eye irritation was found to be the most significant effect. Subjective sensory irritation was perceived at as low as 0.38 mg/m$^3$ for the eyes and 0.63 mg/m$^3$, with peaks up to 1.25 mg/m$^3$, for the nose. Adjustment for the personal trait of negative affectivity (e.g. anxiety), however, led to a value of 0.63 mg/m$^3$ for the eyes at constant exposure and 0.38 mg/m$^3$ plus four brief peak exposures at 0.63 mg/m$^3$. An increase in eye blink frequency, which reflects sensory stimulation of the trigeminal nerve but not necessarily in perception thereof, was observed at 0.63 mg/m$^3$ formaldehyde baseline exposure plus four brief peak exposures at 1.25 mg/m$^3$, but not without the peak exposures. The nasal flow resistance and lung function remained unaffected. Eye and nasal irritation did not occur in parallel in the low dose range because eyes are more sensitive; it also to some extent depended on personal factors (e.g. trait and odour). The authors concluded that a corrected lowest observed effect level (LOEL) is 0.63 mg/m$^3$ without peak exposure, which agrees with the observations of Kulle et al. (99). Lang et al. (79) also concluded that the NOAEL for both subjective and objective eye irritation would be close to the LOEL, i.e. 0.63 mg/m$^3$ at constant exposure; the effects were considered weak, because “less” and “somewhat” were ranked nearly equal. In addition, a slightly lower NOAEL was considered to be 0.38 mg/m$^3$ with peaks of 0.75 mg/m$^3$ formaldehyde. Sensory irritation in humans can be predicted from airway responses in mice (100). Further support for the Lang et al. (79) estimate is obtained from the mouse bioassay (72), because the NOAEL was found experimentally to be 0.38 mg/m$^3$.

As a first approximation, the sensory effect of formaldehyde together with other sensory airway irritants is additive (101). However, in a study of 130 women (mean age 27 years) exposed to 0.04 mg/m$^3$ formaldehyde in a mixture of 23 typical indoor VOCs at a total of 25 mg/m$^3$ plus ozone (0.08 mg/m$^3$) for about 140 minutes, neither significant reported sensory irritation nor indication of nasal inflammation was observed (102,103).

No epidemiological study has been identified that unequivocally shows a direct association between formaldehyde and sensory irritation. In general, mixed exposures have encumbered definite conclusions about the effects of formaldehyde (104–107) and other explanations have been proposed for the reported symptoms, including psychosocial factors (108). Further, two

studies reported no correlation between sensory irritation and formaldehyde concentrations in 23 offices (30) and in 59 kitchens (109). Mixed exposures also occur in the wood industry and hamper the interpretation of the effect of formaldehyde. Nasal irritation dominated relative to that of the eyes and throat and was highest among those working with medium-density fibreboard and other wood products. It was concluded that 0.17 mg/m$^3$ formaldehyde was of minor importance for the reporting of symptoms (110).

The threshold for objective sensory irritation appears to be about 1 mg/m$^3$ for workers. For the indoor environment (24 hours), a value of 0.125 mg/m$^3$ was considered safe for the entire population against sensory irritation, including chronic sensory irritation (66,77). This value agrees with results obtained from a recent controlled human exposure study, where no subjective sensory irritation occurred in the eyes and upper airways below 0.38 mg/m$^3$ formaldehyde (79). Two approaches have been used to protect the potentially more sensitive part of the population. An assessment factor of 4 has been suggested for extrapolation from the NOAEL to a level below the threshold for sensory irritation (101). An assessment factor of 5 has been derived from the standard deviation of nasal pungency thresholds (111). Thus, applying an assessment factor of 5 on the suggested NOAEL of 0.63 mg/m$^3$ from the studies by Lang et al. (79) and Kulle et al. (99), a value of 0.125 mg/m$^3$ is obtained. This value is also considered valid for children, because there is no indication that children are more susceptible to formaldehyde exposure than adults.

There is no indication that extending exposure beyond four hours would increase the formaldehyde irritative response or the sensitivity. This is based on the fact that the chemical reaction of formaldehyde on the TRPA1 receptor site is reversible (112,113). Inflammation may increase the receptor sensitivity, but neither eye nor airway inflammation has been reported at indoor concentrations of formaldehyde. Further, neither nasal damage nor inflammation was observed in rats during life-long exposure to 1.2 mg/m$^3$ (1 ppm) formaldehyde (114).

***Nasal histopatological changes.*** A Swedish study (115) investigated 70 workers in a chemical plant in which formaldehyde and products based on formaldehyde were produced as resins and, for example, used for impregnation of paper. Additionally, 100 workers employed in the furniture industry were investigated. The 36 controls were mainly clerks. The mean formaldehyde concentration was 0.3 mg/m$^3$ (range 0.05–0.5 mg/m$^3$) with frequent formaldehyde peaks above 1 mg/m$^3$ in the chemical plant. The mean duration of exposure was 10.4 years. The furniture workers were exposed to 0.2–0.3 mg/m$^3$ formaldehyde that seldom exceeded 0.5 mg/m$^3$. The mean wood dust concentration was 1–2 mg/m$^3$ and the mean duration of exposure was 9 years. Controls were exposed to a mean formaldehyde concentration of 0.09 mg/m$^3$. Nasal biopsies were performed and evaluated by means of a nine-point scale (score 0–8), where category 1 was “stratified cuboid epithelium with loss of ciliated epithelium” and category 2 “mixed stratified cuboid/stratified squamous epithelium”.

The mean nasal biopsy score was 1.56 (range 0–4) in the controls, 2.07 (range 0–6) in the furniture workers (not statistically significant) and 2.16 (range 0–4) in the chemical plant (statistically significant). Within the formaldehyde exposure groups themselves, the histopathology scores were not exposure-dependent; exposure metrics were current formaldehyde concentrations (both formaldehyde groups were divided into exposure groups 0.1–0.24, 0.25–0.49 and ≥ 0.5 mg/m$^3$ formaldehyde), current wood dust concentrations (furniture workers were divided into exposure groups 0.1–1, 1.1–2 and 2.1–4.9 mg/m$^3$), cumulative formaldehyde exposures (both formaldehyde groups were divided into < 1.5, 1.5–4.99 and ≥ 5 mg/m$^3$.years) and duration of exposure (< 5, 5–14, 15–24 and ≥ 25 years). Overall, this study cannot be used for risk assessment owing to the lack of an exposure-dependent effect.

### Lung effects (non-cancer)

Formaldehyde alone does not cause IgE sensitization (116,117). Recent epidemiological studies of the occupational environment have not indicated an increase in sensitization to formaldehyde

exposure (see below). Nevertheless, formaldehyde-induced sensitization has been hypothesized. Two causes have been suggested, inflammation and formaldehyde acting as an adjuvant for allergens, but they are not supported at normal indoor air concentrations. Inflammatory mediator response was absent on the exposure of human lung epithelial cells at 0.25 mg/m$^3$ formaldehyde compared to clean air (118) and inflammation was not observed in life-long exposure of rats to 1.25 mg/m$^3$ formaldehyde (119). However, increased lung inflammation, reduced lung function and higher allergen-specific IgE antibody levels have been reported in rodents immunized by intraperitoneal administration to the allergen ovalbumin and followed by different airborne formaldehyde exposures (116,120,121). The interpretation of these studies is not clear in terms of the risk assessment of combined human indoor exposure to formaldehyde and allergens due to intraperitoneal administration in the animals. Thus, evidence of lung effects must depend on human data.

***Experimental studies.*** A number of human exposure studies have been carried out with lung function testing during the last decade (see Table 3.1).

The human exposure studies generally show that lung function is unaffected in both healthy and asthmatic people exposed for 1–4 hours to formaldehyde below 1 mg/m$^3$ (79,83,84,88). The limited effect on lung function and rhinitis is in agreement with a study in which formaldehyde inhalation had no effect on 95 patients with both upper and lower airway symptoms, when adjusted for placebo effects (86); further, the authors concluded that IgE-mediated formaldehyde allergy was nearly non-existent.

Two studies with asthmatics sensitive to grass pollen and dust mites (Der p 1), respectively, were investigated, in which formaldehyde exposure was combined with post-exposure to the allergens (in a season without grass pollen). In one study, increasing doses of inhaled grass pollen after exposure to 0.5 mg/m$^3$ formaldehyde for one hour did not affect the lung function over an 8-hour period; a non-significant protective effect of formaldehyde was observed (82). The particle size distribution of the grass pollen was 20–40 μm (V. Ezratty, personal communication, 2010). In the other study, oral breathing of 0.09 mg/m$^3$ formaldehyde for 30 minutes followed by exposure to dust mites (mean particle size 11 μm) resulted in a bronchial response at a lower dust mite allergen concentration relative to background air with 0.03 mg/m$^3$ formaldehyde; the geometric mean $PD_{20}$ for Der p 1 was 34 ng after formaldehyde and 45 ng after placebo ($P$ = 0.05) (80). An alternative statistical test (Wilcoxon signed-rank test) of the published data showed no significance, thus illustrating how sensitively the statistical outcome depends on the test applied. Further, the effect is considered to have no clinical relevance, because an estimated inhaled allergen dose for 8 hours while resting would be less than 1 ng, based on standard respiratory rates for males, sampled dust mites, e.g. in mattresses (122) and assuming a room particle concentration of 100 μg/m$^3$. This agrees with measured airborne concentrations of dust mites (Der f 1) in bedrooms (123).

***Epidemiological studies (children and adults).*** Gilbert (69) reviewed epidemiological studies on formaldehyde and lung effects in the indoor environment. Studies from the occupational environment have also been evaluated (1,68). Key studies with objective lung function testing are summarized in Table 3.1.

***Children.*** Some case-control and cross-sectional studies have indicated a possible association between low formaldehyde exposure and asthma or sensitization to certain allergens (106,124–128). Briefly, these studies have complex co-exposures, which encumber the establishment of direct cause–effect and dose–response relationships for formaldehyde and the evaluation of confounding effects (69).

Formaldehyde measured in the bedrooms of 224 healthy children aged 6–13 years was not found to be associated with effects on lung function (FEV), but an increase in exhaled nitric oxide was associated with formaldehyde levels greater than 0.06 mg/m$^3$ (124). Another study was carried out in 80 homes with 148 children aged 7–14 years, of which 53 were asthmatics. An association (OR = 1.40) between formaldehyde exposure and atopy was found with a 0.01-mg/m$^3$ increase in

formaldehyde in the bedrooms. However, no association was identified between formaldehyde in the bedrooms and asthma incidents and lung effects (125). The result is difficult to interpret, because about one third of the children were also exposed to environmental tobacco smoke and possibly pollutants from nearby coal mines and power stations (129). In a third case-control study, formaldehyde was measured twice in homes (bedroom and living room) of 88 asthmatic children under three years of age and a non-asthmatic control group of 104 children (126). A formaldehyde concentration > 0.06 mg/m$^3$ in the bedroom was found to be associated with an increased risk of asthma. Potential bias could be created by gas heating and new materials in the homes, and the general difficulty of diagnosis in children. Further confounding factors are discussed by Gilbert (69). The most important confounding factor, however, is the presence of combustion products as indicated by reported high concentrations of traffic pollutants such as benzene, toluene, xylenes, nitrogen dioxide and sulfur dioxide in the homes of the children (130). Such pollutants are known to be associated with asthma in children (131), that is, the reported cases may be different apart from asthma and formaldehyde exposure (132). For further information about this particular study and the impact of combustion products and lung effects, see Nielsen et al. (133).

Measured formaldehyde in living rooms and bedrooms did not differ in a univariate analysis between 90 matched pairs of homes of young asthmatics and non-asthmatics aged 4–17 years (134).

The formaldehyde-specific IgE level decreased in 8-year-old children when they moved to a new school with a lower formaldehyde level (128), although no association was identified between formaldehyde and reported symptoms, which encumbers the interpretation. One school study indicated an association between low formaldehyde values and airway effects (106), while another study failed to do so (135). However, the multiple co-exposure of animal allergens, moisture damage (fungi), traffic pollution and socioeconomic factors encumbers interpretation. In addition, chance significance is possible because of the high number of comparisons.

Formaldehyde-specific IgE was measured in 155 Japanese children randomly recruited from outpatient clinics, 122 asthmatics (mean age 9.5 years) and 33 without allergy (mean age 8.8 years) (136). No correlation was found between severity of asthma and IgE levels and formaldehyde, which agrees with the findings of Kim et al. (137). Formaldehyde-specific IgE was detected in only two asthmatic children and only at low levels. One child suffered from severe asthma, while the other had mild asthma.

In a cross-sectional case-control study, comparison of formaldehyde, total volatile organic compounds and dampness in the homes of 193 children (aged 9–11 years) with persistent wheezing and 223 controls showed that formaldehyde may increase wheezing. However, this may be interfered with or dominated by the effects of dampness (138).

In a similar cross-sectional case-control study of children aged 9–11 years, 245 with asthma symptoms within the last year and 329 controls, no association was found between formaldehyde exposure (median concentration 0.037 mg/m$^3$) in the home and reported asthma, allergy, adverse lung function, bronchial hyper-reactivity or sensitization (139).

***Adults.*** Mean exposures of 1.4 ± 0.7 mg/m$^3$ caused a minor decrease in lung function among students dissecting cadavers (85), an effect that diminished over weeks. Three other studies with exposed students and controls failed to find dose–response relationships (87–89). A limited effect on lung function, and rhinitis, is in accord with a study of 95 patients with both upper and lower airway symptoms related to work that were challenged with inhaled formaldehyde (86). Formaldehyde had no effect when adjusted for placebo effects, and the authors concluded that IgE-mediated formaldehyde allergy was nonexistent.

In a prospective study of 998 pregnant Japanese women, a possible association was identified between formaldehyde levels (median 0.030 mg/m$^3$, maximum 0.164 mg/m$^3$) and atopic eczema, but not with asthma, allergy or rhinitis (140). Another prospective study involved 143 Japanese medical students exposed to 3.0 mg/m$^3$ formaldehyde that responded to a questionnaire before

and after a course in anatomy. Two students, one of whom was atopic, showed skin reaction to 1% formaldehyde solution (141). No association was found between reported asthma in 182 inhabitants from 59 homes and measured formaldehyde levels in their kitchens (109). Eczema, but not allergic respiratory effects, was reported in a study among Finish metal workers exposed to, inter alia, formaldehyde and metalworking fluids (142).

In a cross-sectional study, VOCs and formaldehyde emitted from newly painted surfaces were found to be associated with exacerbated asthma in a study of 252 asthmatics that were compared with 310 non-asthmatics (127). The low number of affected people, multiple exposures (e.g. wood smoke and pets), socio economic status and the possibility of chance significance have been suggested as potential sources of bias (133).

In summary, consistent cause-effect and dose-response relationships between formaldehyde and measurable lung effects have not been found in controlled human exposure studies and epidemiological studies below 1 mg/m$^3$. In general, associations between formaldehyde and lung effects or sensitization in children in homes and schools have not been convincing owing to confounding factors and chance effects (17,77,132).

***Release of formaldehyde from wood particles.*** It has been proposed that particles, such as allergens, may carry formaldehyde down to the lower airways (132,143). Indeed, combined effects between formaldehyde and particles have been reported.

In the only human exposure study, subjects reported more coughing and effects on the lungs when exposed to 0.5 mg/m$^3$ active charcoal particles (1.4 µm diameter) and 3.5 mg/m$^3$ formaldehyde (144). These effects are supported by studies on mice and guinea-pigs (145-147), although the results are difficult to interpret for risk assessment because the concentrations are in general orders of magnitude higher than normally found indoors. Further, the amount of releasable formaldehyde from wood particles (> 6 µm) into the respiratory tract has been estimated to be negligible under the conditions in which the particles (5 mg/m$^3$) were exposed to 0.4 mg/m$^3$ formaldehyde (148).

The release of formaldehyde from medium-density fibreboard has been measured to lie between 100 and 1000 µg/g dust during 6 hours in water at 35–37 °C (110,149). This shows that the maximum amount of releasable formaldehyde from inhaled dust particles is 2 µg/day for a respirable particle concentration of 100 µg/m$^3$ and a respiratory rate of 20 m$^3$/day Thus, estimated formaldehyde release is insignificant compared to the inhaled amount of gaseous formaldehyde per day (1 mg) at a concentration of 0.05 mg/m$^3$ (45,150) and in agreement with formaldehyde on ambient particles (151).

In summary, the reported studies on formaldehyde in the wood industry indicate that release of formaldehyde into the airways from inhaled particles in indoor environments is negligible compared to the inhalable formaldehyde.

## Susceptible groups (non-cancer)

### Formaldehyde exposure alone

Paustenbach et al. (77), in their comprehensive review, concluded that hypersensitive groups (elderly people, asthmatics and children) could not be identified, nor could they identify any indication of sensitization by exposure to formaldehyde. This has been supported by comprehensive reviews during the last decade (66,67). Increased sensitivity is not considered biologically plausible. No studies on formaldehyde have been reported that show elderly people to be more susceptible; on the contrary, the elderly are generally less sensitive to sensory irritation (95), possibly decreasing after the age of 60 years (152,153).

Children may breathe more oronasally than adults, in addition to having higher respiration. DNA–protein cross-linking (DPX) has been shown in a computational fluid dynamic nasal model to be about 1.5 higher in adults than in children (154). This suggests that children are not

more susceptible than adults, which agrees with predicted formaldehyde adsorption rates per unit surface area of the nasal cavity being equal in children and adults (73).

### Combined exposure

One study showed that asthmatics sensitive to grass pollen are insensitive to formaldehyde prior to inhalation of grass pollen (82). Another study indicated that dust mite asthmatics may be more sensitive to a dust mite dose after formaldehyde exposure by mouth (80). The effect is not considered to have clinical relevance. Healthy people that suffer from nasal distress in their homes have been shown to exhibit swelling of the mucosa following exposure to 0.13 mg/m$^3$ formaldehyde for two hours when compared with a control group (78).

In summary, the experimental and epidemiological literature on formaldehyde does not indicate an increase in susceptibility among children, elderly people and asthmatics. Nevertheless, people with a personal trait of negative affectivity may report more symptoms.

## Long-term (carcinogenic) effects of exposure to formaldehyde at indoor levels

Formaldehyde is classified by IARC as carcinogenic to humans (Group 1) (1). In addition to sufficient evidence in experimental animals for upper airway carcinogenicity, IARC concluded that there is sufficient epidemiological evidence that formaldehyde causes nasopharyngeal cancer in humans. This was based on results from the U.S. National Cancer Institute (NCI) cohort and supported by the primarily positive findings in other studies. IARC (1) found only limited epidemiological evidence that formaldehyde causes sinonasal cancer in humans and the overall balance of epidemiological evidence did not support a causal role for formaldehyde-induced cancer at other sites, including the oral cavity, oro- and hypopharynx, pancreas, larynx, lung and brain. IARC recently accepted that there is sufficient evidence that formaldehyde may cause myeloid leukaemia in humans (155). The change in classification of myeloid leukaemia was supported by two new studies (156,157).

Formaldehyde is genotoxic in multiple in vitro models and in exposed humans and laboratory animals (1,64). Studies in humans showed increased DPX in workers exposed to formaldehyde, and genotoxicity and cytotoxicity are considered to play important roles in the carcinogenesis of formaldehyde in nasal tissues (1), where cell proliferation due to cytotoxicity is considered a key element in the development of airway cancer (64,158). For this type of carcinogenic effect, the NOAEL and the use of assessment factors are considered appropriate for setting standards or guidelines for airborne exposures (159). On the contrary, the early risk assessments used linear low-dose extrapolations, which do not account for the sub-linearities in the observed concentration–response relationship (1). The NOAEL approach has been used for setting health-based occupational exposure limits for formaldehyde, for example in Europe (64), Germany (160), Japan (161) and the United States (162), and for setting outdoor air standards in Germany (66).

### Biological mechanisms

Formaldehyde is a normal component of the blood. In humans, exposure to about 2.5 mg/m$^3$ airborne formaldehyde did not increase the blood level and exposure to less than 0.6 mg/m$^3$ did not increase urinary formate excretion owing to rapid metabolism (1). From a mathematical model describing the absorption and removal of inhaled formaldehyde in the human nose, it was predicted that exposures in the range of 0.125–12.5 mg/m$^3$ cause only extremely small increases in blood formaldehyde levels compared to pre-exposure levels (50). In monkeys, 7.5 mg/m$^3$ formaldehyde for 6 hours a day, 5 days a week for 4 weeks produced no increase in blood formaldehyde level. In rats, the half-time of formaldehyde is about one minute in the plasma after intravenous administration (1). This indicates that normal indoor air levels of formaldehyde are not expected to increase internal organ exposures.

The mucosal effect in Wistar rats was studied at exposures to 0, 0.125, 1.25 or 12.5 mg/m$^3$ formaldehyde for 6 hours a day, 5 days a week for 1 year (163) and 28 months (119). No

histological effect was apparent at 1.25 mg/m$^3$. In another study, nasal epithelial effects were observed at 2.5 mg/m$^3$ in Fischer 344 rats exposed for 6 hours a day, 5 days a week for 6–24 months (164). This indicates a NOAEL of 1.25 mg/m$^3$ for histopathological changes.

In the nasal tissue, formaldehyde reacts with glutathione to form S-(hydroxymethyl)glutathione, which is oxidized by the formaldehyde-dependent alcohol dehydrogenase to produce formate (1). The half saturation of the enzyme is estimated to occur at 3.25 mg/m$^3$ formaldehyde in the air (60) and, thus, higher exposure levels are expected to cause a disproportionate increase in cellular levels of formaldehyde. Formaldehyde causes DPX formation, which is non-linearly related to formaldehyde concentration. A conspicuous increase in DPX formation occurs above 2–4 mg/m$^3$ (1). In the nasal tissue of animals, DPX is removed rapidly and not accumulated over the exposure period (1).

### Nasal cancer in inhalation studies in rats

Chronic exposure to about 7.5 mg/m$^3$ formaldehyde and above caused squamous cell carcinoma of the nasal cavity of rats (67,158,165) with a non-linear concentration–response relationship (66,158,165). Exposure-dependent squamous cell carcinoma has not been observed at 2.5 mg/m$^3$ (2 ppm) and lower formaldehyde concentrations (1). Further, animal data mostly suggest that organs that are not in direct contact with formaldehyde do not develop neoplasms, presumably due to the fact that formaldehyde is highly reactive and rapidly metabolized locally (158).

The development of squamous cell carcinoma is considered to be related to a genotoxic effect that may be due to DPX (63,156,164) in addition to cytolethality-regenerative cellular proliferation (156,165); increased cell proliferation in the rat nose is considered to occur at about 2.5 mg/m$^3$ formaldehyde and above (67,158).

### Lymphohaematopoietic malignancies in animals

***Drinking-water studies.*** Formaldehyde was administered in the drinking-water in a 2-year study in Wistar rats (168). Males were dosed with 0, 1.2, 15 or 82 mg/kg per day and females with 0, 1.8, 21 or 109 mg/kg per day. Each group comprised 50 rats of each sex. Treatment-related pathological effects were limited to changes in the stomach and the kidney in both sexes in the high-dose group; the kidney effect was considered secondary to the reduced intake of liquid. The incidence of tumours did not vary markedly between the groups. Thus, the number of tumour-bearing rats and the total number of tumours were lower in the high-dose males than in the control males.

Haematological tumours were limited to generalized histiocytic sarcoma in one male and myeloid leukaemia in another male, both in the high-dose group. No lymphoma appeared in the high-dose group and no exposure-dependent lymphoma appeared from the study of the auxiliary lymph nodes and the small intestine.

In another study (169), formaldehyde was administered to Wistar rats for up to 24 months at 0, 10, 50 or 300 mg/kg per day. Each group comprised 20 males and 20 females. None of the animals survived 24 months of exposure in the 300-mg/kg group and severe lesions were observed in the stomach. Additionally, serum urea nitrogen increased significantly in both sexes, suggesting an effect on the kidneys. There was no significant difference in the incidence of any kind of tumour among the groups.

In a 104-week study (170), Sprague-Dawley rats were exposed to 10, 50, 100, 500, 1000 or 1500 mg formaldehyde per litre drinking-water. Another group was treated with 15 mg methanol per litre. The treated groups each consisted of 50 males and 50 females, while a control group given tap water consisted of 100 males and 100 females. The animals were observed until they died. There was no difference in survival among the groups, but the number of tumour-bearing animals was significantly higher among males in the highest exposure group. In the female control, methanol and 10, 50, 100, 500, 1000 and 1500 mg/l formaldehyde groups, the percentages of animals with haemolymphoreticular neoplasia were 7, 10, 10, 14, 16, 14, 22[1] and 20[1],

respectively. In the males, the percentage was 8, 20, 8, 20, 26[2], 24[1], 22[1] and 46[2], respectively. The study has a number of limitations (1). This applies to the "pooling" of lymphomas and leukaemias ("haemolym-phoreticular neoplasia"), the lack of reporting of non-neoplastic lesions, and the absence of information on the incidence of haemolymphoreticular tumours in the historical controls. Further, the incidence in comparison with the methanol-treated group was significantly increased only in the high-dose males, but the dose–response relationship was statistically significant.

Overall, the drinking-water studies showed no consistent increase in lymphohaematopoietic malignancies. Where significant, the effects were at the high formaldehyde levels and exposure–response relationships were apparently nonlinear.

***Inhalation studies.*** Groups of approximately 120 male and 120 female Fischer 344 rats and C57BL/6 × $C3HF_1$ mice were exposed to 0, 2.5, 7 or 18 mg/$m^3$ formaldehyde for 6 hours a day, 5 days a week for 24 months. The exposure period was followed by up to 6 months of non-exposure. Gross pathological examinations were performed on all animals that died or were sacrificed; histopathology was performed on 50 tissue samples per animal in the control and highly exposed groups.

Significantly increased mortality was observed both in male and female rats in the high-dose group and in males in the intermediate group. Survival in female mice was not affected by formaldehyde exposures. Exposed male mice had a slightly poorer survival, but this was not statistically significant. The significant formaldehyde-induced lesions were restricted to the nasal cavity and proximal trachea in both species (164).

The slides from the Kerns et al. (164) study were re-evaluated by Woutersen (114) as well as by a recent IARC working group (see Baan et al. (155) for a list of the working group members) to investigate the occurrence of lymphohaematopoietic malignancies. A mortality-adjusted trend test (the Peto mortality-prevalence test) was used to take into account early deaths due to nasal cancer that might have limited the detection of lymphohaematopoietic malignancies (114). No associations between formaldehyde exposure and leukaemia were seen in male or female rats at the end of the 24-month exposure period or in the 6-month recovery period. In male mice, rare lymphomas were seen at the end of the 24-month exposure period (1%, 1%, 1% and 0%, respectively, in the 0-, 2.5-, 7- and 18-mg/$m^3$ exposure groups), whereas the trend was highly significant in female mice (17%, 16%, 9% and 29%, respectively). It was concluded that formaldehyde may induce lymphoma in female mice, which is clearly driven by the incidence in the top exposure group.

The IARC working group noted that 12, 17, 16 and 7 out of 120 female rats developed undifferentiated leukaemia in the 0-, 2.5-, 7- and 18-mg/$m^3$ exposure groups, respectively, and that there was a markedly decreased survival in the 18-mg/$m^3$ group. Based on a survival-adjusted analysis, the incidence of leukaemia in females exposed to 18 mg/$m^3$ was increased compared to controls ($P = 0.0056$; Tarone extension of the Cox test, $P < 0.0167$). The working group noted that this is a very common, spontaneously occurring neoplasm in the F344 rat strain.

These re-evaluations permit two conclusions. First, leukaemia may or many not be induced in Fischer 344 rats at 24 months of exposure to 18 mg/$m^3$, at which a high incidence of nasal tumours occurred. Second, if lymphoma is induced by formaldehyde in female mice, the occurrence is at the very high exposure level at which there was high incidence of nasal tumours in rats. Thus, in rats the occurrence of nasal tumours is a more sensitive end-point than lymphohaematopoietic malignancies.

In another study, 100 Sprague-Dawley rats were exposed to 18 mg/$m^3$ formaldehyde for 6 hours a day, 5 days a week for life. Complete necropsy was performed on each animal. Histological sections were performed from each lobe of the lung, trachea, larynx, liver, kidney, testes and other organs where gross pathology was present. There was an increased mortality in the formaldehyde group compared with the control group. In the formaldehyde group, three

malignant lymphomas were observed. In the similar control group of 99 rats, two malignant lymphomas were observed, while three were observed in 99 colony controls (171).

In a 28-month study, male F-344 rats in groups of 32 were exposed to formaldehyde for 6 hours a day, 5 days a week at 0, 0.38, 2.5 or 18.8 mg/m$^3$, plus a room control group. The number of rats alive at 18 months or later and thus available for histopathology was 19, 22, 17, 7 and 16, respectively. Haematological, biochemical and pathological examinations were performed. Tissues for histopathology were pituitary, thyroid, nasal region, trachea, oesophagus, stomach, small and large intestine, prostate gland, urinary bladder, muscle, femur, sciatic nerve, spinal cord, mesenteric lymph nodes and any other gross lesion. Increased mortality was observed at the highest exposure concentration. No microscopic lesions were attributed to formaldehyde exposure except those in the nasal cavity. Also, there was no exposure-related abnormal haematological finding (172).

Overall, the occurrence of lymphohaematopoietic malignancies in inhalation studies in rats and mice is not convincing. In general, there is lack of consistency across species (165,173). Nevertheless, if it is assumed that there is a causal association, the association was seen at high exposure levels, which caused a high incidence of nasal cancer in rats. Also, the exposure–response relationship seems to be non-linear.

### Assessment of cancer hazards in meta-analyses

***Oral cavity and pharynx, sinus and nasal cavity, and lung.*** Bosetti et al. (63) conducted a meta-analysis based on six cohorts of industrial workers and professionals (pathologists, anatomists, embalmers and undertakers). No significant excess cancer risk was found in industrial workers and professionals for all cancers or for oral and pharyngeal cancer. The lung cancer risk was not affected in industrial workers (RR 1.06; 95% CI 0.92–1.23), whereas the risk was reduced in the professionals (RR 0.63; 95% CI 0.47–0.84). The study concluded that there was no appreciable risk for cancer of the oral cavity and pharynx, sinus and nasal cavity and lung. IARC (1) also concluded that the overall balance of epidemiological evidence did not support a causal role for formaldehyde in cancer in the oral cavity, oro- and hypopharynx and lungs.

In the meta-analysis by Bosetti et al. (63), the nasopharyngeal cancer risk was increased in industrial workers, but this was not statistically significant (RR 1.33; 95% CI 0.69–2.56). This was based on eight cancers in one study where six cancers were in one of ten plants and one cancer was from another cohort. No excess brain cancer risk was apparent in the industrial workers (RR 0.92; 95% CI 0.75–1.13) but the risk was significantly increased in the professionals (RR 1.56; 95% CI 1.24–1.96). The brain cancer risk is not consistent across the two types of study and it is not biologically plausible that formaldehyde causes brain cancer. This is in agreement with the evaluation of IARC (1).

Pancreatic cancer was addressed in a meta-analysis that comprised 14 epidemiological studies. No exposure-dependent effect was apparent (174). This is in agreement with the IARC evaluation (1).

Leukaemia was studied in a meta-analysis comprising 18 epidemiological studies (175). Heterogeneity was observed across studies and differences appeared between the RR of formaldehyde exposures in American (RR 1.2; 95% CI 1.0–1.4) and European workers (RR 0.9; 95% CI 0.7–1.1). Furthermore, the RR was different for various types of job: industrial workers (RR 0.9; 95% CI 0.8–1.0), embalmers (RR 1.6; 95% CI 1.2–2.0) and pathologists and anatomists (RR 1.4; 95% CI 1.0–1.9). Only three of the studies (176–178) evaluated leukaemia rates by exposure level. This meta-analysis concluded that the data do not provide consistent support for a relationship between formaldehyde exposure and leukaemia.

In the meta-analysis by Bosetti et al. (63), significantly reduced risks of lymphatic and haematopoietic cancer were observed in the industrial workers (RR 0.85; 95% CI 0.74–0.96). In contrast, the risk was significantly increased in the professionals (RR 1.31; 95% CI 1.16–1.48), comprising pathologists, anatomists and embalmers. No excess in leukaemia risk appeared in

industrial workers (RR 0.90; 95% CI 0.75–1.07) but the risk was significantly increased in the professionals (RR 1.39; 95% CI 1.15–1.68).

The most recent meta-analysis that includes all relevant cohort and case-control studies published through May 2009 found no increase in leukaemia. The meta-analysis summary RR was 1.05 (95% CI 0.93–1.20) for cohort studies and the summary OR was 0.99 (95% CI 0.71–1.37) for case-control studies (179).

While the three meta-analyses discussed above reported on the contrast between ever- vs never-exposed subjects and various combinations of lymphohaematopoietic cancers, a recent meta-analysis evaluated especially myeloid leukaemia from the highest exposure group of each study (180). Where several RRs were reported in a study, one RR was selected from each study in the order: peak exposure, average exposure intensity, cumulative exposure, exposure duration. For example, the accepted study groups were exposed to more than 2 ppm on average, with peak exposures above 4 ppm, or were exposed for more than 10 years. In the analysis by Zhang et al. (180), the fixed effects model and the random effect model showed similar results, and therefore the results are from the fixed effects model. Thus, an increased risk was observed for all types of cancer combined (RR 1.25; 95% CI 1.12–1.39; N = 19), for all leukaemia (RR 1.54; 95% CI 1.24–1.91; N = 15), for myeloid leukaemia (RR 1.90; 95% CI 1.41–2.55; N = 6) and for multiple myeloma (RR 1.31; 95% CI 1.02–1.67; N = 9) but not for Hodgkin's lymphoma (RR 1.23; 95% CI 0.67–2.29; N = 8) or non-Hodgkin's lymphoma (RR 1.08; 95% CI 0.86–1.35; N = 11).

The increases in leukaemia, myeloid leukaemia and multiple myeloma in the Zhang et al. (180) study were not consistently observed in the other studies (63,175). This may be explained by the fact that, if these types of cancer are caused by formaldehyde, they appear at high levels of formaldehyde.

### Cancer hazard studies in occupational cohorts

To obtain concentration–response relationships for formaldehyde exposures based on human experiences, the cancer risk due to formaldehyde exposure is reviewed from the three largest and recently updated occupational cohorts, which were identified from IARC (1), from the formaldehyde documentation for setting a health-based occupational exposure limit by the Scientific Committee on Occupational Exposure Limits (64) and a recent review (63). The NCI cohort comprised 25 619 workers employed in 10 facilities producing or using formaldehyde. Workers were employed prior to 1 January 1966 and were followed through to 31 December 1994 (177,181) and recently through to 31 December 2004 for lymphohaematopoietic malignancies (182). A cohort from six British factories, comprising 14 014 men employed after 1937, was followed through to December 2000 (176). The U.S. National Institute for Occupational Safety and Health (NIOSH) established a cohort of 11 039 employees in three garment facilities; the study was updated through to 31 December 1998 (178).

The cancer risks obtained from the three studies are shown in Table 3.3. The table is limited to anatomical sites that are directly exposed to airborne formaldehyde and to other sites where excess risks have been reported.

**Table 3.3**

Cancer risks from formaldehyde exposure.

### Nasopharyngeal cancer

The relative risk of nasopharyngeal cancer was further evaluated by four metrics: average exposure intensity (mg/m$^3$), highest peak exposure (mg/m$^3$), cumulative exposure (mg/m$^3$-years) and duration of exposure (years). In the average exposure intensity metric and the highest peak exposure metric, RRs were obtained with the unexposed group as the reference group. In the three average intensity exposure groups, > 0 to < 0.63 mg/m$^3$, 0.63 to < 1.25 mg/m$^3$ and ≥ 1.25 mg/m$^3$, the respective RRs were: not obtainable (0/3640 deaths), 0.38 (1/1405 deaths) and 1.67

(6/1450 deaths). Apparently, the increased risk was due to exposures ≥ 1.25 mg/m$^3$, although the trend was not statistically significant. With the peak exposure metric, all exposed deaths were in the highest peak exposure group (≥ 5 mg/m$^3$) and the trend was statistically significant. An exposure-dependent trend was found for the cumulative exposure metric (181), which was apparently driven by the highest exposure level.

Later, it was shown that the excess occurrence of nasopharyngeal cancer in the NCI study was driven by one of the 10 plants studied, where 6 of the 10 cases occurred. In this plant, the cases might or might not have been caused by formaldehyde exposure but by other risk factors such as "silver smithing" and "silver smithing or other metal work" (184). The only established occupational risk factor, wood dust, was considered a priori, but dropped because of very small numbers (184). Additionally, a low number of nasopharyngeal cancers in the reference group can cause unstable RR estimates (185). However, a recent IARC working group noted that it was unlikely that confounding or bias could explain the observed association (186).

It can be considered, however, for the purposes of indoor air guideline setting, that no excess nasopharyngeal cancer was reported at a mean formaldehyde exposure level at or below 1.25 mg/m$^3$ and with peak exposures below 5 mg/m$^3$.

### Lymphohaematopoietic malignancies

The NCI study also evaluated the effect of average intensity and peak exposures on the occurrence of lymphohaematopoietic malignancies leading to 178 deaths (177). The lowest exposure groups were used as reference for evaluation of RRs. For the average exposure intensity, the reference group comprised exposures of 0.125–0.5 mg/m$^3$.

The two higher exposure groups comprised exposures of 0.6–1.1 and ≥ 1.25 mg/m$^3$. Lymphohaematopoietic malignancies were significantly increased in both groups, with a borderline significant trend. Hodgkin's lymphoma was significantly increased in the 0.6–1.1-mg/m$^3$ group, with a significant exposure-dependent trend. Myeloid leukaemia was significantly increased at the highest exposure level, but the trend was not significant. For the peak exposure, the exposure in the reference group was 0.125–2.4 mg/m$^3$ and the exposure in the two higher exposure groups was 2.5–4.9 and 5 mg/m$^3$, respectively. Significantly increased RRs were observed for lymphohaematopoietic malignancies and leukaemia in the two highest exposure groups.

In the highest exposure group, the RR for myeloid leukaemia was also increased. For these three diseases, the trend in exposure-dependent effect was statistically significant. Additionally, the exposure-dependent trend was statistically significant for Hodgkin's lymphoma. The RR for leukaemia was not significantly associated with cumulative exposure.

When the study by Hauptmann et al. (177) was reanalysed by Marsh & Youk (187), it was shown that excess leukaemia and myeloid leukaemia were strongly influenced by a lower death rate in the reference groups compared to the national and local county SMRs. Using the national and local ratios, the SMRs for all leukaemia and myeloid leukaemia were very close to unity and were not significantly increased in the highest peak exposure category (≥ 5 mg/m$^3$). To evaluate the robustness of the categorizations, new average exposure intensity categories were constructed whereby the highest exposure category was ≥ 0.93 mg/m$^3$. Again, using the national and local county rates showed that the SMRs for all leukaemia and myeloid leukaemia were very close to unity and not significantly increased. Also, in this case, cumulative formaldehyde exposures were not associated with the development of leukaemia or myeloid leukaemia. Although this reanalysis does not support a causal association between formaldehyde exposure and leukaemia and myeloid leukaemia, for indoor air guideline setting one can take into account the fact that no excess lymphohaematopoietic malignancies occurred at a mean exposure level of formaldehyde below 0.93 mg/m$^3$ and where peak exposures were below 5 mg/m$^3$.

Recently, the NCI study updated lymphohaematopoietic risks through to 31 December 2004 (182). SMRs were estimated from the United States mortality rate (Table 3.3). For lymphohaematopoietic malignancies, the 319 deaths resulted in similar SMRs in exposed and unexposed people: 0.94 (95% CI 0.84–1.06) and 0.86 (95% CI 0.61–1.21), respectively. Exposure-dependent trends were evaluated from exposure categories similar to the previous follow-up. For lymphohaematopoietic malignancies in the average formaldehyde intensity metric, neither of the two highest exposure groups showed an increased RR, nor was the exposure trend statistically significant. In the new follow-up, the RR for Hodgkin's lymphoma was significantly increased in the 0.63- to < 1.25-mg/m$^3$ group but not in the highest exposure group (≥ 1.25 mg/m$^3$). The trend was statistically significant. Similar results appeared in the previous follow-up. Multiple myeloma was significantly increased among the non-exposed but not in the exposed groups. In the previous follow-up, the increase was not significant. In the peak exposure metric, lymphohaematopoietic malignancies were increased significantly in the highest exposure group (≥ 5 mg/m$^3$) and the trend was significant. Apparently, it is driven by the highest exposure group. Thus, the RR in the next highest exposure group was not remarkably increased (1.17 (95% CI 0.86–1.59)) and close to the RR among the unexposed, which was 1.07 (95% CI 0.7–1.62). In the previous follow-up, the RRs in the two highest exposure groups were similar (1.71 and 1.87, respectively) and significantly increased in both groups. The trend was also significant. In the new follow-up, the RR of Hodgkin's lymphoma was increased significantly in the two highest exposure groups: 3.30 (95% CI 1.04–10.50) in the 2.5- to < 5.0-mg/m$^3$ group and 3.96 (95% CI 1.31–12.02) in the ≥ 5-mg/m$^3$ group) with an exposure-dependent trend. In the previous follow-up, the trend was increased significantly but the RRs were approximately of the same size as in the recent follow-up. Except for a statistically increased RR of multiple myeloma in the non-exposed, no other remarkable RR appeared in the peak exposure group in the new follow-up study. For example, the RRs for multiple myeloma were 2.74 (95% CI 1.18–6.37) among the non-exposed, 1.0 in the reference group (≥ 0.13 to < 2.5 mg/m$^3$), 1.65 (95% CI 0.79–3.61) in the 2.5- to < 5.0-mg/m$^3$ group and 2.04 (95% CI 1.01–4.12) in the highest peak exposure group (≥ 5 mg/m$^3$) with no exposure-dependent trend. In this case, the RRs in the exposed groups were lower than in the non-exposed group, which does not support a formaldehyde-dependent effect. In the similar peak exposure groups, the RRs of myeloid leukaemia were 0.82 (95% CI 0.25–2.67), 1.0, 1.30 (95% CI 0.58–2.92) and 1.78 (95% CI 0.87–3.64) with a non-significant trend. In the earlier follow-up, myeloid leukaemia was significantly increased in the highest exposure group (3.46 (95% CI 1.27–9.43)) with a highly significant trend ($P \leq 0.009$).

Summarizing the NCI study, it is of note that the RRs for Hodgkin's lymphoma increase abruptly from that in the reference group (peak exposure > 0 to < 2.5 mg/m$^3$ and average intensity > 0 to < 0.63 mg/m$^3$). Overall, as the RRs in the reference group and the non-exposed group were not significantly different, an exposure guideline for formaldehyde should consider that peak exposures should be below 2.5 mg/m$^3$ and average exposures below 0.63 mg/m$^3$ to protect against lymphohaematopoietic malignancies in general.

The United Kingdom cohort from six British factories comprised 14 014 men employed after 1937 and followed through to December 2000 (176). By the end of the follow-up, 5185 of the men had died. The overall mortality from all cancers was slightly higher than expected from national death rates (SMR 1.10; 95% CI 1.04–1.16), as was that from lung cancer (SMR 1.22; 95% CI 1.12–1.32) and from stomach cancer (SMR 1.31; 95% CI 1.11–1.54) (see Table 3.3). Lung and stomach cancers were further analysed using the local geographical variations in mortality. Lung cancer increased significantly (SMR 1.28; 95% CI 1.13–1.44) only in the highest exposed group where the formaldehyde level was greater than 2.5 mg/m$^3$. No trend was seen at lower levels and, for example, the SMR in the range 0.75–2.5 mg/m$^3$ was 0.99 (95% CI 0.74–1.30). However, there was a statistically non-significant decrease in the risk of death from lung cancer with duration of high exposure. The risk showed no increasing trend with time since first exposure. The authors interpreted lung cancer in the highest exposed group to be “rather large to be explained simply by a confounding effect of smoking” (which was not taken into account). Using the local mortality rate, stomach cancer was not exposure-dependent and was considered

by the authors to be a less plausible outcome. For setting an indoor air guideline, the key information from this study is that no increase in lung cancer was apparent at formaldehyde levels of 5 mg/m$^3$ or lower. No results on peak exposures and risk for myeloid leukaemia were provided.

NIOSH established a cohort of 11 039 employees in three garment facilities (The USA garment worker cohort). The study was updated through to 31 December 1998, by which time 2206 of the employees had died. The mortality from all malignant neoplasms was significantly less than expected (SMR 0.89; 95% CI 0.82–0.97), as was that for all digestive neoplasms (SMR 0.77; 95% CI 0.63–0.92). Myeloid leukaemia (ICD-9: 205) was significantly increased (13 deaths; SMR 1.91) after 20 or more years since first exposure, but the trend was not significant. Among workers with both 10 or more years of exposure and 20 years or more since first exposure, multiple-cause mortality from leukaemia was significantly increased almost two-fold (15 deaths; SMR 1.92; 95% CI 1.08–3.17). In addition to underlying cause of death, all causes listed on the death certificate were analysed using multiple cause mortality. Multiple cause mortality from myeloid leukaemia was significantly increased among this group (8 deaths; SMR 2.55; 95% CI 1.10–5.03) (178).

#### Recent studies on lymphohaematopoietic effects

Haematopoietic tissue damage was studied in 43 formaldehyde-exposed workers and 51 controls. The 8-hour time-weighted average was 1.6 and 0.03 mg/m$^3$ and the 90 percentile 3.14 and 0.03 mg/m$^3$, respectively. Peak exposure concentrations were not reported. Formaldehyde exposures were associated with reduced blood lymphocyte, granulocyte, platelet, red blood cell and total white blood cell counts; the total white blood cell count was reduced by 13.5% in the formaldehyde-exposed workers. Urinary benzene concentrations were low in both groups, thus excluding benzene exposure as a confounder. The findings were considered consistent with a bone-marrow-toxic effect due to formaldehyde. Peripheral blood cells from formaldehyde-exposed and control workers were cultivated to derive blood myeloid progenitor cells. The colony formation fell non-significantly by 20% in the formaldehyde-exposed workers and this was considered a toxic effect on the myeloid progenitor cells. Blood mononuclear cells from volunteers were cultivated in vitro to derive different lines of progenitor cells.

The addition of different dilutions of formalin to the cultures showed that formaldehyde reduced the number of generated colonies from all progenitor cell lines. This showed that formaldehyde can inhibit the proliferation of all progenitor cells if the endogenous formaldehyde level is increased due to formaldehyde exposure. Blood progenitor cells of the myeloid line were derived from 10 highly exposed workers (8-hour time-weighted median concentration 2.67 mg/m$^3$ and 90th percentile 5.18 mg/m$^3$) and 12 controls (8-hour time-weighted median concentration 0.03 mg/m$^3$ and 90th percentile 0.03 mg/m$^3$). Formaldehyde-exposed workers showed increased monosomy (loss) of chromosome 7 and an increase in trisomy of chromosome 8; these cytogenic changes are observed in myeloid leukaemia and myelodysplastic syndromes (154).

It should be noted that the study has limitations in relation to risk assessment of formaldehyde exposure at indoor air concentrations. First, the exposures are extremely high and thus the unreported peak exposure concentrations may have been at extremes. Second, no exposure–response relationship is established. Third, the very high exposure concentrations may be expected to cause mucosal damage that may influence both the nasal metabolism and absorption into the blood compartment; no information is available on the mucosal tissue. Fourth, the in vitro cell culture study is relevant for mechanistic considerations only, because no increase in formaldehyde has been observed in the blood compartment of humans due to formaldehyde exposure. This is supported by model calculations at about 2.5 mg/m$^3$ (50). Similar results were reached for extrapolations up to 12.5 mg/m$^3$, but such extrapolations may be invalidated by the toxic effects on the mucosal membrane above 2.5 mg/m$^3$. Overall, the interpretation of this study in relation to risk assessment is unclear. For the sake of transparency, it would have been desirable that all measured exposures other than to formaldehyde had been reported.

In a case-control study in the United States (157), 168 professionals employed in the funeral industry who died from lymphohaematopoietic malignancies were compared with 265 deceased matched controls from the same industry. The 8-hour time-weighted average formaldehyde intensity was about 0.125–2.5 mg/m$^3$, the average intensity while embalming was about 1.9–2.25 mg/m$^3$ and peak exposure was about 10–13 mg/m$^3$. Four people died from nasopharyngeal cancer, but only two had been involved in embalming (OR 0.1 (95% CI 0.01–1.2)). No increase was observed in lymphoid malignancies (ICD-8 200–204), including Hodgkin's lymphoma (OR 0.5 (95% CI 0.1–2.6)), which was consistently elevated in the previous industrial cohort studies (177,182). The study observed a specific association between embalming and myeloid leukaemia (ICD-8 205). Thus, using a reference group of newer exposed with one case subject, the OR was 11.2 (95% CI 1.3–95.6).

The first analysis of myeloid leukaemia used a reference group of subjects that had not performed embalming. The duration of working in jobs that involved embalming showed a significant trend ($P = 0.02$): in the categories > 0–20, > 20–34 and > 34 years, the OR was 5.0 (95% CI 0.5–51.6), 12.9 (95% CI 1.4–117.1) and 13.6 (95% CI 1.6–119.7), respectively. No significant trend was observed with the number of embalmings. However, several significant ORs were observed. Thus, the number of performed embalmings were divided into > 0–1422, > 1422–3068 and > 3068, where the OR was 7.6 (95% CI 0.8–73.5), 12.7 (95% CI 1.4–116.7) and 12.7 (95% CI 1.4–112.8), respectively. Exposure–response relationships for the different formaldehyde metrics were established. The peak exposure metric was the only metric that showed a significant trend ($P = 0.036$). Peak formaldehyde exposures were divided into > 0–8.75 mg/m$^3$, > 8.75–11.6 mg/m$^3$ and > 11.6 mg/m$^3$, where the OR was 15.2 (95% CI 1.6–141.6), 8.0 (95% CI 0.9–74.0) and 13.0 (95% CI 1.4–116.9), respectively. The cumulative formaldehyde exposures (mg/m$^3$-hours) were divided into > 0–5073, > 5073–11 566 and > 11 566, where the OR was 10.2 (95% CI 1.1–95.6), 9.4 (95% CI 1.0–85.7) and 13.2 (95% CI 1.5–115.4), respectively. The average formaldehyde intensity while embalming was > 0–1.75 mg/m$^3$, > 1.75–2.38 mg/m$^3$ and > 2.38 mg/m$^3$, where the OR was 11.1 (95% CI 1.2–106.3), 14.8 (95% CI 1.6–136.9) and 9.5 (95% CI 1.1–86.0), respectively. The 8-hour time-weighted formaldehyde intensity was divided into > 0–0.125 mg/m$^3$, > 0.125–0.225 mg/m$^3$ and > 0.225 mg/m$^3$, where the OR was 8.4 (95% CI 0.8–79.3), 13.6 (95% CI 1.5–125.8) and 12.0 (95% CI 1.3–107.4), respectively. The cumulative formaldehyde exposure, the average formaldehyde intensity while embalming and the 8-hour time-weighted average intensity showed no statistically significant formaldehyde exposure-dependent trend. It is noted that, within each of the formaldehyde exposure metrics, the ORs showed little difference and had highly overlapping confidence intervals. This suggests that the statistical significances are driven mainly by exposure vs non-exposure and less by differences in exposure levels. Also, in each of the formaldehyde metrics, none of the trend tests within the formaldehyde groups themselves was statistically significant.

Because of the small number of exposed cases and related instability of the reference group, the authors performed additional exposure–response analyses with a larger reference group, including subjects with low exposure. The second analysis of myeloid leukaemia used a reference group whose members had performed fewer than 500 lifetime embalmings, allowing 5 case subjects in the reference group.

The duration of working in jobs with embalming showed a significant trend ($P = 0.02$). In the categories < 20, > 20–34 and > 34 years, the OR was 0.5 (95% CI 0.1–2.9), 3.2 (95% CI 1.0–10.1) and 3.9 (95% CI 1.2–12.5), respectively. No significant trend was observed with the number of embalmings, but significant ORs were observed at the highest exposure level. Thus, the numbers of performed embalmings were divided into ≥ 500–1422, > 1422–3068 and > 3068, where the OR was 1.2 (95% CI 0.3–5.5), 2.9 (95% CI 0.9–9.1) and 3.0 (95% CI 1.0–9.2), respectively.

The peak exposure metric was the only formaldehyde metric that showed a significant trend ($P = 0.036$). Peak formaldehyde exposures were divided into ≤ 8.75 mg/m$^3$, > 8.75–11.6 mg/m$^3$ and ≥ 11.6 mg/m$^3$, where the OR was 2.9 (95% CI 0.9–9.8), 2.0 (95% CI 0.6–6.6) and 2.9 (95% CI

0.9–9.5), respectively. The trend was not statistically significant in the cumulative formaldehyde exposure, the average formaldehyde intensity while embalming and the 8-hour time-weighted intensity group. Only the highest cumulative formaldehyde exposure group (> 11 566 mg/m$^3$-hours) had a statistically elevated OR of 3.1 (95% CI 1.0–9.6). Except for this, the ORs were elevated (2.0–2.9) and very similar within each of the metrics, but none was significantly increased.

Also, in each of the metrics, none of the trend tests within the formaldehyde groups themselves was statistically significant. It is noted that the overall picture was similar to that in the first analysis except for the fact that the ORs fell by one third in this analysis, where a higher number of case subjects were available in the control group. Only one significant OR appeared in the formaldehyde exposure metrics, which was in strong contrast to the 10 significantly elevated ORs in the first analysis.

It is noted that there is a lack of exposure-dependent differences in OR within the different formaldehyde exposure levels in the different metrics. A lack of exposure-dependent effect could be due either to an inappropriate exposure assessment or to a lack of causality between formaldehyde exposure and myeloid leukaemia; the reference groups contained a low number of case subjects. The method of formaldehyde exposure has limitations, as the estimates were predicted by means of interviews and mathematical modelling rather than being based on measured exposures. Also, it is mentioned by the authors that the peak model was not validated. On the whole, this study cannot be used for risk assessment as it does not provide a convincing exposure–response relationship.

Comparison of the Zhang et al. (156) and the Hauptmann et al. (157) studies reveals some differences. The Zhang et al. study suggests an effect on all progenitor cells that results in decreased production of lymphocytes, granulocytes, platelets and red blood cells. Similar results were obtained from the in vitro cell cultures with different progenitor cell lines. In the Hauptmann et al. study, the effect was selective at the myeloid progenitor line. Overall, these studies have very high exposure intensities and thus do not contradict the fact that lymphohaematopoietic malignancies are not observed at lower levels, as derived from the 2003 study by Hauptmann et al. (177) and its re-analysis by Marsh & Youk (187).

The meta-analysis based on the highest exposure levels reported that formaldehyde caused leukaemia and especially myeloid leukaemia (180). Three hypotheses were proposed. First, formaldehyde could be transported by the blood to the bone marrow, where it could cause initiation in a stem or progenitor cell. Second, as a portion of the bone marrow stem and progenitor cells circulate in the peripheral blood, they may be initiated by formaldehyde absorbed into the blood. Third, initiation of the primitive pluripotent stem cells presented within the nasal mucosa could occur, followed by transport to the bone marrow. Similar arguments were analysed by Pyatt et al. (173) and the two first hypotheses were not considered likely owing to the negligible amount of formaldehyde reaching the blood. However, nasal (portal-of-entry) effects caused by high formaldehyde exposure levels could be a plausible mechanism for Hodgkin's lymphoma. However, this was not consistent with the Zhang et al. meta-analysis (180). In summary, potentially offending levels can be considered to be in the range where formaldehyde has shown nasal effects in rats, as no lymphohaematopoietic malignancies were observed with mean exposures below 0.63 mg/m$^3$ and peak exposures below 2.5 mg/m$^3$, if caused by formaldehyde at all.

### Prediction of nasal cancer

Formaldehyde can induce squamous cell carcinoma of the nasal cavity in rats. As a nasal effect would be consistent across species, it is considered the key to setting an indoor air guideline for carcinogenic effects of formaldehyde. The NOAEL approach for setting a guideline value is based mainly on the strongly non-linear relationship between formaldehyde exposure and development of squamous cell carcinoma in rats, largely corroborated by epidemiological studies. This approach accepts that the fall-off of the carcinogenic effect is so rapid that the

observed NOAEL resembles a true NOAEL. Accepting these arguments, an indoor air guideline value can be set by dividing the appropriate NOAEL by one or more assessment factors (159). This approach considers the NOAEL for squamous cell carcinoma in rats (2.5 mg/m$^3$), the NOAEL for nasal cytotoxicity in rats (1.25 mg/m$^3$) and the potential development of malignancies in humans, which have not been encountered at mean exposures below 0.63 mg/m$^3$ and peak exposures below 2.5 mg/m$^3$ formaldehyde.

To obtain a deeper knowledge and thus a better risk assessment, a biologically motivated model has been developed that models exposures by computational fluid dynamics and the development of cancer from a two-stage clonal growth model (17,167,188). Formaldehyde was assumed to act as a direct mutagen with the effect considered proportional to the concentration of the pro-mutagenic DPX lesion. The DPX formation is considered linearly related to the formaldehyde concentration; the linear relation between formaldehyde and DPX concentrations can be considered a worst-case scenario in the low-dose range. At high concentrations, the model includes that cytolethality is followed by cell proliferation. Mutations are considered to occur during cell division, and a tumour cell arises when an initiated cell (modelled by DPX levels) acquires a second mutation (17,167). The relationship between formaldehyde exposure and the average cell division rate was J-shaped in rats. The rapid increase in cell proliferation occurred at a level that was not significantly different from a threshold model with a NOAEL set above 2.5 mg/m$^3$ (167). The two-stage clonal growth model was shown to predict nasal tumours in rats using a lifetime cumulative probability of squamous cell carcinoma with 13 animals with squamous cell carcinoma among 7684 control rats from the U.S. National Toxicology Program historical control database, and where several of the parameters were estimated from the best fit of the model to the experimental data.

The biologically motivated model was extended to humans and took into account that humans are oronasal breathers (17,188). For the general population, the predicted additional risk of upper respiratory tract cancer for non-smokers, associated with an 80-year continuous exposure to 0.125 mg/m$^3$ formaldehyde, was about $2.7 \times 10^{-8}$ (17). The additional risk was estimated to be $10^{-6}$ or less for non-smokers exposed continuously to 0.25 mg/m$^3$ formaldehyde (188).

The robustness of the model has been challenged by sensitivity analyses (189–191). Thus, the estimate is sensitive to the DPX half-life in the nose (190); the DPX half-life was accepted as 1.78 hours in the 2003 study by Conolly et al. (167) that was based on in vivo rat studies, but it was assumed to be 12.3 hours in the sensitivity analysis (190) on the basis of the half-life in immortalized cell lines (192). The estimated risks were sensitive to the incidence of squamous cell carcinoma in the rat control group data (189,190) and to the data used for rates of nasal cell replication and death (189,191). For example, the instability of the estimates was seen when the current control group, comprising no squamous cell carcinoma among 341 controls, was used (189), although this frequency is in overall agreement with what would have been expected from the cumulative group by proportional scaling (0.57/341). Overall, the sensitivity analyses highlight the limited possibility of predicting risks from the rare events in the unexposed control group.

The importance of the replication rate of the initiated cell was addressed (189,191). Introducing a minor arbitrarily selected increase in cell division rate by formaldehyde exposure and using the entire historical control group of rats, the predicted human risk of respiratory cancer by the age of 80 years from lifetime exposure varied from about 0.02 to about 1 at 0.1 ppm formaldehyde. Thus, the sensitivity analysis showed that the assumed cell division rate of the initiated cell has a tremendous effect on the predicted risk. This led to the conclusion that the Conolly et al. model (175) is not reliable for estimating human risk, irrespective of whether the predictions by Crump et al. (193) are at odds with human epidemiology, which was the main point of critique of the sensitivity analyses (194).

The 2004 estimate of Conolly et al. (188) has to be taken cautiously. It is not an upper boundary ("worst-case consideration"), which can reach values – depending on the assumptions in the sensitivity analysis – that are incompatible with epidemiological findings. Beside the key event

of cell proliferation in formaldehyde-induced nasal cancer identified in animal studies, the estimates by the International Programme on Chemical Safety (17) and Conolly et al. (188) qualify the discussion about the size of the formaldehyde-induced risk as well as providing input to the selection of the assessment factor in the NOAEL approach.

A recent model study showed that formaldehyde exposure of children would result in less DPX formation than it would in adults exposed at the same level (154). Consequently, children are not expected to be more sensitive to any carcinogenic effect of formaldehyde than adults and are thus not considered separately in the further evaluation.

## Health risk evaluation

### Exposure evaluation

The major exposure route for formaldehyde is inhalation. Although concentrations above 0.2 mg/m$^3$ may be encountered in new or renovated buildings, in new furnishings and at hot and humid times of the year, levels on the average are less than 0.05 mg/m$^3$ in homes and about half that in public buildings (Table 3.4). The most important way to control the formaldehyde concentration is the air exchange rate and the use of low-emitting materials and products. Environmental tobacco smoke and ozone-initiated reactions of alkene compounds may contribute to temporary peak levels. Outdoor concentrations are considerably lower, except in some major cities.

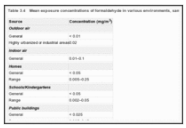

**Table 3.4**

Mean exposure concentrations of formaldehyde in various environments, sampled over several days.

Formaldehyde is a normal component of blood. Exposure to 2.4 mg/m$^3$ did not increase the blood level and exposure to 0.5 mg/m$^3$ did not result in an increase in urinary formate excretion due to rapid local metabolism (1,37,43).

### Critical health outcomes

Effects of formaldehyde in indoor air are generally expected to be limited to effects at the site of contact, specifically the eyes and nasal and upper airways. Effects are due to direct reactions with formaldehyde itself and do not appear to require metabolism.

#### Non-cancer

The acute symptom of formaldehyde at indoor exposure concentrations is sensory irritation of the eyes and upper airways. Human exposure studies indicate that 0.63 mg/m$^3$ is the threshold for trigeminal stimulation of the eyes (e.g. increased blink frequency) and 0.38 mg/m$^3$ is the threshold for subjective sensory irritation.

In general, the concentration perceived by the olfactory system is lower than that triggering sensory irritation of the eyes and airways, and people may therefore report symptoms at levels below its sensory irritation threshold.

Irritation effects of formaldehyde are not cumulative, based on the reversibility of the chemical reactions of formaldehyde-induced irritation and the lack of detectable accumulation of DNA protein cross-links during repeated exposures.

There is no evidence indicating an increased sensitivity to sensory irritation to formaldehyde among people often regarded as susceptible (asthmatics, children and older people).

Although some studies suggest that formaldehyde plays a role in airway sensitization, an association between formaldehyde and lung effects or sensitization in children have not been

convincing owing to confounding factors in the studies, including exposure to traffic-related co-pollutants.

Lung function remains unaltered in adults at exposures below 1 mg/m$^3$ formaldehyde.

#### Cancer

Formaldehyde can induce squamous cell carcinoma of the nasal cavity in rats and nasopharyngeal cancer in humans. Long-term exposure to 7.5 mg/m$^3$ formaldehyde and above caused squamous cell carcinoma of the nasal cavity of rats with a non-linear, biphasic concentration–response relationship having the break point at or above 2.5 mg/m$^3$. In humans, no excess nasopharyngeal cancer has been observed at mean exposure levels at or below 1.25 mg/m$^3$ and with peak exposures below 5 mg/m$^3$.

Exposure to formaldehyde has been suspected of leading to lymphohaematopoetic malignancies. However, most long-term inhalation carcinogenicity studies in rats, mice and hamsters do not suggest induction of lymphohaematopoetic malignancies by formaldehyde at levels associated with nasal cancer. In humans, the overall conclusions from three meta-analyses, as well as a recent study in embalmers, suggest that formaldehyde may be causally associated with lymphohaematopoetic malignancies. The recent study in embalmers found evidence of myeloid leukaemia but not other haematopoietic malignancies; the 8-hour time-weighted average formaldehyde intensity was 0.125–0.25 mg/m$^3$, the average formaldehyde intensity while embalming was about 1.9–2.25 mg/m$^3$, and peak exposure was about 10–13 mg/m$^3$. This suggests that an effect on bone marrow or blood progenitor cells is possible at high exposure concentrations. However, since exposure to formaldehyde concentrations up to 2.5 mg/m$^3$ has negligible influence on the endogenous formaldehyde blood level, protection against nasal cancer should also protect against leukaemia.

### Relevance for health of indoor air exposure

The major exposure route of formaldehyde is inhalation from indoor sources. Formaldehyde is a normal component of blood. Exposure of humans to 2.5 mg/m$^3$ formaldehyde did not increase the blood levels and exposure to 0.5 mg/m$^3$ did not result in an increase in urinary formate excretion due to rapid metabolism. This suggests that formaldehyde levels normally encountered in indoor air, not exceeding 0.2 mg/m$^3$, are not expected to increase internal organ exposure.

### Conclusions of other reviews

Regulatory agencies in many countries have established guideline values for concentrations of formaldehyde in indoor air. IARC has classified formaldehyde as a human carcinogen (Group 1) based on sufficient epidemiological evidence of nasopharyngeal cancer, and a recent IARC working group also found sufficient evidence for myeloid leukaemia.

## Guidelines

An indoor air guideline for formaldehyde is appropriate because indoor exposures are the dominant contributor to personal exposures through inhalation and indoor concentrations may be high enough to cause adverse health effects.

The lowest concentration reported to cause sensory irritation of the eyes in humans is 0.38 mg/m$^3$ for four hours. Increases in eye blink frequency and conjunctival redness appear at 0.6 mg/m$^3$, which is considered equal to the NOAEL. There is no indication of accumulation of effects over time with prolonged exposure.

The perception of odour may result in some individuals reporting subjective sensory irritation, and individuals may perceive formaldehyde at concentrations below 0.1 mg/m$^3$. However, this is not considered to be an adverse health effect. The NOAEL of 0.6 mg/m$^3$ for the eye blink response is adjusted using an assessment factor of 5 derived from the standard deviation of nasal

pungency (sensory irritation) thresholds, leading to a value of 0.12 mg/m$^3$, which has been rounded down to 0.1 mg/m$^3$. Neither increased sensitivity nor sensitization is considered plausible at such indoor concentrations in adults and children. This value is thus considered valid for short-term (30-minute) duration, and this threshold should not be exceeded at any 30-minute interval during a day.

Thus, a short-term (30-minute) guideline of 0.1 mg/m$^3$ is recommended as preventing sensory irritation in the general population.

There is sufficient evidence that formaldehyde causes nasal cancer in animals and nasopharyngeal cancer in humans with a non-linear, biphasic concentration-response relationship. Carcinogenicity studies in rats, mice and hamsters do not show a consistent association between formaldehyde and lymphohaematopoetic malignancies. Associations between exposure to formaldehyde and nasopharyngeal malignancies and leukaemia in humans are limited to high exposure concentrations.

Increased cell proliferation due to cell damage is considered a key mechanism for the development of nasal malignancies following exposure to formaldehyde. Overall, indoor air effects of formaldehyde are expected to be limited to the site of contact, generally the nasal and upper airways. Increasing cell proliferation in the nasal mucosa of rats occurs at concentrations at and above 2.5 mg/m$^3$ formaldehyde. The NOAEL for cell proliferation is 1.25 mg/m$^3$ for long-term exposures.

Thus a threshold approach to setting a guideline for cancer effects is appropriate. Starting with the NOAEL of 1.25 mg/m$^3$, assessment factors are applied. An interspecies assessment factor of 3 is proposed because the effect is local (non-systemic) and directly due to formaldehyde itself; for inter-individual variation, an assessment factor as low as 2 is proposed because sensitivity differences are not seen among different populations (asthmatics, children and older people). This would lead to a proposed guideline of 0.21 mg/m$^3$ for the protection of health for long-term effects, including cancer.

An alternative approach was taken by several other groups, using a biologically motivated model. Their assessments led to a predicted additional risk of $2.7 \times 10^{-8}$ for continuous lifetime exposure to 0.125 mg/m$^3$ and a predicted additional risk of $10^{-6}$ or less for non-smokers continuously exposed to 0.25 mg/m$^3$.

These two assessments (using a NOAEL/assessment factor approach and estimates from the biologically motivated models) yield similar results, with values of approximately 0.2 mg/m$^3$. These values are above the guideline for short-term effects of 0.1 mg/m$^3$. Thus use of the short-term (30-minute) guideline of 0.1 mg/m$^3$ will also prevent long-term health effects, including cancer.

The use of low-emitting building materials and products, and preventing exposures to environmental tobacco smoke and other combustion emissions, will minimize exposure-related risk. In addition, ventilation can reduce indoor exposure to formaldehyde.

The guidelines section was formulated and agreed by the working group meeting in November 2009.

## Summary of main evidence and decision-making in guideline formulation

### Critical outcome for guideline definition

Sensory irritation.

### Source of exposure–effect evidence

Experimental study reporting conjunctival redness and increases in eye blink frequency at a four-hour exposure of 0.63 mg/m$^3$ considered as the NOAEL (79). This was adjusted using an assessment factor of 5 derived from the standard deviation of nasal pungency (sensory irritation) thresholds, leading to a value of 0.12 mg/m$^3$, which has been rounded down to 0.1 mg/m$^3$.

#### Supporting evidence

- Several reviews on sensorial irritation at exposure levels between 0.15 and 1.25 mg/m$^3$ (66,67,77).
- 12 controlled, mostly double-blind studies on respiratory effects at exposures of 0.08–11.2 mg/m$^3$ (78–89).

#### Results of other reviews

IARC: Group I (known human carcinogen) (1,155,186).

#### Guidelines

0.1 mg/m$^3$ (30-minute average concentration).

#### Comments

- The short-term guideline will also prevent effects on lung function as well as long-term health effects, including nasopharyngeal cancer and myeloid leukaemia.
- No change in the guideline as compared to *Air quality guidelines for Europe*, 2nd ed.

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## Footnotes

1 $P < 0.05$.

2 $P < 0.01$.



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