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132. Formaldehyde

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Nordic Council of Ministers

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Preface

An agreement has been signed by the Dutch Expert Committee on Occupational Standards (DECOS) of the Health Council of the Netherlands and the Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals (NEG). The purpose of the agreement is to write joint scientific criteria documents, which could be used by the national regulatory authorities in both the Netherlands and in the Nordic countries.

The document on health effects of formaldehyde was written by Anton Wibowo, Coronel Institute, Academic Medical Centre, University of Amsterdam, the Netherlands, and has been reviewed by DECOS as well as by NEG.

The joint document is published separately by DECOS and NEG. The NEG version presented herein has been adapted to the requirements of NEG and the format of Arbete och Hälsa. The editorial work and technical editing has been carried out by Anna-Karin Alexandrie, and Jill Järnberg, scientific secretary of NEG, at the National Institute for Working Life in Sweden.

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
CI	confidence interval
CNS	central nervous system
CRR	combined relative risk
EPA	United States Environmental Protection Agency
FEV_1	forced expiratory volume in one second
FEV_3	forced expiratory volume in three seconds
FVC	forced vital capacity
IARC	International Agency for Research on Cancer
IHF	Industrial Health Foundation
IPCS	International Programme on Chemical Safety
LOAEL	lowest observed adverse effect level
MAK	maximale Arbeitsplatzkonzentration
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no observed adverse effect level
OR	odds ratio
OSHA	Occupational Safety and Health Association
RD_{50}	concentration associated with a 50% decrease in respiratory rate
SMR	standard mortality ratio
SPIR	standardised proportionate incidence ratio
SRR	standardised rate ratio
TLV	threshold limit value
TWA	time weighted average
WHO	World Health Organisation

Contents

1. Introduction

Formaldehyde is a colourless gas at room temperature and normal atmospheric pressure. It is flammable, reactive and polymerises readily at room temperature. It forms explosive mixtures with air and oxygen at atmospheric pressure. The substance occurs naturally in the environment and is produced physiologically by mammalian cells during metabolism.

Formaldehyde is used as a raw material in chemical reactions, and as an intermediate in the manufacture of numerous products. It has also a medical application as a disinfectant and is used as a preservative in various consumer products.

A criteria document on formaldehyde was written for the Nordic Expert Group for Documentation of Occupational Exposure Limits (NEG) in 1982 (66).

The present document is a co-production between NEG and the Dutch Expert committee on Occupational Standards (DECOS) hereafter called the committees, and the document is an up-date of the previus DECOS publication from 1987 (34).

2. Identity, properties and monitoring

2.1 Identity and chemical properties

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

2.2 Physical characteristics (27, 59)

Relative molecular mass:	30.03
Boiling point:	-20°C
Melting point:	-92°C
Relative density (water=1):	0.8
Solubility in water:	miscible
Relative vapour density (air = 1):	1.08
Flash point:	flammable gas, 60°C

Auto-ignition temperature:	300°C
Explosive limits:	7-73 vol% in air
Vapour pressure:	0.2 kPa at 20°C, 101.3 kPa at -19°C, 52.6 kPa at -33°C
Conversion factors: (25°C, 1066 mbar)	1 ppm = 1.2 mg/m^3 1 mg/m^3 = 0.83 ppm

Formaldehyde is a colourless gas at room temperature and normal atmospheric pressure. It is flammable, reactive and readily polymerises at room temperature. It forms explosive mixtures with air and oxygen at atmospheric pressure.

Formaldehyde is present in aqueous solutions as a hydrate and tends to polymerise. At room temperature, and a formaldehyde content of 30% and more, the polymers precipitate and render the solution turbid. Under atmospheric conditions, formaldehyde is readily photo-oxidised in sunlight to carbon dioxide.

2.3 Validated analytical methods

2.3.1 Environmental exposure monitoring

The most widely used methods for the determination of formaldehyde are based on photometric measurements. The sampling method depends on the medium in which formaldehyde is to be determined.

The International Programme on Chemical Safety/World Health Organisation (IPCS/WHO) reported a number of different methods for determination of formaldehyde, using spectrophotometric, colorimetric, fluorometric, high performance liquid chromatographic, polarographic, gas chromatographic, infrared, and visual analytical methods (59). On each method the analytical sensitivity was reported.

Formaldehyde in air may be collected in an absorbing medium by diffusion (passive sampling). Aqueous or 50% 1-propanol solutions are also used for formaldehyde sampling. For active sampling, aqueous solutions and solutions containing sulphite, 3-methyl-2-benzothiazolene hydrazine, chromotropic acid or 2,4-dinitrophenylhydrazine are generally used as the absorbing solution. For passive sampling sodium bisulphite, triethanolamine and 2,4-dinitrophenyl-hydrazine are used and sorbents such as silica gel, aluminium oxide and activated carbon, sometimes specially treated, may be useful for taking samples at the workplace.

2.3.2 Biological exposure monitoring

Until present, biological monitoring methods for exposure to formaldehyde have not been fully examined. Considering the critical effects and the target organs biological monitoring seems to be irrelevant.

3. Sources

3.1 Natural sources

Formaldehyde is naturally formed in the troposphere during the oxidation of hydrocarbons.

Formaldehyde is one of the volatile compounds formed in the early stages of decomposition of plant residues in the soil.

3.2 Man-made sources

The most important man-made source of formaldehyde is automotive exhaust from engines not fitted with catalytic converters.

3.2.1 Production

Formaldehyde is produced by oxidising methanol using two different procedures: (a) oxidation with silver crystals or silver nets at 600-720°C, and (b) oxidation with iron molybdenum oxides at 270-380°C. Formaldehyde can be produced as a by-product of hydrocarbon oxidation processes.

In 1992 worldwide formaldehyde production was estimated to be 12 million tonnes. Major formaldehyde producing countries in 1990 were the United States and Japan with 3 million and 1.5 million tonnes, respectively. Other production numbers were: Germany 680 000; China 467 000; Sweden 244 000; Finland 48 000 and Denmark 3 000 tonnes (58).

3.2.2 Uses

Formaldehyde is an inexpensive starting material for a number of chemical reactions, and a large number of products are made using formaldehyde as a base.

As an intermediate product, formaldehyde is used in the manufacture of particleboard, fibreboard, plywood, paper treatment, textile treatment, moulding compounds, surface coatings, foam, plywood adhesive, insulation, foundry binders, phenolic thermosetting, resin curing agents, explosives, lubricants, automobile applications, plumbing components, alkyd resins, synthetic lubricants, tall oil esters, foundry resins and controlled release fertilisers.

Furthermore, formaldehyde has medical applications as a preservative and disinfectant and it is used as a preservative in various consumer products.

4. Exposure

4.1 General population

The possible sources of exposure to formaldehyde of the general population are tobacco smoke, automobile emissions, building and insulating materials, food products, cosmetics, household cleaning agents, medicinal products, and in nature (59). Routes of exposure are inhalation, ingestion and dermal absorption.

The IPCS/WHO made the following estimation on the contribution of various atmospheric environments to the total formaldehyde intake by inhalation of an individual (Table 1) (59).

Guicherit and Schulting reported an average concentration of 7.4 $\mu g/m^3$ (0.006 ppm) of formaldehyde in the ambient air of Terschelling Island, Delft and Rotterdam, the Netherlands, in the 1980s (45).

The IPCS/WHO estimated that smoking 20 cigarettes per day would lead to an average daily intake of 1 mg formaldehyde per day (59). Formaldehyde produced by cigarettes may also mean considerable exposure for non-smokers through passive smoking. The more so since it has been reported that the effects of gaseous formaldehyde are potentiated by smoke particles and aerosols.

4.2 Working population

Exposure to formaldehyde in the workplace can be caused by either the production or handling of this compound or products containing it. Concentrations of formaldehyde in occupational settings in the United States were reported by the ICPS/WHO (59), these are presented in Appendix 1.

The following represents more recent occupational exposure data.

Akbar-Khanzadeh *et al*. reported concentrations ranging from 0.08 to 3.53 mg/m^3 (0.07-2.94 ppm) formaldehyde in a gross anatomy laboratory of the Medical College in Ohio, United States (3). The 8-hour time weighted average (TWA) exposure of 31.7% of the subjects working in the laboratory exceeded the action level of 0.6 mg/m^3 (0.5 ppm) set by the Occupational Safety and Health Association (OSHA).

The mean concentration of formaldehyde in area samples of an anatomy laboratory in Singapore was 0.6 mg/m^3 (0.5 ppm) with a range of 0.5-0.7 mg/m^3

Table 1. Contribution of various atmospheric environments to the total formaldehyde intake by inhalation of an individual (59).

Source	Average intake (mg/day)
Ambient air (10% of the time)	0.02
Indoor air, home (65% of the time)	
prefabricated (particle board)	1-10
conventional home	0.5-2
Workplace air (25% of the time)	
without occupational exposure[a]	0.2-0.8
occupational exposure to 1 mg/m^3	5
environmental tobacco smoke	0.1-1.0
Smoking (20 cigarettes/day)	1.0

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

(0.4-0.6 ppm). The mean of personal samples was 0.9 mg/m^3 (0.74 ppm) with a range of 0.5-1.4 mg/m^3 (0.41-1.20 ppm) during a session of 2.5 hours (28).

Kilburn *et al*. reported 0.24-6.0 mg/m^3 (0.2-5 ppm) formaldehyde levels in the workplace air by area sampling in 10 representative histology laboratories in Los Angeles, United States, in 1983 (64). The sampling duration was not reported. The levels were highest during selection of tissue samples for processing.

Kriebel *et al*. reported formaldehyde exposures in the breathing zone ranging from 0.59-1.12 mg/m^3 (0.49 to 0.93 ppm) with a geometric mean of 0.88 mg/m^3 (0.73 ppm) during a clinical anatomy laboratory course at the University of Massachusetts in the United States (67).

Suruda *et al*. studied 29 mortician students who were taking a course in embalming (105). During an 85-day study period, the subjects performed an average of 62.9 embalmings and had average cumulative formaldehyde exposures of 14.8 ppm·hour, with an average air concentration of 1.68 mg/m^3 (1.4 ppm) during embalming. Since the average time spent embalming was 125 minutes, formaldehyde exposures calculated as an 8-hour TWA were 0.40 mg/m^3 (0.33 ppm).

Mean levels of 8-hour TWA exposure to formaldehyde ranged from about 0.09 mg/m^3 (0.08 ppm) in the sawmill and shearing-press departments to 0.39 mg/m^3 (0.32 ppm) in the warehouse area of a plywood factory in Italy (10).

Herbert *et al*. examined the concentrations of formaldehyde from particles and vapour at five sampling sites in an oriented strand board plant in Canada (54). In the manufacture they used wood fibre derived from Aspen trees bonded by phenol formaldehyde. The highest total concentration of formaldehyde was 0.32 mg/m^3 (0.27 ppm) recorded at the preheat conveyor. The lowest was 0.08 mg/m^3 (0.07 ppm) recorded at the saw line. The samples were collected for 21 hours continuously at the sites.

5. Kinetics

5.1 Absorption

There are limited human data regarding absorption of formaldehyde through inhalation. Under normal conditions, absorption is expected to occur in the upper respiratory tract (nasal passages in obligate nose-breathers; trachea and bronchi in oral breathers).

From animal data absorption of formaldehyde through the upper respiratory tract is estimated to be 100% as concluded from the removal of formaldehyde from the air (59). Detailed studies on the distribution of ^{14}C-formaldehyde in the rat nasal cavities have confirmed that it is absorbed primarily in the upper respiratory system.

Another study investigated the retention of formaldehyde gas in the nasal passages of anaesthetised male rats exposed in a nose-only system to

^{14}C-formaldehyde at 2.4-60 mg/m^3 (2-50 ppm) for 30 minutes. More than 93% of the substance was retained, regardless of airborne concentrations.

Loden performed an *in vitro* experiment to study the permeability of human skin to formaldehyde using excised skin in a flow-through diffusion cell (70). The rate of resorption was determined by measuring the amount of substance found in the receptor fluid beneath the skin at steady state. The resorption rates of formaldehyde were: from a concentrated solution of formalin, 319 mg/cm^2 per hour, from a solution of 10% formalin[1] in phosphate buffer, 16.7 mg/cm^2 per hour. The fact that formaldehyde induces denaturation of the skin proteins may have influenced the absorption of the compound.

5.2 Distribution and biotransformation

The IPCS/WHO cited a study on rats, which were exposed by inhalation for 6 hours to 18 mg/m^3 (15 ppm) ^{14}C-formaldehyde (59). The distribution of radioactivity in the tissues was determined. The highest concentrations occurred in the oesophagus, followed by the kidneys, liver, intestines, and lungs.

There are no data available on the distribution of formaldehyde in the human body. The mean formaldehyde concentration in human blood after inhalatory exposure to 2.3 mg/m^3 (1.9 ppm) formaldehyde vapour during 40 minutes was approximately 2.61 ± 0.14 mg/100 ml. However, no statistical difference was found with pre-exposure levels (59). No increases in blood concentrations of formaldehyde were detected in rats or human beings exposed to formaldehyde through inhalation due to rapid metabolism.

The overall metabolism of formaldehyde is summarised in Figure 1. Of importance are the oxidation of formaldehyde into formic acid and carbon dioxide, the reaction with glutathione, and the covalent linkage with proteins and nucleic acids.

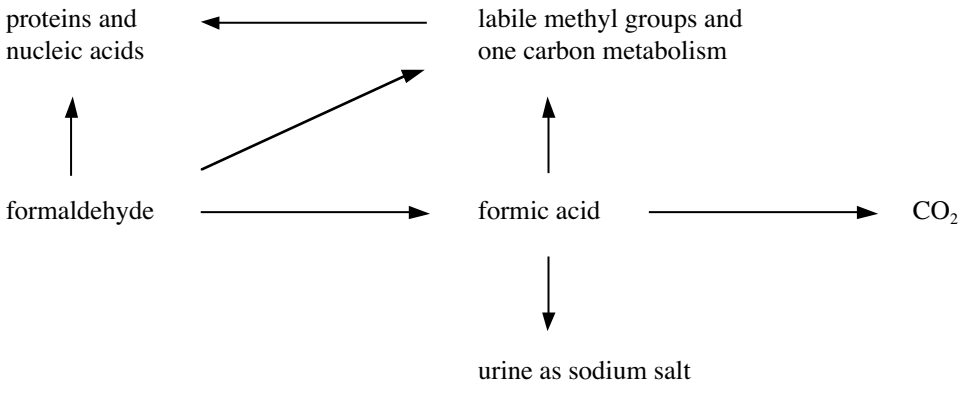

Figure 1. Overall metabolism of formaldehyde (65).

[1] Formalin is defined as 37% formaldehyde in water containing 10-15% methanol

Formaldehyde is an endogenous metabolite in mammalian systems and it is rapidly metabolised to formate, which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidised to carbon dioxide.

5.3 Elimination

After absorption formaldehyde is rapidly metabolised to formate or enters the one-carbon pool to be incorporated into other molecules. Besides this, there are two pathways of final elimination, via exhalation or renal elimination. There are no human data available on the elimination of formaldehyde, but the IPCS/WHO reported that 81% of subcutaneously administered ^{14}C-formaldehyde to rats was found again as carbon dioxide and a small amount in choline (59).

5.4 Possibilities for biological monitoring

At present there are no biological monitoring methods available to determine the magnitude of past exposure to formaldehyde.

There have been a number of cytologic and cytogenetic studies of formaldehyde exposure in man. These studies examined nasal and buccal cells and blood lymphocytes of occupationally exposed workers and unexposed control volunteers. These studies will be evaluated in the respective chapters.

5.5 Summary

Under normal conditions it is expected that formaldehyde in ambient air is absorbed through inhalation in the upper respiratory tract. In animals absorption has been found to be 100%. From *in vitro* experiments using human skin, it is estimated that the absorption of a concentrated solution of formalin through the skin amounted to 319 mg/cm^2 per hour.

After inhalation of radioactive formaldehyde by the rat the radioactivity is distributed in the tissues, with the highest concentration in the oesophagus, followed by the kidney, liver, intestines, and lung. Retention in the nasal passage of the rat is estimated at 93% of the dose, regardless of airborne concentrations.

Formaldehyde is an endogenous metabolite in mammalian systems and it is rapidly metabolised to formate, which is partially incorporated via normal metabolic pathways into the one-carbon pool of the body or further oxidised to carbon dioxide. There are two pathways for elimination: via exhalation and via the kidneys.

There are no biological monitoring methods at present to determine the magnitude of past exposure to formaldehyde.

6. Effects

6.1 Observation in man

Only a selection of the most adequate human studies from the review of Paustenbach *et al*. is discussed in this chapter (92).

6.1.1 Odour

At high concentrations, e.g. 6-12 mg/m^3 (5-10 ppm), formaldehyde has a distinct and pungent odour. The odour of formaldehyde is detectable and/or recognisable by most individuals at concentrations around 1.2 mg/m^3 (1 ppm) (59). The odour threshold (i.e. the concentration at which a group of observers can detect the odour in 50% of the presentations) of formaldehyde ranges from 0.06 to 0.22 mg/m^3 (0.05-0.18 ppm).

6.1.2 Sensory irritation

For most odorous irritants, the trigeminal nerve has a higher threshold than the olfactory nerve. However, when the formaldehyde concentration is increased, sensory irritation is first experienced in the eyes, then the odour is perceived, and finally nasal irritation occurs (59).

Surveys

Akbar-Khanzadeh *et al*. studied 34 workers employed in a gross anatomy laboratory in Toledo, Unites States (3). They were exposed to formaldehyde at (TWA) concentrations ranging from 0.08 to 3.53 mg/m^3 (0.07-2.94 ppm) (duration of exposure not described). More than 94% of the subjects were exposed to formaldehyde concentrations exceeding 0.36 mg/m^3 (0.3 ppm). By more than 70% of the exposed subjects, irritation of the eyes (88%) and nose (74%) were reported.

Kriebel *et al*. investigated students exposed to formaldehyde during a clinical anatomy laboratory course when dissecting cadavers for 3 hours per week over a 10-week period (67). Formaldehyde exposures in the breathing zone ranged from 0.59-1.12 mg/m^3 (0.49-0.93 ppm), with a geometric mean of 0.88 mg/m^3 (0.73 ppm). Symptoms of irritation increased strongly during the day, and the effects were stronger at the beginning than at the end of the semester. The prevalence of symptoms at the start of the laboratory session ranged from 15% for cough to 46% for nose irritation. At the end of the session the prevalences were 20 and 67, respectively. The average increase in symptoms prevalence from beginning to end of laboratory session was greatest for eye irritation, with an increase of 43%. No statistical analyses were reported.

Wilhelmsson and Holmström performed a cross-sectional study on 66 employees of a formaldehyde producing plant in Sweden to determine whether chronic exposure to formaldehyde often causes symptoms by direct irritation (120). The workers were exposed almost exclusively to formaldehyde. Mean duration of exposure was 10 years (range 1-36 years). Thirty-six community

clerks served as a reference group. The exposure level of the exposed group as measured by personal sampling was between 0.05 to 0.60 mg/m^3 (0.04-0.50 ppm) formaldehyde, with a mean of 0.26 mg/m^3 (0.22 ppm). The reference group was exposed to an average concentration of 0.09 mg/m^3 (0.07 ppm) formaldehyde over the year. From a (not specified) questionnaire, it appeared that 67% of the exposed group experienced general nasal discomfort compared to 25% of the reference group ($p<0.001$). Nasal discomfort strictly connected to the workplace occurred in 53% of the exposed group and in 3% of the reference group ($p<0.001$). However, the questionnaire was not published. Therefore, the committees are of the opinion that this study might only suggest that after long-term occupational exposure (0.26 mg/m^3 formaldehyde), more than 50% of the exposed workers complained of nasal discomfort, which was attributed to their occupation.

Liu *et al*. studied the irritant effects associated with formaldehyde exposure in mobile homes in California (69). Week-long integrated formaldehyde concentrations were measured in summer (663 mobile homes with 1 394 residents) and winter (523 mobile homes with 1 096 residents), using passive monitors while the mobile home residents continued their normal activities. The concentrations varied from below the detection limit (0.0012 mg/m^3) to 0.55 mg/m^3. Irritant effects were found to be significantly associated with formaldehyde exposure after controlling for age, sex, smoking status, and chronic illnesses. Effects included complaints of burning/tearing eyes, stinging/burning skin, fatigue, and sleeping problems in summer and burning/tearing eyes, chest pain, dizziness, sleeping problems, and sore throat in winter. For the three weekly ranges of formaldehyde exposure that were distinguished (less than 8.4 mg/m^3·hour, between 8.4-14.4 mg/m^3·hour, more than 14.4 mg/m^3·hour), the percentages of people with burning/tearing eyes in the summer increased from 13.3% to 17.1% and then to 21.4%. In winter, percentages increased from 10.8% to 14.7% and then to 20.6%.

Controlled human studies

Weber-Tschopp *et al*. exposed healthy volunteers to increasing concentrations of formaldehyde from 0.036 to 4.8 mg/m^3 (0.03-4 ppm) (116). Thirty-three subjects were continuously exposed for 35 minutes and 48 subjects were exposed for 1.5 minute. The irritating effects were determined by the eye-blinking rate of the individuals. The authors found that the irritating effects increased as a function of the formaldehyde concentration. The irritation threshold of formaldehyde was placed in the range between 1.2 and 2.4 mg/m^3 (1 and 2 ppm). The authors suggested that adaptation to the irritation occurred after a few minutes in subjects after prolonged exposure to formaldehyde.

Bender *et al*. studied eye irritation in groups of volunteers (n= 5-28 per group) exposed to 0, 0.42, 0.67, 0.84, 1.08 and 1.2 mg/m^3 (0, 0.35, 0.56, 0.7, 0.9 and 1.0 ppm) formaldehyde for 6 minutes (12). The authors reported that the subjective measurements of eye irritation may be affected by a variety of psychological and physiological factors, such as air flow over the eyes, dust particles, length of sleep the previous night, etc. In spite of the large variation in response time, there was still a significant relationship between formaldehyde concentration and time to

detection of response. The authors concluded that eye irritation occurred at exposure concentrations of 0.42-1.1 mg/m^3 (0.35-0.9 ppm) formaldehyde. The response was slight until a concentration of 1.2 mg/m^3 (1 ppm) was reached.

Andersen and Mølhave conducted a study in which 16 healthy subjects (5 smokers) were exposed to 0.29, 0.48, 0.97 or 1.92 mg/m^3 (0.24, 0.4, 0.81 or 1.6 ppm) formaldehyde for 5 hours (4). The purpose of the study was to determine the concentration at which eye irritation occurred. Nineteen percent of the respondents reported eye irritation at 0.29 mg/m^3 (0.24 ppm). Discomfort increased during the first 2 hours of exposure up to 0.97 mg/m^3 (0.81 ppm); then irritation stabilised for the remaining 3 hours. A decrease in discomfort was observed at 1.92 mg/m^3 (1.6 ppm), indicating acclimatisation. After 5 hours of exposure, 38% of the subjects had no complaints at 1.92 mg/m^3 (1.6 ppm), and 63% had no discomfort at 0.97 mg/m^3 (0.81 ppm). This study illustrates the relatively wide variation in individual susceptibility to irritation from formaldehyde.

6.1.3 Rhinitis

Pazdrak *et al*. tried to characterise the nature of formaldehyde induced nasal response consisting of symptoms of rhinitis and changes in nasal lavage fluid (93). Eleven healthy subjects and 9 patients with specific skin sensitisation were provoked in an experimental chamber with formaldehyde at a concentration of 0.48 mg/m^3 (0.4 ppm) for 2 hours. Nasal lavage was performed prior to and immediately after provocation, and 4 and 8 hours later. It was found that the provocation caused transient symptoms of rhinitis and prolonged changes in nasal washing. There were increases in the relative number of eosinophils, and in albumin and total protein levels in the nasal fluid, 4 and 8 hours after provocation. No difference was found between the healthy subjects and patients. These data confirm the irritant effects of inhaled formaldehyde and might suggest that inhaled formaldehyde is capable of inducing non-specific inflammatory changes at a concentration of 0.48 mg/m^3 (0.4 ppm).

6.1.4 Effects on pulmonary function in healthy and asthmatic subjects

Witek Jr *et al*. evaluated the respiratory effects in asthmatics after exposure to formaldehyde (123). Fifteen asthmatic volunteers were exposed in a double-blind manner to room air or 2.4 mg/m^3 (2 ppm) formaldehyde for 40 minutes. These exposures were repeated on a separate day during moderate exercise (450 kpm/minutes) for 10 minutes. Pulmonary function was assessed by using partial and maximal flow volume curves. The following parameters were determined: vital capacity, residual volume, total lung capacity, forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), peak expiratory flow rate, and maximal flow at 50% of vital capacity. No significant airway obstruction or airway resistance was noted in this group during and immediately after exposure. However, bad odour, sore throat, and eye irritation were common during exposure, but the symptoms were infrequent afterwards. No delayed bronchoconstriction was detected with measurements of peak expiratory flow.

The results of this study were substantiated by Sauder *et al*. (98). In their study on 9 non-smoking asthmatic volunteers, they also found no significant changes in the pulmonary function [FVC, FEV_1, mean forced expiratory flow during the middle half of the FVC (25-75%), specific airway conductance or functional residual capacity] or airway reactivity when the volunteers were exposed to 3.6 mg/m^3 (3 ppm) formaldehyde vapour for 3 hours. However, there was a significant increase in nose and throat irritation at the 30th minute and eye irritation at the 60th and 180th minutes of exposure.

Harving *et al*. studied the possible effects of acute formaldehyde exposure on the lung function of asthmatic subjects. They exposed 15 non-smoking asthmatic subjects, with documented bronchial hyperresponsiveness, to 0.08, 0.12 or 0.85 mg/m^3 formaldehyde for 90 minutes (47). All except one subject required bronchodilator therapy and none were using methylxanthines or corticosteroids. Exposure occurred in a climate chamber and the protocol was double blind. No control group was used in this experiment. Lung function tests were carried out before the exposure period and repeated near the end. The results showed no significant changes in the FEV_1, functional residual capacity, airway resistance, specific airway resistance, and flow-volume curves during formaldehyde exposure. Furthermore, histamine challenge performed immediately after formaldehyde exposure showed no evidence of changes in bronchial hyper-reactivity. No late reactions were registered during the first 14-16 hours after exposure. There was no association of subjective ratings of symptoms, if any, with increasing exposure. The rating of symptoms did not differ significantly when the three exposure levels were compared. The results of this study suggest that the exposure levels of formaldehyde used were of minor, if any, importance in the emergence of pulmonary symptoms in asthmatic subjects.

Chia *et al*. examined 150 first-year medical students exposed to formaldehyde during dissection of cadavers in a gross anatomy laboratory (28). As a reference group they used 189 third- and fourth-year medical students matched for sex, ethnic group, and age. The mean concentration of formaldehyde in the area was 0.60 mg/m^3 (0.50 ppm) and the mean concentration of personal samples was 0.89 mg/m^3 (0.74 ppm). The latter had a range of 0.49 to 1.44 mg/m^3 (0.41-1.20 ppm). No differences were found in FEV_1 and FVC among 22 randomly selected male and female subjects, when the measurements were compared between the first day after two weeks vacation and after the dissection period. Significant differences, however, were observed in the exposed group for symptoms of decreased ability to smell, eye irritation, and dry mouth in comparison with the reference group.

Herbert *et al*. performed a cross-sectional study on 99 workers employed in the manufacture of oriented strand board (54). The reference group consisted of 165 unexposed workers from a petroleum industry. Both groups were investigated using questionnaires, spirometry and skin prick tests to common environmental antigens. Environmental monitoring showed dust levels with a mean of 0.27 mg/m^3. The mass mean aerodynamic diameter of the particles was 2.5 mm. The concentration of formaldehyde was between 0.08 and 0.32 mg/m^3 (0.07-0.27 ppm) in the strand board factory. Lung function tests showed significant differences

between strand board workers and workers from the petroleum industry in the FEV_1/FVC ratio and reductions of FEV_1 (p=0.044) and FVC (p=0.022) during the shift work. Also, the strand board workers complained of self-reported asthma and of lower respiratory tract symptoms significantly more frequent than the oil workers. The prevalence of atopy did not differ between both groups. Lung function was significantly better in the strand board workers who had no symptoms, compared with symptomatic workers. Since the complaints of self-reported asthma and of lower respiratory tract symptoms by the exposed group occurred at rather low concentrations of formaldehyde and dusts, the authors concluded that the effects may have been related to small particles containing formaldehyde that penetrated deep into the airways.

Horvath *et al*. surveyed 109 workers (exposed to formaldehyde from 1 to 20 years) for symptoms of respiratory tract irritation (57). Estimates of the exposure ranged from 0.2 to 3.5 mg/m^3 (0.17-2.93 ppm) (mean 0.83 mg/m^3 (0.69 ppm)). The percentage of the exposed workers reporting respiratory irritation was significantly higher than in the non-exposed group (n=264).

6.1.5 Sensitisation

Respiratory tract sensitisation

Grammer *et al*. evaluated the immunological response to formaldehyde exposure in a group of 37 workers in a cross-sectional study (44). The durations of employment were not reported. Concentrations of formaldehyde in air sampling in several work areas at various times ranged from 0.004 to 0.087 mg/m^3 (0.003-0.073 ppm) as TWAs. The workers were also exposed to phenol and organic solvents. A clinical assessment included review of a summary of medical history, physical examination, chest X-ray films, and pulmonary function studies. Serologic assessment was made with an enzyme linked immunosorbent assay for IgE and IgG to formaldehyde-human serum albumin. It was found that none of the workers had IgE or IgG antibodies to formaldehyde-human serum albumin or an immunologically mediated respiratory or ocular disease caused by formaldehyde.

Thrasher *et al*. studied four groups of patients with long-term inhalation exposure to formaldehyde consisting of (1) mobile home residents, (2) office workers who had worked in a new office building, (3) subjects who had moved from mobile homes for at least one year, and (4) subjects who had worked in jobs with possible exposure to formaldehyde (110). All patients in this study had sought continuous medical attention because of multiple complaints involving the central nervous system (CNS). They were compared with a group of students who had been exposed to formaldehyde for 13 hours per week for 28 weeks while studying anatomy. No measurements of formaldehyde in air were performed. When compared to the controls it was found that the patients had significantly higher autoantibodies and antibody titers and B-cell titers to formaldehyde-human serum albumin.

Sixty-three practising pathologists in Alberta, Canada, were studied regarding atopy and sensitivity to formaldehyde (97). Serum samples were assayed for total IgE levels and the presence of IgE with specificity towards formaldehyde.

Twenty-nine of the subjects (46%) had a history of atopy that was confirmed in 12 by either IgE levels or a positive radio-allergosorbent test. Twenty-nine (46%) complained of formaldehyde sensitivity. In this study, none of the pathologists had allergen-specific IgEs directed against formaldehyde, and there was no evidence of a tendency for atopic subjects to be more prone to sensitivity to formaldehyde. However, the authors confirmed that this might have been related to the deliberate reduction in exposure by individuals experiencing adverse effects.

A case-report was described by Grammer *et al*. (43). The subject was a worker with clinical symptoms compatible with bronchospasm caused by formaldehyde exposure. An enzyme linked immunosorbent assay showed that the worker had positive IgE and IgG titers to formaldehyde-human serum albumin. The worker had a positive intracutaneous test for formaldehyde-human serum albumin. The cutaneous reactivity could be transferred to a rhesus monkey through the worker's serum. The worker had a negative metacholine challenge at 25 mg/ml and negative formaldehyde inhalation challenges at 0.36, 1.2, 3.6, and 6 mg/m^3 (0.3, 1, 3, and 5 ppm) for 20 minutes. The authors concluded that the worker's symptoms were probably not caused by immunologically mediated asthma. Based on their experience, they stated that immunologically mediated asthma caused by formaldehyde is extremely rare, if it exists at all.

In 1991, Bardana Jr and Montanaro made an extensive review and analysis of the immunological effects of formaldehyde (11). They concluded that formaldehyde is capable of acting as a respiratory irritant. But according to the authors of the review, there is no consistent evidence indicating that formaldehyde is a respiratory sensitiser. Formaldehyde does not induce transient or permanent bronchial hyperreactivity, which has been associated with e.g. exposure to ozone or nitrogen dioxide. Almost the same conclusions were drawn by IPCS/WHO (59). They commented that there are a few case-reports of asthma-like symptoms caused by formaldehyde, but none of these demonstrated a sensitisation effect (neither Type I nor Type IV) and the symptoms were considered to be due to irritation.

Garrett *et al*. studied a group of 148 children (age 7-14), 53 of whom were asthmatic, in houses in Australia between March 1994 and February 1995 (42). The mean indoor formaldehyde exposure level was 15.8 mg/m^3 and an association between formaldehyde exposure and atopy [odds ratio (OR) 1.4; 95% confidence interval (CI): 0.98-2.00] was observed. The committees noted, however, the potential selection bias in this study.

Skin sensitisation

According to the IPCS/WHO skin sensitisation by formaldehyde has been shown only by direct skin contact with formaldehyde solutions in concentrations of 20 g/l (2%) and higher (59). The lowest patch test challenge concentration in an aqueous solution reported to produce a reaction in sensitised persons was 0.05% formaldehyde.

Flyvholm and Menné interviewed 11 patients with eczema and a positive patch test to formaldehyde (40). All patients used one or more products containing formaldehyde or formaldehyde releasers. Sources of exposure were cosmetics and personal care products, dishwashing liquids, water-based paints, photographic products etc.

Liden *et al*. reported absence of specific IgE antibodies in allergic contact sensitivity to formaldehyde (68). They studied 23 patients with positive epicutaneous test reactions to formaldehyde, recruited from dermatologic departments in Sweden. The patients were between 21-74 years old and 19 were women. The tests had been performed 6 months to 10 years before inclusion in the study. On re-testing, 15 showed a positive reaction. Eight patients showed atopic diathesis, and 8 had a history of ongoing atopic dermatitis. In the radio-allergo-sorbent test only 2 non-atopic patients had specific IgE antibodies to formaldehyde. In cellular infiltrates from biopsies of epicutaneous test sites cells reactive with monoclonal antibodies against IgE were found in positive and in negative formalin tests, both in atopics and non-atopics, as well as in control biopsies from non-lesional skin. Double immunofluorescence staining experiments showed that IgE occurred on Langerhans cells. The proportion of IgE-positive cells correlated to the level of serum IgE, but not to atopy. These cells were also found in the epidermis and in the dermis of non-atopic patients. The authors concluded that this study did not support the hypothesis that specific IgE antibodies are active in the pathogenesis of contact sensitivity to formaldehyde, neither in atopic nor in non-atopic patients.

Cronin performed an investigation in the St John Dermatology Center in London to determine the prevalence of formaldehyde sensitivity and to establish whether there is a significant correlation between formaldehyde sensitivity and hand eczema (33). The study spanned 6 years, from 1984 to 1989. In this period a total of 4 553 men were patch tested with a 1% aqueous solution of formaldehyde. The prevalence of sensitisation was approximately 2-3% each year. During these 6 years, 98 men (2.2%) were sensitised. During the same period 6 479 women were patch tested with a 1% aqueous solution of formaldehyde. The prevalence of sensitisation was remarkably constant at approximately 4% each year. During these 6 years 235 women (3.6%) showed a positive reaction and 117 women were primarily sensitised by formaldehyde, of whom 61 (52%) had hand eczema. Of this group 2% was occupationally exposed and 88% domestic.

In their review Bardane and Montanaro pointed out that the threshold for induction of delayed hypersensitivity contact dermatitis has not been determined precisely (11). The frequency of allergic contact dermatitis to formaldehyde was estimated by the authors to range between 3% and 6% in the general population. Cross reactivity with other aldehydes has not yet been demonstrated; glutaraldehyde does not cross react. Formaldehyde has also been reported to cause contact urticaria, but the mechanism of action has never been clearly demonstrated.

6.1.6 Toxicity due to acute and short-term exposures

No cases of death from formaldehyde inhalation have been published (59).

The IPCS/WHO summarised the clinical features of formaldehyde intoxication including weakness, headache, abdominal pain, vertigo, anaesthesia, anxiety, burning sensation in the nose and throat, thirst, clammy skin, central nervous system depression, coma, convulsions, cyanosis, diarrhoea, dizziness, dysphagia, irritation and necrosis of mucous membranes and gastrointestinal tract, vomiting, hoarseness, nausea, pallor, shock, and stupor (59).

Effects on the respiratory system caused by high formaldehyde concentrations are pneumonia, dyspnoea, wheezing, laryngeal and pulmonary oedema, bronchospasm, coughing of frothy fluid, respiratory depression, obstructive tracheobronchitis, laryngeal spasm, and sensation of substernal pressure.

Acute ingestion may cause renal injury (dysuria, anuria, pyuria, and haematuria) and leads to an increase in formate levels in the urine.

6.1.7 Epidemiological studies

Cross-sectional morbidity studies

A summary of cross-sectional morbidity studies of workers occupationally exposed to formaldehyde is presented in Table 2.

From these studies it may be concluded that symptoms of irritation of the upper respiratory tract already occurred after acute exposure to levels below 1.2 mg/m^3 (1 ppm) formaldehyde. After exposure for a few hours decreases of the FEV_1 and FVC have been observed.

Of interest are the cross-sectional morbidity studies performed by Wilhelmsson and Holmström (120), Herbert *et al*. (54), and Boysen *et al*. (22).

The study by Wilhelmsson and Holmström (120) on 66 workers occupationally exposed to formaldehyde during formaldehyde production is described in section 6.1.2. Beside irritation, the authors were also interested in whether chronic exposure affected exposed people through hyperreactivity in atopic persons, through formaldehyde-induced hyperreactivity in non-atopic persons, or through immunologically mediated, immediate Type I reactions to formaldehyde itself. Among the 53% of the exposed workers experiencing nasal discomfort through hyperreactivity, atopics were not significantly overrepresented. Two workers with occasional occupational nasal discomfort, and sensitised by long-term inhalation, had a positive radio-allergosorbent test for formaldehyde. Of the occupationally exposed group 20% experienced general eye problems. The frequency in the control group was 0%. Thirty-six percent of the exposed group had dermatological problems such as eczema or itching, while the corresponding frequency among the control group was 11%. The authors concluded that in certain circumstances formaldehyde can induce an IgE-mediated Type I reaction in the nose, but in most cases the annoying nasal symptoms are caused by formaldehyde induced hyperreactivity, which can cause problems in about 50% of a population exposed to formaldehyde at an average level of 0.26 mg/m^3 (0.22 ppm). Another interesting finding was that atopics run approximately the same risk of suffering from this hyperreactivity as non-atopics. However, these results were obtained

Table 2. Cross-sectional morbidity studies of workers occupationally exposed to formaldehyde.

Factory or professions (country)	Number of subjects (C=controls)	Levels of exposure in ppm (mg/m^3)	Confounding factors	Effects	Reference
Airplane production (United States)	37 (no control group)	0.003-0.073 (0.004-0.088)	Co-exposure to phenol and organic solvents	14 workers with irritant syndrome. None of them had respiratory or ocular disease that was immunologically mediated.	(44)
Plywood factory (Italy)	15 (C=15, matched for age and sex)	0.08-0.32 (0.09-0.39)	Co-exposure to wood dusts (0.23-0.73 mg/m^3)	Higher frequency of micronucleated cells in nasal respiratory cells. Chronic inflammation of the nasal mucosa. Higher frequency of squamous metaplasia cells.	(10)
Formaldehyde producing plant (Sweden)	66 (36% smokers) (C=36, 28% smokers)	0.04-0.50 (0.05-0.60) mean 0.22 (0.26)		53% of exposed group had nasal discomfort (3% in control group). 33% of exposed group had general lower respiratory tract discomfort (C=1%). 20% of exposed group had eye problems (C=0%).	(120)
Oriented strand board manufacture (Canada)	99 (C=165)	0.07-0.27 (0.08-0.32)	Dust level 0.27 mg/m^3 with mass mean aero-dynamic diameter 2.5 μm	Significant lower FEV_1/FVC, and cross-shift reduction of FEV_1 and FVC. Elevated reports of "asthma" and higher frequency of lower respiratory tract symptoms. No difference in atopy.	(54)
Paper mill (India)	22 (C=27)	0.025 8-hour TWA (0.03)		Exposed subjects showed more respiratory symptoms and complaints pertaining to gastrointestinal, musculoskeletal and cardiovascular systems. No difference in hematology.	(102)

Table 2. Cont.

Factory or professions (country)	Number of subjects (C=controls)	Levels of exposure in ppm (mg/m^3)	Confounding factors	Effects	Reference
Chemical company (Norway)	37 (C=37, matched for age, no difference in smoking habits)	0.5 – >2 (0.6 – >2.4)		Exposed group showed more pronounced metaplastic alterations in nasal mucosa. Three of 17 workers exposed to 0.5-2 ppm showed epithelial dysplasia.	(22)
Anatomy laboratory (United States)	34 (C=12) all were non-smokers	0.07-2.94 (0.08-3.53) Exposure to form-aldehyde at least 6 weeks. Mean 1.24 (1.49)	Embalming fluid consisted of 36% formaldehyde, 8.6 % methanol and 1.2% phenol	No difference in basic lung functions between both groups. During shift there was a decrease of FVC and FEV_3.	(3)
Histology laboratory (United States)	280 all were non-smokers (compared to normal subjects in the same state)	0.2-1.9 (0.24-2.28) with peaks of 5 ppm (6)	Co-exposure to chloroform, xylene and toluene	Exposed group showed steeper reduced vital capacity and flows from age 20 to 60.	(63)
Students during anatomy course (United States)	24 (no control group)	0.49-0.93 (0.59-1.12) Geom. mean 0.73 (0.88) 3 h/week, 10 weeks		Increase of irritant symptoms, stronger in the beginning. Decline in the peak expiratory flow rates over the semester. Reports of “asthma” and throat irritation.	(67)
Students anatomy class (Singapore)	150 (C=189, matched for age, sex and ethnic group	0.41-1.20 (0.49-1.44) Mean 0.74 (0.89)		No difference between the groups in FEV_1 and FVC. Significant differences in symptoms of decreased ability to smell, eye irritation, throat irritations and dry mouth.	(28)

from a not published questionnaire and therefore the results are of limited use.

The cross-sectional study by Herbert *et al*. (54) on workers employed in a manufacture of oriented strand board is described in section 6.1.4. The workers showed reduced lung functions and complained more of self-reported asthma and of lower respiratory tract symptoms compared to the reference group.

Boysen *et al*. (22) reported on a study on nasal biopsies of 37 workers occupationally exposed to formaldehyde (chemical company producing formaldehyde and formaldehyde resin). The workers were exposed for more than 5 years, and they were compared to 37 age-matched controls. The level of exposure of the exposed group ranged from 0.6 to more than 2.4 mg/m^3 formaldehyde. The two groups did not differ as to other environmental influences, smoking habits, and previous nasal disease. The authors found that the degree of metaplasia of the nasal mucosa cells was more pronounced among the exposed workers than among the controls. Three cases of dysplasia out of 17 workers (18%), all of the squamous type, were observed in the formaldehyde group (zero cases in the control group). These workers had been exposed daily to formaldehyde concentrations ranging from 0.6 mg/m^3 to more than 2.4 mg/m^3 for more than 22 years. According to the committees the study, however, is too small to draw any conclusions. Since only a small area of the nasal mucosa can be examined histologically, the number of dysplastic lesions found can not be expected to reflect the real prevalence of dysplasia and therefore the committees are of the opinion that the real prevalence of dysplasia could even be higher.

Longitudinal/prospective morbidity studies

Nunn *et al*. followed a group of 164 workers exposed daily to formaldehyde during the production of urea-formaldehyde resin, together with 129 workers not exposed to formaldehyde, for 6 years (87). Exposure was classified as high (TWA more than 2.4 mg/m^3), medium (0.72-2.4 mg/m^3) or low (0.12-0.6 mg/m^3). Twenty-five % of the workers had high exposure during several periods and 17% moderate exposure. The annual assessment included lung function testing. The proportion of self-reported respiratory symptoms was similar in the two groups. The initial FEV_1 was within 0.5 litre of the predicted value (by age and height) in 65% of the exposed and 59% of the unexposed workers, and more than 0.5 litre below the predicted value in 9% of the exposed and 11% of the unexposed workers. The mean decline in FEV_1 was 42 ml/year in the exposed group and 41 ml/year in the unexposed group. The authors found no association between the rate of decline and indices of exposure to formaldehyde in the exposed group. In interpreting these results it is important to assess any possible bias in the conduct of the study. Workers with adverse respiratory effects from exposure to high concentrations of formaldehyde may have left employment so that only "survivors" are included in the study (healthy worker effect).

The effect of low-level exposure to formaldehyde on oral, nasal, and lymphocytic biological markers were studied prospectively by Suruda *et al*. in a group of 29 mortician students who were about to take a course in embalming (105). During the 85-day study period the subjects performed an average of 69

embalmings and had an average cumulative formaldehyde exposure of 14.8 ppm·hour, with an average air concentration of 1.7 mg/m^3 (1.4 ppm) formaldehyde during embalming. The calculated 8-hour TWA was 0.40 mg/m^3 (0.33 ppm) on days when embalmings were done. Epithelial cells from the buccal area of the mouth as well as nasal epithelial cells showed an increase of micronucleus frequency. In the lymphocytes the micronucleus frequency increased while sister chromatid exchanges decreased. In this study no control group was used. Each subject had been used as his or her own control. The study was limited due to the small number of measurements, other formaldehyde exposures, and due to prior embalming exposure to formaldehyde of subjects.

Retrospective cohort mortality/morbidity studies

A summary of retrospective cohort mortality studies is presented in Table 3.

Most attention was given to a retrospective cohort mortality study on workers of 10 formaldehyde-producing or -using facilities in the United States by several authors, who came to different conclusions (16-19, 74, 75, 103, 104).

The first report of the study was done by Blair *et al*. (17). This historical cohort study evaluated the mortality of 26 561 workers, comprising approximately 600 000 person-years. The cohort consisted of all workers first employed before January 1, 1966. Subjects were traced to January 1, 1980, to determine vital status. Historical exposure to formaldehyde was estimated by job-related monitoring data available from participating plants. There were five ranked categories: (1) trace, (2) <0.12 mg/m^3 (<0.1 ppm), (3) 0.12–<0.6 mg/m^3 (0.1–<0.5 ppm), (4) 0.6–<2.4 mg/m^3 (0.5–<2.0 ppm), and (5) ≥2.4 mg/m^3 (≥2.0 ppm). The standard mortality ratio (SMR) was calculated by comparison with the mortality rates of the total United States population, local population, and non-exposed workers. No statistically significant increases occurred of specific cancers. Two deaths from nasal cancer occurred (both among the exposed), whereas three were expected. The risk of lung cancer was higher in each exposure category compared to the non-exposed, due to the lower risk among the non-exposed (in comparison to the general population). But no trend of increasing lung cancer risk was seen with cumulative exposure.

In 1987, the authors reported an analysis of the excess mortality from cancers of the nasopharynx and oropharynx (19). Four of 7 workers with nasopharynx cancer and 2 of 5 workers with oropharynx cancer occurred in a single plant producing moulding compounds, which was a dusty operation. The authors concluded that the patterns for nasopharyngeal cancer suggested that simultaneous exposure to formaldehyde and particulates may be a risk factor for these tumours. For persons exposed to particulates, the risk of death from cancer of the nasopharynx increased with cumulative exposure to formaldehyde from SMR of 192 for 0.6 mg/m^3·years (0.5 ppm·years) to 403 for concentrations between 0.6 and 6.6 mg/m^3·years (0.5 and 5.5 ppm·years) and to 746 for 6.6 mg/m^3·years (5.5 ppm·years). This trend was not significant, however.

Table 3. A summary of retrospective cohort mortality studies of workers occupationally exposed to formaldehyde.

Factories or occupations (country)	Estimation of exposure	Characteristics of cohort	Results	Reference
10 formaldehyde production and use facilities (United States)	Based on job titles. Using available monitoring data from participating plants. 5 ranked categories of exposure.	26 561 workers (approx. 600 000 person-years). Follow-up 1966 to 1980. Comparison with US population, local population and non-exposed workers. Information on smoking habits was not available.	No significant excesses for specific cancers. SMRs for cancer of the respiratory system are 112 (95% CI: 97-128) for white men, 121 (95% CI: 52-238) for white women, 68 (95% CI: 34-124) for black men. There is no trend of increasing lung cancer risk with cumulative exposure level. Mortality from cancer of the nasal cavity was not excessive. The pattern of nasopharyngeal cancer suggests that simultaneous exposure to formaldehyde and "particulates" may be a risk factor for this tumour.	(17-19)
Automotive iron foundry (United States)	Based on job titles, 4 categories (high, medium, low and none).	3 929 workers. Follow-up period 1960-1989. Comparison with US population and non-exposed workers (n = 2 032). Smoking status ascertained in 65.4% of exposed and 55.1% of the unexposed cohort.	No association between formaldehyde exposure and deaths from malignant or non-malignant disease of the respiratory system. SMRs for cancer of buccal cavity and pharynx: exposed workers 131 (95% CI: 48-286); unexposed workers 169 (95% CI: 54-395). SMRs for cancer of trachea, bronchus and lung: exposed workers 120 (95% CI: 89-158); unexposed workers 119 (95% CI: 84-163).	(5, 6)
Chemical and plastic industry (United Kingdom)	Based on job titles, 4 categories (high, moderate, low and background).	7 660 men first employed before 1965, and 6 357 men first employed after 1964 (total 14 017). Follow-up until 1989. Comparison with death rates from England and Wales, also local rates.	There were no deaths from cancer of nasopharynx (expected 1.3). Among earlier group of workers there was no suggestion of a trend in mortality due to lung cancer with increasing exposure. The high exposure group, however, did have the highest SMR (124, 95% CI: 107-144), which was largely due to data from one factory. There was no relation between mortality from lung cancer and cumulative dose.	(41)

In 1990, the same authors again performed additional analyses to determine whether the association with formaldehyde may have occurred in a subgroup of the cohort and/or to identify other occupational risk factors that might have been involved (18). This report includes only 20 714 white men, the race-sex group that had an excess of lung cancer. Cumulative exposure was used to assess total dose. The SMRs and standardised rate ratios (SRRs) were estimated. The authors found that, in general, the relative risk for lung cancer (both SMRs and SRRs) 20 or more years after first exposure did not rise with increasing exposure to formaldehyde. There was a lack of consistency among the various plants for risk of lung cancer. Mortality from lung cancer was more strongly associated with exposure to other substances, including phenol, melanine, urea, and wood dust than with exposure to formaldehyde.

In 1992, Marsh *et al*. (75) performed an additional analysis from the same data collected from Blair *et al*. (17) by using regression analysis of lung cancer mortality. There were 242 lung cancer deaths in the cohort of 20 067 white male workers. SMRs were computed by plant, age, calendar time, and job type for several time-dependent formaldehyde exposures, including formaldehyde exposures in the presence of twelve selected co-exposures to other agents. A 1.6-fold increase in lung cancer risk was found (significant with $p<0.01$), beginning approximately 16-20 years after first employment. For workers who were never co-exposed to any of the ten other agents associated with increased lung cancer risk, an inverse relation was found between the estimated lung cancer risk ratios and (cumulative) formaldehyde exposure.

Two years later the same authors (74) performed an enlarged and updated investigation on one of the plants from the study of Blair *et al*. (17), which revealed an excess of nasopharyngeal cancer (4 cases). The cohort consisted of 7 359 workers first employed between the plant start-up in 1941 and 1984. Vital status was determined on December 31, 1984 for 96% of the cohort and death certificates were obtained for 93% of 1531 deaths. The statistical analyses focused on 6 039 white males for the 1945-1984 period. SMRs were calculated based on both United States and local county death rates. A significantly increased SMR (550 by local comparison) was found for nasopharyngeal cancer based on the same 4 cases found earlier. But when the workers were divided into long-term and short-term employed workers, there were no significant excesses or deficits in the mortality of long-term workers (n=2 590). In contrast, the short-term workers (n=3 449) had significantly elevated SMRs for total mortality, ischemic heart disease, non-malignant respiratory disease, and accidents, and for cancers of the lung, skin, and CNS. The authors claimed that these increases are difficult to interpret due to the brief employment of the workers. The results provided little evidence that the risk of lung cancer and nasopharyngeal cancer was associated with formaldehyde exposure alone or in combination with particulate or pigment exposures.

In 1994, Sterling and Weinham (103), using the same data from Blair *et al*. (17), compared the more exposed to less exposed workers to compute relative risks for respiratory and lung cancers using a multiple, log-linear model,

incorporating factors for job type, cumulative exposure, length of exposure, and age. Models were fit for all workers, all males, all workers less than 65 years of age, and for all males less than 65 years of age. The results showed that while only at high levels of cumulative exposure a significant elevation in relative lung cancer risk was observed, trend analyses of the coefficients of log-linear models indicated a significant trend of increasing risk with increasing formaldehyde exposure.

Shortly after this publication, Blair and Stewart (16) stated that it is unclear why the results from Sterling and Weinham's calculations were different from those performed by others using other approaches which failed to note an exposure-response gradient. Blair and Stewart noted that apparently the authors had not considered exposures other than formaldehyde in their analyses and Blair and Stewart disagreed with their conclusions for several reasons: (1) the exposure-response gradient was not confirmed by others, (2) the findings differed from those of other major studies on formaldehyde in several countries, and (3) there was a stronger linkage between lung cancer and exposures to agents other than formaldehyde than with formaldehyde itself.

In 1995, Sterling and Weinham replied to the comments (104). They acknowledged that there were a number of crucial procedural differences between Blair *et al*. and theirs. Their analysis showed a trend in relative lung and respiratory cancer risks with increasing cumulative exposure; Blair's did not. Besides, trend analysis by Blair *et al*. was performed on white males and on white male wage earners, and theirs on all employees and all males. Sterling and Weinham attributed Blair's failure to find such a trend to failing to adequately adjust for the "healthy worker effect", to restricting their analysis to white males and white male hourly workers only, and to possible misclassification bias due to their use of less precise exposure computations.

Hansen and Olsen studied the risk of cancer morbidity in Denmark during 1970-1984 from standardised proportionate incidence ratios (SPIR) among men in 265 companies in which formaldehyde was used (46). The longest employment had been held since 1964, at least 10 years before diagnosis of cancer. A total of 126 347 men with cancer, born between 1897 and 1964, were identified in the files of the nationwide Danish Cancer Registry. Individual employment histories were established for the patients through comprehensive data linkage with Supplementary Pension Fund. Only 91 182 male cancer cases (72.2%) were found in the files of the latter, of the rest no record of employment was found. The results did not show an association between formaldehyde exposure and lung cancer (SPIR 1.0; 95% CI: 0.9-1.1). However, significantly elevated risks were found for cancers of the colon (SPIR 1.2; 95% CI: 1.1-1.4), kidney (SPIR 1.3; 95% CI: 1.0-1.6), and sinonasal cavities (SPIR 2.3; 95% CI: 1.3-4.0). For sinonasal cancer, a relative risk of 3.0 (95% CI: 1.4-5.7) was found among blue collar workers with no probable exposure to wood dust, the major confounder. The authors concluded that formaldehyde may increase the risk of sinonasal cancer in humans. Because of the rarity of nasopharyngeal cancer, it was not possible to evaluate the risk in this study. According to the committees there are

some serious shortcomings in this study. First, the exposure classification was based on the unusual criterion of having been employed at a company that annually used over one kilogram of formaldehyde per employee. Clearly, only a small proportion of these employees had been exposed to formaldehyde. Secondly, job histories were only collected for exposed cases and not for exposed controls. Thus, an actual comparison of job histories between cases and controls is not possible. In addition, several of the job histories of the 13 "exposed" cases provided no evidence for formaldehyde exposure. For instance it is quite unlikely that a representative of a glue manufacturing company had been exposed to formaldehyde.

Case-control studies

Partanen *et al*. performed a nested case-control study in a woodworker cohort in Finland (91). The cohort consisted of all male production workers who entered and were employed for at least a year in these plants between January 1944 and December 1965. Cases (n=136) of respiratory cancers were newly diagnosed among the cohort members between 1957 and 1982. Three controls (408 in all) were individually matched to each case according to year of birth. The study size was determined prior to the start in such a way that an OR of at least 2 would be detected for respiratory cancer and formaldehyde exposure at an alpha of 0.05 (one-sided) and a power of 0.8. The occupational exposure of the cases ranged from less than 0.12 to 3.6 mg/m^3 (0.1-3 ppm) formaldehyde. The results showed that the most relevant figure was the OR adjusted for both vital status and smoking with provision for a latency period of at least 10 years. This OR was 1.4 (95% CI: 0.4-4.1), which did not differ significantly from unity (=1). The OR for lung cancer was near unity. The number of cases exposed to repeated peak exposures to formaldehyde was small, and no excess risk was observed. No significant exposure-response relationship was observed.

Luce *et al*. conducted a case-control study of cancer of the nose and paranasal sinuses in France (71). There were 207 histologically confirmed cases, which were diagnosed between January 1986 and February 1988. The controls were obtained from two sources, the first being hospital controls consisting of patients with cancers at other sites, matched for age and sex (control to case ratio 3:2), and the second coming from a list provided by the cases, matched in sex, age and residence (n = 233). Occupational exposure to formaldehyde and 14 other substances was assessed by an occupational hygienist, and the levels of exposure categorised into low, medium and high. The results indicated that the OR estimates for formaldehyde exposure and squamous cell carcinomas of nasal cavities among males, adjusted for exposure to wood dust and glues, did not significantly differ; the highest OR was below 1.5. The ORs decreased when the duration and the cumulative levels of exposure increased. This study confirmed the association between nasal adenocarcinoma and exposure to wood dust. The authors suggested that interaction between formaldehyde and wood dust is plausible, since the action of wood dust, by impairing the nasal mucosa, might enhance the effect of formaldehyde.

Recently, Andjelkovich *et al*. reported a nested case-control study in the United States to identify the determinants of lung cancer mortality in a cohort of 8 147 male foundry workers among whom an excess of lung cancer deaths was observed previously (7). This study consisted of 220 lung cancer deaths that occurred in this cohort between 1950 and 1989. Both living and dead controls, matched on race and attained age, were selected in the ratio 10:1 (n = 2 200). Smoking history was obtained for about 71% of the study objects. The formaldehyde exposures were categorised into high, medium, low, and none. The same was done for silica exposure. The results showed that cigarette smoking was a strong predictor of lung cancer mortality. Neither exposure to formaldehyde nor silica, nor employment in any of the six major work areas within the foundry indicated an association with lung cancer.

A population-based case-control study on cases of bladder cancer was carried out in Montreal, Canada by Siemiatycki *et al*. (100). Between 1979 and 1986, 484 persons with pathologically confirmed cases of bladder cancer and 1 879 controls with cancers at other sites were interviewed, as well as a series of 533 controls of the general population. The job histories of the subjects were evaluated by a team of chemist/hygienists for exposure to 294 workplace chemicals, and information on relevant non-occupational compounds was obtained. One of the substances, which showed no evidence of an association, was formaldehyde. The estimated OR for "non-substantial" exposure to formaldehyde was 1.2 (95% CI: 0.9-1.6) and for "substantial" exposure was 1.2 (95% CI: 0.7-2.0). The results were adjusted for age, ethnicity, socio-economic status, smoking, coffee, and status of the respondent.

From these case-control studies the committees conclude that no clear relations can be found between occupational exposure to formaldehyde and cancer of the respiratory tract, including cancers of the nose, paranasal sinuses, the lung, and bladder cancer.

Meta-analysis studies

Three meta-analyses of the carcinogenicity data have been published (15, 31, 90). The committees decided to use these data as a starting point for the evaluation of the carcinogenicity and completed with more recent epidemiological studies (if relevant), which were not discussed in the meta-analysis. The first two meta-analyses took similar approaches to analysing the data.

Blair *et al*. performed a meta-analysis of 30 epidemiological studies to evaluate cancer risks associated with formaldehyde exposure (15). In some studies excesses were reported for: leukaemia and cancers of the nasal cavities, nasopharynx, lung, and brain. However, no consistent pattern emerged for any given cancer across the 30 studies. Inconsistencies among and within studies impeded assigning formaldehyde a convincing causal role for the excesses of lung cancer found among industrial workers. The authors divided the exposed groups into two categories: the professionals, like embalmers, anatomists, pathologists and funeral professionals, and the industrial workers, subjects employed in the production of formaldehyde, formaldehyde resins, formaldehyde adhesives,

paraform, and alcoforms. In the analyses, the observed and expected numbers were summed for studies of professional and industrial groups separately to create combined relative risk (CRR) estimates. The summation approach weighs the risks estimates by study size. The authors found that among the professionals, significant excesses occurred for leukaemia (CRR 1.6, $p<0.05$), brain cancer (CRR 1.5, $p<0.05$), and colon cancer (CRR 1.3, $p<0.05$). Fewer deaths from lung cancer occurred among the professionals (CRR 0.9, $p<0.05$). In contrast to the professionals, industrial workers did not show elevated mortality from leukaemia (CRR 1.1) or brain cancer (CRR 0.9). A small but significant excess of lung cancer (CRR 1.1, $p<0.05$) was seen among industrial workers. A non-significant increase was observed for nasopharyngeal cancer (CRR 1.2), nasal cavity cancer (CRR 1.1), and bladder cancer (CRR 1.1). The risk of nasal cancer was evaluated by exposure level or duration. The results showed no exposure-related response gradient. On the other hand, for nasopharyngeal cancer, the CRR values rose to 2.1 in the high-exposure category (higher than 6.6 $mg/m^3 \cdot$year cumulative exposure), a trend which was significant. The authors concluded that: (1) a causal association between exposure to formaldehyde and lung cancer could not be entirely discounted; (2) a causal role for formaldehyde is most probable for cancers of the nasopharynx; (3) the association with nasal cancer is plausible, but somehow less persuasive than that for nasopharyngeal cancer; (4) the absence of excesses for leukaemia and cancers of colon and brain among industrial workers suggests that the association seen among professional workers may not be due to formaldehyde.

Partanen (90) also performed a meta-analysis using the same sources as Blair *et al*. (15) with some updating. The overlaps between the studies were removed, as in the earlier study. The aggregated risk ratios were estimated as aggregated observed-to-expected ratios, and the 95% CIs were set for the risk ratio values. The main difference between the earlier (original) analysis and the reanalysis was the selection of the input values. In the reanalysis, of both sinonasal and nasopharyngeal cancers, a significant increase was associated with "substantial" exposure category (risk ratios 1.7 for sinonasal cancers and 2.7 for nasopharyngeal cancers, respectively). Neither an increased risk nor an exposure-response relation was suggested by the aggregated data for the combined category of oropharynx, hypopharynx, lip, tongue, salivary glands, and mouth cancer. Analyses for lung cancer showed a decreased risk for professionals (aggregated risk ratios = 0.3 and 1.0), for industrial workers the aggregated risk ratio was 1.1 (95% CI: 1.0-1.2). Further analyses for industrial workers alone showed an aggregated risk ratio of 1.2 for "low-medium" exposure and 1.1 for "substantial" exposure. The authors concluded that it did remain unlikely that workplace exposures to formaldehyde pose any substantial lung cancer hazard among humans. On the other hand, an exposure-response gradient was revealed on sinonasal cancer; risk in the category of substantial exposure was significantly elevated. However, according to both committees, in this meta-analysis the authors did not correct for the unreported studies in which no cases of nasal

cancers were found. This method must have led to an overestimation of the overall relative risk for nasopharyngeal cancer.

Collins *et al*. reported a review of 47 epidemiological studies in which the carcinogenic risk after occupational exposure to formaldehyde was studied (31). These 47 studies included studies of industrial cohorts of exposed workers, of exposed medical specialists, and exposed embalmers case-control studies. After correction for underreporting a meta relative risk of 1.0 for nasal cancer was found in the cohort studies and a relative risk of 1.3 for the case-control studies. The authors concluded that the available studies do not support a causal relation between formaldehyde exposure and nasopharyngeal cancer. In addition to the literature review the investigators provide four factors that explain the discrepancy with the two earlier positive literature reviews. Since this well conducted (more recent) meta-analysis includes more studies (positive and negative) than the previous literature reviews and the exposure potential for jobs included in the general population case-control studies was evaluated, the committees give preference to the review of Collins *et al*. over the earlier reviews.

In 2000, Vaughan *et al*. published a case-control study at five cancer registries in the Unites States (113). Cases (n=196) with nasopharyngeal cancer diagnosed between 1987-1993 and controls (n=244) were questioned. The authors concluded that the results of this study support the hypothesis that occupational exposure to formaldehyde, but not to wood dust, increases the risk of nasophryngeal cancer (specific for squamous cell carcinomas). However, no actual exposures to formaldehyde were measured, the authors used self-reported occupational histories for assessing exposure concentration. Thus, misclassification was inevitable.

Finally, the committees conclude that although a small number of studies produce limited evidence for the association between nasopharyngeal cancer and exposure to formaldehyde, the overall total body of epidemiological data does not support a causal relationship for a nasal cancer risk at the experienced exposure levels.

Genotoxicity

Several studies were identified that described the positive and negative genotoxic effects after exposure to formaldehyde.

Ying *et al*. studied the frequency of micronuclei in the cells of nasal mucosa, oral mucosa, and in lymphocytes of 25 students exposed to formaldehyde (127). The concentration of formaldehyde was 0.508 ± 0.299 mg/m^3. A higher frequency of micronuclei was observed in nasal and oral exfoliative cells but not in lymphocytes. In 1999, Ying *et al*. evaluated the effects of formaldehyde on peripheral lymphocytes of 23 non-smoking students (128). No significant difference was reported between lymphocyte proliferation and sister chromatid exchange.

Vasudeva *et al*. examined the effect of formaldehyde in the incidence of chromosome aberrations in peripheral blood lymphocytes of 30 medical students exposed to concentrations of less than 1.2 mg/m^3 (112). There was no difference in incidence of chromosomal aberrations between the exposed and control group.

He *et al*. examined human peripheral lymphocytes of 13 students exposed to formaldehyde (3.17 mg/m^3) for abnormalities (48). Lymphocytes of 10 students of the same school without formaldehyde exposure served as controls. The micronuclei rate (6.38 ± 2.5, $p<0.01$), chromosome aberration rate (5.92 ± 2.4, $p<0.01$), and sister chromatid exchange rate (3.15 ± 1.57, $p<0.05$) in the exposed group was increased.

In conclusion, evidence for genotoxic potential of formaldehyde in humans exposed to occupational levels is insufficient and conflicting.

6.2 Animal experiments

6.2.1 Sensory irritation

Kane and Alarie exposed Swiss Webster mice for 10 minutes to concentrations of formaldehyde ranging from 0.62 to 13.4 mg/m^3 (0.52-11.2 ppm) to evaluate sensory irritation after single exposures (61). The concentration associated with a 50% decrease in respiratory rate (RD_{50}) appeared to be 3.6 ± 0.34 mg/m^3 (3.0 ± 0.28 ppm).

Wood and Coleman studied the irritant properties of formaldehyde in mice (n=8) by observing their behaviour (124). The animals were initially trained to terminate exposure to ammonia by poking their nose five times into a conical sensor. In this experiment, mice were exposed to a series of concentrations from 1.2 to 12 mg/m^3 (1-10 ppm) formaldehyde for a maximum of 60 seconds followed by a 60 seconds washout period; this cycle was repeated 25 times per session. As the concentration of formaldehyde increased, the time span after which the animals terminated their exposure shortened. This study showed that formaldehyde was aversive to mice at concentrations, which approximate those at which humans reported sensory irritation.

6.2.2 Airway reactivity

Adult male Cynomolgus monkeys (n=9) exposed to an average of 3.1 mg/m^3 (2.6 ppm) formaldehyde for 10 minutes showed significant pulmonary function deficits immediately after the challenge (14). The design of this experiment included a pre-exposure metacholine challenge to determine whether responses to formaldehyde were associated with pre-existing bronchial hyperreactivity. A significant increase of the average pulmonary flow resistance was observed 2, 5, and 10 minutes after formaldehyde challenge.

The hyperreactivity of the respiratory smooth muscle after exposure to formaldehyde was studied by Swiecichowski *et al*. (109). Groups of 5-7 guinea pigs were exposed to (I) 1, 4, 11.3, or 37.3 mg/m^3 (0.86, 3.4, 9.4, or 31.1 ppm) formaldehyde for 2 hours, or to (II) 0.1, 0.4, 0.7 or 1.3 mg/m^3 (0.11, 0.31, 0.59 or 1.05 ppm) formaldehyde for 8 hours. The airway reactivity was assessed before exposure to formaldehyde and 1 and 24 hours after exposure, using *in vivo* and *in vitro* methods. The authors found that the specific pulmonary resistance and airway reactivity (to infused acetylcholine) increased with increasing formaldehyde exposure. Formaldehyde exposure caused bronchoconstriction and

hyperreactivity at lower concentrations when exposure was extended from 2 to 8 hours. Exposure to concentrations of formaldehyde higher than 0.37 mg/m^3 for 8 hours was sufficient to produce a significant increase in airway reactivity, while similar effects after 2 hours exposure only occurred at concentrations above 11 mg/m^3. Formaldehyde exposure also heightened airway smooth muscle responsiveness to acetylcholine or carbachol *in vitro*. These effects occurred with no evidence of epithelial damage or inflammation up to 4 days after formaldehyde exposure. From this study the committees conclude that the no observed adverse effect level (NOAEL) for airway reactivity in guinea pigs is 0.13 mg/m^3 (0.11 ppm) formaldehyde vapour.

6.2.3 Sensitisation

Hilton *et al*. studied the sensitising property of formaldehyde (56). They reported that the compound elicited strong positive responses in three independent methods: the guinea pig maximisation test (n=10), the guinea pig occluded patch test of Buehler (n=10), and the mouse local lymph node assay (n=4). In contrast, formaldehyde was negative in the mouse IgE test (n=6), which is a novel predictive test method for assessment of respiratory sensitisation potential. The authors concluded that, although formaldehyde is a potent contact allergen, it lacks a significant potential to cause sensitisation of the respiratory tract.

Boman *et al*. (21) studied the potency of contact allergens, including formaldehyde, by using the guinea pig maximisation test (21). For each chemical five groups of 5 animals each were treated intradermally with concentrations per group reduced with increments of a factor three from the highest concentration that could be applied intradermally. Two of the five groups were treated topically with the highest non-irritating concentration and the three other groups with a 100 times lower concentration. All groups were challenged and re-challenged with the highest non-irritating concentration. For each chemical a vehicle control group was included for comparison. Measurements were performed in two different laboratories. A highly significant dose response relationship was obtained and the curves were similar at both laboratories and corresponded well with earlier reported test results supporting that multidose design gives reproducible results.

6.2.4 Acute cytotoxic effects on nasal epithelium

In vitro experiments have been performed by Colizzo *et al*. to study the alterations of specific ciliated epithelial cell surface components after exposure to formaldehyde levels, which decreased respiratory ciliary function (30). In this experiment, bovine trachea was exposed to 0, 16, 33, and 66 mg formaldehyde per cm^2 epithelial surface for 30 minutes. The results showed that the axoneme proteins (i.e. part of the cilia) decreased with increased formaldehyde concentrations and the biotinylated proteins proportionally increased. Membrane fractions showed little change in protein. The data suggest that increasing formaldehyde exposure reduced both extractable ciliary axonemes and detergent-soluble surface components.

Bhalla *et al*. investigated the distribution of epithelial cells over the turbinates in the rat nasal cavity and their injury following exposure to formaldehyde in a nose-only manner (13). Rats were exposed to either purified air or to 12 mg/m^3 (10 ppm) formaldehyde for a period of 4 hours. Changes were seen in the various regions of the turbinates in the form of ciliary destruction and cell separation (especially in the naso- and maxilloturbinates), cellular swelling (throughout the turbinate), mucous release by the goblet cells (in the naso turbinate), and in some cases pores on the cell surface or between adjacent cells (evident in the meates). The authors concluded that the degree of deleterious effects of formaldehyde on the nasal epithelia of rats is dependent upon cell type and location.

6.2.5 Toxicity during short-term exposure

Major short-term inhalation toxicity studies of formaldehyde in experimental animals are summarised in Table 4.

The critical effects of short-term exposure to airborne formaldehyde in experimental animals are damage to and increased proliferation of the nasal epithelium. The histopathological changes range from slight hyperplasia and squamous cell metaplasia of the ciliated and non-ciliated respiratory epithelium in specific areas (found at low effective exposure concentrations, i.e. 2.4-3.6 mg/m^3) to severe rhinitis, necrosis, and extensive hyper/metaplasia of major portions of the nasal epithelium (found at exposure concentrations of about 7.2 mg/m^3 and higher). Substantial increases in epithelial cell turnover rates occur in rats at exposure concentrations of 7.2 mg/m^3 and higher. Marginally and only transiently increased cell turnover rates have occasionally been found at levels of 0.6-2.4 mg/m^3.

Table 4 shows that the majority of NOAELs are between 1.2 and 2.4 mg/m^3 (1-2 ppm). Table 4 also reveals that in all studies with a NOAEL of 1.2 mg/m^3 (1 ppm) the lowest observed adverse effect level (LOAEL) is higher than 2.4 mg/m^3 (2 ppm), indicating a steep dose-response relation (it is possible that in these studies a NOAEL of 2.4 mg/m^3 might have been obtained if this exposure concentration would have been included in these experiments). However, occasionally (107, 108, 129) increased cell proliferation has been found at exposure levels of 0.6 or 1.2 mg/m^3 (0.5 or 1 ppm), while the findings of Woutersen *et al*. (125) turned out to be inconclusive with respect to 1.2 mg/m^3 (1 ppm) being a NOAEL or a LOAEL.

Table 4. Short-term inhalation toxicity studies of formaldehyde in rats, mice or monkeys.

Study design	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Critical effect	Reference
Groups of 50 male and 50 female rats exposed to; 0, 0.3, 1 or 3 ppm (0, 0.36, 1.2 or 3.6 mg/m^3); 6 h/day; 5 days/week; 13 weeks. Satellite groups of 5 males and 5 females exposed to the same concentrations for 3 days or 13 weeks.	1.2 (13-week study) 0.36 (3-day study)	3.6 (13-week study) 1.2 (3-day study)	Histopathological changes in nasal cavity and increased epithelial cell proliferation in nasal cavity (13-week study). Increased epithelial cell proliferation in nasal cavity (3-day study).	(129)
Groups of 10 male rats exposed to; 0, 0.3, 1.1 or 3.1 ppm (0, 0.36, 1.3 or 3.7 mg/m^3); 22 h/day for 3 consecutive days	1.3	3.7	Histopathological changes and increased epithelial cell proliferation in the nasal cavity.	(95)
Groups of 5-6 male rats exposed to; 0, 1, 3.2 or 6.4 ppm (0, 1.2, 3.8 or 7.7 mg/m^3); 6 h/day, 3 consecutive days	1.2	3.8	Histopathological changes and increased epithelial cell proliferation in the nasal cavity.	(26)
Groups of 25 male rats exposed to either 0, 1 or 2 ppm (0, 1.2 or 2.4 mg/m^3) for 8 h/day ("continuous exposure") or to 2 or 4 ppm (2.4 or 4.8 mg/m^3) for 8 30-min. exposure periods separated by 30-min. intervals ("intermittent exposure"); 5 days/week; 13 weeks	2.4	4.8	Histopathological changes and increased epithelial cell proliferation in the nasal cavity; squamous metaplasia with basal cell hyperplasia in nasal epithelium.	(122)
Groups of 10 male rats exposed to; 0, 6, or 12 mg/m^3 (0, 5, 10 ppm); for 8 h/day ("continuous exposure") or to; 10 or 20 ppm (12 or 24 mg/m^3); for 8 30-min. exposure periods separated by 30-min. intervals ("intermittent exposure"); 5 days/week; 4 weeks		6	Histopathological effects and increased cell turnover rates, squamous metaplasia with cellular hyperplasia, minimal to moderate rhinitis. In rats with the same daily cumulative dose, the effects were greater in rats exposed intermittently to the higher concentration.	(121)
Groups of 6 male rats exposed to; 0, 0.6, 2.4, 7.1 or 17.3 mg/m^3 (0, 0.5, 2, 5.9 or 14.4 ppm); 6 h/day, 5 days/week; 1, 2, 4, 9 or 14 days	2.4	7.1	Histopathological effects in nasal cavity. Inhibition of mucociliary clearance.	(83)

Table 4. cont.

Study design	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Critical effect	Reference
Groups of 10 male rats exposed to; 0, 0.7, 2, 5.9, 10.5 or 14.5 ppm (0, 0.8, 2.4, 7.1, 12.6 or 17.4 mg/m^3); 6 h/day; 5 days/week for 11 weeks	2.4	7.1	Histopathological changes and increased epithelial cell proliferation in the nasal cavity.	(24)
Groups of 3 male Rhesus monkeys exposed to; 0 or 6 ppm (0 or 7.2 mg/m^3); 6 h/day; 5 days/week for 1 or 6 weeks		7.2	Histopathological changes and increased epithelial cell proliferation in upper respiratory tract.	(80)
Groups of 36 male rats exposed to; 0, 0.7, 2, 6.2, 9.9 or 14.8 ppm (0, 0.8, 2.4, 7.4, 11.9 or 17.8 mg/m^3); 6 h/day; 5 days/week for 1, 4 or 9 days or 6 weeks	2.4	7.4	Histopathological changes and nasal epithelial cell necrosis, neutrophil infiltration, epithelial hyperplasia, squamus metaplasia, increased cell proliferation.	(79)
Rats and mice (no. and sex not specified) exposed to; 0, 0.6, 2.4, 7.2, 18 mg/m^3 (0, 0.5, 2, 6, 15 ppm); 6 h/day; 3 days	*mice:* 7.2	*mice:* 18 *rats:* permanent effects at 7.2, and transient effects at 0.6 and 2.4.	Increased epithelial cell proliferation in nasal cavity.	(107, 108)
Groups of 10 male rats exposed to; 0, 0.1, 1 or 9.4 ppm (0, 0.12, 1.2 or 11.3 mg/m^3); 6 h/day; 5 days/week for 13 weeks	1.2	11.3	Histopathological changes in nasal cavity (rhinitis, hyperplasia and metaplasia).	(8)
Groups of 10 male and 10 female rats exposed to; 0, 1.2, 11.6 or 23.8 mg/m^3 (0, 1, 9.7 or 19.8 ppm); 6 h/day, 5 days/week; 13 weeks	1.2 however, doubtful according to authors	11.6	Histopathological effects in nasal cavity.	(125)

6.2.6 Toxicity due to long-term exposure and carcinogenicity

Major long-term inhalation toxicity and/or carcinogenicity studies in rats and mice are summarised in Table 5.

Critical effects of long-term inhalation exposure to formaldehyde include inflammatory, degenerative and regenerative changes of the nasal mucosa, and squamous cell carcinomas of the nasal respiratory epithelium. The non-neoplastic nasal changes range from a minimal degree of hyperplasia and squamous cell metaplasia of the nasal respiratory epithelium (occasionally seen at concentrations of approximately 2.4 mg/m^3 or lower) to rhinitis, necrosis and extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium invariably seen at concentrations of about 7.2 to 18 mg/m^3 (6-15 ppm). High incidences of squamous cell carcinomas have been found in rats at exposure levels of 12 mg/m^3 (10 ppm) or higher.

In most long-term studies, a NOAEL of 1.2 or 2.4 mg/m^3 have been reported (Table 5). However, in one long-term study in rats 2.4 mg/m^3 (2 ppm) appeared to be a LOAEL (62) and in another long-term rat study a LOAEL as low as 0.36 mg/m^3 (0.3 ppm) was reported (60).

6.2.7 Genotoxicity

The mutagenic properties of formaldehyde have been investigated in many test systems. A summary as presented by the International Agency for Research on Cancer (IARC) and WHO is shown in Appendix 2 (58).

After the appearance of the IARC/WHO document (58), more data on the genotoxicity of formaldehyde have been published. Vock *et al*. studied the induction of DNA double-strand breaks in cultured human lung epithelial cells by pulse-field gel electrophoresis, and the viability was evaluated by the MTT (dimethylthiazol-diphenyltetrazolium bromide) cytotoxicity test (115). They reported induction of DNA double-strand breaks by formaldehyde when cell viability was reduced to less than 60% of the control values, indicating that DNA double-strand breaks were the consequence of extragenomic damage and viability loss.

Merk and Speit studied formaldehyde induced DNA-protein cross-links in V79 Chinese hamster cells (77). They observed that formaldehyde, parallel to the induction of cytotoxicity, induced significant numbers of DNA-protein cross-links, sister chromatid exchanges, and micronuclei in the same range of concentrations. In contrast, treatment of V79 cells with formaldehyde did not induce gene mutations in the HPRT test, even after variations of the treatment protocol. The authors concluded that formaldehyde induced DNA-protein cross-links seem to be related to cytotoxicity and clastogenicity, but do not lead to the formation of gene mutations in mammalian cells.

In an *in vivo* experiment Casanova *et al*. reported covalent binding of formaldehyde to DNA in the respiratory tract of rhesus monkeys (25). The DNA-protein cross-links were formed after exposure by inhalation (head only) to 0.8, 2.4 or 7.2 mg/m^3 (0.7, 2 or 6 ppm) formaldehyde for 6 hours (n=3 per group).

Table 5. Long-term inhalation toxicity and/or studies of formaldehyde in rats and mice.

Study design	NOAEL (mg/m^3)	LOAEL (mg/m^3)	Major effect	Reference
Groups of 32 male rats exposed to; 0, 0.3, 2 or 15 ppm (0, 0.36, 2.4 or 18 mg/m^3) 6 h/days; 5 days/week; 28 months		0.36	Histopathological changes in nasal cavity. The effect seen at 0.36 mg/m^3 was not statistically significantly different from that in the controls but was nevertheless considered formaldehyde related by the authors due to a clear dose-response relationship for these nasal findings. Nasal squamous cell carcinoma: 13/29 rats exposed to 18 mg/m^3.	(60)
Groups of 119-120 male and 120 female rats, and 119-120 male and 120-121 female mice exposed to; 0, 2.0, 5.6 and 14.3 ppm (0, 2.4, 6.7 or 17.2 mg/m^3) 6 h/day; 5 days/week; up to 24 months	*mice:* 2.4	*mice:* 6.7 *rats:* 2.4	Histopathological changes in nasal cavity. Nasal squamous cell carcinoma: 2/17 male mice exposed to 17.2 mg/m^3 and killed at 24 months. Nasal squamous cell carcinoma: 51/117 male and 52/115 female rats exposed to 17.2 mg/m^3. Nasal polypoid adenoma: 1/232, 8/236, 6/235 and 5/232 rats exposed to 0, 2.4, 6.7 or 17.2 mg/m^3, resp.	(62)
Groups of approximately 90-150 male rats exposed to; 0, 0.7, 2, 6, 10 or 15 ppm (0, 0.8, 2.4, 7.2, 12 or 18 mg/m^3) 6 h/day; 5 days/week; up to 24 months	2.4	7.2	Histopathological changes in nasal cavity and increased proliferation of nasal epithelial cells. Nasal squamous cell carcinoma: 20/90 and 69/147 rats exposed to 12 and 18 mg/m^3, resp.	(81)
Groups of 30 male rats exposed to; 0, 0.1, 1 or 9.2 ppm (0, 0.12, 1.2 or 11 mg/m^3) 6 h/day; 5 days/week for 3 months and then observed for a further 25 months	1.2	11	Histopathological changes in nasal cavity. No nasal tumours.	(126)
Groups of 10 male rats exposed to; 0, 0.1, 1 or 9.4 ppm (0, 0.12, 1.2 or 11.3 mg/m^3); 6 h/day; 5 days/wk; 52 weeks	1.2	11.3	Histopathological changes in nasal cavity. No nasal tumours.	(8)
Groups of 30 male rats exposed to; 0, 0.1 or 9.8 ppm (0, 0.12 or 11.8 mg/m^3) 6 h/day; 5 days/week; 28 months	1.2	11.8	Histopathological changes in nasal cavity. No nasal tumours.	(126)
Three groups of 90-100 male rats exposed to; 0, 0 (colony controls) or 14.2 ppm (0, 0 or 17.5 mg/m^3) 6 h/day; 5 days/week for life		17.5	Histopathological changes in nasal cavity. Nasal squamous cell carcinoma: 38/100 rats exposed to 17.5 mg/m^3.	(99)

Odeigah performed two short-term *in vivo* mutagenicity tests (sperm head abnormality and dominant lethal mutation assays) in isogenic strains of albino rats (88). Five daily intraperitoneal injections of formaldehyde resulted in a statistically significant increase of sperm head abnormalities at doses of 0.125-0.500 mg/kg body weight. The frequency of dominant lethal mutations in female rats sired by males exposed to formaldehyde was significantly higher than in the control group.

In summary, no adequate data are available on genetic effects of formaldehyde in humans. Formaldehyde is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents. Formaldehyde given by inhalation or gavage to rats *in vivo* induced chromosomal aberrations in lung cells, micronuclei in the gastrointestinal tract, and sperm-head anomalies. Formaldehyde induced DNA-protein cross-links, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchanges, and gene mutations in human cells *in vitro*. It induced cell transformation, chromosomal aberrations, sister chromatid exchanges, DNA strand breaks, DNA-protein cross-links and gene mutations in rodent cells *in vitro*. Administration of formaldehyde to *Drosophila melanogaster* in the diet induced lethal and visible mutations, deficiencies, duplications, inversions, translocations, and crossing-over in spermatogonia. Formaldehyde induced mutations, gene conversion, DNA strand breaks and DNA-protein cross-links in fungi, and mutations and DNA damage in bacteria. Inhalation of formaldehyde leads to formation of DNA-protein cross-links in the nasal respiratory mucosa of rats and monkeys. The formation of DNA-protein cross-links is a sublinear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3 (0.71-15.27 ppm), 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 exposures.

6.2.8 Mechanism of formaldehyde nasal carcinogenesis

From the above data it is clear that formaldehyde is a highly cytotoxic, genotoxic carcinogen capable of inducing nasal carcinomas in rats and possibly in mice. The nasal toxicity of formaldehyde is characterised by inhibition of mucociliary function (83), reaction with small proteins present in nasal mucus (20), reaction with glutathione followed by detoxification by formaldehyde dehydrogenase (53), and, when biotransformation is overwhelmed or even inactivated, rhinitis, degeneration and necrosis followed by regenerative hyperplasia and metaplasia of the respiratory epithelium (82, 108). These distinct toxic effects have been invariably found in rats after short- and long-term exposure to concentrations of about 2.4 mg/m^3 (2 ppm) and higher (8, 62, 81, 83, 99, 125, 126).

Formaldehyde appears to be a direct-acting genotoxicant capable of inducing DNA-protein cross-links in nasal respiratory epithelium of experimental animals following inhalation exposure ("local genotoxicity") (72). Cross-linking of DNA with proteins might be expected to lead to DNA damage during cell replication, and potential mechanisms for such effects have been reviewed by Heck *et al*. (51).

A series of studies has clearly demonstrated a strong deviation from linearity of the formation of DNA-protein cross-links in the nasal epithelium of rats (23, 50, 52). One of the reasons for this non-linearity is inactivation of formaldehyde by glutathione, which apparently is much more effective at low (1.2-2.4 mg/m^3) than at high (7.2-18 mg/m^3) formaldehyde concentrations (51, 52).

High incidences of nasal carcinomas have been found in rats following long-term exposure to concentrations of 12 mg/m^3 (10 ppm) or higher (60, 62, 81, 99). These tumour data and the aforementioned toxicity data demonstrate that exposure levels causing nasal tumours also cause rhinitis, necrosis and epithelial hyperplasia and metaplasia of the nasal mucosa. Moreover, in a study on the more precise localisation of the formaldehyde induced nasal tumours in rats, Morgan *et al*. showed that tumours invariably occurred at locations of mucociliary inhibition, and epithelial hyperplasia and metaplasia (84). The dose-response curve for nasal tumours is very steep and extremely non-linear, while its shape appears to correspond with that of the dose-response curves for DNA-protein cross-links, inhibition of the mucociliary function, increased cell proliferation, and hyperplasia and metaplasia of the nasal respiratory epithelium. Obviously, an association exists between the cytotoxic, genotoxic, and carcinogenic effects (82). In other words, the steep non-linear dose-response curve for nasal tumours – indicating a more than proportionate decrease in cancer incidence at low concentrations – is most probably due to the fact that defence mechanisms of the nose (mucociliary clearance, detoxification by dehydrogenase, DNA repair) are very effective at low concentrations, but can be overwhelmed and inactivated at high concentrations; consequently, cell and tissue damage and finally tumours occur at high concentrations only.

These data and considerations suggest that the induction of nasal carcinomas by formaldehyde requires long-term exposure to levels that cause considerable damage to the nasal epithelium followed by restorative hyperplasia. This increased cell replication and subsequent cycles of DNA synthesis, provoked by long-term exposure to formaldehyde, may strongly enhance the likelihood of relevant DNA damage, and moreover, may strongly enhance the progression of initiated/preneoplastic cells to cancer. This also means that formaldehyde in concentrations not leading to tissue damage most probably cannot act as a complete carcinogen (causing initiation, promotion, and progression), and as a result is very unlikely to induce cancer by itself. Therefore, it is concluded that cytotoxic effects of formaldehyde play a highly significant, if not an essential role, in the formation of nasal tumours by formaldehyde. This conclusion is strongly supported by the results of a long-term inhalation study, in which male rats with a severely damaged or undamaged nasal mucosa were exposed to 0, 0.12, 1.2 or 12 mg/m^3 (0, 0.1, 1.0 or 10 ppm) formaldehyde for 6 hours/day, 5 days/week, during either 28 months or 3 months followed by a non-exposure, observation period of 25 months (126). The damage to the nasal mucosa was induced by bilateral intranasal electrocoagulation. Treatment related nasal tumours (squamous cell carcinomas) only occurred in the 12 mg/m^3 group of rats with a damaged nasal mucosa and exposed to formaldehyde for 28 months. Obviously, severe damage to

the nasal mucosa in combination with prolonged exposure to a relatively high cytotoxic concentration of formaldehyde leads to tumour formation. In this study, 12 mg/m^3 formaldehyde induced extensive and severe hyperplasia and metaplasia in the intact nasal mucosa, but no tumours. Clearly, for tumour formation "drastic" conditions seem to be required: severe damage plus a relatively high concentration (dose) of formaldehyde (38, 39).

6.2.9 Reproductive toxicity

In 1987, DECOS concluded in its previous document on formaldehyde that, based on studies available at that time, formaldehyde had not been demonstrated to cause adverse reproductive outcomes, even though foetotoxicity but not teratogenic effects had been observed, following administration of high doses of a known precursor of formaldehyde (hexamethylene tetramine). Therefore, it was suggested that additional studies in this field should be conducted. In 1989, the IPCS/WHO concluded that animal experiments did not show any evidence of the embryo, it being unusually sensitive to formaldehyde, and there was no information to show that formaldehyde was teratogenic in rodents when administered orally or applied dermally in non-toxic amounts to the dams (59). Furthermore, the data did not provide any evidence indicating that formaldehyde caused terata at exposure concentrations that were not toxic for the adult.

Saillenfait *et al*. studied the reproductive toxicity of formaldehyde in Sprague-Dawley rats (96). Groups of 25 pregnant rats were exposed by inhalation to 0, 6, 12, 24 or 48 mg/m^3 (0, 5, 10, 20 or 40 ppm) formaldehyde, 6 hours/day, from day 6 to 20 of gestation. No effect was found on embryonic or foetal lethality, nor significant alterations in the external, visceral or skeletal appearances of the foetuses. Significant concentration related reduction of foetal body weight occurred at 24 and 48 mg/m^3 (20 and 40 ppm). Maternal toxicity was observed at 48 mg/m^3 (40 ppm), as indicated by reduction of body weight and body weight gain.

Martin exposed groups of 25 mated rats by (whole-body) inhalation to 2.4, 6.0 or 12 mg/m^3 (2, 5 or 10 ppm) formaldehyde 6 hours/day, from day 6 to day 15 of gestation (76). Two control groups were used. The pregnancy rate in all groups was at least 80%. At the highest dose (12 mg/m^3) there was a significant decrease in maternal food consumption and body weight gain. Pregnancy parameters, including numbers of corpora lutea, implantation sites, live foetuses and resorptions, foetal weights, sex ratios, and preimplantation and postimplantation losses were unaffected by the treatment. The overall incidences of litters and foetuses with major malformations, minor external and visceral anomalies, and minor skeletal anomalies were not affected by treatment with formaldehyde. There was no evidence of maternal toxicity at 2.4 and 6 mg/m^3 (2 and 5 ppm) exposure levels. At the 6 and 12 mg/m^3 (5 and 10 ppm) dose levels, an apparently significant concentration related decrease in ossification was detected in the foetal bones of the pelvic girdle, which was associated with larger litter sizes with decreased foetal weights in both these groups. Also the slightly lower foetal weights were considered to be due to the larger litter sizes.

Recently, Majumber and Kumar reported inhibitory effects of formaldehyde on the reproductive system of male rats (73). In their experiment, adult male rats were treated intraperitoneally with formaldehyde at a dose of 10 mg/kg body weight per day given for 30 days. After the exposure period they found a fall in tissue protein contents of the epididymis and prostate, while these were not affected in testes and seminal vesicles. On the other hand, the DNA content had significantly decreased only in the testes and prostate of treated rats compared to control rats. The sperm count had decreased by 50% in treated rats. The sperm viability was also significantly affected and only 30% of viable sperms in the treated group were motile as compared to 86% in the control group. The authors also performed an *in vitro* study in which equal volumes of sperm suspension of normal rats and different concentrations of formaldehyde were mixed and incubated at ambient temperature for different time intervals. In this study, 80% sperms were viable over a period of 1 hour in the control group. At concentrations of 5 ng/ml formaldehyde only 50% spermatozoa were viable over a period of 30 minutes. At 500 ng/ml formaldehyde 50% spermatozoa were viable over a period of 6 minutes and at 2.5 mg/ml the effect was profound and instantaneous, and sperm viability dropped to zero within 10 minutes. Clearly, direct contact of high concentrations of formaldehyde with sperm affected sperm viability.

From the data the committees conclude that there is no evidence that formaldehyde may induce teratogenicity or may affect reproduction by inhalation exposure.

6.2.10 Other studies

Vargova *et al*. studied the immunotoxicity of formaldehyde in male rats (111). The animals were exposed to doses of 0, 20, 40, and 80 mg/kg body weight per day by oral administration (gastric tube) for 28 days. The body weights of rats exposed to the highest dose were slightly decreased. The lymph node weights were significantly increased, but the cellularity of lymphoid organs was not influenced after 28 days of exposure to formaldehyde. There was a dose dependent reduction of antibody response (IgG and IgM) at doses of 20, 40, and 80 mg/kg body weight per day. However, there was no significant reduction of the spleen cells producing IgM antibodies in exposed rats. The hepatocytes of the exposed animals showed increased cytoplasmic vacuolisation. Histochemistry revealed narrowing of the thymus-dependent zone in the spleen.

6.3 Summary

The odour threshold of formaldehyde varies from 0.06 to 0.22 mg/m^3 (0.05-0.18 ppm) (59).

6.3.1 Human studies

Sensory irritation

Sensory irritation in man is first (at low concentrations) experienced in the eyes, then (at higher concentrations) the odour of formaldehyde is perceived, and finally

nasal and throat irritation occur (59). After long-term occupational exposure to an average concentration of 0.26 mg/m^3 (0.22 ppm) formaldehyde (range 0.05-0.6 mg/m^3) more than 50% of the workers complained of nasal discomfort (120). However, in this (not well controlled) study the questionnaire used was not published. From cross-sectional morbidity studies it appeared that symptoms of irritation of the upper respiratory tract may occur after acute exposure to formaldehyde levels below 1.2 mg/m^3 (1 ppm) (28, 102, 120). Also from controlled studies in volunteers it appeared that at exposure levels for a short period lower than 1.2 mg/m^3 (1 ppm) sensory irritation may still occur in a substantial percentage of exposed individuals (4, 12). In one study (4), 19% of the exposed persons reported eye irritation at an exposure level of 0.29 mg/m^3 (0.24 ppm).

Rhinitis

Transient rhinitis has been found in volunteers exposed to 0.48 mg/m^3 (0.4 ppm) formaldehyde for 2 hours (93). A cross-sectional study on workers exposed to formaldehyde levels between 0.6 and 2.4 mg/m^3 (0.5-2 ppm) for more than 22 years revealed that 3 of 37 workers (18%) showed epithelial dysplasia in nasal biopsies; in all 3 cases the dysplasia was of the squamous type (22).

Pulmonary function

No changes in pulmonary function have been found in humans exposed to formaldehyde concentrations up to 3.6 mg/m^3 (3 ppm) (47, 98, 123).

Sensitisation

There is no consistent evidence of formaldehyde being capable of sensitising the respiratory tract. Under certain circumstances formaldehyde induced an IgE-mediated Type I reaction in the nose, but in most cases the annoying nasal symptoms were caused by formaldehyde induced hyperreactivity (120). An interesting finding was that atopics run approximately the same risk of suffering from this hyperreactivity as non-atopics (120). Formaldehyde did not induce transient or permanent bronchial hyperreactivity (11). Symptoms of the lower respiratory tract, like decreases of lung function parameters, were suggested to be related to exposure of workers to respirable particles containing formaldehyde penetrating deep into the airways (54).

Skin sensitisation by formaldehyde has been shown only by direct skin contact with formaldehyde solutions in concentrations higher than 2% (59). The threshold for induction of delayed hypersensitivity contact dermatitis has not been determined precisely. Formaldehyde induced allergic contact dermatitis has been estimated to occur in 3 to 6% of the population. Formaldehyde has also been reported to cause contact urticaria, but the mechanism is unknown (11).

Carcinogenic effects

An extensive retrospective cohort mortality study consisting of 26 561 workers from 10 formaldehyde-producing or -using facilities in the United States showed no statistically significant excess for specific cancers (17). There was no trend of

rising lung cancer risk with increasing levels of cumulative exposure to formaldehyde. Further analysis showed that 4 of 7 workers with nasopharynx cancer and 2 of 5 workers with oropharynx cancer occurred in a single plant producing moulding compounds, which was a dusty operation (19). The authors suggested that simultaneous exposure to formaldehyde and particulates may be a risk factor for these tumours. Using the same data, other authors calculated there was a 1.6-fold increase in lung cancer risk beginning approximately 16-20 years after first employment (75). For workers who were never co-exposed to any of the ten substances associated with increased lung cancer risk, the cumulative formaldehyde exposure was inversely related with the estimated lung cancer risk ratios. An update of the investigation by the same authors provided little evidence that the risk of lung cancer and nasopharyngeal cancer was associated either with formaldehyde exposure alone or in combination with particulate or pigment exposures (74). At the same time, other authors using a different statistical technique on the same data concluded that only high levels of cumulative exposure showed a significant elevation in relative lung cancer risk (103). Trend analysis indicated a significant trend of increasing risk of lung cancer and respiratory cancer with increasing formaldehyde exposure.

These results have been strongly opposed by the original investigators (16) who commented that Sterling *et al*. (103) apparently had not considered exposures other than formaldehyde in their analysis. Differences in the outcome might have been attributable to differences in the target population confounded by the healthy worker effect (104).

A cancer morbidity study showed that formaldehyde may increase the risk for sinonasal cancer in humans (46). Because of the rarity of nasopharyngeal cancer, it was not possible to evaluate the risks. There were some serious shortcomings in this study. Various case-control studies have been performed using end-points as: respiratory cancer, cancer of the nose and paranasal sinuses, lung cancer, and bladder cancer. In these studies no firm relationships could be found between occupational exposure to formaldehyde and these cancers.

A meta-analysis of 30 epidemiological studies indicated no exposure-related response gradient for CRR on nasal cancer (15). On the other hand, on nasopharyngeal cancer the CRR value rose to 2.1 in the highest exposure category; the trend was significant. The results of this study were substantiated by another meta-analysis (90). However, in this meta-analysis the authors did not correct for the unreported studies in which no cases of nasal cancers were found. It is likely that this may have caused an overestimation of the true relative risk. In a recent meta-analysis of 47 epidemiological studies a correction for underreporting was made (31). Relative risks for nasal cancers in cohort and case-control studies were 1.0 and 1.3, respectively. The authors concluded that these studies do not support a causal relation between formaldehyde exposure and nasopharyngeal cancer.

6.3.2 Animal studies

Sensitisation

For formaldehyde a 10-minutes RD_{50} in mice of 3.6 ± 0.3 mg/m^3 (3.0 ± 0.28 ppm) has been reported (61).

Studies in mice and guinea pigs produced no evidence of formaldehyde being a respiratory tract sensitiser (56).

Formaldehyde has been shown to be a contact sensitiser (21, 56).

Short-term exposure

The critical effects of short-term exposure to airborne formaldehyde in experimental animals are damage to and increased proliferation of the nasal epithelium. The histopathological changes range from slight hyperplasia and squamous cell metaplasia of the ciliated and non-ciliated respiratory epithelium in specific areas, found at low effective exposure concentrations, i.e. 2.4-3.6 mg/m^3 (2-3 ppm), to severe rhinitis, necrosis and extensive hyperplasia and metaplasia of major portions of the nasal epithelium, found at exposure concentrations of about 7.2 mg/m^3 (6 ppm) and higher (8, 24, 26, 79, 80, 83, 95, 121, 122, 125, 129).

Substantial increases in epithelial cell turnover rates occur in rats at exposure concentrations of 7.2 mg/m^3 (6 ppm) and higher (24, 79, 80, 107, 108). The majority of NOAELs found in these short-term studies are 1.2 or 2.4 mg/m^3 (1 or 2 ppm). In all studies with a NOAEL of 1.2 mg/m^3 (1 ppm) the LOAEL was higher than 2.4 mg/m^3 (2 ppm), indicating the possibility that also in these studies a NOAEL of 2.4 mg/m^3 might have been obtained if indeed this exposure level would have been included in these experiments. However, occasionally (marginally and transiently) increased cell proliferation has been found at exposure levels of 0.6 or 1.2 mg/m^3 (0.5 or 1 ppm) (107, 108, 129), while the histopathological changes observed by Woutersen *et al*. turned out to be inconclusive with respect to 1.2 mg/m^3 (1 ppm) being a NOAEL or a LOAEL (125).

Long-term exposure

Critical effects of long-term inhalation exposure to formaldehyde include inflammatory, degenerative and regenerative changes of the nasal mucosa, and squamous cell carcinomas of the nasal respiratory epithelium. The non-neoplastic nasal changes range from a minimal degree of hyperplasia and squamous cell metaplasia of the nasal respiratory epithelium (occasionally seen at concentrations of approximately 2.4 mg/m^3 (2 ppm) or lower) to rhinitis, necrosis and extensive restorative hyperplasia and metaplasia of the nasal respiratory epithelium invariably seen at concentrations of about 7.2 to 18 mg/m^3 (6-15 ppm).

High incidences of squamous cell carcinomas have been found in rats at exposure levels of 12 mg/m^3 (10 ppm) or higher (60, 62, 81, 99). In most long-term studies, a NOAEL of 1.2 or 2.4 mg/m^3 have been reported. However, in one long-term study in rats 2.4 mg/m^3 (2 ppm) appeared to be a LOAEL (62) and in another long-term rat study a LOAEL of 0.36 mg/m^3 (0.3 ppm) was reported (60).

Genotoxicity

No adequate data were available on genetic effects of formaldehyde in humans. Formaldehyde has been investigated for genotoxic properties in many test systems (58). It is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents *in vivo*. Formaldehyde given by inhalation or gavage to rats induced chromosomal aberrations in lung cells, micronuclei in gastro-intestinal tract cells, and sperm-head anomalies. Inhalation of formaldehyde leads to formation of DNA-protein cross-links in the nasal respiratory epithelium of rats and monkeys. The formation of DNA-protein cross-links is a sub-linear function of the formaldehyde concentration in inhaled air from 0.86 to 18.4 mg/m^3 (0.71-15.3 ppm), 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 exposures (58). In V79 Chinese hamster cells, formaldehyde induced DNA-protein cross-links, sister chromatid exchanges, and micronuclei, but no gene mutations, in concentrations similar to those inducing cytotoxicity, suggesting that formaldehyde induced DNA-protein cross-links are related to cytotoxicity and clastogenicity (77). In cultured human lung epithelial cells, DNA double-strand breaks were induced by formaldehyde only when cell viability was reduced to 60%, indicating that the double-strand breaks were caused by extragenomic damage and viability loss (115). Recio suggested that the nasal inflammation and proliferation induced by formaldehyde exposure may contribute to the induction of genetic alterations through a variety of mechanisms including generation of reactive oxygen species, alterations in nucleotide pools, free radical formation, and clonal expansion with further mutation of genetically altered cells (94).

With respect to the mechanism underlying the nasal carcinogenicity of formaldehyde in rats, there is a large body of data suggesting an association between the cytotoxic, genotoxic, and carcinogenic effects of formaldehyde (29, 38, 39, 51, 53, 82, 84, 126). The steep non-linear dose-response curve for nasal tumours – indicating a disproportionate decrease in carcinoma incidence at low concentrations – is most probably due to the fact that defence mechanisms of the nose (mucociliary clearance, detoxification by dehydrogenase, DNA repair) are very effective at low concentrations, but can be overwhelmed and inactivated at high concentrations; consequently, cell and tissue damage and finally tumours occur at high concentrations only. This also means that formaldehyde in concentrations not leading to tissue damage most probably cannot act as a complete carcinogen (causing initiation, promotion and progression), and as a result is very unlikely to induce cancer by itself.

In several animal studies, inhalation of formaldehyde was not found to affect reproduction.

7. Existing guidelines, standards and evaluations

7.1 General population

The following recommendation was forwarded by IPCS/WHO (59): "The formaldehyde air concentration allowed in living, sleeping and working rooms should not be higher than 0.12 mg/m^3 (0.1 ppm), in order to minimise the risk of repeated or continuous low concentration exposure to formaldehyde".

Using a linear-at-low-dose extrapolation, the United States Environmental Protection Agency (EPA) developed an upper-limit unit-risk estimate of 1.6×10^{-2} /ppm continuous exposure to formaldehyde, in 1987 (32). This approach was based solely on the dose-response for formaldehyde induced tumour formation, assuming a five-stage model for carcinogenesis. The EPA subsequently changed its risk estimate using a three-stage model, resulting in an upper-limit risk of 6.1×10^{-3}/ppm formaldehyde exposure. In 1991, the EPA further revised its risk estimate using the levels of DNA-protein cross-links in the rat and monkey as an indicator of delivered formaldehyde dose. The use of this information in a two-stage model, based upon the goodness-of-fit of the data, yielded an upper-limit unit risk estimate of 3.3×10^{-4}/ppm. Thus, the use of mechanistic information resulted in a 50-fold reduction in the estimation of carcinogenic risk to humans from formaldehyde.

In 2002, the WHO/IPCS has published a review on formaldehyde (CICAD) (119). They concluded that based on studies in both animals and humans, formaldehyde is weakly genotoxic, with good evidence of an effect at site of contact. Epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde and human cancer, although the possibility of increased respiratory cancer cannot be excluded. Therefore, based primarily upon data derived from laboratory studies, the inhalation of formaldehyde under conditions that induce cytotoxicity and sustained regenerative proliferation is considered to present a carcinogenic hazard to humans.

7.2 Working population

Occupational exposure standards in various countries are shown in Table 6.

7.3 Evaluations of standards

7.3.1 The Netherlands

In 1981, DECOS concluded that formaldehyde is a proven genotoxic carcinogen in experimental animals and that the induction of cancer in humans could not be excluded (117). DECOS estimated that exposure to 0.1 mg/m^3 or 0.5 mg/m^3 formaldehyde, 8 hours/day, 5 days/week for 40 years with a life span of 75 years, would result in maximal cancer risks of 1:40 000 and 1:10 000, respectively.

In 1987, however, DECOS updated the previous document and concluded that an occupational exposure limit not exceeding 1.2 mg/m^3 (1 ppm) formaldehyde,

Table 6. Occupational exposure standards in various countries.

Country -organisation	Occupational exposure limit		Averaging time	Note[a]	Year of adoption[b]	Reference[c]
	ppm	mg/m^3				
The Netherlands	1	1.5	8 h		1986	(78)
	2	3.0	15 min			
Germany	0.30	0.37	8 h	4[d] Sens	Unknown	(35)
Great Britain	2	2.5	8 h		Unknown	(49)
	2	2.5	15 min			
Sweden	0.5	0.6	8 h	Sens	1987	(106)
	1.0	1.2	Ceiling	Carc		
Denmark	0.3	0.4	Ceiling	Carc	Unknown, before 1994	(9)
Finland	0.3	0.37	8 h		Unknown	(101)
	1	1.2	Ceiling			
Norway	0.5	0.6	8 h	Sens	1984	(36)
	1.0	1.2	Ceiling	Carc		
Iceland	0.3	0.4	8 h	Sens	1999	(114)
	1.0	1.2	Ceiling			
United States						
–ACGIH	0.3	0.37	Ceiling	Group A_2[d]	1992	(2)
–OSHA	0.75	0.9	8 h		Unknown	(89)
–NIOSH	0.016	0.02	8 h	Carc	Unknown	(85)
	0.10	0.12	15 min			
European Union				Carc Cat 3	Unknown	(86)

a. Sens, substance can cause sensitisation.
Carc, classification of carcinogenic properties.
b. Year that this limit was officially adopted.
c. Reference to the most recent official publication of occupational exposure limits.
d. Genotoxicity playing no or at most a minor part.

15 minutes TWA, virtually should not constitute an increased nasal cancer risk (34). From studies in rats DECOS concluded that at subcytotoxic levels the risk of induction of nasal cancer appears to be negligibly small.

7.3.2 United States

In 1989, the American Conference of Governmental Industrial Hygienists (ACGIH) revised their assessment on formaldehyde. The proposed threshold limit value (TLV) for formaldehyde was 0.37 mg/m^3 (0.3 ppm) as a ceiling, with a notation "suspected human carcinogen" (A_2) (1). In the opinion of the ACGIH this TLV as a ceiling should reduce the risk of sensory irritation for workers handling formaldehyde or formaldehyde containing products. They also advised to reduce formaldehyde workplace exposure to the lowest possible level in view of the

reported dose-dependent carcinogenic effect in rats and mice, and the inadequate epidemiological data on the cancer risk in man.

In 1992, OSHA responded to a remand by the Unites States Court of Appeals for the DC Circuit (89). The final amendments lowered the permissible exposure level for formaldehyde from 1 ppm as an 8-hour TWA to an 8-hour TWA of 0.75 ppm (0.9 mg/m^3). It should be noted that the former standard had been challenged in Unites States Court by both industry and labour. Four unions had challenged the standard as being insufficiently protective. They contended that the former permissible exposure limit was not low enough to eliminate all significant risk of harm, from both cancer and from formaldehyde irritant effects.

The National Institute for Occupational Safety and Health (NIOSH) recommended an exposure limit of 0.02 mg/m^3 (0.016 ppm) (8-hour TWA) and a 0.12 mg/m^3 (0.1 ppm) 15 minutes limit (85).

7.3.3 Germany

In 2000, Deutsche Forschungsgemeinschaft set a "Maximale Arbeitsplatzkonzentration" (MAK) value of 0.37 mg/m^3 (0.3 ppm) for formaldehyde. Formaldehyde is classified in category 4, which contains substances with carcinogenic potential, for which genotoxicity plays no or at most a minor part. No contribution to human cancer risk is expected at the MAK-value. The classification is supported especially by evidence that increases in cellular proliferation or changes in cellular differentiation are important in the mode of action. To characterise the cancer risk, the manifold mechanism contributing to carcinogenesis and their characteristic dose-time response relationships are taken into consideration. Furthermore, formaldehyde is classified in germ cell mutagenicity category 5. A risk of damage to developing embryos or foetuses is not to be expected at concentrations below the MAK value. Therefore formaldehyde is classified in group C for compounds which may influence pregnancy.

7.3.4 Sweden

The most current consensus report for formaldehyde by the National Board of Occupational Safety and Health was dated 25-8-1982. It was concluded that the basis for occupational exposure standards should be the irritating effects of formaldehyde on the respiratory organs and eyes. Formaldehyde has been shown to be carcinogenic in animal studies. Epidemiological studies provide inadequate evidence and cannot be used to assess carcinogenic effects on man.

7.3.5 IARC / WHO

The most recent evaluation by IARC on formaldehyde concluded that there was limited evidence in humans for the carcinogenicity of formaldehyde (58). There is sufficient evidence in experimental animals for the carcinogenicity of formaldehyde. The overall evaluation was that formaldehyde is probably carcinogenic to humans (Group 2A).

7.3.6 European Union

The European Union has classified the carcinogenic effects of formaldehyde in category 3 (substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment) (Appendix 3).

8. Hazard assessment

8.1 Assessment of the health hazard

Formaldehyde occurs naturally in the environment and is produced physiologically by mammalian cells during metabolism. It has been used by man for over a century in a variety of products and activities. The human cell can rapidly detoxify lower levels of formaldehyde.

Airborne formaldehyde exposures can occur as vapour or as particles (solids or mists) or as a combination of both. The relative intensities of vapour and particle exposures vary with the industry and the job activities. The anatomic site of tissue contact as well as the intensity of exposure depend on the physical form of the compound. Inhaled formaldehyde vapour is usually efficiently removed by the nose, mouth, and trachea, but in analogy with sulphur dioxide, some vapour probably penetrates into the lower airways with mouth breathing during moderately heavy or heavy work (55). Inhaled particles containing formaldehyde are deposited in the respiratory system as a function of their aerodynamic characteristics and, given an appropriate aerodynamic diameter, may result in exposures deep within the respiratory tract. The biological behaviour of formaldehyde deposited in particulate form is unknown.

From the toxicological data base on formaldehyde it is evident that the critical effects of formaldehyde are sensory irritation, and cytotoxicity induced regenerative hyperplasia (increased cell proliferation/increased cell turnover rates) and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats and possibly in mice after long-term exposure to high cytotoxic concentrations.

Symptoms of formaldehyde exposure in humans start with sensory irritation first experienced in the eyes, followed by perception of the odour, and then irritation of the nose and throat, accompanied by discomfort, lachrymation, sneezing, coughing, nausea and dyspnoea. A panel of independent experts convened by the Industrial Health Foundation (IHF) studied all available data on sensory irritation related to formaldehyde exposure (92). This IHF-panel concluded that for most persons eye irritation does not occur until at least 1.2 mg/m^3 (1.0 ppm) formaldehyde. This panel also observed that from controlled studies in volunteers, it appears that moderate to severe eye, nose and throat irritation does not occur for most individuals until exposure concentrations of formaldehyde exceed 2.4-3.6 mg/m^3 (2.0-3.0 ppm). The panel further concluded that an occupational exposure limit of less than 0.6 mg/m^3 (0.5 ppm) may be

needed to prevent sensory irritation in a diverse working population, and therefore recommended for formaldehyde an occupational exposure limit of 0.36 mg/m^3 (0.3 ppm) as an 8-hour TWA with a ceiling value of 1.2 mg/m^3 (1.0 ppm) (92). However, according to the committees (DECOS and NEG) the database on sensory irritation of formaldehyde reveals that at lower exposure levels sensory irritation may still occur in substantial percentages of exposed individuals. For instance, in a not well-documented study, more than 50% of occupationally exposed workers complained of nasal discomfort after long-term exposure to an average concentration of 0.26 mg/m^3 (0.22 ppm; range 0.05-0.6 mg/m^3 or 0.04-0.5 ppm) (120). Moreover, from a controlled study in volunteers it appeared that 19% (n=3) of the exposed subjects (n=16) reported eye irritation at an exposure concentration of 0.29 mg/m^3 (0.24 ppm) (4). However, according to the IHF-panel such a response is often considered of doubtful toxicological significance because irritation responses of 15-20% may be obtained in unexposed volunteers as well (92).

In experimental animals, irritation of eyes, nose, throat, and lungs were observed at exposure concentrations higher than 2.4 mg/m^3 (2.0 ppm). Kane and Alarie determined in mice a 10-minutes RD_{50} for formaldehyde of 3.6±0.43 mg/m^3 (3.0±0.28 ppm) (61). Compared to humans, experimental animals seem to be less sensitive to stimulation of the trigeminal nerve by formaldehyde. Moreover, in view of the wealth of reliable data on sensory irritation in humans, the irritation data on formaldehyde in experimental animals are considered of secondary importance in terms of both hazard identification and risk assessment.

Overall, weighing the total body of data on sensory irritation, the committees estimate that 0.3 mg/m^3 (0.25 ppm) formaldehyde is the lowest exposure concentration at which sensory irritation may occur in low but significant percentages of exposed workers

Nasal carcinomas in rats have only been found at high, cytotoxic exposure concentrations causing rhinitis, necrosis and regenerative hyperplasia and squamous metaplasia of the nasal respiratory epithelium (60, 62, 81, 99). The crucial role of tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium in formaldehyde carcinogenesis has been demonstrated in a convincing way (38, 39, 126) and has meanwhile been widely recognised (92, 118) and should therefore be included in human cancer risk assessment (29). Despite differences in anatomy and physiology of the nose between rats and humans, the upper respiratory tract defence systems are similar in both species (82). It is, therefore, reasonable to conclude that the response of the respiratory tract to formaldehyde will be qualitatively similar in rats and humans. If in humans exposure of formaldehyde were to be accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have carcinogenic potential in man. Correspondingly, if the respiratory tract tissue is not recurrently injured, exposure of humans to relatively low non-cytotoxic levels of formaldehyde can be assumed to be associated with a negligible cancer risk.

The committees observe that the majority of short- and long-term inhalation toxicity studies with formaldehyde in experimental animals reveal a NOAEL of

1.2 or 2.4 mg/m^3 (1 or 2 ppm). However, in one 24-month inhalation study in rats, 2.4 mg/m^3 (2 ppm) formaldehyde (lowest level tested) induced mild squamous metaplasia of the epithelium lining the nasal turbinates (62). Moreover, a 13-week inhalation toxicity study with formaldehyde, 1.2 mg/m^3 (1 ppm), in rats was inconclusive with respect to its effects on the nasal respiratory epithelium (125). Furthermore, in two short-term inhalation studies in rats, slightly (and only transiently) increased cell proliferation of the respiratory epithelium was seen in a specific area of the nasal mucosa at formaldehyde exposure concentrations of 0.6 or 1.2 mg/m^3 (0.5 or 1 ppm) (107, 108, 129). Finally, in one recently published long-term inhalation toxicity/carcinogenicity study on formaldehyde in rats (60), a low incidence of hyperplasia with or without squamous metaplasia of the nasal respiratory epithelium was found at 0.36 mg/m^3 (0.3 ppm). This low incidence (4/32) was not statistically significantly different from that in controls (0/32), but was nevertheless considered toxicologically relevant (i.e. formaldehyde induced) because there was a clear dose-response relationship with the increased incidences at the higher exposure levels being statistically significantly different from that in controls.

The data in humans are less clear. Three meta-analyses of epidemiological studies have shown inconsistent results. In two of them a significant relation between exposure to formaldehyde and nasopharyngeal cancer risk was observed. The association between formaldehyde exposure and nasal cancer was ambiguous (15, 90). However, according to the committees in these meta-analyses the authors did not correct for the unreported studies in which no cases of nasal cancers were found. This most likely led to an overestimation of the overall relative risk of nasopharyngeal cancer. In the third, more recent, published meta-analysis, relative risks of 1.0 and 1.3 were found for nasal cancer in cohort and case-control studies, respectively (31). In this meta-analysis a correction was made for underreporting. Moreover, the authors evaluated the exposure potential for jobs included in the general population case-control studies. The authors concluded that there was no support for a causal relation between formaldehyde exposure and nasopharyngeal cancer. The committees (both DECOS and NEG) endorse this conclusion and further conclude that the currently available epidemiological database does not provide support for a nasal cancer risk at the exposure levels lower than 0.3 mg/m^3. Also from the epidemiological database it seems unlikely that exposure to formaldehyde affects lung cancer risk (5, 6, 15, 18, 41, 46, 90). Overall, both committees conclude that the currently available epidemiological database on formaldehyde does not provide evidence for a respiratory tract cancer risk at the experienced exposure levels. In correspondence to the previous evaluation of formaldehyde by DECOS in 1987 (34), the committees endorse the conclusion from 1987 that with prevention of cytotoxicity, carcinogenic effects will not occur.

8.2 Groups at extra risk

Allergic dermal sensitisation to formaldehyde in man occurs in 3 to 6% of the general population. It is not possible to identify individuals with elevated risk for allergic sensitisation *a priori* with a simple screening test. Skin sensitisation constitutes a health risk in workers occupationally exposed to formaldehyde.

8.3 Scientific basis for an occupational exposure limit

The critical effect of formaldehyde is sensory irritation (LOAEL 0.25 ppm). Another concern is cytotoxicity induced regenerative hyperplasia and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats and possibly in mice after long-term exposure to high cytotoxic concentrations.

High, cytotoxic formaldehyde vapour concentrations (≥10 ppm) can induce nasal cancer in rats. A large body of data suggests an association between the cytotoxic, genotoxic and carcinogenic effects of formaldehyde. Tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium has a crucial role in formaldehyde carcinogenesis. Thus, formaldehyde in non-cytotxic concentrations not leading to tissue damage most probably cannot act as a complete carcinogen. However, if human exposure of formaldehyde is accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have a carcinogenic potential in man.

Formaldehyde is a skin sensitiser.

9. Summary

Wibowo, Anton. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 132. Formaldehyde*. Arbete och Hälsa 2003;11:1-76.

Formaldehyde is a colourless, flammable, reactive gas, which readily polymerises, and forms explosive mixtures with air and oxygen. It is used as a raw material in chemical reactions, and as an intermediate in the manufacture of numerous products. It has also a medical application as a disinfectant or preservative.

Inhaled formaldehyde is almost completely absorbed in the upper respiratory tract in rodents. Formaldehyde is a normal metabolite in mammalians and is rapidly metabolised to formate, which may be further oxidised to carbon dioxide. Final elimination occurs via exhalation and via the kidneys.

The target organs of formaldehyde vapour are the eyes, nose, and throat. The effects of concern are sensory irritation and cytotoxicity-induced regenerative hyperplasia and metaplasia of the nasal respiratory epithelium accompanied by nasal carcinomas in rats. Weighting the total body of data 0.25 ppm formaldehyde is the LOAEL at which sensory irritation may occur in a low but significant percentage of exposed workers. The majority of short- and long-term inhalation animal studies reveal a NOAEL of 1-2 ppm. However, in a few studies slight histopathological changes of the nasal respiratory epithelium were observed at 0.3-2 ppm.

Formaldehyde is genotoxic in a variety of experimental systems, including rodents *in vivo*. There is overwhelming evidence that high, cytotoxic formaldehyde vapour concentrations (≥10 ppm) can induce nasal cancer in rats. A large body of data suggests an association between the cytotoxic, genotoxic, and carcinogenic effects of formaldehyde. The crucial role of tissue damage followed by hyperplasia and metaplasia of the nasal respiratory epithelium in formaldehyde carcinogenesis has been demonstrated in a convincing way. Thus, formaldehyde in non-cytotxic concentrations most probably cannot act as a complete carcinogen. However, if human exposure to formaldehyde is accompanied by recurrent tissue damage at the site of contact, formaldehyde may be assumed to have carcinogenic potential in man.

Formaldehyde-induced allergic contact dermatitis has been estimated to occur in 3-6% of the population, and skin sensitisation by direct skin contact has been induced with formaldehyde solutions. There is no consistent evidence of formaldehyde being a respiratory sensisitiser.

Key words: allergy, cancer, contact dermatitis, cytotoxicity, formaldehyde, genotoxicity, irritation, nasal, occupational exposure limit, review, risk assessment

10. Summary in Swedish

Wibowo, Anton. *The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals and the Dutch Expert Committee on Occupational Standards. 132. Formaldehyde*. Arbete och Hälsa 2003;11:1-76.

Formaldehyd är en färglös, lättantändlig, reaktiv gas som lätt polymeriserar och bildar explosiva blandningar med luft och syre. Ämnet används som råmaterial i kemiska reaktioner och som intermediär vid tillverkning av ett stort antal produkter. Det har även medicinsk användning som desinfektionsmedel och konserveringsmedel.

Inandad formaldehyd absorberas nästan fullständigt i de övre luftvägarna. Formaldehyd är en normal ämnesomsättningsprodukt hos däggdjur och omvandlas snabbt till format (myrsyra) som kan oxideras vidare till koldioxid. Slutlig eliminering sker via utandning och via njurarna.

Målorgan för formaldehydånga är ögon, näsa och hals. Effekter av betydelse är sensorisk irritation samt cytotoxiskt inducerad regenerativ hyperplasi och metaplasi i nässlemhinnan, följt av näscancer hos råtta. Sammantaget bedöms 0,25 ppm vara den lägsta nivå (LOAEL) vid vilken sensorisk irritation uppträder hos en liten men signifikant andel av exponerade arbetare. Merparten inhalationsstudier, såväl kort- som långtidsstudier, rapporterar en icke-effektnivå (NOAEL) på 1-2 ppm. I några studier har man dock observererat små histopatologiska förändringar av nässlemhinnan vid 0,3-2 ppm.

Formaldehyd är genotoxiskt i en rad experimentella system inklusive gnagare *in vivo*. Det finns överväldigande bevis för att höga, cytotoxiska formaldehydkoncentrationer (≥10 ppm) kan inducera näscancer hos råtta. En mängd data pekar på ett samband mellan de celltoxiska, genotoxiska och carcinogena effekterna av formaldehyd. Vävnadsskada följt av hyperplasi och metaplasi i näsans respiratoriska epitel spelar en avgörande roll i carcinogenesen vid formaldehydexponering, vilket har visats på ett övertygande sätt. Formaldehyd i icke-cytotoxiska concentrationer är därför troligen inte en komplett carcinogen. Om människor exponeras för formaldehyd med upprepad vävnadsskada vid kontaktstället som följd kan formaldehyd emellertid antas ha carcinogen potential.

Formaldehyd-inducerat allergiskt kontakteksem beräknas uppträda hos 3-6% av befolkningen och hudsensibilisering har inducerats via direkt hudkontakt med formaldehydlösningar. Det finns inga entydiga bevis för att formaldehyd kan ge sensibilisering via inandning.

Nyckelord: allergi, cancer, kontakteksem, cytotoxicitet, formaldehyd, genotoxicitet, gränsvärden, irritation, näs-, riskbedömning, översikt

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12. Data

A number of reviews on formaldehyde were the starting point in searching literature on the health effects to formaldehyde (32, 37, 58, 59, 92).

Unless otherwise indicated, data were derived from these documents. Data considered to be critical were evaluated by reviewing the original publications. In addition, literature was retrieved from the on-line databases Medline (starting at 1966) and Mbase (from 1988 onwards) prior to January 1997, and from NIOSH-TIC and HSE-line from 1996 backwards.

In addition, Toxline and Medline were searched for studies published between January 1997 and October 1999. Those studies that were considered relevant to the conclusion of the committee were included in the document. A final search was performed in October 2002. Studies published between October 1999 and October 2002 were no reason for the committees to adjust their conclusions and are therefore not included in this document.

Appendix 1

Formaldehyde monitoring data in occupational settings (59).

Appendix 2

Genetic and related effects of formaldehyde (58).

Appendix 3

Classification of substances with respect to carcinogenicity (guideline 93/21/EEG of the European Community).

Submitted for publication October 13, 2003.

Appendix 1. Formaldehyde monitoring data in occupational settings[a] (59).

Industry	Job or work area	Exposure levels mg/m^3 (ppm)			Area or personal monitoring	No. of observations	Method[b]	Reference
		Range	Mean	Median				
Formaldehyde production	Production operator	–	1.68 (1.4)	–	Personal	–	CT, IC	NIOSH (1980a)
	Laboratory technician	–	1.57 (1.31)	–	Personal	–	CT, IC	NIOSH (1980a)
Resin and plastic materials production	Production operator	–	1.67 (1.39)	–	Personal	–	CT, IC	NIOSH (1980a)
	Resin plant	0.06-0.44 (0.05-0.37)	0.29 (0.24)	–	Area	8	BI, CT, GC	NIOSH (1976a)
	Resin plant	0.11-0.20 (0.09-0.17)	0.16 (0.13)	–	Area	2	BI, CO	NIOSH (1978a)
	UF resin production (2 plants)	0.14-0.66 (0.12-0.55)	–	–	Area	–	SS, IC	Herrick *et al.* (1983)
		0.22-6.48 (0.18-5.4)	–	–	Area	–	SS, IC	Herrick *et al.* (1983)
		0.24-0.89 (0.2-0.74)	–	–	Area	–	SS, IC	Herrick *et al.* (1983)
		0.072-0.41 (0.06-0.34)	–	–	Area	–	SS, IC	Herrick *et al.* (1983)
	UF resin production	0.14-6.48 (0.12-5.4)	1.08 (0.90)	–	Personal	18	BI, CA	NIOSH (1980b)
		0.24-0.89 (0.20-0.74)	0.47 (0.39)	–	Personal	5	BI, CA	NIOSH (1980b)
		0.07-0.41 (0.06-0.34)	0.23 (0.19)	–	Personal	5	BI, CA	NIOSH (1980b)
Textile finishing	Textile warehouse	0.05-0.88 (0.04-0.73)	0.37 (0.31)	–	Area, Personal	11	CT, SP	NIOSH (1979a)
		0.10-0.61 (0.08-0.51)	0.30 (0.25)	–	Area, Personal	11	BI, SP	NIOSH (1979a)
	Textile facilities	<0.12-1.56 (<0.1-1.3)	–	0.96 (0.8)	Area, Personal	28	–	NIOSH (1979b)
		<0.12-1.68 (<0.1-1.4)	–	0.84 (0.7)	Area, Personal	15	–	NIOSH (1979b)
	Textile manufacture	0.13-1.60 (0.11-1.33)	0.83 (0.69)	0.77 (0.64)	Personal	6	–	NIOSH (1981)
		0.18-1.44 (0.15-1.2)	0.64 (0.53)	0.54 (0.45)	Area	13	–	NIOSH (1981)

Appendix 1. Cont.

Industry	Job or work area	Exposure levels mg/m^3 (ppm)			Area or personal monitoring	No. of observations	Method[b]	Reference
		Range	Mean	Median				
Clothing production	Permanent press	0.18-0.46 (0.15-0.38)	0.37 (0.31)	–	Area	9	BI, I	US DHEW (1966)
		0-3.24 (0-2.7)	0.89 (0.74)	–	Area	32	BI, I	US DHEW (1968)
	Warehouse	0.13-0.68 (0.11-0.57)	0.47 (0.39)	0.44 (0.37)	Personal	13	–	NIOSH (1979a)
		0.05-0.23 (0.04-0.19)	0.14 (0.12)	0.18 (0.15)	Area	9	–	NIOSH (1979a)
	Sewing machine operators	0.61-1.09 (0.51-0.91)	0.86 (0.72)	0.85 (0.71)	Personal	16	–	NIOSH (1979a)
		0.36-2.16 (0.3-1.8)	1.44 (1.2)	1.44 (1.2)	Personal	41	–	NIOSH (1979a)
	Clothing pressers	0.006-1.14 (0.005-0.95)	0.08 (0.07)	0.065 (0.054)	Personal	40	–	NIOSH (1976a)
Plywood particle-board production	All workers	–	1.2-3.0 (1-2.5)	–	Area	–	–	NIOSH (1979b)
Wood furniture manufacture	Particle board veneering	0.01-0.3 (0.008-0.25)	0.14 (0.12)	–	Area	11	BI, CA	Herrick *et al.* (1983)
		1.08-7.68 (0.9-6.4)	3.30 (2.75)	–	Area	–	BI, CA	Herrick *et al.* (1983)
		0.24-0.66 (0.2-0.55)	0.48 (0.40)	–	Area	9	BI, CA	Herrick *et al.* (1983)
		0.24-3.0 (0.2-2.5)	0.84 (0.70)	–	Area	13	BI, CA	Herrick *et al.* (1983)
Plastic moulding	Injection mould	0.01-0.12 (0.01-0.1)	0.044 (0.037)	–	Personal	9	CA	NIOSH (1973a)
	Area samples	0.01-0.64 (0.01-0.53)	0.24 (0.20)	–	Area	8	CA	NIOSH (1973a)
	Operators	<2.4 (<2)	<2.4 (<2)	<2.4 (<2)	Personal	28	DT	NIOSH (1973a)
	Near grinder hopper	2.4-4.8 (2-4)	3.6 (3)	3.6 (3)	Area	3	DT	NIOSH (1973a)
	Sand mould production	0.12-0.84 (0.1-0.7)	0.37 (0.31)	0.24 (0.2)	Personal	28	–	NIOSH (1976a)
		ND-1.32 (ND-1.1)	0.20 (0.17)	0.12 (0.1)	Area	29	–	NIOSH (1976a)

Appendix 1. Cont.

Industry	Job or work area	Exposure levels mg/m^3 (ppm)			Area or personal monitor	No. of observations	Method[b]	Reference
		Range	Mean	Median				
Paper and paperboard manufacture	Paper treatment (resin impregnated)	0.05-0.19 (0.04-0.16)	0.10 (0.08)	–	Personal	15	BI, CT, CA	NIOSH (1976b)
		0.04-0.08 (0.03-0.07)	0.07 (0.06)	–	Area	7	BI, CT, CA	NIOSH (1976b)
		0.01-0.28 (0.01-0.23)	0.06 (0.05)	–	Personal	30	BI, CT, CA	NIOSH (1976b)
		0.02-0.34 (0.02-0.28)	0.06 (0.05)	–	Personal	10	BI, CT, CA	NIOSH (1976b)
	Treated paper products	0.17-1.19 (0.14-0.99)	–	0.70 (0.59)	Area	64	–	NIOSH (1979b)
		0.17-1.08 (0.14-0.90)	–	0.41 (0.34)	Personal	37	–	NIOSH (1979b)
	Coating preparation	<0.01-3.6 (<0.01-3)	1.2 (1.0)	0.01 (0.01)	Area	7	–	NIOSH (1980a)
		0.96-0.50 (0.8-0.42)	0.61 (0.51)	0.50 (0.42)	Area	4	–	NIOSH (1980a)
Foundries (steel, iron, and non-ferrous)	Bronze foundry, core machine operators	0.29-0.96 (0.24-0.80)	0.64 (0.53)	0.66 (0.55)	Personal	4	BI, CA	NIOSH (1976c)
		0.14-0.83 (0.12-0.69)	0.47 (0.39)	0.47 (0.39)	Area	11	BI, CA	NIOSH (1976c)
	Iron foundry, core machine operators	<0.02-22.0 (0.02-18.3)	–	0.52 (0.43)	Personal	14	–	NIOSH (1979b)
		0.08-0.40 (0.07-0.33)	0.19 (0.16)	–	Personal	3	BI, CA	NIOSH (1973b)
	Moulding	0.04-0.16 (0.03-0.13)	0.11 (0.09)	–	Personal	6	BI, CO	NIOSH (1977a)
		0.08-0.94 (0.07-0.78)	0.25 (0.21)	–	Area	6	BI, CO	NIOSH (1977a)
Rubber hose production		ND-0.05 (ND-0.04)	0.05 (0.04)	–	Personal	10	BI, CO	NIOSH (1977b)
Asphalt shingle production	Producers	0.04-0.08 (0.03-0.07)	0.06(0.05)	0.06 (0.05)	Area	2	BI, CO	NIOSH (1978b)
Fibreglass insulation	Installers	0.008-0.04 (0.007-0.033)	0.028 (0.023) (TWA)	0.023 (0.019)	Personal	13	–	NIOSH (1980a)

Appendix 1. Cont.

Industry	Job or work area	Exposure levels mg/m^3 (ppm)			Area or personal monitoring	No. of observations	Method[b]	Reference
		Range	Mean	Median				
Urea-Formaldehyde foam insulation dealing and installation	Suburban shopping centre insulated with UF foam	0.08-2.4 (0.07-2)	–	–	–	–	IC	Herrick *et al.* (1983)
		0.96-1.92 (0.8-1.6)	1.26 (1.05)	–	Area	36	BI, CA	NIOSH (1979b)
		0.36-3.72 (0.3-3.1)	1.73 (1.44)	–	Area	30	CT, IC	NIOSH (1979b)
		<0-6.36 (<0-5.3)	1.87 (1.56)	–	Area	16	DT	NIOSH (1979b)
Fertilizer manufacturing		0.24-2.28 (0.2-1.9)	1.08 (0.9)	–	Area, Personal	11	–	NIOSH (1979b)
Mushroom farming		<0.61-12+ (<0.51-10+)	3.22 (2.68)	–	Area	12	DT	NIOSH (1980b)
		ND-3.24 (ND-2.7)	–	–	Personal	3	CT, IC	NIOSH (1980b)
		ND-5.92 (ND-4.93)	–	–	Area	3	CT, IC	NIOSH (1980b)
Funeral homes	Embalmers	0.1-6.3 (0.09-5.26)	0.89 (0.74)	–	Area	187	CA	Kerfoot and Mooney (1975)
		0.24-4.79 (0.20-3.99)	1.32 (1.1)	0.65 (0.54)	Area, Personal	8	CT	NIOSH (1980c)
		1.56-4.72 (1.30-3.99)	3.24 (2.7)	2.99 (2.49)	Area, Personal	5	CT	NIOSH (1980c)
Pathology	Autopsy room	0.07-9.5 (0.06-7.9)	5.76 (4.8)	–	Area	10	BI, CA	Covino (1979)
		2.64-9.5 (2.20-7.9)	5.22 (4.35)	–	Area	6	–	NIOSH (1979b)
Biology teaching	Laboratory	3.30-17.76 (2.75-14.8)	9.96 (8.3)	–	Area	8	BI, CA	US EPA (1981)
Hospital	Laboratory	2.64-2.76 (2.2-2.3)	2.70 (2.25)	–	Personal	2	BI	Blade (1983)
		2.28 (1.9)	–	–	Personal	1	CT	Blade (1983)
		2.64 (2.2)	2.40 (2)	–	Area	2	CT	Blade (1983)

Appendix 1. Cont.

Industry	Job or work area	Exposure levels mg/m^3 (ppm)			Area or personal monitoring	No. of observations	Method[b]	Reference
		Range	Mean	Median				
Goverment	Laboratory	2.88 (2.4)	–	–	Personal	1	CT	Blade (1983)
		0.96 (0.8)	–	–	Area	1	CT	Blade (1983)
Hospital	Dialysis unit	ND-1.08 (ND-0.90)	0.50 (0.42)	–	Area	9	CT	Blade (1983)
		0.32-0.76 (0.27-0.63)	0.49 (0.41)	–	Personal	5	CT	Blade (1983)
		0.05-0.60 (0.04-0.05)	0.61 (0.51)	–	Area		CEA	Blade (1983)
Animal dissection	Laboratory	<0.46-1.25 (<0.38-1.04)	–	–	Personal	15	CA	Blade (1983)
		0.06-0.48 (0.05-0.40)	0.18 (0.15)	–	Area	6	BI	Blade (1983)
		0.13-0.22 (0.11-0.29)	0.22(0.18)	–	Area	3	CEA	Blade (1983)
Garment manufacturing (3 plants)		<0.17-0.76 (<0.14-0.63)	0.28-0.40 (0.23-0.33)	–	Personal	40	CT	Blade (1983)
		<0.04-0.48 (<0.03-0.40)	0.23-0.31 (0.19-0.26)	–	Area	43	CT	Blade (1983)
		0.04-0.48 (0.03-0.40)	0.25 (0.21)	–	Area	43	BI	Blade (1983)
		0.06-1.34 (0.05-1.2)	0.55 (0.46)	–	Area	42	CEA	Blade (1983)
Chemical manufacturing		0.05-1.92 (0.04-1.6)	0.66 (0.55)	–	Personal	3	BI	Blade (1983)
		0.04-0.52 (0.03-0.43)	0.20 (0.17)	–	Area	5	BI	Blade (1983)
Glass manufacturing		0.50 (0.42)	0.50 (0.42)	–	Personal	1	CT	Blade (1983)
		0.54-0.80 (0.45-0.64)	0.65 (0.54)	–	Area	2	CT	Blade (1983)
Hospital work		0.44-0.88 (0.37-0.73)	0.66 (0.56)	–	Area	2	BI	Blade (1983)

Appendix 1. Cont.

Industry	Job or work area	Exposure levels mg/m^3 (ppm)			Area or Personal monitoring	No. of observations	Method[b]	Reference
		Range	Mean	Median				
Paraformaldehyde packaging		<0.30-1.02 (<0.25-0.85)	0.66 (0.55)	–	Personal	10	CA	Blade (1983)
		0.34-4.08 (0.28-3.4)	1.40 (1.17)	–	Area	8	CEA	Blade (1983)
Office work (3 locations)		0.02-0.14 (0.02-0.12)	0.07 (0.06)	–	Area	39	BI	Blade (1983)
		<0.05 (<0.04)	<0.05 (<0.04)	–	Area	9	CT	Blade (1983)
Autopsy rooms	Resident	–	1.90[c] (1.58)	–	Personal	10	CA	Makar *et al*. (1975)
	Pathologist	–	1.50[c] (1.24)	–	Personal	9	CA	Makar *et al*. (1975)
	Technician	–	0.68[c] (0.57)	–	Personal	2	CA	Makar *et al*. (1975)
	Assistants	0.16-16.28 (0.13-13.57)	0.86 (0.72)	–	Area	23	CA	Makar *et al*. (1975)

a. From: Consensus Workshop of Formaldehyde (1984).
b. Abbrevations for analytical procedure: BI, bisulphite impingers; CA, chromotropic acid procedure; CEA, CEA instruments Model 555; CO, colorimetric analysis; CT, charcoal tubes; DT, Draeger tubes; GC, gas cromatography; IC, ion cromatography; SP, spectrophotometric procedure; SS, solid sorbents.
c. Average.

Appendix 2. Genetic and related effects of formaldehyde (58).

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

Appendix 2. Cont

Test system		Result[a]		Dose[b]	Reference
		Without exogenous metabolic system	With exogenous metabolic system	(LED/HID)	
SAO	*Salmonella typhimurium* TA100, reverse mutation	(+)	+	3	Schmid *et al.* (1986)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	10	Marnett *et al.* (1985)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	10	Le Curieux *et al.* (1993)
SA2	*Salmonella typhimurium* TA102, reverse mutation	+	0	35.7	O´Donovan & Mee (1993)
SA4	*Salmonella typhimurium* TA104, reverse mutation	+	0	10	Marnett *et al.* (1985)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	–	–	30	Gocke *et al.* (1981)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	–	–	50	Haworth *et al.* (1983)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	0	–[c]	9	Pool *et al.* (1984)
SA5	*Salmonella typhimurium* TA1535, reverse mutation	–	0	143	O´Donovan & Mee (1993)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	–	–	30	Gocke *et al.* (1981)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	–	–	50	Haworth *et al.* (1983)
SA7	*Salmonella typhimurium* TA1537, reverse mutation	–	0	143	O´Donovan & Mee (1993)
SA8	*Salmonella typhimurium* TA1538, reverse mutation	–	–	30	Gocke *et al.* (1981)
SA8	*Salmonella typhimurium* TA1538, reverse mutation	–	0	143	O´Donovan & Mee (1993)
SA9	*Salmonella typhimurium* TA98, reverse mutation	+	0	5	Marnett *et al.* (1985)
SA9	*Salmonella typhimurium* TA98, reverse mutation	–	–	30	Gocke *et al.* (1981)
SA9	*Salmonella typhimurium* TA98, reverse mutation	–	(+)	16.6	Haworth *et al.* (1983)
SA9	*Salmonella typhimurium* TA98, reverse mutation	–	(+)	30 (toxic above 100 µg/plate)	Connor *et al.* (1983)
SA9	*Salmonella typhimurium* TA98, reverse mutation	0	(+)[c]	3	Pool *et al.* (1984)
SA9	*Salmonella typhimurium* TA98, reverse mutation	+	0	17.9	O´Donovan & Mee (1993)
SAS	*Salmonella typhimurium* TA97, reverse mutation	+	0	5	Marnett *et al.* (1985)
SAS	*Salmonella typhimurium* (other miscellaneous strains), reverse mutation	–	–	100 (toxic at 250 µg/ml)	Connor *et al.* (1983)

Appendix 2. Cont.

Test system		Result[a]		Dose[b]	Reference
		Without exogenous metabolic system	With exogenous metabolic system	(LED/HID)	
ECW	*Escherichia coli* WP2 *uvrA*, reverse mutation	+	0	15	Takahashi *et al.* (1985)
ECW	*Escherichia coli* WP2 *uvrA*(pKM101), reverse mutation	+	0	17.9	O´Donovan & Mee (1993)
EC2	*Escherichia coli* WP2, reverse mutation	+	0	1.2	Nishioka (1973)
EC2	*Escherichia coli* WP2(pKM101), reverse mutation	+	0	35.7	O´Donovan & Mee (1993)
EC2	*Escherichia coli* WP2, reverse mutation	+	0	60	Takahashi *et al.* (1985)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	900	Panfilova *et al.* (1966)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	80	Demerec *et al.* (1951)
ECR	*Escherichia coli* (other miscellaneous strains), reverse mutation	+	0	30	Takahashi *et al.* (1985)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	990	Magana-Schwencke (1978)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	500	Magana-Schwencke & Ekert (1978)
SSB	*Saccharomyces* species, DNA strand breaks, cross-links or related damage	+	0	500	Magana-Schwencke & Moustacchi (1980)
SCH	*Saccharomyces cerevisiae*, gene conversion	+	0	540	Chanet *et al.* (1975)
SCH	*Saccharomyces cerevisiae*, homozygosis by mitotic recombination or gene conversion	+	0	18.5	Zimmermann & Mohr (1992)
NCF	*Neurospora crassa*, forward mutation	+	0	100	de Serres *et al.* (1988)
NCR	*Neurospora crassa*, reverse mutation	–	0	732	Dickey *et al.* (1949)
NCR	*Neurospora crassa*, reverse mutation	+	0	37 500	Jensen *et al.* (1952)
NCR	*Neurospora crassa*, reverse mutation	–	0	300	Kölmark & Westergaard (1953)
PLM	Plants (other), mutation	+	0	0.0	Auerbach *et al.* (1977)

Appendix 2. Cont.

Test system		Result[a]		Dose[b]	Reference
		Without exogenous metabolic system	With exogenous metabolic system	(LED/HID)	
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		2700	Ratnayake (1970)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		420	Alderson (1967)
DMG	*Drosophila melanogaster*, genetic crossing over or recombination	+		1260	Sobels & van Steenis (1957)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		420	Alderson (1967)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	(+)		1940	Ratnayake (1968)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		2380	Ratnayake (1970)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1940	Auerbach & Moser (1953)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1080	Kaplan (1948)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		420	Khan (1967)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		270	Stumm-Tegethoff (1969)
DMX	*Drosophila melanogaster*, sex-linked recessive lethal mutations	+		1260	Sobels & van Steenis (1957)
DMH	*Drosophila melanogaster*, heritable translocation	+		2700	Ratnayake (1970)
DMH	*Drosophila melanogaster*, heritable translocation	+		420	Khan (1967)
DML	*Drosophila melanogaster*, dominant lethal mutation	+		1940	Auerbach & Moser (1953)
DML	*Drosophila melanogaster*, dominant lethal mutation	+		1400	Srám (1970)
*	*Caenorhabditis elegans*, recessive lethal mutation	+		700	Johnsen & Baillie (1988)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	6	Ross & Shipley (1980)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	3.75	Ross *et al*. (1981)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	22.5	Demkowicz-Dobrzanski & Castonguay (1992)
DIA	DNA strand breaks, cross-links or related damage, animal cells *in vitro*	+	0	7.5	O´Connor & Fox (1987)
G9H	Gene mutation, Chinese hamster V79 cells, *hprt* locus	+	0	9	Grafström *et al*. (1993)

Appendix 2. Cont.

Test system		Result[a]		Dose[b]	Reference
		Without exogenous metabolic system	With exogenous metabolic system	(LED/HID)	
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	0	1	Obe & Beek (1979)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	3.2	Natarajan *et al.* (1983)
SIC	Sister chromatid exchange, Chinese hamster cells *in vitro*	+	+	1.8	Basler *et al.* (1985)
CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*	+	+	6.5	Natarajan *et al.* (1983)
CIC	Chromosomal aberrations, Chinese hamster cells *in vitro*	+	0	18	Ishidate *et al.* (1981)
TCM	Cell transformation, C3H10T1/2 mouse cells	+[d]	0	0.5	Ragan & Boreiko (1981)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	24	Fornace *et al.* (1982)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	1.5	Craft *et al.* (1987)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Grafström *et al.* (1986)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Snyder & van Houten (1986)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Saladino *et al.* (1985)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	3	Grafström *et al.* (1984)
DIH	DNA strand breaks, cross-links or related damage, human cells *in vitro*	+	0	12	Grafström (1990)
UIH	Unscheduled DNA synthesis, human bronchial epithelial cells *in vitro*	–	0	3 (>0.1 mmol/L was lethal)	Doolittle *et al.* (1985)
GIH	Gene mutation, human cells *in vitro*	+	0	3	Grafström *et al.* (1985)
GIH	Gene mutation, human cells *in vitro*	+	0	3.9	Goldmacher & Thilly (1983)
GIH	Gene mutation, human cells *in vitro*	+	0	0.9	Craft *et al.* (1987)
GIH	Gene mutation, human cells *in vitro*	+	0	4.5	Crosby *et al.* (1988)
GIH	Gene mutation, human cells *in vitro*	+	0	4.5	Liber *et al.* (1989)
GIH	Gene mutation, human cells *in vitro*	+	0	3	Grafström (1990)
RIH	DNA repair exclusive of unscheduled DNA synthesis, human cells *in vitro*	+	0	6	Grafström *et al.* (1984)

Appendix 2. Cont.

Test system		Result[a]		Dose[b]	Reference
		Without exogenous metabolic system	With exogenous metabolic system	(LED/HID)	
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	0	5.4	Obe & Beek (1979)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	0	5	Kreiger & Garry (1983)
SHL	Sister chromatid exchange, human lymphocytes *in vitro*	+	+	3.75	Schmid *et al.* (1986)
CHF	Chromosomal aberrations, human fibroblasts *in vitro*	+	0	60	Levy *et al.* (1983)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	0	10	Miretskaya & Shvartsman (1982)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	+	7.5	Schmid *et al.* (1986)
CHL	Chromosomal aberrations, human lymphocytes *in vitro*	+	0	3.75	Dresp & Bauchinger (1988)
DVA	DNA-protein cross-links, rat cells *in vivo*	+		1.5 inhal. 6h	Casanova-Schmitz *et al.* (1984b)
DVA	DNA-protein cross-links, rat cells *in vivo*	(+)		1.5 inhal. 6h	Larn *et al.* (1985)
DVA	DNA-protein cross-links, rat cells *in vivo*	+		0.25 inhal. 3h	Heck *et al.* (1986)
DVA	DNA-protein cross-links, rat cells *in vivo*	+		0.25 inhal. 3h	Casanova & Heck (1987)
DVA	DNA-protein cross-links, rat cells *in vivo*	+		0.08 inhal. 6h	Casanova *et al.* (1989)
DVA	DNA-protein cross-links, rhesus monkey nasal turbinate cells *in vivo*	+		0.05 inhal. 6h	Heck *et al.* (1989)
DVA	DNA-protein cross-links, rhesus monkey nasal turbinate cells *in vivo*	+		0.05 inhal. 6h	Casanova *et al.* (1991)
*	DNA-protein cross-links, rat tracheal implant cells *in vivo*	+		2 mg/ml instil.	Cosma *et al.* (1988)
SVA	Sister chromatid exchange, rat cells *in vivo*	–		3.9 inhal. 6h/d x 5	Kligerman *et al.* (1984)
*	Micronucleus induction, newt (*Pleurodeles waltl*) *in vivo*	–		5 µg/ml, 12 d	Siboulet *et al.* (1984)
MVM	Micronucleus induction, mouse *in vivo*	–		25 ip x 1	Natarajan *et al.* (1983)
MVM	Micronucleus induction, mouse *in vivo*	–		30 ip x 1	Gocke *et al.* (1981)
MVR	Micronucleus induction, rat (gastrointestinal tract) *in vivo*	+		200 po x 1	Migliore *et al.* (1989)
CBA	Chromosomal aberrations, mouse bone-marrow cells *in vivo*	–		25 ip x 1	Natarajan *et al.* (1983)
CBA	Chromosomal aberrations, rat bone-marrow cells *in vivo*	+		0.07 inhal. 4h/d, 4 month	Kitaeva *et al.* (1990)

Appendix 2. Cont.

Test system		Result[a]		Dose[b]	Reference
		Without exogenous metabolic system	With exogenous metabolic system	(LED/HID)	
CBA	Chromosomal aberrations, rat bone-marrow cells *in vivo*	–		3.9 inhal. 6h/d x 5, 8 weeks	Dallas *et al*. (1992)
CLA	Chromosomal aberrations, rat leukocytes *in vivo*	–		3.9 inhal. 6h/d x 5	Kligerman *et al*. (1984)
CCC	Chromosomal aberrations, mouse spermatocytes treated *in vivo,* spermatocytes observed	–		50 ip x 1	Fontignie-Houbrechts (1981)
CVA	Chromosomal aberrations, mouse spleen cells *in vivo*	–		25 ip x 1	Natarajan *et al*. (1983)
CVA	Chromosomal aberrations, rat pulmonary lavage cells *in vivo*	+		3.9 inhal. 6h/d x 5	Dallas et al. (1992)
GVA	Gene mutation, rat cells *in vivo* (*p53* point mutations in nasal carcinomas)	+		3.9 inhal. 6h/d, 2 years	Recio *et al*. (1992)
MST	Mouse spot test	–		3.9 inhal. 6h/d x 3	Jensen & Cohr (1983) (Abstract)
DLM	Dominant lethal mutations, mouse	(+)		50 ip x 1	Fontignie-Houbrechts (1981)
DLM	Dominant lethal mutations, mouse	–		20 ip x 1	Epstein *et al*. (1972)
DLR	Dominant lethal mutations, rat	(+)		0.2 inhal. 4h/d x 120	Kitaeva *et al*. (1990)
DLM	Dominant lethal mutations, mouse	–		20 ip x 1	Epstein & Shafner (1968)
MVH	Micronucleus formation, human lymphocytes *in vivo*	(+)		0.06[e] inhal. 8h-TWA	Suruda *et al*. (1993)
MVH	Micronucleus formation, human cells (buccal epithelium) *in vivo*	+		0.06[e] inhal. 8h-TWA	Suruda *et al*. (1993)
MVH	Micronucleus formation, human cells (nasal epithelium) *in vivo*	–		0.06[e] inhal. 8h-TWA	Suruda *et al*. (1993)
MVH	Micronucleus formation, human cells (nasal epithelium) *in vivo*	+		0.06[e] inhal. 8h-TWA	Ballarin *et al*. (1992)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	–		0.5 inhal. 8h-TWA	Thomson et al. (1984)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	–		0.5 inhal. 8h-TWA	Bauchinger & Schmid (1985)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	+		0.2 inhal. 8h-TWA	Yager *et al*. (1986)
SLH	Sister chromatid exchange, human lymphocytes *in vivo*	–		0.06[e] inhal. 8h-TWA	Suruda *et al*. (1993)

Appendix 2. Cont.

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

*. Not on profile.
a. +, positive; (+), weak positive; –, negative; 0, not tested.
b. In vitro tests, μg/ml; in vivo tests, mg/kg bw.
c. Tested with S9 without co-factors.
d. Positive only in presence f 12-*O*-tetradecanoylphorbol 13-acetate (TPA).
e. Based on a mean 8-h TWA of 0.33 ppm (range, 0.1-0.96 ppm); peak exposures up to 6.6 ppm.

Appendix 2. Summary table of genetic and related effects of formaldehyde.

Non-mammalian systems				Mammalian systems			
				In vitro		*In vivo*	
Pro-karyotes	Lower eukaryotes	Plants	Insects	Animal cells	Human cells	Animal	Human
D G	D R G A	D G C	R G C A	D G S M C A T I	D G S M C A T I	D G S M C DL A	D S M C A
+ +	+ + +	+[1]	+ + +	+ +[1] + + +[1]	+ + + +	+ –[1] +[1] ? ?	? ?[1] ?

A, aneuploidy; C, chromosomal abberations; D, DNA damage; DL, dominant lethal mutation; G, gene mutation; I, inhibition of intercellular communication; M, micronuclei; R, mitotic recombination and gene conversion; S, sister chromatid exchange; T, cell transformation.

In completing the table, the following symbols indicate the concensus of the Working group with regard to the results for each end-point:

+ considered to be positive for the specific end-point and level of biological complexity.
+[1] considered to be positive, but only one valid study was available to the Working group.
– considered to be negative.
–[1] considered to be negative, but only one valid study was available to the Working group.
? considered to be equivocal or inconclusive (e.g. there were contradictory results from different laboratories; there were confounding exposures; the results were equivocal.

Appendix 3

Classification of substances with respect to carcinogenicity

Guideline 93/21/EEG of the European Community

4.2 Criteria for classification, indication of danger, choice of risk phrases

4.2.1 Carcinogenic substances

For the purpose of classification and labelling, and having regard to the current state of knowledge, such substances are divided into three categories:

Category 1:

Substances known to be carcinogenic to man.

There is sufficient evidence to establish a causal association between human exposure to a substance and the development of cancer.

Category 2:

Substances which should be regarded as if they are carcinogenic to man.

There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of:

- appropriate long-term animal studies
- other relevant information.

Category 3:

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment.

There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

4.2.1.1 The following symbols and specific risk phrases apply:

Category 1 and 2:

T; R45 May cause cancer

However for substances and preparations which present a carcinogenic risk only when inhaled, for example, as dust, vapour or fumes, (other routes of exposure e.g. by swallowing or in contact with skin do not present any carcinogenic risk), the following symbol and specific risk phrase should be used:

T; R49 May cause cancer by inhalation

Category 3:

Xn; R40 Possible risk of irreversible effects

4.2.1.2 Comments regarding the categorisation of carcinogenic substances

The placing of a substance into Category 1 is done on the basis of epidemiological data; placing into Categories 2 and 3 is based primarily on animal experiments.

For classification as a Category 2 carcinogen either positive results in two animal species should be available or clear positive evidence in one species; together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises 2 sub-categories:

a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classification in Category 2. Additional experiments would not be expected to yield further relevant information with respect to classification.
b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between Categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in Category 3, even though tumours have been induced in animals:

- carcinogenic effects only at very high levels exceeding the “maximal tolerated dose”. The maximal tolerated dose is characterised by toxic effects which, although not yet reducing life span, go along with physical changes such as about 10% retardation in weight gain;
- appearance of tumours, especially at high dose levels, only in particular organs of certain species is known to be susceptible to a high spontaneous tumour formation;
- appearance of tumours, only at the site of application, in very sensitive test systems (e.g. intraperitoneal or subcutaneous application of certain locally active compounds); if the particular target is not relevant to man;
- lack of genotoxicity in short-term tests *in vivo* and *in vitro*;
- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation;
- existence of a species - specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between Category 3 and no classification arguments are relevant which exclude a concern for man:

- a substance should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man;
- if the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories;
- particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence.