Formaldehyde

Major Uses and Sources of emissions
Sources of formaldehyde include; motor vehicle exhaust, manufacturing plants that produce or use formaldehyde or substances that contain formaldehyde (eg. glues), petroleum refineries, coking operations, incineration, wood-burning, tobacco smoke. Formaldehyde is also released from pressed wood products (chipboard, wood veneers) and carpets.

Critical health end point.
The end points chosen were the irritation of the eyes and the upper respiratory tract. It was considered that by protecting persons from the irritative effects of formaldehyde, then they would be protected from the more serious nasal cellular changes in humans and animals and potential carcinogenic effects that are seen to arise in animals with long periods of formaldehyde exposure.

Concise International Chemical Assessment Document (CICAD) No. 40 Formaldehyde WHO 2002.
Published under the joint sponsorship of the United Nations Environment Programme, the International Labour Organization, and the World Health Organization,

This document contains the most recent data assessed on formaldehyde and therefore is considered to replace the 1989 IPCS Environmental Health Criteria document 89 – Formaldehyde. This CICAD has been based on the Government of Canada: Environment Canada, Health and Welfare Canada,; Priority Substances List Assessment Report, Formaldehyde (2001)

Effects On Humans

Irritant effects
There are numerous reports that exposure to formaldehyde vapour causes direct irritation of the respiratory tract. However, precise thresholds have not been established for the irritant effects of inhaled formaldehyde.

In a number of clinical studies, generally mild to moderate sensory eye, nose, and throat irritation was experienced by volunteers exposed for short periods to levels of formaldehyde ranging from 0.25 to 3.0 ppm (0.30 to 3.6 mg/m^3) (Andersen & Mølhave, 1983; 1986; Kulle, 1993; Pazdrak et al., 1993).

Carcinogenicity
There are a large number of cohort and case–control studies of professionals, including pathologists and embalmers, and industrial workers. In addition, several authors have conducted meta-analyses of the available data. In most epidemiological studies, the potential association between exposure to formaldehyde and cancer of the respiratory tract has been examined.

In case–control studies, while some-times no increase was observed overall (Vaughan et al., 1986), significantly increased risks of nasopharyngeal cancer (up to 5.5-fold) were observed among workers with 10–25 years of exposure or in the highest exposure category in three out of four investigations (Vaughan et al., 1986; Roush et

al., 1987; West et al., 1993), although there were limitations associated with most of these studies.

In the only investigation in which the association between exposure to formaldehyde and adenocarcinoma of the nasal cavity was examined, there was a non-significant increase that was exacerbated in the presence of wood dust (Luce et al., 1993), although possible residual confounding by wood dust exposure could not be excluded.

In the most extensive investigation of exposure–response, there were no increases in lung cancer in workers subdivided by latency period, although there was a non-significant increase for those coexposed to wood dust. There was no statistically significant increased risk for "all respiratory cancer" by level, duration, cumulative exposure, duration of repeated exposures to peak levels, or duration of exposure to dust-borne formaldehyde, except in one category (Partanen et al., 1990).

In smaller cohort studies of professional and industrial workers there have been no significant excesses of cancers of the trachea, bronchus, or lung (Hayes et al., 1990; Andjelkovich et al., 1995), the buccal mucosa or pharynx (Matanoski, 1989; Hayes et al., 1990;

In a cohort of 14 000 workers employed at six chemical and plastic factories in the United Kingdom for which 35% of the cohort was exposed to >2 ppm there was a non-significant excess (comparison with local rates) of lung cancers in workers first employed prior to 1965. Among groups employed at individual plants, the standardised mortality ratio for lung cancer was significantly increased only in the "highly exposed" subgroup at one plant. However, there was no significant relationship with years of employment or cumulative exposure (Gardner et al., 1993).

In the largest industrial cohort mortality study of 26 561 workers first employed before 1966 at 10 plants in the USA (4% of cohort exposed to 2 ppm), Blair et al. (1986) observed a slight but significant, 1.3- fold excess of deaths due to lung cancer among the subcohort of white male industrial workers with 20 years since first exposure. However, results of a number of follow-up studies within this industrial group have provided little additional evidence of exposure–response (cumulative, average, peak, duration, intensity), except in the presence of other substances.

Meta-analyses of data from epidemiological studies published between 1975 and 1991 were conducted by Blair et al. (1990b) and Partanen (1993). Blair et al. (1990b) indicated that the cumulative relative risk of nasal cancer was not significantly increased among those with lower (RR = 0.8) or higher (RR = 1.1) exposure to formaldehyde, while Partanen (1993) reported that the cumulative relative risk of sinonasal cancer among those with substantial exposure to formaldehyde was significantly elevated, RR = 1.75. In both meta-analyses, there was a significantly increased cumulative relative risk (ranging from 2.1 to 2.74) of nasopharyngeal cancer among those in the highest category of exposure to formaldehyde; in the lower or low-medium exposure categories, the cumulative relative risks for nasopharyngeal cancer ranged from 1.10 to 1.59. Both meta-analyses revealed no increased risk of lung cancer among professionals having exposure to formaldehyde; however, among industrial workers, the cumulative relative risk for lung cancer was marginally (but significantly) increased for those with lower and low-medium exposure (both RR =

1.2) to formaldehyde, compared with those with higher (RR = 1.0) or substantial exposure (RR = 1.1) (Blair et al., 1990b; Partanen, 1993).

More recently, Collins et al. (1997) determined the cumulative relative risks of death due to nasal, nasopharyngeal, and lung cancer associated with potential exposure to formaldehyde, based upon a meta-analysis of data from case–control and cohort investigations published between 1975 and 1995. For nasal cancer, cumulative relative risks (designated as meta RR) were 0.3 (95% confidence interval [CI] = 0.1–0.9) and 1.8 (95% CI = 1.4–2.3), on the basis of the cohort and case–control studies, respectively.

In contrast to the findings of Blair et al. (1990b) and Partanen (1993), Collins et al. (1997) concluded that there was no evidence of increased risk of nasopharyngeal cancer associated with exposure to formaldehyde. The differing results were attributed to inclusion of additional more recent studies for which results were negative (Gardner et al., 1993) and correction for under-reporting of expected numbers. The authors also considered that the previous analyses of exposure–response were questionable, focusing on only one cohort study and combining the unquantified medium/high-level exposure groups from the case–control studies with the quantified highest exposure group in the one positive cohort study. Although an analysis of exposure–response was not conducted by Collins et al. (1997), the authors felt that the case–control data should have been combined with the low-exposure cohort data.

Genotoxicity
An increased incidence of micronucleated buccal or nasal mucosal cells has been reported in some surveys of individuals occupationally exposed to formaldehyde (Ballarin et al., 1992; Ying et al., 1997).

Evidence of genetic effects (ie., chromosomal aberrations, sister chromatid exchanges) in peripheral lymphocytes from individuals exposed to formaldehyde vapour has also been reported in some studies (Dobiáš et al., 1989), but not others (Vasudeva and Anan, 1996).

Available data are consistent with a pattern of weak positive responses, with good evidence of effects at the site of first contact and equivocal evidence of systemic effects, although contribution of coexposures cannot be precluded.

Laboratory animal studies

Short term exposures
Histopathological effects and an increase in cell proliferation have been observed in the nasal and respiratory tracts of laboratory animals repeatedly exposed by inhalation to formaldehyde for up to 13 weeks. Most short- and medium-term inhalation toxicity studies have been conducted in rats, with histopathological effects (eg., hyperplasia, squamous metaplasia, inflammation, erosion, ulceration, disarrangements) and sustained proliferative response in the nasal cavity at concentrations of 3.1 ppm and above. Effects were generally not observed at 1 or 2 ppm, although there have been occasional reports of small, transient increases in epithelial cell proliferation at lower concentrations (Swenberg et al., 1983; Zwart et al., 1988).

Long term exposures
The principal non-neoplastic effects in animals exposed to formaldehyde by inhalation are histopathological changes (eg., squamous metaplasia, basal hyperplasia, and rhinitis) within the nasal cavity and upper respiratory tract. Most chronic inhalation toxicity studies have been conducted in rats, with the development of histopathological effects in the nasal cavity being observed at concentrations of formaldehyde of 2 ppm and higher (Monticello et al., 1996; Kerns et al., 1983; Kamata et al 1997; Woutersen et al., 1989).

Exposure–response in these investigations was similar and highly non-linear, with sharp increases in tumour incidence in the nasal cavity occurring only at concentrations greater than 6 ppm formaldehyde, noted at 10 ppm in the Monticello et al 1996 study. The most extensive bioassay conducted to date in which proliferative responses in the epithelium of various regions of the nasal cavity were investigated is that by Monticello et al. (1996).

Mode of action
The mechanisms by which formaldehyde induces tumours in the respiratory tract of rats are not yet fully understood. Inhibition of mucociliary clearance is observed in rats exposed acutely to concentrations of formaldehyde greater than 2 ppm (Morgan et al., 1986a). A sustained increase in proliferation of nasal epithelial cells has not been observed following the exposure of rats to concentrations of formaldehyde of 2 ppm irrespective of the exposure period. In rats exposed to formaldehyde, increased respiratory epithelial cell proliferation in the nasal cavity was more closely related to the concentration to which the animals were exposed than to the total cumulative dose (Swenberg et al., 1983). There is also evidence that glutathione-mediated detoxification of formaldehyde within nasal tissues becomes saturated in rats at inhalation exposures above 4 ppm (Casanova and Heck, 1987). This correlates with the non-linear increase in DNA–protein crosslink formation at exposures above this level.

A sustained increase in nasal epithelial cell regenerative proliferation as a consequence of cellular toxicity and mutation, for which DNA–protein crosslinks serve as markers of potential, have been identified as likely, although not sufficient, factors contributing to the induction of nasal tumours in rats induced by formaldehyde. This hypothesis is based primarily on observation of consistent, non-linear dose response relationships for all three end-points (DNA–protein crosslinking, sustained increases in proliferation, and tumours) and concordance of incidence of these effects across regions of the nasal passages.

Evaluation of Human Health Risks

Non-neoplastic effects

There are considered to be sufficient data from clinical studies and cross-sectional surveys of human populations, as well as supporting observations from experimental studies conducted with laboratory animals, to indicate that the irritant effects of formaldehyde on the eyes, nose, and throat occur at low concentrations. Although individual sensitivity and exposure conditions such as temperature, humidity, duration, and co-exposure to other irritants are likely to influence response levels, in

well conducted studies, only a very small proportion of the population experiences symptoms of irritation following exposure to 0.1 ppm formaldehyde. This is less than the levels that reduce mucociliary clearance in the anterior portion of the nasal cavity in available clinical studies in human volunteers (0.25 ppm) and induce histopathological effects in the nasal epithelium in cross-sectional studies of formaldehyde exposed workers (0.25 ppm).

Carcinogenicity
The weight of evidence indicates that formaldehyde is carcinogenic only at concentrations that induce the obligatory precursor lesion of proliferative regenerative response associated with cytotoxicity, although interaction with DNA must also be taken into account.

Epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde exposure and human cancer, although the possibility of increased risk of respiratory cancers, particularly those of the upper respiratory tract, cannot be excluded on the basis of available data. 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.

In case–control studies, associations between cancers of the nasal or nasopharyngeal cavities and formaldehyde exposure have been observed that fulfil, at least in part, traditional criteria of causality; significantly elevated odds ratios of an association were found for workers with the highest level or duration of exposure. It should be noted, though, that measures of exposure in these population-based investigations are rather less reliable than those in the larger, most extensive cohort studies of occupationally exposed populations; moreover, methodological limitations complicate interpretation of several of the case–control studies. Excesses of cancers of the nasal or nasopharyngeal cavities have not been observed consistently in cohort studies. In epidemiological studies of occupationally exposed populations, there has been little evidence of a causal association between exposure to formaldehyde and lung cancer. Indeed, results of studies in a rather extensive database of cohort and case–control studies do not fulfil traditional criteria of causality in this regard, such as consistency, strength, and exposure–response

Observation of tumours at the site of contact is consistent with toxicokinetic considerations. Formaldehyde is a highly water-soluble, highly reactive gas that is locally absorbed quickly at the site of contact. It is also rapidly metabolised, such that exposure to even high concentrations of atmospheric formaldehyde does not result in an increase in formaldehyde concentrations in the blood.

Because formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance when extrapolating across species that have significantly different anatomical features of the nasal and respiratory passages and patterns of flow of inhaled air. Since humans as well as other primates are oronasal breathers, compared with rats, which are obligate nose breathers, effects associated with the inhalation of formaldehyde are likely to be observed in a larger area, including deeper parts of the respiratory tract. Indeed, in rats exposed to moderate levels of formaldehyde, histopathological changes, increased epithelial cell proliferation, and DNA–protein

crosslink formation are restricted to the nasal cavity; in formaldehyde-exposed monkeys (as surrogates for humans), on the other hand, these effects have been observed further along within the upper respiratory tract. While the epidemiological studies taken as a whole do not provide strong evidence for a causal association between formaldehyde exposure and human cancer, the possibility of increased risk of respiratory cancers, particularly those of the upper respiratory tract, cannot be excluded on the basis of available data. biological plausibility for weight of evidence of causality is also satisfied by the convincing evidence in monkeys (Rusch et al., 1983) and rodents of histopathological alterations (degenerative changes consistent with cytotoxicity) within the upper respiratory tract.

Risks of cancer estimated on the basis of a biologically motivated case-specific model for calculated exposure of the general population to formaldehyde in air based on the sample exposure scenario for the source country (Canada) are exceedingly low. This model incorporates two-stage clonal growth modelling and is supported by dosimetry calculations from computational fluid dynamics modelling of formaldehyde flux in various regions of the nose and single-path modelling for the lower respiratory tract.

The carcinogenic risks for humans were evaluated by an International Agency for Research on Cancer ad hoc expert group in 1987. The evaluation was updated in 1995 and it was concluded that there was limited evidence for carcinogenicity to humans and sufficient evidence for carcinogenicity to animals (Group 2A) (IARC, 1987, 1995).

Carcinogenicity in Laboratory Animals

The CICAD concludes that there is indisputable evidence that formaldehyde is carcinogenic in rats following inhalation, with the carcinogenic response being limited to the site of contact (eg., the nasal passages of rodents). While the mechanism of action is not well understood, based primarily upon data derived from laboratory studies, regenerative proliferation associated with cytotoxicity appears to be an obligatory intermediate step in the induction of cancer by formaldehyde. Interaction with genetic material, the potential for which is indicated by DNA–protein cross-linking, likely also contributes, although the probability of mutation resulting from DNA–protein crosslinking is unknown. However, since formaldehyde is highly reactive at the site of contact, dosimetry is of critical importance in predicting interspecies variations in response, as a function of flux to the tissues and the regional tissue susceptibility, due to the significantly different anatomical features of the nasal and respiratory passages between experimental animals and humans.

Californian Environmental Protection Agency, 1999 (CEPA), Office of Environmental Health Hazard Assessment (OEHHA) Determination of Acute Reference Exposure Levels for Airborne Toxicants – Formaldehyde

Acute Toxicity to Humans

Numerous acute controlled and occupational human exposure studies have been conducted with both asthmatic and normal subjects to investigate formaldehyde's irritant effects on the eyes and the upper respiratory tract. Feinman (1988) states that most people cannot tolerate exposures to more than 5 ppm formaldehyde in air

Key Studies

Kulle et al. (1987); Kulle (1993) exposed 19 healthy subjects to 0, 1.0, and 2.0 ppm for 3-hour periods and asked them to note symptoms of eye and nose/throat irritation and to rate severity on a 0-3 scale: 0=none; l=mild (present but not annoying); 2=moderate (annoying); and 3=severe debilitating). Ten of the subjects were also exposed to 0.5 ppm and nine were exposed to 3 ppm for 3-hour periods. The frequencies of subjects reporting eye irritation or nose/throat irritation increased with increasing exposure concentration, especially at concentrations ≥ 1 ppm. Under nonexposed conditions, 3/19 subjects noted mild nose/throat irritation and l/19 noted mild eye irritation. At 0.5 ppm, l/10 subjects noted mild nose/throat irritation, but none reported eye irritation. Frequencies for subjects with mild or moderate eye irritation were 4/19 at 1 ppm (1 moderate), 10/19 at 2 ppm (4 moderate), and 9/9 at 3 ppm (4 moderate). The increased frequency for eye irritation (compared with controls) was statistically significant at .2 ppm. Frequencies for mild nose/throat irritation were l/19 at 1 ppm, 7/19 at 2 ppm, and 2/9 at 3 ppm. Compared with control frequency for nose/throat irritation, only the response at 2 ppm was significantly elevated.

Weber-Tschopp et al. (1977) exposed a group of 33 healthy subjects for 35 minutes to concentrations of formaldehyde that increased during the period from 0.03 to 3.2 ppm; another group of 48 healthy subjects was exposed to 0.03, 1.2, 2.1, 2.8, and 4.0 ppm for 1.5 minute intervals. Eye and nose irritation were reported on a l-4 scale (l=none to 4=strong) in both experiments, and eye blinking rate was measured in the second experiment. Average indices of eye and nose irritation were increased in both experiments to a small, but statistically significant at 1.2 ppm compared with indices for nonexposed controlled conditions. The published report of this study graphically showed average severity scores of about 1.3-l.4 for both indices at 1.2 ppm compared with 1.0-l.1 for non exposed conditions. The average severity score was increased to a greater degree at higher concentrations, but was less than about 2.5 at the highest exposure concentration, 4 ppm. Average rates of eye blinking were not significantly affected at 1.2 ppm, but were statistically significantly increased at 2.1 ppm (about 35 blinks/minute at 2.1 ppm versus about 22 blinks/minutes under nonexposed conditions).

The study reported by Pazdrak and associates (1993) was not selected as the key study because lack of information on the method used to estimate exposure concentrations and additional limitations in reporting data reduce the level of confidence in this study. The study adds weight, however, to the REL and to the conclusion that low-level exposures may cause adverse health effects.

The recommended REL was estimated by a benchmark concentration (BC05) approach, using log-probit analysis (Crump, 1984; Crump and Howe, 1983). The BC05 is defined as the 95% lower confidence limit of the concentration expected to produce a response rate of 5%. The resulting BC05 from this analysis was 0.44 ppm (0.53 mg/m^3) formaldehyde. This value was adjusted to a 1-hour duration using the formula $C^n \times T = K$, where n = 2 (AICE, 1989), resulting in a value of 0.76 ppm. An uncertainty factor (UF) of 10 was used to account for individual variation.

Chronic Toxicity

Long term exposure to elevated levels of formaldehyde in the occupational setting has been shown to result in upper and lower airway irritation and eye irritation in humans; degenerative, inflammatory and hyperplastic changes of the nasal mucosa in humans and animals

Symptoms of irritation were reported by 66 workers exposed for 1 to 36 years (mean = 10 years) to a mean concentration of 0.17 ppm (0.03 - 0.4 ppm) formaldehyde (Wilhelmsson and Holmstrom, 1992). Controls (36 subjects) consisted of office workers in a government office and were exposed to a mean concentration of 0.06 ppm formaldehyde.

An increase in severity of nasal epithelial histological lesions, including loss of cilia and goblet cell hyperplasia (11%), squamous metaplasia (78%), and mild dysplasia (8%), was observed in wood products workers exposed to between 0.07 and 0.7 ppm formaldehyde for a mean duration of 10.5 years, compared to control subjects (Edling *et al*., 1988). Only three exposed men had normal mucosa. A high frequency of symptoms relating to the eyes and upper airways was reported in exposed workers. The mean histological score was about the same regardless of years of employment, in addition, no difference in the histological scores was found between workers exposed only to formaldehyde and those exposed to formaldehyde and wood dust.

Ritchie and Lehnen (1987) reported a dose-dependent increase in health complaints (eye and throat irritation, and headaches) in 2000 residents living in 397 mobile and 494 conventional homes, that was demonstrated by logistic regression. Complaints of symptoms of irritation were noted at concentrations of 0.1 ppm formaldehyde or above.

Chronic Reference Exposure Level (REL)

The Wilhelmsson and Holmstrom (1992) study was selected by OEHHA for their derivation of a Chronic (REL) because it was a human occupational study that contained a LOAEL of 0.17 ppm (0.03 - 0.4 ppm)and a NOAEL of 0.06 ppm (0.09 mg/m^3), was recent, and contained a reasonable number of subjects. Critical effects were considered to be nasal and eye irritation, nasal obstruction, and lower airway discomfort; histopathological nasal lesions including rhinitis, squamous metaplasia, and dysplasia The average occupational concentration 0.032 mg/m^3 for NOAEL group (0.09 x 10/20 x 5/7) and using only an intraspecies uncertainty factor of 10, gave them the Chronic Inhalation Reference Level of 0.003 mg/m^3 (3 $\mu g/m^3$; 0.002 ppm; 2 ppb)

The supporting occupational study by Edling *et al*. (1988) noted similar sensory irritation results due to long-term formaldehyde exposure. In addition, nasal biopsies from exposed workers in the study exhibited nasal epithelial lesions similar to those found in subchronic and chronic animal studies.

For comparison, we estimated a REL from Edling *et a*l. (1988). A median concentration of 0.6 mg/m^3 was determined for the LOAEL from the TWA range of 0.1-1.1 mg/m^3 as a NOAEL was not reported. The average continuous occupational concentration was 0.2 mg/m^3 (0.6 x 10/20 x 5/7) Application of a UF of 10 for

intraspecies variability and a UF of 10 for estimation of a NOAEL from the LOAEL would result in a REL of 2 $\mu g/m^3$ (2 ppb).

Agency for Toxic Substances and Disease Registry.1999 (ATSDR) Toxicological profile for Formaldehyde, US Department of Health and Human Services, Public Health Service,

The respiratory tract, especially the upper respiratory tract, is a critical target of the toxicity of airborne formaldehyde as shown by acute controlled exposure human studies, by studies of humans exposed acutely or repeatedly under occupational or residential conditions, and by studies of animals (including primates) exposed by inhalation for acute, intermediate, and chronic durations.

ATSDR has derived an acute inhalation Minimal Risk Level (MRL) on the basis of clinical symptoms (increased itching, sneezing, mucosal congestion, transient burning sensation of the eyes and of the nasal passages) and nasal alterations (elevated eosinophil counts and a transient increase in albumin content of nasal lavage fluid) in a study of human volunteers (Pazdrak et al. 1993). This MRL is based on a minimal LOAEL of 0.4 ppm and an uncertainty factor of nine (three for use of a minimal LOAEL and three for human variability as a sensitive sub group was used in the study).

Key Study for an Acute MRL
Pazdrak, K, et al (1993) study investigated the effects of formaldehyde exposure on the severity of symptoms of nasal and eye irritation and the cellular makeup of nasal discharge in occupationally exposed patients with skin hypersensitivity to formaldehyde and unexposed controls. The study was comprised of 2 study groups, all of whom were non-smokers. Group 1 consisted of 7 male and 3 female volunteers, all of whom suffered from skin hypersensitivity to formaldehyde; group 2 consisted of 11 healthy males with no history of allergic diseases, normal serum IgE levels, and negative skin tests to common allergens. Nasal washings were performed in both groups immediately before and after a 2-hour exposure to 0 and 0.4 ppm. formaldehyde, and at 4 and 18 hours after completion of the 2-hour exposure periods. Symptoms of were evaluated through the exposure period and through 4- and 18-hour periods after the exposure period (maximum score = 7). In both groups, placebo inhalation periods were without effects on nasal wash cellular contents or symptom score. During exposure to 0.4 ppm formaldehyde, both groups showed statistically significantly increased average symptom scores compared with average placebo scores (about 4 versus <0.5). Symptom scores were no longer elevated 18 hours after exposure. In both groups, eosinophil counts were elevated at all time points after 0.4 ppm formaldehyde exposure, while the proportion of epithelial cells declined after formaldehyde exposure. Albumin levels also increased in both groups after formaldehyde exposure, but remained elevated only briefly (10 minutes). There were no significant differences between allergic and healthy patients in nasal washing characteristics after formaldehyde exposure. No changes in basophil numbers were noted in either patient group and there was no evidence of mast cell degranulation. The authors concluded that the symptoms observed were the result of a non-specific, non-allergic process in response to low-level formaldehyde vapour exposure. The authors also noted that further study is required to understand the significance of the

increased release of eosinophils noting that eosinophils may have both protective (eg., they can neutralise histamine) and damaging (eg., they may liberate mediators that damage epithelial surfaces) properties.

The Andersen and Molhave (1983) study identified an apparent effect level (0.2 ppm), based on subjective reports of irritation that is lower than the effect levels (0.35-0.4 ppm) in the studies by Pazdrak et al. (1993), Krakowiak et al. (1998), and Bender et al. (1983), which used more objective measures of acute irritation (eosinophil counts and protein concentrations in nasal lavage fluid or time to first reporting of irritation). Because of the use of objective measures of toxicity and the general weight of the available data indicating that some people will not experience eye or upper respiratory tract irritation from formaldehyde even at 1 ppm (Day et al. 1984; Kulle et al. 1987, Weber Tschopp et al. 1977), the Pazdrak et al. (1993) study LOAEL of 0.4 ppm was considered a minimal LOAEL in a group of potentially sensitive individuals (some subjects had dermal hypersensitivity to formaldehyde) and selected as the basis of the acute MRL

Chronic MRL
A chronic inhalation MRL of 0.008 ppm was also derived based on a minimal LOAEL of 0.24 ppm for mild irritation of the eyes and upper respiratory tract and histological evidence of mild damage to the nasal epithelial tissue (squamous metaplasia, loss of ciliated cells, goblet cell hyperplasia, and mild dysplasia in biopsied tissue) in formaldehyde exposed chemical workers (Holmstrom et al. 1989). To derive the MRL, the minimal LOAEL was divided by an uncertainty factor of 30 (3 for the use of a minimal LOAEL and 10 for human variability).

Human Studies
Carcinogenicity
The potential for occupational exposure to formaldehyde to cause cancer in humans has been examined in more than 40 epidemiology studies (cohort mortality and case-control studies). In general, these studies have provided inconsistent evidence for carcinogenicity in humans chronically exposed to low levels of formaldehyde in workplace air. In most studies finding statistically significant associations between occupational formaldehyde and human cancer, the associations have not been strong. The epidemiological studies each have shortcomings, such as limited follow-up, limited exposure information, possible misclassification of disease, presence of confounding risk factors, or small numbers of subjects, that make the establishment of a causal relationship between occupational exposure to formaldehyde and human cancer difficult. Some of the epidemiological studies have found some scattered evidence for extra-respiratory site cancers in groups of formaldehyde-exposed workers, but the data are not consistent across studies and adjustment for potential confounding factors often has not been possible.

Three meta-analyses of the epidemiological data are available (Blair et al. 1990a; Collins et al. 1997; Partanen 1993). Each meta-analysis has focused on findings for respiratory cancer deaths based on the premise that the respiratory tract is the most biologically plausible site for cancer from exposure to airborne formaldehyde. Strong support for this premise comes from animal studies showing that chronic inhalation exposure to formaldehyde concentrations between approximately 6 and 15 ppm, but

not lower concentrations, induces carcinogenic responses in rats that are restricted to the nasal cavity.

Assessment

Other reviewers also have arrived at differing conclusions regarding the evidence from the epidemiological studies. On one side, IARC (1995) and US EPA (1991) judged that there was limited evidence in humans and NTP (1998) judged that formaldehyde was reasonably anticipated to be a human carcinogen; whereas McLaughlin (1994) and ECETOC (1995), on the other side, concluded that a causal relationship was not established by the available data. A more recent collaborative review of the data by US EPA and CIIT (1998) appears to take a middle stand concluding that "it appears that a weak association between nasopharyngeal cancer and formaldehyde exposure cannot be completely ruled out".

In contrast to the equivocal, limited, or weak nature of the evidence in humans, replicated inhalation studies have consistently shown that formaldehyde induces nasal tumours in rats exposed to high concentrations (10–15 ppm) that also induce nasal epithelial necrosis and cellular proliferation, but not when exposed to lower concentrations (0.3–2 ppm) that do not markedly damage nasal epithelial tissue (Albert et al. 1982; Kamata et al. 1997; Kerns et al. 1983; Monticello et al. 1996; Wouterson et al. 1989). Exposure-related cancer or non-cancer lesions at sites distant from the portal-of-entry were not found in these studies, consistent with the water solubility and reactivity of formaldehyde and the ubiquity of rapid cellular metabolism of formaldehyde.

Mechanistic studies indicate that the carcinogenic response to inhaled formaldehyde in rats originates in regions of the nasal cavity epithelium that initially show non-neoplastic damage and provide support for the hypothesis that formaldehyde-induced, cancer will occur only at exposure levels that extensively damage epithelium tissue Monticello et al. (1996). Comparison of the non-neoplastic upper respiratory tract response in rats and monkeys to intermediate-duration formaldehyde exposure has indicated that both monkeys and rats are similarly susceptible to formaldehyde cytotoxicity but display some regional differences in sites of tissue damage within the upper respiratory tract (Casanova et al.1989, 1991; Monticello et al. 1989). These observations support the use of data from rodent studies to estimate risks for nasal tissue damage and nasal cancer with human exposure scenarios.

The application of dosimetric models (eg., models of airflow and uptake in nasal passages and PBPK models of nasal disposition of formaldehyde) currently under development holds promise of reducing uncertainties in estimating human cancer risks from the available rodent data . Ongoing efforts (CIIT 1998; Conolly et al. 1992; Conolly and Andersen 1993) to develop two-stage clonal-growth cancer models (ie., pharmacodynamic models) incorporating data on formaldehyde-induced cell proliferation rates, numbers of cells at risk, tumour incidence, and site-specific flux of inhaled formaldehyde are also likely to reduce uncertainties in estimating the risks for neoplastic damage to the upper respiratory tract in humans exposed to low levels of airborne formaldehyde.

Laboratory Animal Studies.

Acute Inhalation
Studies in animals confirm that the upper respiratory tract is a critical target for inhaled formaldehyde and describe exposure-response relationships for upper respiratory tract irritation and epithelial damage in several species. Acute inhalation animal studies show that inhaled formaldehyde, at appropriate exposure concentrations, damages epithelial tissue in specific regions of the upper respiratory tract in rats, mice, and monkeys (Chang et al. 1983; Monticello et al. 1989, 1991)

Monticello et al. (1991) found no evidence for histological nasal epithelial damage in rats exposed to 0.7 or 2 ppm, 6 hours/day for 1, 4, or 9 days, but damage was observed at 6, 10, and 15 ppm. Regions of epithelium showing histological lesions also showed increased rates of cellular proliferation at concentrations greater than 6 ppm.

Site-specific damage to nasal epithelial cells after acute exposure (6 hours/day for 1 to 3 weeks) of rats to formaldehyde was correlated with inhibition of mucociliary function at concentrations of 2, 6, and 15 ppm, but no effects on these end points were found at 0.5 ppm (Morgan et al. 1986a, 1986b).

Upper respiratory tract epithelial lesions similar to those observed in rats have been observed in Rhesus monkeys exposed to 6 ppm, 6 hours/day, 5 days/week for 1 week; the regional distribution of these lesions was not restricted to the nasal cavity, as they were in rats exposed to 6 ppm (Monticello et al. 1991), but extended to the trachea and major bronchi (Monticello et al. 1989). Lesions were most severe in the nasal passages and were minimal in the lower airways (larynx, trachea, and carina). Regions of epithelium with lesions corresponded with regions in which high rates of cellular proliferation were measured.

Intermediate duration Inhalation
Rusch *et al.* (1983) exposed groups of male Cynomolgus monkeys, rats, and hamsters to 0, 0.2, 1.0, or 2.95 ppm formaldehyde vapour for 22 hours/day, 7 days/week for 26 weeks. There was no treatment-related mortality during the study. In monkeys, the most significant findings were hoarseness, congestion and squamous metaplasia of the nasal turbinates in all monkeys exposed to 2.95 ppm. There were no signs of toxicity in the lower exposure groups. In the rat, squamous metaplasia and basal cell hyperplasia of the nasal epithelia were significantly increased in rats exposed to 2.95 ppm. The same group exhibited decreased body weights and decreased liver weights. In contrast to monkeys and rats, hamsters did not show any signs of response to exposure, even at 2.95 ppm.

Chronic Inhalation
Chronic exposure to formaldehyde concentrations ranging from about 6 ppm to 15 ppm induced increased incidences of nasal tumours (squamous cell carcinomas, squamous cell papillomas, or polyploid adenomas) in three bioassays with Fisher 344 rats (Kamata et al. 1997; Kerns et al. 1983; Monticello et al. 1996; Swenberg et al. 1980). Increased incidences of lower respiratory tract tumours or distant site tumours were not found in these studies, and exposure to concentrations of 2 ppm and lower induced no malignant nasal tumours.

In the earliest chronic inhalation rat bioassay (Kerns et al. 1983; Swenberg et al. 1980), polyploid adenomas in the nasal cavity were found in rats exposed to formaldehyde up to 14.3 ppm, for 24 months. Malignant nasal tumours (predominantly squamous cell carcinomas) were found in 2/235 (5.6-ppm), and 106/232 (14.3-ppm) rats (Kerns et al. 1983).

Kamata et al. (1997) exposed groups rats to formaldehyde up to 15 ppm, for up to 28 months, and found nasal squamous cell carcinomas only in the 15-ppm group (13/32 rats). In contrast to the studies by Kerns et al. (1983) and Monticello et al. (1996), no polyploid adenomas were found, but squamous cell papillomas were found in 3/32 rats.

Air Quality Guidelines for Europe, *2nd edition* -WHO Regional Office for Europe, 2000 (WHO 2000)

The WHO Working Group concluded that the predominant symptoms of formaldehyde exposure in humans are irritation of the yes, nose and throat, together with concentration dependent discomfort, lachrymation, sneezing, coughing, nausea dyspnea and finally death.

Damage to the nasal mucosa, such as squamous cell metaplasia and mild dysplasia of the respiratory epithelium, have been reported in humans, but these findings may have been confounded by concomitant exposures to other substances (IARC 1995). There is also epidemiological evidence of associations between relatively high occupational exposure to formaldehyde and both nasopharyngeal and sinonasal cancers (Blair et al 1990b; Partanen 1993; McLaughlin 1994). There is substantial variation in individual responses to formaldehyde in humans. Significant increases in signs of irritation occur at levels above 0.08 ppm in healthy subjects. At concentrations above 1 ppm, a progression of symptoms and effects occurs.

There is evidence of formaldehyde inducing pathological and cytogenetic changes in the nasal mucosa of humans in studies with reported mean exposures ranged from 0.02 ppm to 2 ppm, with peaks between 4.2 ppm and 15 ppm. Epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases (Blair et al 1990b; Partanen 1993; McLaughlin 1994). IARC (1995) has interpreted the available cancer data as limited evidence for the carcinogenicity of formaldehyde in humans, and classified formaldehyde in Group 2A.

There is convincing evidence of high concentrations of formaldehyde being a nasal carcinogen in rats. A highly significant incidence of nasal cancer was found in rats exposed to a level of 13.9 ppm, but the dose–response curve was non linear, the risk being disproportionately low at low concentrations. It also appears that the dose–response curves were nearly identical for neoplastic changes, cell turnover, DNA–protein cross-links and hyperproliferation, when the relationship between non-neoplastic and neoplastic lesions in the nasal respiratory epithelium was analysed. This close concordance indicates an association among the observed cytotoxic, genotoxic and carcinogenic effects. It is thus likely that hyperproliferation induced by

cytotoxicity plays a significant role in the formation of nasal tumours by formaldehyde.

Despite differences in the anatomy and physiology of the respiratory tract between rats and humans, the respiratory tract defence mechanisms are similar. It is therefore reasonable to assume that the response of the human respiratory tract mucosa to formaldehyde will be similar to that of the rat. Thus, if the respiratory tract tissue is not repeatedly damaged, exposure of humans to low, non cytotoxic concentrations of formaldehyde can be assumed to be associated with a negligible cancer risk. This is consistent with epidemiological findings of excess risks of nasopharyngeal and sinonasal cancers associated with concentrations above about 0.84 ppm.

Conclusions

The lowest concentration (LOAEL) which has been recorded as associated with nose and throat irritation after short-term exposure is 0.08 ppm (IPCS, 1989).

The working group, in its assessment of a guideline value for formaldehyde in ambient air, adopted the recommendation of IPCS and concluded that in order to prevent sensory irritation in the general population, an Air Quality Guideline value of 0.08 ppm is recommended. Since this recommended guideline value is more than one order of magnitude lower than a presumed threshold for cytotoxic damage to the nasal mucosa, this guideline value is considered low enough to avoid any significant risk of upper respiratory tract cancer in humans.

International Agency for Research on Cancer (IARC) 1995. - Summaries & Evaluations, Formaldehyde (IARC Vol 62 1995)

IARC (1995) has determined that formaldehyde is probably carcinogenic to humans (Group 2A) based on specific evaluations that there is limited evidence in humans for the carcinogenicity of formaldehyde and sufficient evidence in experimental animals.

Human carcinogenicity data

Excess numbers of nasopharyngeal cancers were associated with occupational exposure to formaldehyde in two of six cohort studies of industrial or professional groups, in three of four case-control studies and in meta-analyses. In one cohort study performed in 10 plants in the United States, the risk increased with category of increasing cumulative exposure. In the cohort studies that found no excess risk, no deaths were observed from nasopharyngeal cancer. In three of the case-control studies, the risk was highest in people in the highest category of exposure and among people exposed 20-25 years before death.

Of the six case-control studies in which the risk for cancer of the nasal cavities and paranasal sinuses in relation to occupational exposure to formaldehyde was evaluated, three provided data on squamous-cell tumours and three on unspecified cell types. Of the three studies of squamous-cell carcinomas, two (from Denmark and the Netherlands) showed a positive association, after adjustment for exposure to wood dust, and one (from France) showed no association.

The two case-control studies that considered squamous-cell tumours and gave positive results involved more exposed cases than the other case-control studies combined. In the studies of occupational cohorts overall, however, fewer cases of cancer of the nasal cavities and paranasal sinuses were observed than were expected. Because of the lack of consistency between the cohort and case-control studies, the epidemiological studies can do no more than suggest a causal role of occupational exposure to formaldehyde in squamous-cell carcinoma of the nasal cavities and paranasal sinuses.

The meta-analyses found a significantly higher risk among people estimated to have had substantial exposure than among those with low/medium or no exposure. The observed associations between exposure to formaldehyde and risk for cancer cannot reasonably be attributed to other occupational agents, including wood dust, or to tobacco smoking. Limitations of the studies include misclassification of exposure and disease and loss to follow-up, but these would tend to diminish the estimated relative risks and dilute exposure-response gradients.

Taken together, the epidemiological studies suggest a causal relationship between exposure to formaldehyde and nasopharyngeal cancer, although the conclusion is tempered by the small numbers of observed and expected cases in the cohort studies.

Animal carcinogenicity data

Several studies in which formaldehyde was administered to rats by inhalation showed evidence of carcinogenicity, particularly induction of squamous-cell carcinomas of the nasal cavities, usually only at the highest exposure. Similar studies in hamsters showed no evidence of carcinogenicity. Studies in mice either showed no effect or were inadequate for evaluation.

Acute or subacute exposure of rats to a concentration of 2.1 ppm appears to cause no detectable damage to the nasal epithelium and does not significantly increase rates of cell turnover. Cell turnover rates in rat nose during subchronic or chronic exposures to formaldehyde do not increase at 2.1 ppm, increase marginally at concentrations of 3.1-6.2 ppm and increase substantially at concentrations of 10.3-15.4 ppm.

Concentration is more important than length of exposure in determining the cytotoxicity of formaldehyde. Inhalation of formaldehyde leads to the formation of DNA-protein cross-links in the nasal respiratory mucosa of rats and monkeys. Much lower levels of DNA-protein cross-links were found in the nasopharynx, trachea and carina of some monkeys, in decreasing concentrations with passage through the respiratory tract, but none were found in the maxillary sinus.

In rodents and monkeys, there is a no-observable-effect level (2.1 ppm) of inhaled formaldehyde with respect to cell proliferation and tissue damage in otherwise undamaged nasal mucosa. These effects are considered to contribute to subsequent development of cancer. Although these findings provide a basis for extrapolation to humans, conclusive data demonstrating that such cellular and biochemical changes occur in humans exposed to formaldehyde are not available.

Other effects
IARC considers that formaldehyde is comprehensively genotoxic in a variety of experimental systems, ranging from bacteria to rodents, in vivo. Formaldehyde induced DNA-protein crosslinks, DNA single-strand breaks, chromosomal aberrations, sister chromatid exchange and gene mutation in human cells in vitro. It induced cell transformation, chromosomal aberrations, sister chromatid exchange, DNA strand breaks, DNA-protein crosslinks and gene mutation in rodent cells in vitro. There are no conclusive data showing that formaldehyde is toxic to the immune system, to the reproductive system or to developing foetuses in humans

Environment Canada Health and Welfare Canada (2001): Priority Substances List Assessment Report, Formaldehyde

This assessment is not reviewed as a separate evaluation as it forms the basis for the Concise International Chemical Assessment Document No. 40 Formaldehyde WHO 2002.

Formaldehyde however has been considered to be ' toxic' as defined in Paragraph 64 (c) of the Canadian Environmental Protection Act 1999. The reason for this is that 'although other factors (such as sustained cellular proliferation) play an important role, there is likely a genetic component (i.e., mutation, for which DNA-Protein crosslinks serve as a marker for potential) in the induction of tumours following the inhalation of formaldehyde'.

US EPA IRIS Summary – Formaldehyde (June 2002)

Reference Concentration for Chronic Inhalation Exposure (RfC) Not available at this time.

Key Studies not previously detailed

Human studies

Edling et al. (1988) found histological evidence of epithelial damage in biopsied specimens from the nasal mucosa of 75 workers from two particle board processing plants and a laminate plant. From air measurements occasionally made during an 8-year period before the study, estimates of TWA concentrations were calculated ranging from 0.08 to 0.9 ppm. (A mean TWA concentration was not reported, but the midpoint of this range is 0.49 ppm). Peaks of up to 4.07 ppm were measured during the 8-year period. Air concentrations were qualitatively assessed as being “somewhat higher” during earlier periods. Wood dust air concentrations in the particle board plants ranged from 0.5 to 1 ppm; air in the laminate plant was reported to be without wood dust. Employment durations ranged from 1 to 39 years with a mean of 10.5 years. Runny nose, nasal crusting, and runny eyes when at work were reported by 60 and 75% of the exposed subjects, respectively, but frequencies were not compared in the report with frequencies of symptoms for a control group of 25 nonexposed subjects. Little information was given about the selection of the control group, except that they were “selected with regard to age and smoking habits”, however, 35% of

exposed versus 48% of controls were smokers. Gross clinical examination showed that 25% of exposed workers had either swollen nasal mucosa or dry nasal mucosa; prevalence of this condition in the control group was not reported. Normal ciliated epithelium was found only in 3/75 exposed subjects; whereas a loss of ciliated cells and goblet cell hyperplasia was noted in 59/75 subjects, and 6/75 exposed subjects showed mild dysplasia. No subjects displayed severe dysplasia or carcinoma. Edling et al. (1988) did not report incidences of nasal lesions found in the control group. Histological scores did not increase with increasing employment duration in the exposed group. The authors reported that there was no difference in average histological scores between the exposed workers from the particle board plants, where confounding exposure to wood dust occurred, and those from the laminate plant without wood dust exposure. This observation supports the hypothesis that the observed nasal epithelial lesions were caused by formaldehyde and not by an interaction between formaldehyde and wood dust.

Partanen et al. (1990) performed a retrospective study that attempted to determine the association of respiratory cancer (136 cases, 408 controls) with formaldehyde exposure; this case control study was nested in a total cohort of 7,307 woodworkers having had a minimum level of 0.1 ppm and a minimum cumulative exposure of 3 ppm months to formaldehyde. The odds ratio for respiratory cancers in exposed versus unexposed workers, when corrected for vital status, smoking, and a latency period of 10 years, was not statistically significant.

Gardner et al. (1993) assessed the risk of disease and cancers among British male chemical worker exposed to formaldehyde. The cohort for the study consisted of 7,660 men who began employment prior to 1965 and 6,357 men who began employment after 1964. Formaldehyde exposure ranged from<0.1 to >2 ppm. There was one death from nasal cancer and no deaths from nasopharyngeal cancer, nor were any non fatal cases of nasopharyngeal reported. Among lung cancer cases, there was no association of cancer with formaldehyde exposure. Among men classified as exposed to the higher end of possible exposure levels of formaldehyde, there was no indication of a relationship between cancer and duration of employment, and no association between cancer and cumulative dose. In those employed prior to 1965, there was a significant excess of lung cancer, with the authors stating that the increase was probably due to smoking and other environmental pollution. This appears to be related to one factory in which more men were exposed to high levels of formaldehyde. The determination of exposure levels in this study was crude and the information on coexposure to other chemicals was not analysed. Weaknesses of this study included the observation that no actual measurements of formaldehyde exposure levels occurred, but the investigators did undertake a detailed estimation procedure for classifying expected exposure levels.

Holmstrom et al. (1989) examined histological changes in nasal tissue specimens from a group of 70 workers in a chemical plant that produced formaldehyde and formaldehyde resins for impregnation of paper, a group of 100 furniture factory workers working with particle board and glue components, and a nonexposed, control group of 36 office workers in the same village as the furniture factories. Mean durations of employment in the groups were 10.4 years (range 1–36 years) for the chemical workers and 9.0 years (range 1–30 years) for the furniture workers. Estimates of personal breathing zone air concentrations ranged from 0.04 to 0.4 ppm

(median 0.24±0.13 ppm) for the chemical workers, from 0.16 to 0.4 ppm (median 0.20±0.04 ppm) for the furniture workers, and from 0.07 to 0.13 ppm in the late summer for the office workers with a year-round office worker median reported as 0.07 ppm . The mean wood dust concentration in the furniture factory was reported to have been between 1 and 2 mg/m ^{3}. Nasal mucosa specimens were taken from the medial or inferior aspect of the middle turbinate. Histology scores were assigned to each specimen based on a 0–8 scale as used by Edling et al. (1988). Nasal histology scores ranged from 0 to 4 (mean 2.16, n=62) for the chemical workers, from 0 to 6 (mean 2.07, n=89) for the furniture workers, and from 0 to 4 (mean 1.46, n=32) for the office workers. The mean histological score for the chemical workers, but not the furniture workers, was significantly different from the control score, thus supporting the hypothesis that the development of the nasal lesions is formaldehyde-related and not obligatorily related to a possible interaction between formaldehyde and wood dust. The most severe epithelial change noted (light or moderate epithelial dysplasia) was found in two furniture workers. Among the chemical workers (not exposed to wood dust), loss of cilia, goblet cell hyperplasia, and cuboidal and squamous cell metaplasia replacing the columnar epithelium occurred more frequently than in the control group of office workers. Within both groups of formaldehyde-exposed workers, no evidence was found for associations between histological score and duration of exposure, index of accumulated dose, or smoking habit.

Andersen and Molhave (1983) exposed a group of 16 healthy subjects to 0.2, 0.4, 0.8, and 1.6 ppm for 4-hour periods preceded by a nonexposed period of two hours. Subjects were asked to assess “discomfort” on a 0-100 scale ranging from 0=no discomfort to l00=intolerable discomfort (scores between 1 and 33 were rated as “slight discomfort”). Average peak discomfort scores for the group generally increased with exposure concentration, but the average discomfort score for the highest exposure concentration (1.6 ppm) never exceeded 18. Numbers of subjects who reported “no discomfort” ratings at the end of exposure periods were 7, 13, 10, and 6, respectively for 0.2, 0.4, 0.8, and 1.6 ppm; respective numbers of subjects reporting “conjunctival irritation and dryness in the nose and throat” were 3, 5, 15, and 15 of the 16 subjects exposed to each respective concentration. A statistical analysis of these data was not reported.

Gorski et al. (1992) reported that, after exposure to 0.4 ppm for 2 hours, l/5 healthy subjects and 3/3 subjects with formaldehyde-sensitive contact dermatitis experienced nose irritation, sneezing, or eye irritation. Similar exposure produced statistically significant increases in the average number and proportion of eosinophils and the concentration of albumin and total protein in nasal lavage fluid, both in groups of 9 sensitised subjects and in groups of 11 nonexposed subjects; the responses in the two groups were not significantly different (Pazdrak et al. 1993).

Laboratory animal studies

Rusch et al. (1983) histologically examined the lungs, trachea, and nasal turbinates of groups of 6 or 12 male Cynomolgus monkeys, 20 male and 20 female Fischer 344 rats, and 10 male and 10 female Golden Syrian hamsters exposed to 0, 0.2, 0.98, or 2.95 ppm for 22 hours/day, 7 days/week for 26 weeks. Examination of other organs and tissues at necropsy for gross lesions revealed no exposure-related effects, but

these tissues were not microscopically examined. Monkeys exposed to 2.95 ppm showed an increased incidence of hoarseness, congestion, and nasal discharge. Monkeys in the lower exposure groups showed a greater incidence of nasal discharge than control monkeys, but the discharge was "only a minimal grade" and was noted sporadically throughout the study. The study authors judged that the nasal discharge at the two lowest exposure levels was not of biological significance. Body weights of exposed monkeys were not significantly different from body weights of controls. Monkeys and rats exposed to 2.95 ppm, but not the lower concentrations, showed a significantly increased incidence of squamous metaplasia and/or basal cell hyperplasia of the nasal cavity epithelium; the response was reported to be most clearly seen in both species in the mid-region of the nasoturbinates. No lesions were found in the most anterior sections of the nose or in the ethmoturbinates. Incidences of monkeys with squamous metaplasia/hyperplasia in nasal turbinate epithelium were 0/12, 0/6, 1/6, or 6/6 at 0, 0.2, 0.98, and 2.95 ppm, respectively. Respective incidences of rats with squamous metaplasia/hyperplasia were 5/77, 1/38, 3/36, and 23/37. Ultrastructural examinations were made of the nasal turbinates, trachea, and lungs from rats in the control and 0.98-ppm group; no exposure-related changes were found. No histological changes were found in the nasoturbinates, trachea, or lungs of the exposed hamsters compared with controls.

Kerns et al., (1983), in a study in which groups of male and female F344 rats were exposed to 0, 2.0, 5.6, or 14.3 ppm formaldehyde for 6 h/day, 5 days/week, for up to 24 months, followed by an observation period of 6 months, the incidence of squamous cell carcinoma in the nasal cavity was markedly increased only in the high-concentration groups compared with the unexposed controls. The incidence of this tumour was 0/118, 0/118, 1/119 (1%), and 51/117 (44%) in males and 0/118, 0/118, 1/116 (1%), and 52/119 (44%) in females in the control, low-, mid-, and high-concentration groups, respectively. Precise histopathological analysis revealed that in animals exposed to the highest concentration of formaldehyde, more than half of the nasal squamous tumours were located on the lateral side of the nasal turbinate and adjacent lateral wall at the front of the nose (Morgan et al., 1986b). Two nasal carcinomas (in male and female rats) and two undifferentiated carcinomas or sarcomas (in male rats) were also observed in animals from the high-concentration groups.

In a follow-up study, Monticello et al. (1996) exposed male F344 rats to 0, 0.7, 2, 6, 10, or 15 ppm formaldehyde for 6 h/day, 5 days/week, for up to 24 months. Epithelial cell proliferation at seven sites within the nasal was determined after 3, 6, 12, and 18 months of exposure. The overall incidence of nasal squamous cell carcinoma in animals exposed to 0, 0.7, 2, 6, 10, or 15 ppm formaldehyde was 0/90, 0/90, 0/90, 1/90 (1%), 20/90 (22%), and 69/147 (47%), respectively. Tumours were located primarily in the anterior lateral meatus, the posterior lateral meatus, and the mid-septum.

Woutersen et al., (1989) reported that compared with unexposed controls, the incidence of nasal squamous cell carcinoma was not significantly increased in male Wistar rats. The rats were exposed to formaldehyde at concentrations of 0, 0.1, 1, or 9.8 ppm for 6 h/day, 5 days/week, for 28 months (0% and 4% of the controls and animals exposed to 9.8 ppm, respectively, had nasal squamous cell carcinomas). However, consistent with the hypothesised role of tissue damage in formaldehyde-

induced nasal tumours, when animals with noses damaged by electrocoagulation were similarly exposed, the incidence of this tumour type was markedly increased in the high-concentration group (1/54, 1/58, 0/56, and 15/58 in animals exposed to 0, 0.1, 1, or 9.8 ppm, respectively).

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