SCOEL/SUM/125
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Recommendation from the Scientific Committee on

Occupational Exposure Limits

for Formaldehyde

8 hour TWA:	0.2 ppm
STEL (15 mins):	0.4 ppm
Additional classification:	skin sensitiser

Substance Identity and Properties:

Formaldehyde CH_2O

Classification: Carc. Cat. 3; R40 Limited evidence of a carcinogenic effect.
T; R23/24/25 Toxic by inhalation, in contact with skin and if swallowed.
C; R34 Causes burns.
R43 May cause sensitization by skin contact.

Synonyms: methanal, oxomethane, oxymethylene, methylene oxide, methyl aldehyde

Chemical Name	formaldehyde
CAS Number:	50-00-0
Molecular Weight:	30.03
Melting point:	-92°C
Boiling point:	-21°C
Conversion factor:	1 ppm ≈ 1.23 mg/m^3

Occurrence and Use:

Formaldehyde is a colourless gas with a pungent odour (Reuss et al. 1988). Its widest use is in the production of resins with urea, phenol and melamine and, to a small extent, their derivatives. Based on its chemical reactivity, formaldehyde is also used for preservation and disinfection, as well as an antimicrobial agent (preservative) in cosmetic products.

Formaldehyde is a ubiquitous compound in the environment, and it is an important endogenous chemical that occurs in most life forms, including humans (IARC 1995).

Health Significance:

As a result of its reactivity in target tissues with direct contact with the substance, formaldehyde causes local irritation, acute and chronic toxicity and has genotoxic and cytotoxic properties (DFG 2000, DECOS 2003, Nordic Expert Group 2003).

Studies with volunteers yielded threshold concentrations for odour perception of less than 0.5 ppm, for eye irritation of 0.5 to l ppm and for nose and throat irritation of l ppm; eye irritation was observed in some cases also at lower concentrations. In workers exposed long-term to formaldehyde at the workplace, lesions were observed in the nasal mucosa even at average exposure concentrations below 1 ppm (DFG 2000). The experimental no-effect-level of sensory irritation in BALB/c mice has been determined to be 0.3 ppm (Damgård Nielsen et al. 1999).

Formaldehyde causes sensitisation of the skin and to a lesser extent bronchial asthma (Lemière et al. 1995).

Toxicokinetics and mechanisms of formaldehyde inactivation

Several mechanisms are involved in the inactivation of formaldehyde. The inhaled hydrophilic gas dissolves first of all in the layer of mucus covering the nasal epithelium; reactions with components of the mucus (Bogdanffy *et al.* 1987) and mechanical clearance of the mucus represent the first barrier. From a certain exposure concentration mucociliary clearance is impaired. In inhalation studies with rats exposed to 15 ppm, the mucociliary function in the frontal nasal region was inhibited and marked mucostasis was observed. After 6 ppm only certain areas were affected. After 2 ppm minimal changes in the mucus flow rate were observed, whilst 0.5 ppm had no effect (Morgan *et al.* 1986). With sufficiently high exposure concentrations, a concentration gradient of free formaldehyde was established within the layers of the nasal epithelium. Under these circumstances, in the fully differentiated cells near the surface, the actual concentration is higher than in the lower-lying proliferating stem cells. In the rostral third of the respiratory epithelium, however, the epithelium consists of only two cell layers with few basal cells (Hermann 1997). In the epithelial cells there are several ways inactivation can take place. Direct reactions with protein and RNA in the cytosol probably remove a large amount of free formaldehyde (Casanova-Schmitz *et al.* 1984a). The molecule may enter the C_1 pool of cell metabolism, and there is effective GSH-dependent oxidation by formaldehyde dehydrogenase (Heck and Casanova-Schmitz 1984, Heck and Casanova 2004).

The concentration of endogenous formaldehyde in human blood is about 2-3 mg/l; similar concentrations are found in monkeys and in rats. Exposure of humans, monkeys or rats to formaldehyde by inhalation has not been found to alter the concentration of formaldehyde in the blood. The average level of formate in the urine of people not occupationally exposed to formaldehyde is 12.5 mg/l and varies considerably both within and between individuals. No

significant changes of urinary formate were detected after exposure to 0.4 ppm formaldehyde for up to 3 weeks in humans (IARC 2005).

Acute toxicity

Studies of the sensory irritation caused by formaldehyde in mice and rats showed the mouse to be markedly more sensitive (Barrow *et al.* 1983, 1986, Chang *et al.* 1981, 1984). The concentration, which after short-term exposure leads to a reduction in the respiration rate to 50 % (RD_{50}) in mice, was found to be between 3 and 5 ppm (Chang *et al.* 1981, Schaper 1993). A clear no-effect level for nasal irritation in mice was found to be at 0.3 ppm (Damgård Nielsen et al. 1999). In rats, RD_{50} values between 10 and 30 ppm have been reported (Cassee 1995, Cassee *et al.* 1996a, Chang *et al.* 1981, 1984, Schaper 1993).

Subacute, subchronic and chronic toxicity

Studies of the subchronic and chronic toxicity of inhaled formaldehyde have been documented by DFG (2000) and jointly by DECOS (2003) and the Nordic Expert Group (2003). In all animal experiments, the most noticeable toxic effects of formaldehyde were observed in the upper respiratory tract; these effects have been investigated in numerous studies.

In rats exposed to formaldehyde concentrations of 10 ppm, daily for 6 hours on 5 days a week, rhinitis, hyperplasia and squamous metaplasia of the respiratory epithelium of the nasal mucosa were described in all studies. In rats exposed to 1.0 ppm for 2 years no histopathological changes were observed (no observed adverse effect level, NOAEL; Woutersen *et al.* 1989). From concentrations of 2 ppm, rhinitis, epithelial dysplasia and even papillomatous adenomas and squamous metaplasia of the respiratory epithelium of the nose were found, from 6 ppm squamous cell carcinomas (Kerns *et al.* 1983, Swenberg *et al.* 1980). At this concentration also the cell proliferation rate in the nasal mucosa was increased transiently, and from 10 ppm increased permanently (Monticello *et al.* 1996).

Uninterrupted exposure of rats for 8 hours/day ("continuous") was compared with 8 exposures for 30 minutes followed by a 30-minute phase without exposure ("intermittent") in two 13-week studies with the same total dose. Effects were seen only after intermittent exposure to formaldehyde concentrations of 4 ppm, but not after continuous exposure to 2 ppm. The authors concluded that the toxicity in the nose depends on the concentration and not on the total dose (Wilmer *et a,*. 1989). In mice exposed to formaldehyde concentrations of 2.0, 5.6 or 14.3 ppm for 2 years (6 hours/day, 5 days/week), rhinitis and epithelial hyperplasia was observed, from 5.6 ppm dysplasia, metaplasia and atrophy. Squamous cell carcinomas were observed only after concentrations of 14.3 ppm and above (Kerns *et al.* 1983).

In hamsters exposed to formaldehyde concentrations of 10 ppm (5 hours/day, 5 days per week) for life, survival was reduced and the incidence of hyperplasia and metaplasia (4/88, 5 %) was slightly increased, but not that of tumours (Dalbey 1982).

In cynomolgus monkeys exposed almost continuously to formaldehyde concentrations of 0.2, l or 3 ppm for 26 weeks, metaplasia and hyperplasia were observed in 1/6 and 6/6 animals of the 1 and 2 ppm groups, respectively. In the animals exposed to concentrations of 0.2 ppm, no histopathological changes were found (Rusch *et al.* 1983a, 1983b).

Reduced body weight gains were reported in rats exposed to formaldehyde concentrations from 10 ppm for 6 hours a day in a 13-week inhalation study (Woutersen *et al.* 1987) and in those exposed to concentrations from 5.6 ppm in a 2-year inhalation study (Kerns *et al.* 1983, Swenberg *et al.* 1980). In mice, reduced body weight gains were found in a 13-week inhalation study only at concentrations from 20 ppm. Other systemic effects were not observed in these studies. Only in a 26-week inhalation study with continuous exposure (22 hours a day, 7 days a week) were reduced absolute and relative liver weights observed from concentrations as low as 3 ppm (in addition to reduced body weight gain and lesions in the nasal region) (Rusch *et al.* 1983a, 1983b).

Single and repeated exposures in humans

Studies with the controlled exposure of volunteers must be distinguished from epidemiological studies of persons exposed at the workplace or under certain environmental conditions. The most reliable data are obtained in controlled studies with volunteers. Studies of persons exposed at the workplace are less suitable for making quantitative statements, mainly because of uncertain levels of exposure. The available studies have been documented by a panel of independent experts convened by the Industrial Health Foundation (IHF; Paustenbach *et al*. 1997). The data were indicative of a relatively wide individual susceptibility to irritation from formaldehyde. Data available for eye irritation from a total of 17 studies have been compiled and evaluated. A concentration-effect curve (Paustenbach *et al.* 1997) was constructed that shows that at concentrations between 0.5 and l ppm, exposure for up to 6 hours can produce eye irritation in 5% to 25% of the exposed persons. It was concluded by the group from the available data that with maximum concentrations at the workplace of 0.3 ppm for 8 hours “almost all the workers” are protected against eye irritation. Significant increases in eye irritation are reported, however, only at concentrations of at least l ppm, which is the reason that this concentration is often regarded as a ceiling value.

Very recently, the question of a threshold for chemosensory irritation was experimentally addressed by Lang et al. (2008). This study was made available to SCOEL by FORMACARE. Twenty-one volunteers (11 m, 10 f) were examined over a 10 weeks period using a repetitive design. Each subject was exposed to 10 exposure conditions on 10 consecutive working days, each for 4 h. During 4 of the 10 sessions, ethyl acetate (12-16 ppm) was used as a masking agent for formaldehyde exposure. Measurements were related to conjunctival redness, blinking frequency, nasal flow and resistance, pulmonary function and reaction times. Subjective assessments included discomfort, and the influence of personality factors on subjective scoring was also evaluated. Blinking frequency and conjunctival redness, ranging from slight to moderate, were significantly increased by short-term peak exposures of 1.0 ppm that occurred at a baseline exposure of 0.5 ppm formaldehyde. Results of subjective ratings indicated eye and olfactory symptoms at concentrations as low as 0.3 ppm. Nasal irritation was reported at concentrations of 0.5 ppm plus peaks of 1.0 ppm, as well as at levels of 0.3 ppm and 0.5 ppm with co-exposure to ethyl acetate. The ethyl acetate exposure was also perceived as irritating. No significant treatment effects were noted regarding nasal flow and resistance, pulmonary function and reaction times. When negative affectivity was introduced as a covariate, the level of 0.3 ppm was no longer an effect level, but 0.5 ppm with peaks of 1.0 ppm was. The authors concluded that eye irritation was the most sensitive parameter recorded, and that the no-observed-adverse-effect levels for subjective and objective eye irritation were 0.3 and 0.5 ppm, respectively.

Carcinogenic effects in experimental animals

In a 2-year inhalation study with F344 rats, squamous cell carcinomas of the nose were observed. Exposure was to formaldehyde concentrations of 0, 2.0, 5.6 and 14.3 ppm, for 6 hours/day on 5 days/week. All the animals exposed to formaldehyde developed rhinitis, epithelial dysplasia and metaplasia in the nasal cavity. After 18 months, 15/40 animals of the high exposure group had developed hyperplasia. In all the groups exposed to formaldehyde, metaplasia preceded dysplasia. If the exposure was interrupted for longer than 3 months, the rhinitis and metaplasia began to regress. After 24 months, squamous cell carcinomas were found in the nasal cavities only in the middle dose group (0.9 %) and in the high dose group (44 %). In the high dose group, undifferentiated carcinomas and sarcomas were also found. Also the number of polypoid adenomas was slightly increased in the male animals. The total tumour incidence in the high dose group was 48.7 % (Kerns *et al.* 1983, Swenberg *et al.* 1980). The formation of nasal tumours in the rat after high level exposure to formaldehyde (> 6 ppm) has been confirmed in other studies (Feron *et al.* 1988, Monticello *et al.* 1996, Woutersen *et al.* 1989).

In another long-term study over 28 months, F344 rats were exposed to formaldehyde concentrations of 0, 0.3, 2.0 and 15 ppm for 6 hours/day, 5 days/week. Although keratinizing squamous cell carcinomas were found only in the high dose group (in 13 of 32 animals), the incidence of epithelial hyperplasia and metaplasia of the nasal respiratory mucosa was significantly increased in all exposed groups. As inflammatory infiltration of the nasal mucosa, erosion and oedema were described in both the controls and the exposed animals, the possibility cannot be excluded that the hyperplasia and metaplasia were caused by the interaction of formaldehyde and inflammatory damage to the nasal mucosa (Kamata *et al.* 1997). Therefore, this study cannot be included in the present assessment.

In a 2-year inhalation study with B6C3F1 mice exposed to formaldehyde concentrations of 0, 2.0, 5.6 or 14.3 ppm for 6 hours/day on 5 days/week, squamous cell carcinomas of the nasal cavity were found in only 2/240 animals (0.8 %) of the high dose group. Epithelial metaplasia and dysplasia of the respiratory epithelium were, however, also observed (Kerns *et al.* 1983).
In hamsters exposed to concentrations of 10 or 30 ppm, no tumours were found (Dalbey 1982, IARC 1995, WHO 1989) and the incidence of non-neoplastic changes of the nasal epithelium was low.

Formaldehyde was administered in the drinking water for 2 years to Wistar rats in doses of 0, 10, 50 or 300 mg/kg body weight and day (Tobe *et al.* 1989) and 0, 1.2, 15 or 82 mg/kg body weight and day for male animals and 0, 1.8, 21 or 109 mg/kg body weight and day for female animals (Til *et al.* 1989). No changes were produced with doses up to 10 mg/kg body weight and day, and 15 and 21 mg/kg body weight and day, respectively. In almost all animals given doses from 50 mg/kg body weight, and 82 and 109 mg/kg body weight, histopathological changes in the forestomach (hyperplasia, keratinisation) and inflammation and ulcers of the glandular stomach were found. In addition, at doses of 82 and 109 mg/kg body weight per day, food and liquid consumption, and body weight gains were reduced. There was no increase in the incidence of tumours (Tobe *et al.* 1989, Til *et al.* 1989). Til and associates note, however, that some of the histopathological changes they classified as hyperplasia could have been classified as papillomas by other pathologists. In the study of Til *et al.* (1989), also renal changes (increased relative kidney weights, necrosis), and changes in the composition of the urine were observed in the female animals of the high dose group; the authors attribute this to the reduced drinking-water consumption.

In another drinking-water study, formaldehyde was administered to 7-week-old male and female Sprague-Dawley rats for 104 weeks in concentrations of 0, 10, 50, 100, 500, 1000 or 1500 mg/l drinking-water. In addition, 25-week-old male and pregnant female animals, and later their offspring were given formaldehyde in concentrations of 0 or 2500 mg/l. Reduced body weights were found only in the animals (offspring) exposed from the embryonal phase. In the animals of the groups exposed to formaldehyde concentrations of 50 mg/l and above and the animals of the 2500 mg/l group, the incidence of leukaemia (lymphoblastic leukaemia, lymphosarcomas) was increased in a dose-dependent manner (controls 3.5%, 10 mg/l: 3.0%, 50 mg/l: 9%, 500 mg/l: 12%, 1000 mg/l: 13%, 1500 mg/l: 18%, 2500 mg/l: 11.1 %). Data for the statistical significance of the findings or for the historical controls were not given by the authors (Soffritti *et al.* 1989). Despite criticism of this study, IARC (1995) regarded these data as being dose-dependent and significantly different from the data for the controls. Benign and malignant gastrointestinal tumours, which according to Sofritti *et al.* are very rare in this strain of rat (all incidences < 0. l%), were increased in particular in the animals of the following groups: 1000 mg/l (l%: leiomyosarcomas), 1500 mg/l (2%: adenomas) and 2500 mg/l (parent animals: 2.8%: papillomas and acanthomas, 2.8%: adenocarcinomas; offspring: 1.4%: adenomas, 1.4%: squamous cell carcinomas, 1.4%: adenocarcinomas, 2.7%: leiomyosarcomas) (Soffritti *et al.* 1989). The validity of this study has been questioned as a result of its conduct and the methods used (Feron *et al.* 1990).

Soffritti et al. (1989, 2002) reported about a 104 week study in male and female Sprague-Dawley rats exposed to 10, 50, 100, 500, 1000, 1500 and 2500 mg/l formaldehyde in drinking water. Animals were kept until spontaneous death. An increase of malignant tumours at various sites was noted, in particular of gastro-intestinal tumours and leukaemias. The study is difficult to evaluate because it was not conducted according to GLP standards and documentation has not been sufficient.

Human epidemiology

Over 25 cohort studies concerning professionals or industrial workers have examined the association between formaldehyde and cancer. Some have been conducted on workers exposed to formaldehyde in the chemical, garment, fibreglass, iron, woodworking, plastics and paper, pulp and plywood industries. Others are studies of professional groups (mainly health professionals, embalmers and funeral directors). Case–control studies have also been used to examine the association of formaldehyde with various cancers and, for rarer tumours such as sinonasal and nasopharyngeal cancer, they have the potential to provide greater statistical power than can normally be achieved in cohort studies. Against this advantage, however, must be set the difficulties in assessing retrospectively exposure to formaldehyde in community-based studies.

The carcinogenicity of formaldehyde has recently been re-evaluated by IARC (2006). In particular, three major cohort studies previously evaluated (IARC 1982, 1995), and since then updated for follow-up and for exposure assessment, were considered.

NCI cohort and leukaemias and lymphohematopoietic cancers

A cohort studied by the U.S. National Cancer Institute (NCI) consisted of 25,619 workers (865 708 person-years) employed before January 1, 1966, at one of 10 U.S. industrial plants and followed through December 31, 1994. Among the cohort, there were 178 deaths from

lymphohematopoietic malignancies. Relative risks for leukemia (69 deaths), particularly for myeloid leukaemia (30 deaths), increased with formaldehyde exposure. Compared with workers exposed to low peak levels of formaldehyde (0.1-1.9 ppm), relative risks for myeloid leukemia were 2.43 (95% CI = 0.81 to 7.25) and 3.46 (95% CI = 1.27 to 9.43) for workers exposed to peak levels of 2.0-3.9 ppm and > or = 4.0 ppm, respectively (P(trend) =.009). Compared with workers exposed to low levels of average exposure intensity of formaldehyde (0.1-0.4 ppm), workers exposed to 0.5-0.9 ppm and > or = 1.0 ppm average intensity had relative risks of 1.15 (95% CI = 0.41 to 3.23) and 2.49 (95% CI = 1.03 to 6.03), respectively (P(trend) =.088). The relative risk for leukemia was not associated with cumulative exposure but was weakly associated with duration of exposure (Hauptmann et al. 2003).

Marsh and Youk (2004) re-analysed the data from the updated NCI cohort (Hauptmann *et al*., 2003) and reproduced the results presented by Hauptmann *et al*. (2003). Three additional analyses were performed. Exposure category-specific SMRs, based on mortality rates for the general US population, increased with increasing peak and average intensity of exposure for all leukaemias combined and for myeloid leukaemia. Findings were similar when regional mortality rates were used. The use of alternative cut-points for categories of average intensity of exposure in order to achieve similar numbers of deaths from the combined group of all leukaemias in each exposed category resulted in similar relative risk estimates to those previously observed by Hauptmann *et al*. (2003). Analyses of duration of time worked in the highest peak category did not generally indicate higher risks among those who had experienced high peaks for a longer time.

<u>NCI cohort and nasopharyngeal cancers</u>

A second publication focussed on solid cancers observed in the same cohort. In this extended follow-up of formaldehyde-exposed workers, the authors evaluated mortality from solid cancers (1,921 deaths) among 25,619 workers (865,708 person-years) employed in 10 US formaldehyde-producing or -using facilities through 1994. Exposure assessment included quantitative estimates of formaldehyde exposure. Standardized mortality ratios and relative risks were calculated. Compared with that for the US population, mortality from solid cancers was significantly lower than expected among subjects exposed and non-exposed to formaldehyde (standardized mortality ratios = 0.91 and 0.78, respectively). Relative risks for nasopharyngeal cancer (nine deaths) increased with average exposure intensity, cumulative exposure, highest peak exposure, and duration of exposure to formaldehyde (p-trend = 0.066, 0.025, <0.001, and 0.147, respectively). Formaldehyde exposure did not appear to be associated with lung (744 deaths), pancreas (93 deaths), or brain (62 deaths) cancer. Although relative risks for prostate cancer (145 deaths) were elevated for some measures of formaldehyde exposure, the trend was inconsistent. Regarding solid cancers, some evidence was found in this cohort of formaldehyde-industry workers of an exposure-response relation with mortality from nasopharyngeal cancer (based on small numbers) but not for cancers of the pancreas, brain, lung, or prostate (Hauptmann et al. 2004).

In 2002, Marsh et al. published a follow-up of their independent analysis conducted at one of the 10 plants included in the NCI cohort, the Wallingford plant or Plant 1, together with a case-control analysis (Marsh et al. 2002). They concluded that the pattern of findings suggested that the large, persistent NPC excess observed among the Wallingford workers was

not associated with formaldehyde exposure, and could reflect other (non) occupational risk factors.

A re-analysis of the updated NCI cohort, concerning the mortality risks from nasopharyngeal cancer, was later presented by Marsh and Youk (2005). They pointed out that the statistically significant exposure-response relation for this malignancy in the NCI study was driven entirely by a large excess of this tumour in "Plant 1" for the highest peak exposure category (4+ ppm). An independent and larger re-analysis of Plant 1 found that this excess was not associated with formaldehyde exposure. The authors concluded that the re-analysis provided little evidence to support the suggestion of a causal association between formaldehyde exposure and mortality from nasopharyngeal cancer.

Marsh et al. (2007) conducted two additional re-analyses of the NCI cohort data which confirmed their previous conclusions (Marsh et al. 2002) that the elevated NPC risks in plant 1 were more likely due to factors external to the workplace. An additional analysis suggests that the increased risk of NPC might be associated with previous employment in the metal industry (Marsh et al. 2007).

The second major study considered by IARC was also from the United States (NIOSH). To evaluate the mortality experience of 11,039 workers exposed to formaldehyde for three months or more in three garment plants. The mean time weighted average formaldehyde exposure at the plants in the early 1980s was 0.15 ppm but past exposures may have been substantially higher. Vital status was updated through 1998, and life table analyses were conducted. Mortality from all causes (2206 deaths, standardised mortality ratio (SMR) 0.92, 95% CI 0.88 to 0.96) and all cancers (SMR 0.89, 95% CI 0.82 to 0.97) was less than expected based on US mortality rates. A non-significant increase in mortality from myeloid leukaemia (15 deaths, SMR 1.44, 95% CI 0.80 to 2.37) was observed. Mortality from myeloid leukaemia was greatest among workers first exposed in the earliest years when exposures were presumably higher, among workers with 10 or more years of exposure, and among workers with 20 or more years since first exposure. No nasal or nasopharyngeal cancers were observed. Mortality from trachea, bronchus, and lung cancer (147 deaths, SMR 0.98, 95% CI 0.82 to 1.15) was not increased. Mortality from leukaemia was increased almost twofold among workers with both 10 or more years of exposure and 20 years or more since first exposure (15 deaths, SMR 1.92, 95% CI 1.08 to 3.17). Mortality from myeloid leukaemia among this group of workers appeared also significantly increased (8 deaths, SMR 2.55, 95% CI 1.10 to 5.03). It was concluded that the results supported a possible relation between formaldehyde exposure and myeloid leukaemia mortality. Limitations of the study include limited power to detect an excess for rare cancers such as nasal and nasopharyngeal cancers and lack of individual exposure estimates (Pinkerton et al. 2004).

The third major study considered by IARC had been conducted in the U.K. This study extended by 11 years the follow-up of an existing cohort of 14,014 men employed after 1937 at six British factories where formaldehyde was produced or used. Subjects had been identified from employment records, and their jobs had been classified for potential exposure to formaldehyde. Standardized mortality ratios (SMRs) were derived using the person-years method and were compared with the expected numbers of deaths for the national population. During follow-up through December 31, 2000, 5185 deaths were recorded, including two from sino-nasal cancer (2.3 expected) and one from nasopharyngeal cancer (2.0 expected). Relative to the national population, mortality from lung cancer was increased among those who worked with formaldehyde, particularly in men in the highest of four estimated exposure

categories (>2 ppm) (SMR = 1.58, 95% confidence interval = 1.40 to 1.78), and the increase persisted after adjustment for local geographic variations in mortality (SMR = 1.28, 95% confidence interval = 1.13 to 1.44). However, there was a statistically non-significant decrease in the risk of death from lung cancer with duration of high exposure (P(trend) =.18), and this risk showed no trend with time since first high exposure (P(trend) =.99) (Coggon et al. 2003).

The IARC Working Group concluded that there was sufficient evidence in humans that formaldehyde causes nasopharyngeal cancer, on the grounds that there was a statistically significant excess of deaths from nasopharyngeal cancer in the largest and most informative cohort study of industrial workers (Hauptmann et al 2004), with statistically significant exposure-response relationships for peak and cumulative exposure. These conclusions might, however, need to be re-interpreted in light of the recent studies conducted by Marsh and colleagues (Marsh et al. 2002; Marsh and Youk, 2005; Marsh and Youk 2007, Marsh et al. 2007). An excess of deaths from nasopharyngeal cancer was also observed in a proportionate mortality analysis of the largest US cohort of embalmers (Hayes et al 1990), and an excess of cases of nasopharyngeal cancer was observed in a Danish study of proportionate cancer incidence among workers at companies that manufactured or used formaldehyde (Hansen and Olsen 1995). Although other cohort studies reported fewer cases of nasopharyngeal cancer than expected (Walrath and Fraumeni 1983, Coggon et al. 2003, Pinkerton et al. 2004), the Working Group noted that the deficits were small and the studies had low power to detect an effect on nasopharyngeal cancer. Of seven case-control studies of nasopharyngeal cancer (Olsen et al. 1984, Vaughan et al. 1986a, Vaughan et al. 1986b, Roush et al. 1987, West et al. 1993, Armstrong et al. 2000, Vaughan et al. 2000, Hildesheim et al. 2001), five found elevations of risk for exposure to formaldehyde.

It was mentioned that leukaemia mortality, primarily myeloid-type, was increased in six of seven cohorts of embalmers, funeral-parlour workers, pathologists, and anatomists. These findings had previously been discounted by IARC because an increased incidence of leukaemia had not been seen in industrial workers. The recent updates, however, reported a greater incidence of leukaemia in two cohorts of US industrial workers and US garment workers, but not in a third cohort of United Kingdom chemical workers. A recent meta-analysis found that, overall, the relative risk for leukaemia was increased and did not vary significantly among studies (Collins and Lineker 2004). The Working Group concluded that there was “strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde”.

Several case-control studies had associated exposure to formaldehyde with sinonasal adenocarcinoma and squamous-cell carcinoma. However, confounding from wood dust exposure occurred in these studies, and no excess of sinonasal cancer was reported in the updated cohort studies. The IARC Working Group concluded that there was limited evidence in humans that formaldehyde causes sinonasal cancer (IARC 2005).

Genotoxicity

Genotoxic and mutagenic effects of formaldehyde were found in various *in vitro* test systems. As a reactive compound, formaldehyde reacts with nucleic acids and proteins. DNA adducts, DNA-protein crosslinks, strand breaks and the induction of repair were detected *in vitro.* Formaldehyde also produced back mutation and forward mutation in bacteria. High concentrations of formaldehyde (4 mM) produced insertions, deletions and point mutations in GC base pairs in the gpt gene of *Escherichia coli* (Crosby *et al.* 1988). Gene mutations were detected also in lymphoblasts treated with formaldehyde (Liber *et al.* 1989). Most of the mutations were AT —> CG transversions at specific sites. Tests with V79 cells from the Chinese hamster, on the other hand, showed that although cytotoxicity parallels sister chromatid exchange (SCE) and micronucleus (MN) formation results from the formation of DNA-protein crosslinks, no gene mutation occurred (Merk and Speit 1998). Chromosomal aberrations (CA) (Natarajan *et al.* 1983) and SCE (Schmidt *et al.* 1986) were reported. Thus the mutagenic effects of formaldehyde are well-documented from *in vitro* studies.

Results of *in vivo* studies are more difficult to evaluate. Of particular importance is the question whether cytogenetic effects can only occur as the result of local exposure or also as the result of the systemic availability of formaldehyde. In the rat, chromatid breaks are described in cells from lung lavage after repetitive inhalation exposures to 15 ppm, but not at lower levels of exposure (Dallas *et al.* 1992) MN in the gastrointestinal epithelium were reported after gavage of formaldehyde (Migliore *et al.* 1989).

The incidence of MN was increased in cells of the nasal mucosa in non-smoking workers of a plywood factory relative to that in controls. In this case, however, there was mixed exposure to formaldehyde and wood dust (Ballarin *et al.* 1992) and the effects did not correlate with the dose.

In cultures of lymphocytes isolated from blood samples from persons exposed to formaldehyde concentrations of up to 9.8-11.0 mg/m^3 (8-8.9 ppm) in pathological laboratories, the incidences of chromosomal aberrations and SCE were not increased (Thomson *et al.* 1984). In workers from a paper factory, the incidence of CA was increased, but not that of SCE (Bauchinger and Schmid 1985). A slight increase in SCE was observed in the lymphocytes of students of an anatomy course compared to the values before the beginning of the course in which they were exposed to average formaldehyde concentrations of 1.2 ppm (Yager *et al.* 1986). In all three studies the number of cases was very small and the effects slight.

In vivo, DNA-protein crosslinks were detected in the epithelium of sections of the trachea (Cosma *et al.* 1988b) and in the nasal epithelium of rats exposed to formaldehyde (Casanova and Heck 1987, Casanova *et al.* 1989, 1994, Casanova-Schmitz and Heck 1983, Casanova-Schmitz *et al.* 1984a, Heck and Casanova 1995, Lam *et al.* 1985). In monkeys, the levels of DNA-protein crosslinks were highest in the mucosa of the middle turbinates; lower concentrations were produced in the anterior lateral wall/septum and nasopharynx. Very low concentrations were found in the larynx, trachea and *carina tracheae* and in the proximal portions of the major bronchi (Casanova *et al.* 1991). The incidences of DNA-protein crosslinks varied widely in the various regions of the nasal cavity, and in the monkey in the deeper sections of the respiratory passages (Casanova *et al.* 1991, 1994). The distribution of DNA-protein crosslinks correlated with the probability of deposition of formaldehyde dictated by the anatomy and physiology of the various sections of the nose (Hubal et al. 1997).

In the nasal epithelium of F344 rats, DNA-protein crosslinks were still detected at formaldehyde concentrations as low as 0.3 ppm (Casanova *et al.* 1994). In the experiments with rhesus monkeys, they were also found at the lowest concentration of 0.7 ppm (Casanova *et al.* 1991). In the DNA of white blood cells from workers exposed to formaldehyde (average concentrations determined by personal air sampling: 2.8-3.1 ppm), the incidence of DNA-protein crosslinks was significantly higher than in control persons ($p = 0.03$). Assuming that formaldehyde reaches the blood cells via the lungs, it was suggested DNA-protein crosslinks be used as a biomarker for exposure to formaldehyde (Shaham *et al.* 1996). Because of methodological shortcomings, this study has, however, been heavily criticized (the blood samples were allowed to stand for 3 hours, the intra-individual and analytical variability were not determined, formaldehyde-induced DNA-protein crosslinks and DNA-protein crosslinks of other genesis were not differentiated; Casanova *et al.* 1996); however, a more recent study by the same group has been considered (IARC, 2005) to reveal increased DNA protein cross-links in workers exposed to formaldehyde (Shaham et al., 2003).

DNA-protein crosslinks induced by formaldehyde can be removed by repair. Half-lives of 2 to 4 hours have been reported. Accordingly, DNA-protein crosslinks can usually no longer be detected 24 hours after exposure (Cosma and Marchok 1988a,b, Craft *et al.* 1987, Grafström *et al.* 1983, 1984, Magana-Schwenke and Moustacchi 1980, Merk and Speit 1998). In sections of the tracheal epithelium of rats, the DNA-protein crosslinks had been almost completely removed within 48 to 72 hours after the treatment, depending on the concentration of the instilled aqueous formaldehyde solutions (1.7-66.7 mM) (Cosma *et al.* 1988a,b). This corresponds to a half-life of about 7 hours. Histological examination revealed hyperproliferation in the tracheal epithelium. The accumulation of DNA-protein crosslinks was investigated; because of the methods used, however, the results cannot be evaluated conclusively (Casanova *et al.* 1994).

Schmid and Speit (2007) studied the dose-response of genotoxicity of formaldehyde in human blood cultures *in vitro*. DNA-protein crosslinks were induced at formaldehyde concentrations starting from 25 µM. However, DNA-protein crosslinks induced by formaldehyde concentrations up to 100 µM were completely removed before the lymphocytes started to replicate. SCE were induced at concentrations higher than 100 µM, parallel to the induction of cytotoxicity, determined as reduction of the replication index. MN were not induced by formaldehyde concentrations up to 250 µM, the highest concentration that could be tested.

Using a physiologically based pharmacokinetic model, it was calculated that in man fewer DNA-protein crosslinks are formed in the nasal mucosa than in the rat or monkey (Casanova *et al.* 1988, 1991).

In a long-term inhalation study with rats published by Monticello *et al.* (1996), point mutations were found in the p53 gene in 5 of 11 nasal tumours. The tumours expressed only the mutated gene. The role of formaldehyde in causing these mutations is unclear (Recio *et al.* 1992): p53 mutations have been detected in man in tumours of various genesis. In rodents, however, they are rare (Wolf *et al.* 1995), although the finding of p53 mutations in rat nasal SCC and the high prevalence of p53 mutations among human nasal SCC indicates that a common molecular alteration is shared between rodent and human SCC (Recio, 1997). Often the mutations are produced secondarily during the promotion or progression phase. The heterogeneous spectrum of mutations in the nasal tumours of rats suggests, thus, an important contribution of cell proliferation at such high levels.

In brief, there is consistent evidence for the genotoxicity of formaldehyde in *in vitro* systems, laboratory animals and exposed humans. DNA-protein cross links have been reproducibly detected in the nasal mucosa of rats, monkeys and workers exposed to formaldehyde and provide a useful marker of genotoxicity. The biphasic behaviour of the dose-response curve for this genotoxic endpoint points to a steeper slope at 2-3 ppm in Fischer 344 rats; for rhesus monkeys the slope is less well defined. At concentrations above 6 ppm of formaldehyde, genotoxicity is greatly amplified by cell proliferation, resulting in a marked increase of malignant lesions in the nasal passages (IARC, 2005).

Toxic effects on germ cells

The sperm count, sperm morphology and the occurrence of fluorescent bodies were investigated in 11 employees who carried out autopsies and were exposed to average formaldehyde concentrations of 0.61 to 1.32 ppm. No significant differences from the controls were found (Ward ***et al.*** 1983, 1984). The exposure levels were, however, low and the number of persons investigated small.

The toxic effects of formaldehyde on germ cells have been demonstrated in numerous tests with *Drosophila* (Alderson 1965, Herkowitz 1953, 1959), in particular after administration with the diet, and were limited to effects on early spermatocytes of the larvae (see IARC 1982). Gaseous formaldehyde had no effect. In tests for mosaic mutations in *Drosophila* and in the Müller-5 test for recessive lethal mutations, formaldehyde yielded positive results (Szabad ***et al.*** 1983). In a comparative test with the unstable zeste-white assay in *Drosophila melanogaster,* formaldehyde produced somatic mutations, but no germ cell mutations (Rasmuson and Larsson 1992). *In vitro,* during the reaction of formaldehyde with adenosine, a hydroxymethyl adduct was produced. This kind of nucleoside modification is thought to have marked germ-cell-stage-specific mutagenic effects in male *Drosophila* larvae (Alderson 1985).

Few studies have been carried out with mammals. In a review of the dominant lethal test, formaldehyde is listed with substances for which premature death of the foetuses and pre-implantation losses were within the control range (Epstein ***et al.*** 1972). In mice (Q strain) given single intraperitoneal injections of a 35% formaldehyde solution (dose: 50 mg/kg body weight) no chromosomal changes were found in the metaphase I spermatocytes (Fontignie-Houbrechts 1981). In the dominant lethal test, the number of pre-implantation and post-implantation losses in the first week of mating was twice the control value (Fontignie-Houbrechts 1981). In albino rats, marked dose-dependent effects were observed in the dominant lethal test in mating weeks one to three after intraperitoneal administration of 0.125 to 0.5 mg/kg body weight (1/4 to 1/16 of the lethal dose) in the form of a 37% solution stabilized with 10% methanol. Also the fertility of the treated male rats decreased in a dose-dependent manner (Odeigah 1997). In another test the authors found an increase in the number of abnormal sperm.

Thus, positive results were obtained in i.p. studies. This route is likely to lead to direct exposure of germ cells, bypassing the systemic circulation. This is because substances injected into the abdominal cavity can reach the testes directly via the inguinal canal. The relevance for conditions of human inhalation exposure of such results must be questioned.

Formaldehyde can therefore be regarded as a potential germ cell mutagen in rodents, with mutagenic effects when it reaches the target organ and the target structures in sufficient amounts, as was demonstrated in the dominant lethal test with intraperitoneal injection of

high-percentage solutions. Exposure to exogenous formaldehyde at levels which do not significantly increase the endogenous bioavailability of the substance is not expected to produce mutagenic effects on the germ cells. Specifically, this relates to exposures below the recommended OEL of 0.2 ppm. This is supported by toxicokinetic studies by inhalation in several species (see section on Toxicokinetics).

This conclusion is in line with the assessment of the US Agency for Toxic Substances and Disease Registry (ATSDR 1999) that the results of studies in humans and experimental animals indicate that it is very unlikely that low level exposure to formaldehyde can cause developmental or reproductive damage.

Conclusions considering modes of action

Experimental findings: Experimentally, formaldehyde elicits local tumours in the upper respiratory tract. It appears plausible that the occurrence of tumours in the nasal mucosa of rats and mice is the result of chronic proliferative processes caused by the cytotoxic effects of the substance. Evaluation of the data for the carcinogenic effects confirms this assumption. The dose-response relationships for all the parameters investigated, such as damage to the nasal epithelium, cell proliferation, tumour incidence and also the formation of DNA-protein crosslinks, is very flat for low level exposures and becomes much steeper at higher levels of exposure. For all the parameters mentioned, with the exception of the formation of DNA-protein crosslinks, concentrations which did not produce effects were demonstrated in the respective studies. The possibility of the formation of DNA-protein crosslinks cannot be excluded even with low levels of exposure. The data suggest, however, that with concentrations that do not lead to cell proliferation, only few DNA-protein crosslinks are formed. Moreover, formaldehyde-induced DNA-protein crosslinks are rapidly repaired, as evidenced in a number of biological systems (see Genotoxicity section). In addition, the physiological proliferation rate in the respiratory epithelium is low, and as long as this is not increased (which requires exposure to concentrations of more than 2 ppm), the probability that DNA-protein crosslinks are transformed into mutations is low. In the low dose range, which does not lead to an increase in cell proliferation, it has therefore been considered that the observed experimental genotoxicity of formaldehyde plays no or at most a minor part in its carcinogenic potential so that no significant contribution to human cancer risk is expected (Bolt 1987, DFG 2000, Conolly et al. 2004). Such a conclusion is supported by dosimetry modellings (Kimbell et al. 2001a,b) and results of a numerical risk assessment which, for persons exposed to concentrations of 0.3 ppm at the workplace for 40 years, yielded a very low additional cancer risk for non-smokers of 1.3×10^{-8} and for smokers of 3.8×10^{-7} (CIIT 1999).

Epidemiological findings: The increased risk of nasopharyngeal carcinoma induced by formaldehyde in exposed workers, if any, could be based on similar mechanisms as the experimental inductions of nasal tumors in rats. On one hand, dosimetry modellings have indicated that human nasal flux patterns shifted distally as inspiratory flow rate increased (Kimbell et al. 2001b), on the other hand it appears important that the rat breathes only through the nose while humans, expecially upon physical work, show considerable mouth breathing in addition. As a further theory, a contribution of Epstein-Barr virus infections to nasopharyngeal carcinogenesis has been discussed. In essence, it may be concluded that the dose-response of human nasopharyngeal tumours elicited by formaldehyde must be non-linear at low doses, based on the modes of action established experimentally in rodents.

The possible induction of myeloid leukaemias by formaldehyde in humans is not so easy to explain, but there are indications that formaldehyde could induce this kind of malignancy. However, this would require that formaldehyde would act systemically and reach the bone marrow which is the target tissue. Such an action would not be possible within a range where the external dose does not change the physiological level of formaldehyde. No significant changes in formate excretion could be detected over a 3-week period of exposure to formaldehyde at a concentration in air of less than 0.4 ppm (Gottschling et al. 1984, IARC 2005). This indicates that the physiological homeostasis of endogenous formaldehyde is not challenged within this range of external exposure, and consequently, no systemic effects can be expected under such exposure conditions. These considerations are supported by exposure modellings based on data in different species (Heck and Casanova 2004).

Based on the "SCOEL Approach on OEL Recommendations for Carcinogens" (Bolt and Huici-Montagud 2008), SCOEL regards formaldehyde as a “genotoxic carcinogen, for which a practical threshold is supported”. Consequently, a health-based OEL is recommended.

Recommendation:

For the derivation of an OEL for formaldehyde, which takes the carcinogenic risk into account, the avoidance of cell proliferation is critical. The cause of cell proliferation is the irritant effect of formaldehyde on the upper respiratory tract. For this effect, however, the database is insufficient for the establishment of a clear NOAEL value. Nevertheless, the database is much better for the irritant effects of formaldehyde on the eye, a more sensitive parameter (DECOS 2003, Nordic Expert Group 2003). It is generally considered that avoidance of sensory irritation of the eye and the upper respiratory tract will provide a safety margin to avoid irritation-induced local cell proliferation. Different evaluations have been published concerning the NOAEL of eye irritation in humans.

On the basis of an evaluation of a total of 17 controlled studies with volunteers it was concluded by an independent expert panel convened in the USA by the Industrial Health Foundation (IHF) that with daily exposure for 8 hours to maximum formaldehyde concentrations of 0.3 ppm “practically all workers” are protected against eye irritation. Animal data were considered supportive of this conclusion. In consequence, a concentration of 0.3 ppm formaldehyde was regarded as a practical NOAEL and was proposed as an OEL (Paustenbach *et al.* 1997).

By contrast, the identical database for sensory irritation of formaldehyde, as compiled by Paustenbach *et al.* (1997), was viewed by the joint DECOS (2003) and Nordic Expert Group (2003) committees to reveal that “at lower exposure levels sensory irritation may still occur in a substantial percentage of exposed individuals”. The joint committees regarded 0.24 ppm (see below!) formaldehyde to be a LOAEL “at which sensory irritation may occur in a low but significant percentage of exposed workers”. At the same time, it was stated that the majority of short- and long-term animal inhalation studies reveal a NOAEL of 1-2 ppm, with slight histopathological changes of the nasal respiratory epithelium being observed at 0.3-2 ppm. On this basis, DECOS (2003) recommended a health-based OEL (TWA) of 0.12 ppm (0.15 mg/m^3), with a STEL of 0.42 ppm (0.5 mg/m^3).

This discrepancy in evaluations of an identical data set by the IHF *vs*. DECOS/Nordic Expert

groups is mainly influenced by interpretation of two studies from Scandinavia.

The first was a field study on formaldehyde-induced discomfort (Wilhelmsson and Holmström 1992) that was not included in the evaluation by the IHF group, but was considered as a "not well-documented study" by the joint DECOS/Nordic group, showing that "more than 50% of 66 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)". In a reference group, 25% gave such reportings (Wilhelmsson and Holmström 1992). However, the publication neither gives methodological details of the questionnaire used, nor was the way of exposure assessment specified.

The second was a controlled study in volunteers (Andersen and Mølhave 1983) in which 3 out of 16 subjects reported eye irritation at a formaldehyde concentration of 0.24 ppm (see above). This study has the fundamental weakness that no control group with sham exposure was included. Whereas the joint DECOS/Nordic Export groups took this as a hint to sensory irritation in substantial percentages of individuals at less than 0.3 ppm formaldehyde, the IHF group's argumentation was based on a concentration-response curve constructed from the entire body of data from the reported irritation studies. According to their evaluation irritation reportings may be obtained in 15-20% of non-exposed volunteers as well (Paustenbach et al. 1997). Recently, Arts et al. (2006) applied a benchmark approach to the study of Andersen and Mølhave (1983) and arrived at the conclusion that a concentration of 0.24 ppm formaldehyde, based on a 95% confidence interval and assuming a background response of 1/16, would be acceptable.

A very recent experimental study in human volunteers has been published by Lang et al. (2008), using subjective questionnaire ratings and objective methods (for details, see chapter "Single and Repeated Exposures in Humans). This study provides a solid basis for an assessment. Subjective eye and olfactory symptoms were noted at concentrations as low as 0.3 ppm. Nasal irritation was reported at 0.5 ppm plus peaks of 1.0 ppm formaldehyde, as well as at levels of 0.3 ppm and 0.5 ppm with co-exposure to 12-16 ppm ethyl acetate. When the personal trait of negative affectivity was used as a covariate, the level of 0.3 ppm was no longer seen as an effect level. The authors concluded that the NOAEL for objective and subjective eye irritation was at 0.5 ppm formaldehyde in the case of a constant exposure, and at 0.3 ppm with peaks of 0.6 ppm in case of short-term exposures.

In general, SCOEL considers that the onset of eye irritation is a very sensitive parameter that provides a safety margin to the onset of irritation-induced cytotoxicity and cell proliferation. Introduction of a safety margin is essential, and SCOEL considers formaldehyde to be a "genotoxic carcinogen, for which a practical threshold is supported" (see chapter "Conclusions Considering Modes of Action") provided that one can be confident that irritation is avoided.

Regarding the subjective symptoms of eye irritation, the very recent human volunteer study of Lang et al. (2008) has indicated an NOAEL of 0.3 ppm formaldehyde, if the personal trait of negative affectivity was treated as a co-variable.

According to the reasoning given above, the TWA-OEL of formaldehyde should be set at or below the NOAEL for sensory irritancy of the eye. In view of the limited number of persons that can be examined in a laboratory volunteer study (21 persons on the study of Lang et al. 2008), the exclusion of particularly sensitive persons with negative affectivity appears

problematic.

Therefore, SCOEL proposes an 8h-TWA of 0.2 ppm. This especially considers possible interindividual differences in susceptibility to irritation by formaldehyde, which may be expected based on the entire body of data. Short-term irritation may be prevented by a 15min-STEL of 0.4 ppm. This STEL is set below the threshold for objective eye irritation, as outlined by Lang et al. (2007).

At these levels, no systemic effect of formaldehyde is to be expected.

As a result of the exclusively local effects of formaldehyde, a "skin" notation is not required.

Formaldehyde is a well-known contact allergen to the skin. Against the background of a widespread use, respiratory sensitization has been reported only in single cases (DECOS 2003; Nordic Expert Group 2003).

At these levels of exposure, analytical difficulties are not expected.

References

Alderson T (1985) Formaldehyde-induced mutagenesis: a novel mechanism for its action. *Mutat Res 154:* 101-110

Andersen I, Mølhave L (1983) Controlled human studies with formaldehyde. In: Gibson JE, ed., Formaldehyde Toxicity, pp. 154-165. Washington: Hemisphere Publishing Corporation

Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC, Sani S (2000) Nasopharyngeal carcinoma in Malaysian Chinese: Occupational exposures to particles, formaldehyde and heat. Int J Epidemiol 29: 991–998.Alderson T (1965) Chemically induced delayed germinal mutation in *Drosophila. Nature 207:* 164-167

Arts JHE, Rennen MAJ, de Heer C (2006) Inhaled formaldehyde: evaluation of sensory irritation in relation to carcinogenicity. *Regulatory Toxicol Pharmacol 44:* 144-160

ATSDR (Agency for Toxic Substances and Disease Registry) (1999) Public Health Service, US Department of Health & Human Services: *Toxicological Profile for Formaldehyde,* 251-262

Ballarin C, Sarto F, Giacomelli L, Bartolucci GB, Clonfero E (1992) Micronucleated cells in nasal mucosa of formaldehyde-exposed workers. *Mutat Res 280:* 1-7

Barrow CS, Steinhagen WH, Chang JCF (1983) Formaldehyde sensory irritation. In: Gibson JE (Ed.) *Formaldehyde Toxicity,* Hemisphere Publishing Corp., Washington, New York, London, 16-25

Barrow CS, Buckley LA, James RA, Steinhagen WH, Chang JCF (1986) Sensory irritation: studies on correlation to pathology, structure-activity, tolerance development, and prediction of species differences to nasal injury. in: Barrow CS (Ed.) *Toxicology of the Nasal Passages,* Hemisphere Publishing Corp., Washington, New York, London, 101-120

Bauchinger M, Schmid E (1985) Cytogenetic effects in lymphocytes of formaldehyde workers of a paper factory. *Mutat Res 158:* 195-199

Bedford P, Fox BW (1981) The role of formaldehyde in methylene dimethanesulphonate-induced DNA cross-links and its relevance to cytotoxicity. *Chem-Biol Interact 38:* 119-126

Bender JR, Mullin L, Graepel GJ, Wilson WE (1983) Eye irritation response of humans to formaldehyde. *Am Ind. Hyg Assoc J 44:* 463-465

Benyajati C, Place AR, Sofer W (1983) Formaldehyde mutagenesis in *Drosophila.* Molecular analysis of ADH-negative mutants. *Mutat Res 111:*1-7

Bogdanffy MS, Morgan PH, Starr TB, Morgan KT (1987) Binding of formaldehyde to human and rat nasal mucus and bovine serum albumin. *Toxicol Lett 38:* 145-154

Boysen M, Zadig E, Digernes V, Abeier V, Reith A (1990) Nasal mucosa in workers exposed to formaldehyde: a pilot study. *Br J Ind. Med 47:* 116-121

Bolt HM (1987) Experimental toxicology of formaldehyde. *J Cancer Res Clin Oncol* 113: 305-309.
Bolt HM (2006) SCOEL approach on OEL recommendations for carcinogens. *On behalf of SCOEL presented at the Workshop "Setting OELsfor Carcinogens", European Commission, Luxemburg, Oct. 25, 2006*
Bolt HM, Huici-Montagud (2008) Strategy of the scientific committee on occupational exposure limits (SCOEL) in the derivation of occupational exposure limits for carcinogens and mutagens.
*Arch Toxicol 82(1):*61-4.
Casanova-Schmitz M, Heck H d'A (1983) Effects of formaldehyde exposure on the extractability of DNA from proteins in the rat nasal mucosa. *Toxicol Appl Pharmacol 70:* 121-132
Casanova M, Heck H d'A (1987) Further studies of the metabolic incorporation and covalent binding of inhaled [^{3}H]- and [^{14}C]-formaldehyde in Fischer 344 rats: effects of glutathione depletion. *Toxicol Appl Pharmacol 89:* 105-121
Casanova-Schmitz M, Starr TB, Heck H d'A (1984) Differentiation between metabolic incorporation and covalent binding in the labeling of macromolecules in the rat nasal mucosa and bone marrow by inhaled [^{14}C]- and [^{3}H]-formaldehyde. *Toxicol Appl Pharmacol 76:* 26-44
Casanova M, Heck H d'A, Everitt JI, Harrington WW, Popp *Jr* JA (1988) Formaldehyde concentrations in the blood of rhesus monkeys after inhalation exposure. *Food Chem Toxicol 26:* 715-716
Casanova M, Deyo DF, Heck H d'A (1989) Covalent binding of inhaled formaldehyde to DNA in the nasal mucosa of Fischer 344 rats: analysis of formaldehyde and DNA by high-performance liquid chromatography and provisional pharmacokinetic Interpretation. *Fundam Appl Toxicol 12:*397-417
Casanova M, Morgan KT, Steinhagen WH, Everitt JI, Popp JA, Heck H d'A (1991) Covalent binding of inhaled formaldehyde to DNA in the respiratory tract of rhesus monkeys: pharma-cokinetics, rat-to-monkey interspecies scaling, and extrapolation to man. *Fundam Appl Toxicol* 77: 409-428
Casanova M, Morgan KT, Gross EA, Moss OR, Heck H d'A (1994) DNA-protein cross-links and cell replication at specific sites in the nose of F344 rats exposed subchronically to formaldehyde. *Fundam Appl Toxicol 23:* 525-536
Casanova M, Heck H d'A, Janszen D (1996) Comments on "DNA-protein crosslinks, a biomarker of exposure to formaldehyde - *in vitro* and *in vivo* studies" by Shaham *et al. Carcinogenesis 17:* 2097-2101
Cassee FR (1995) *Upper Respiratory Tract Toxicity of Mixtures of Aldehydes.* Doctoral thesis, University of Utrecht, NL
Cassee FR, Arts JHE, Groten JP, Feron VJ (1996a) Sensory irritation to mixture of formaldehyde, acrolein, and acetaldehyde in rats. *Arch Toxicol 70:* 329-337
Cassee FR, Groten JP, Feron VJ (1996b) Changes in the nasal epithelium of rats exposed by inhalation to mixtures of formaldehyde, acetaldehyde and acrolein. *Fundam Appl Toxicol 29:* 208-218
Chang JCF, Steinhagen WH, Barrow CS (1981) Effects of single or repeated formaldehyde exposures on minute volume of B6C3F1 mice and F344 rats. *Toxicol Appl Pharmacol 61:* 451-459
Chang JCF, Gross EA, Swenberg JA, Barrows CS (1983) Nasal cavity deposition, histopathology and cell proliferation after single or repeated formaldehyde exposures in B6C3F1 mice and F344 rats. *Toxicol Appl Pharmacol 68:* 161-176
Chang JCF, Steinhagen WH, Barrow CS (1984) Sensory irritation tolerance in F344 rats exposed to chlorine or formaldehyde gas. *Toxicol Appl Pharmacol 76:* 319-327
CIIT (Chemical Industry Institute of Toxicology) (1999) *Formaldehyde: Hazard Characterization and Dose-Response Assessment for Carcinogenicity by the Route of Inhalation* (revised edition). CIIT, Research Triangle Park, NC, USA
Coggon D, Harris EC, Poole J, Palmer KT (2003) Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *J Natl Cancer Inst* 95: 1608-1615
Collins JJ, Lineker GA (2004) A review and meta-analysis of formaldehyde exposure and leukemia. *Regul Toxicol Pharmacol* 40: 81-91
Conaway CC, Whysner J, Vema LK, Williams GM (1996) Formaldehyde mechanistic data and risk assessment: endogenous protection from DNA adduct formation. *Pharmacol Ther 71:* 29-55
Conolly RB, Kimbell JS, Janszen D, Schlosser PM, Kalisak D, Preston J, Miller FJ (2004) Human respiratory tract cancer risks of inhaled formaldehyde: dose-response predictions derived from biologically-motivated computational modeling of a combined rodent and human dataset. *Toxicol Sci* 82: 279-96.
Cosma GN, Marchok AC (1988a) Benzo[a]pyrene- and formaldehyde-induced DNA damage and repair in rat tracheal epithelial cells. *Toxicology 51:* 309-320
Cosma GN, Wilhite AS, Marchok AC (1988b) The detection of DNA-protein cross-links in rat tracheal implants exposed *in vivo* to benzo(a)pyrene and formaldehyde. *Cancer Lett 42:* 13-21
Costa M (1991) DNA-protein complexes induced by chromate and other carcinogens. *Environ Health Perspect 92:* 45-52
Craft TR, Bermudez E, Skopek TR (1987) Formaldehyde mutagenesis and formation of DNA-protein crosslinks in human lymphoblasts *in vitro. Mutat Res 176:* 147-155

Crosby RM, Richardson KK, Craft TR, Benforado KB, Liber HL, Skopek TR (1988) Molecular analysis of formaldehyde-induced mutations in human lymphoblasts and *E. coli. Environ Mol Mutagen 12:* 155-166
Dalbey WE (1982) Formaldehyde and tumours in hamster respiratory tract. *Toxicology 24:* 9-14
Dallas CE, Scott MJ, Ward JB, Theiss JC (1992) Cytogenetic analysis of pulmonary lavage and bone marrow cells of rats after repeated formaldehyde exposure. *J Appl Toxicol 12:* 199-203
Damgård Nielsen A, Hougaard KS, Larsen ST, Hammer M, Wolkoff P, Clausen PA, Wilkins CK, Alarie Y (1999) Acute airway wffects of formaldehyde and ozone in BALB7c mice. *Hum Exp Toxicol* 18: 400-409
DECOS [Health Council of the Netherlands: Dutch Expert Committee on Occupational Standards] (2003) Formaldehyde. Health-based recommended occupational exposure limit. The Hague; Health Council of the Netherlands, publication no. 2003/02OSH.
DFG (2000) Formaldehyde, in: Occupational Toxicants, vol. 17, pp.163-201
ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) (1995) *Technical Report no. 65: Formaldehyde and Human Cancer Risk.* ISSN-0773-8072-65
Edling C, Ödkvist L, Hellquist H (1985) Formaldehyde and the nasal mucosa. *Br J Ind Med 42:* 570-571
Epstein SS, Arnold E, Andrea J, Bass W, Bishop Y (1972) Detection of chemical mutagens by the dominant lethal assay in the mouse. *Toxicol Appl Pharmacol 23:* 288-325
Feron VJ, Bruyntjes JP, Woutersen RA, Immel HR, Appelman LM (1988) Nasal tumours in rats after short-term exposure to a cytotoxic concentration of formaldehyde. *Cancer Lett 39:* 101-111
Feron VJ, Til HP, Woutersen RA (1990) Formaldehyde must be considered a multipotential experimental carcinogen. *Toxicol Ind Health 6:* 637-639
Fontignie-Houbrechts N (1981) Genetic effects of formaldehyde in the mouse. *Mutat Res 88:* 109-114
Fornace AJ, Lechner JF, Grafström RC, Harris CC (1982) DNA repair in human bronchial epithelial cells. *Carcinogenesis 3:* 1373-1377 Gorski P, Tarkowski M, Krakowiak A, Kiec-Swierczynska M (1992) Neutrophil chemiluminescence following exposure to formaldehyde in healthy subjects and in patients with contact dermatitis. *Allergol Immunopathol (Madr) 20:* 20-23
Gottschling LM, Beaulieu HJ, Melvin WW (1984) Monitoring of formic acid in urine of humans exposed to low levels of formaldehyde. *Am J Hyg Assoc J* 45: 19-23
Grafström RC, Fomace AJ, Autrup H, Lechner JF, Harris CC (1983) Formaldehyde damage to DNA and inhibition of DNA repair in human bronchial cells. *Science 220:* 216-218
Grafström RC, Fornace A, Harris CC (1984) Repair of DNA damage caused by formaldehyde in human cells. *Cancer Res 44:* 4323-4327
Hansen J, Olsen JH (1995) Formaldehyde and cancer morbidity among male employees in Denmark. Cancer Causes Control 6: 354–360
Hauptmann M, Lubin JH, Steward PA, Hayes RB, Blair A (2003) Mortality from lymphohematopoietic malignancies among workers in formaldehyde industries. *J Natl Cancer Inst* 95: 1615-1623
Hauptmann M, Lubin JH, Steward PA, Hayes RB, Blair A (2004) Mortality from solid cancers among workers in formaldehyde industries. *Am J Epidemiol* 159: 1117-1130
Hayes RB, Blair A, Stewart PA, Herrick RF, Mahar H (1990) Mortality of US embalmers and funeral directors. Am J Ind Med 18: 641–652
Heck H d'A, Casanova-Schmitz M (1984) Biochemical toxicology of formaldehyde. *Rev Biochem Toxicol 6:* 155-189
Heck H d'A, Casanova M (1995) Nasal dosimetry of formaldehyde: modeling site specificity and the effects of preexposure. in: Dugger EL, Schweiter C (Eds) *Nasal Toxicity and Dosimetry of Inhaled Xenobiotics: Implications for Human Health,* Taylor & Francis, Washington DC, USA, 159-175
Heck H d'A, Casanova M (1999a) Pharmacodynamics of formaldehyde: arrest of DNA replication by DNA protein crosslinks is the proximal cause of mutation. *Toxicologist 48:* 123 (Abstract)
Heck H d'A, Casanova M (1999b) Pharmacodynamics of formaldehyde: applications of a model for the arrest of DNA replication by DNA-protein cross links. *Toxicol Appl Pharmacol 160:* 86-100
Heck H d'A, Casanova M (2004) The implausibility of leucemia induction by formaldehyde: a critical review of the biological evidence on distant-site toxicity. *Regul Toxicol Pharmacol* 40: 92-106
Heck H d'A, White EL, Casanova-Schmitz M (1982) Determination of formaldehyde in biological tissues by gas chromatography/mass spectrometry. *Biomed Mass Spectrom 9:* 347-353
Herkowitz H (1953) Formaldehyde-induced mutation in mature spermatozoa and early develop-mental stages of *Drosophila melanogaster. Genetics 38:* 668-669
Herkowitz H (1959) The differential induction of lethal mutations by formalin in the two sexes of *Drosophila. Science 112:* 302-303
Hermann R (1997) *Karzinogenese der Nasenschleimhaut durch N-Nitrosodimethylamin - Inhalation bei der Ratte.* Inaugural-Dissertation, Univ. Heidelberg

Hildesheim A, Dosemeci M, Chan CC, Chen CJ, Cheng YJ, Hsu MM, Chen IH, Mittl BF, Sun B, Levine PH, Chen JY, Brinton LA, Yang CS (2001) Occupational exposure to wood, formaldehyde, and solvents and risk of nasopharyngeal carcinoma. Cancer Epidemiol Biomarkers Prev 10: 1145–1153.
Hubal EA, Schlosser PM, Conolly RB, Kimbell JS (1997) Comparison of inhaled formaldehyde dosimetry predictions with DNA-protein cross-link measurements in the rat nasal passages. *Toxicol Appl Pharmacol 143:* 47-55
IARC (International Agency for Research on Cancer) (1982) *Monographs on the Evaluation of the Carcinogenic Risk ofChemicals to Humans, Formaldehyde,* Vol 29, IARC, Lyon
IARC (International Agency for Research on Cancer) (1995) *Monographs on the Evaluation of Carcinogenic Risks to Humans, Wood Dust and Formaldehyde,* Vol 62, IARC, Lyon
IARC (International Agency for Research on Cancer) (2006) *Monographs on the Evaluation of Carcinogenic Risks to Humans, Formaldehyde, 2-Butoxyethanol and 1-tert-Butoxy-2-propanol,* Vol 88, IARC, Lyon
Kamata E, Nakadate M, Uchida O, Ogawa Y, Suzuki S, Kaneko T, Saito M, Kurokawa Y (1997) Results of a 28-month chronic inhalation toxicity study of formaldehyde in male Fisher-344 rats. *J Toxicol Sci 22:* 239-254
Kerns WD, Pavkov KL, Donofrio DJ, Gralla EJ, Swenberg JA (1983) Carcinogenicity of formaldehyde in rats and mice after long-term inhalation exposure. *Cancer Res 43:* 4382-4392
Kimbell JS, Subramaniam RP, Gross EA, Schlosser PM, Morgan KT (2001a) Dosimetry modeling of inhaled formaldehyde: comparisons of local flux predictions in the rat, monkey, and human nasal passages. *Toxicol Sci* 64: 100-110
Kimbell JS, Overton JH, Subramaniam RP, Schlosser PM, Morgan KT, Conolly RB, Miller FJ (2001) Dosimetry modeling of inhaled formaldehyde: binning nasal flux predictions for quantitative risk assessment. *Toxicol Sci 64*: 111-121
Lam CW, Casanova M, Heck H d'A (1985) Depletion of nasal mucosal glutathione by acrolein and enhancement of formaldehyde-induced DNA-protein cross-linking by simultaneous exposure to acrolein. *Arch Toxicol 58:* 67-71
Lang I, Bruckner T, Triebig G (2008) Formaldehyde and chemosensory irritation in humans: a controlled human exposure study. *Regulatory Toxicol Pharmacol 50*: 23-36
Lemière C, Desjardins A, Cloutier Y, Drolet D, Perrault G, Cartier A, Malo JL. (1995) Occupational asthma due to formaldehyde resin dust with and without reaction to formaldehyde gas. Eur Respir J. 8:861-5.
Liber HL, Benforado K, Crosby RM, Simpson D, Skopek TR (1989) Formaldehyde-induced and spontaneous alterations in human hprt DNA sequence and mRNA expression. *Mutat Res 226:* 31-37
Magana-Schwenke N, Moustacchi E (1980) Biochemical analysis of damage induced in yeast by formaldehyde. III. Repair of induced cross-links between DNA and proteins in the wild-type and in excision-deficient strains. *Mutat Res 70:* 29-35
Marsh GM, Youk AO (2004) Reevaluation of mortality risks from leukemia in the formaldehyde cohort study of the National Cancer Institute. *Regul Toxicol Pharmacol 40*: 113-124
Marsh GM, Youk AO (2005) Reevaluation of mortality risks from nasophaqryngeal cancer in the formaldehyde cohort study of the National Cancer Institute. *Regul Toxicol Pharmacol 42*: 275-383
Marsh GM, Youk AO, Buchanich JM, Cassidy LD, Lucas LJ, Esmen NA, Gathuru IM (2002) Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde.Toxicol Ind Health 18: 257-268
Marsh GM, Youk AO, and Morfeld P (2007) Mis-specified and non-robust mortality risk models for nasopharyngeal cancer in the National Cancer Institute formaldehyde worker cohort study. Regul.Toxicol.Pharmacol. 47:59-67
Marsh GM, Youk AO, Buchanich JM, Erdal S, Esmen NA. (2007) Work in the metal industry and nasopharyngeal cancer mortality among formaldehyde-exposed workers. Regul Toxicol Pharmacol. 48:308-19.
Merk O, Speit G (1998) Significance of formaldehyde-induced DNA-protein crosslinks for mutagenesis. *Environ Mol Mutagen 32:* 260-268
Migliore L, Ventura L, Barale, Loprieno N, Castellino S, Pulci R (1989) Micronuclei and nuclear anomalies induced in the gastro-intestinal epithelium of rats treated with formaldehyde. *Mutagenesis 4:* 327-334
Miller CA, Costa M (1989) Analysis of proteins cross-linked to DNA after treatment ofcells with formaldehyde, chromate, and cis-diamminedichloroplatinum (II). *Mol Toxicol 2:* 11-26
Miller CA, Costa M (1990) Immunodetection of DNA-protein crosslinks by slot blotting. *Mutat Res 234:* 97-106
Monticello TM, Swenberg JA, Gross EA, Leininger JR, Kimbell JS, Seilkop S, Starr TB, Gibson JE, Morgan KT (1996) Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. *Cancer Res 56:* 1012-1022
Morgan KT, Gross EA, Patterson DL (1986) Responses of the nasal mucociliary apparatus of F-344 rats to formaldehyde gas. *Toxicol Appl Pharmacol 82:* 1-13
Natarajan AT, Darroudi F, Bussman CJM, van Kasteren-van Leeuwen AC (1983) Evaluation of the mutagenicity of formaldehyde in mammalian cytogenetic assays *in vivo* and *in vitro*. *Mutat Res 122:* 355-360
Nordic Expert Group (2003) The Nordic Expert Group for Criteria Documentation of Health Risks from

Chemicals and The Dutch Expert Committee on Occupational Standards. 132. Formaldehyde, Ed.: Wibiwo A, *Arbete och Hälsa*, Vetenskaplig Skriftserie No. 11: 2003
Odeigah PGC (1997) Sperm head abnormalities and dominant lethal effects of formaldehyde in albino rats. *Mutat Res 289:* 141-148
Olin KL, Cherr GN, Rifkin E, Keen CL (1996) The effects of some redox-active metals and reac-tive aldehydes on DNA-protein cross-links *in vitro. Toxicology 110:* 1-8
Olsen JH, Jensen SP, Hink M, Faurbo K, Breum NO, Jensen OM (1984) Occupational formaldehyde exposure and increased nasal cancer risk in man. Int J Cancer 34: 639–644.
Paustenbach D, Alarie Y, Kulle T, Schachter N, Smith R, Swenberg J, Witschi H, Harowitz SB (1997) A recommended occupational exposure limit for formaldehyde based on Irritation. *J Toxicol Environ Health 50:* 217-263
Pinkerton LE, Hein MJ, Stayner LZ (2004) Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occup Environ Med* 61: 193-200
Rasmuson A, Larsson J (1992) Somatic and germline mutagenesis assayed by the unstable zeste-white test in *Drosophila melanogaster. Mutagenesis 7:* 219-223
Recio L, Sisk S, Pluta L, Bermudez E, Gross EA, Chen Z, Morgan K (1992) p53 Mutations in formaldehyde-induced nasal squamous cell carcinoma in rats. *Cancer Res 52:* 6113-6116
Reuss G, Disteldorf W, Grundler O, Holt A (1988) Formaldehyde. In: *Ullmann's Encyclopedia of Industrial Chemistry*, 5th Rev. Ed., Vol. A11, pp. 619-651. VCH Publishers, Weinheim
Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT, Blair A (1987) Nasopharyngeal cancer, sinonasal cancer, and occupations related to formaldehyde: A case–control study. J Natl Cancer Inst 79: 1221–1224.
Rusch GM, Bolte HF, Rinehart WE (1983a) A 26-week inhalation toxicity study with formaldehyde in the monkey, rat and hamster. in: Gibson JE (Ed.) *Formaldehyde Toxicity,* Hemisphere, New York, 98-110
Rusch GM, Clary JJ, Bolte HF, Rinehart WE (1983b) A 26-week inhalation toxicity study with formaldehyde in the monkey, rat, and hamster. *Toxicol Appl Pharmacol 68:* 329-343
Saladino AJ, Willey JC, Lechner JF, Grafström RC, LaVeck M, Harris CC (1985) Effects of formaldehyde, acetaldehyde, benzoyl peroxide, and hydrogen peroxide on cultured normal human bronchial epithelial cells. *Cancer Res 45:* 2522-2526
Schaper M (1993) Development of a database for sensory irritants and its use in establishing occupational exposure limits. *Am Ind Hyg Assoc J 54:* 488-544
Schmid E, Göggelmann W, Bauchinger M (1986) Formaldehyde-induced cytotoxic, genotoxic and mutagenic response in human lymphocytes and *Salmonella typhimurium. Mutagenesis 1:* 427-431
Schmid O, Speit G (2007) Genotoxic effects induced by formaldehyde in human blood and implications for the interpretation of biomonitoring results. *Mutagenesis* 22: 69-74.
Shaham J, Bomstein Y, Meltzer A, Kaufman Z, Palma E, Ribak J (1996) DNA-protein crosslinks, a biomarker of exposure to formaldehyde - *in vitro* and *in vivo* studies. *Carcinogenesis 17:* 121-125
Shaham J, Bomstein Y, Gurvich R, Rashkovsky M and Kaufman Z (2003) DNA-protein crosslinks and p53 protein expression in relation to occupational exposure to formaldehyde Occupational and Environmental Medicine 60: 403-409
Sofritti M, Maltoni C, Maffei F, Biagi R (1989) Formaldehyde: an experimental multipotential carcinogen. *Toxicol Ind Health 5:* 699-730
Soffritti M, Belpoggi F, Lambertin L, Lauriola M, Padovani M, Maltoni C (2002) Results of long-term experimental studies on the carcinogenicity of formaldehyde and acetaldehyde in rats. *Ann NY Acad Sci* 982: 87-105
Swenberg J, Kerns WD, Mitchell RI, Gralla EJ, Pavkow KL (1980) Induction of squamous cell carcinomas of the rat nasal cavity by Inhalation exposure to formaldehyde vapour. *Cancer Res 40:* 3398-3402
Szabad J, Soos I, Polgar G, Hejja G (1983) Testing the mutagenicity of malonaldehyde and formaldehyde by the *Drosophila* mosaic and the sex-linked recessive lethal test. *Mutat Res 113:* 117-133
Thomson EJ, Shackleton S, Harrington JM (1984) Chromosome aberration and sister-chromatid exchange frequencies in pathology staff exposed to formaldehyde. *Mutat Res 141:* 89-93
Til HP, Woutersen RA, Feron VJ, Hollanders VHM, Falke HE (1989) Two-year drinking-water study of formaldehyde in rats. *Food Chem Toxicol 27:* 77-87
Tobe M, Naito K, Kurokawa Y (1989) Chronic toxicity study on formaldehyde administered orally to rats. *Toxicology 56:* 79-86
Vaughan TL, Strader C, Davis S, Daling JR (1986a) Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I. Occupational exposures. Int J Cancer 38: 677–683.
Vaughan TL, Strader C, Davis S, Daling JR (1986b) Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II. Residential exposures. Int J Cancer 38: 685–688.
Vaughan TL, Stewart PA, Teschke K, Lynch CF, Swanson GM, Lyon JL, Berwick M (2000) Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. Occup Environ Med 57: 376–384.

Walrath J, Fraumeni JF Jr (1983) Mortality patterns among embalmers. Int J Cancer 31: 407–411.
Ward Jr BJ, Legator MS, Chang LW, Periera MA (1983) Evaluation of occupational exposure to formaldehyde using a battery of tests for genetic damage. *Environ Mutagen 5:* 433-434
Ward Jr JB, Hokanson JA, Smith ER, Chang LW, Pereira MA, Whorton Jr EB, Legator MS (1984) Sperm-count, morphology and fluorescent body frequency in autopsy service workers exposed to formaldehyde. *Mutat Res 130:*417-424
West S, Hildesheim A, Dosemeci M (1993) Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: Results from a case–control study. Int J Cancer 55: 722–727.
WHO (World Health Organisation) (1989) International Programme on Chemical Safety, *Environmental Health Criteria 89, Formaldehyde,* WHO, Geneva
Wilhelmsson B, Holmström M (1992) Possible mechanisms of formaldehyde-induced discomfort in the upper airways. *Scand J Work Environ Health* 18: 403-407
Wilmer JWGM, Woutersen RA, Appelman LM, Leeman WR, Feron VJ (1989) Subchronic (13-week) Inhalation toxicity study of formaldehyde in male rats: 8-h hour intermittent versus 8-hour continuous exposures. *Toxicol Lett 47:* 287-293
Wolf DC, Gross EA, Lyght O, Bermudez E, Recio L, Morgan KT (1995) Immunohistochemical localization of p53, PCNA, and TGF-α proteins in formaldehyde-induced rat nasal squamous cell carcinomas. *Toxicol Appl Pharmacol 132:* 27-35
Woutersen RA, Appelman LM, Wilmer JWGM, Falke HE, Feron VJ (1987) Subchronic (13-week) inhalation toxicity study of formaldehyde in rats. *J Appl Toxicol 7:* 43-49
Woutersen RA, van Gardener-Hoetmer A, Bruijntjes JP, Feron VJ (1989) Nasal tumours in rats after severe injury to the nasal mucosa and prolonged exposure to 10 ppm formaldehyde. *J Appl Toxicol 9:* 39-46
Yager JW, Cohn KL, Spear RC, Fisher JM, Morse L (1986) Sister-chromatid exchanges in lymphocytes of anatomy students exposed to formaldehyde-embalming solution. *Mutat Res 174:* 135-139
Zwart A, Woutersen RA, Wilmer JWGM, Spit BJ, Feron VJ (1988) Cytotoxic and adaptive effects in rat nasal epithelium after 3-day and 13-week exposure to low concentrations of formaldehyde vapour. *Toxicology 51:* 87-99

Criteria Documents used: Conolly et al. (2004), DECOS (2003), DFG (2000), ECETOC (1995), IARC (1995, 2005), Nordic Expert Group (2003), Paustenbach et al. (1997)