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# FORMALDEHYDE AND HUMAN CANCER RISK

## CONTENTS

## SUMMARY

Formaldehyde is a natural component in all mammalian cells and because of active enzymatic pathways is rapidly detoxified. Its use by man has been long-term and widespread, finding both medical and industrial applications.

This review examines the cytologic and cytogenetic studies of workers exposed to formaldehyde and examines the epidemiologic studies on cancer risk as they relate to formaldehyde exposure. All studies reviewed were non-experimental in design and as such concerns of bias, confounding and chance must be evaluated thoroughly before any etiologic conclusion can be drawn.

The cytologic and cytogenetic studies of worker volunteers in the formaldehyde industry were inconsistent in their findings, biased in their selection of exposed and non-exposed control subjects, confounded by other exposures and not large enough to allow for the sufficient exclusion of chance. Before these studies can be taken as serious evidence they must be larger in scale, show absence of selection bias and provide proper control of confounding factors and present a detailed and informed analysis.

Epidemiologic studies of formaldehyde and human cancer risk can be divided into three major groups: formaldehyde industry workers, morticians and medical professionals, and community-based case-control studies. These three groups reflect a descending order in the likelihood of exposure, with the formaldehyde industry workers having certain, and for the most part, measured exposure. The medical professionals and morticians are likely to have some exposure with the potential for short-term high peaks in exposure. Community-based case-control studies have no certainty of exposure; all putative exposure to formaldehyde is inferred from job titles.

The cohort studies of formaldehyde industry workers provide no convincing evidence of a link with cancer. There is no evidence of an excess of nasal cancer, the neoplasm reported in animal studies. One study suggesting an association between formaldehyde and nasopharyngeal cancer has been shown to suffer from misdiagnosis and multiple comparison biases.

Studies of medical professionals and morticians report no link with nasal cancer, nasopharyngeal or lung cancer risk, sites that would come into contact with formaldehyde. Based on years of animal experiments, effects on sites distal to those exposed are not considered to be related to formaldehyde due to the highly reactive nature and rapid metabolism of this chemical. Hence the excess of colon and brain cancer and leukaemia found among professionals is not likely to be a result of their exposure to formaldehyde.

Community-based case-control studies provide the weakest evidence of all study approaches because there is no documented exposure, data for the latter is derived from job-titles. In this context it is worth noting that the case-control studies performed within cohorts of formaldehyde industry workers (nested case-control studies) were all uniform in showing no relation to formaldehyde exposure. The community-based studies failed to eliminate bias, confounding and chance as the most likely explanations of their findings. None provides convincing evidence of a causal link.

After a careful review of the cytologic, cytogenic and epidemiological studies there is an absence of evidence to support the judgement of an etiologic relationship between formaldehyde and human cancer risk. Causal criteria used by epidemiologists in evaluating an association, such as strength of an association, consistency of results across studies, dose-response effects, biologic plausibility and coherence have not been met by the studies examined in this report.

# SECTION 1. INTRODUCTION

Formaldehyde is a naturally occurring chemical found in all mammalian cells. It is highly reactive and metabolises quickly on contact with tissue. It has been used in a variety of products and activities for over a century.

ECETOC has earlier reviewed the toxicology of formaldehyde (1981a,b; 1982). A review was conducted by the International Agency for Research on Cancer (IARC) (1982) which indicated that formaldehyde was carcinogenic to rats but there was insufficient evidence to assess its carcinogenic potential to man. A subsequent review by IARC (1987) resulted in a 2A classification (i.e., "probably carcinogenic to humans"). The toxicity, ecotoxicity and epidemiological evidence on formaldehyde has been reviewed by the World Health Organization's International Programme on Chemical Safety (IPCS, 1989). Recently, IARC has reviewed the latest evidence on formaldehyde and human cancer risk and the classification of 2A has remained unchanged (IARC, 1995).

The objective of this report is to critically review the cytologic and cytogenetic studies of workers exposed to formaldehyde and the epidemiological studies of formaldehyde and cancer risk.

A companion publication will review the animal evidence and its relevance to man.

# SECTION 2. STUDIES OF BIOLOGIC MARKERS

## 2.1 Cytologic and Cytogenetic Studies

There have been a number of cytologic and cytogenetic studies of formaldehyde exposure in man. These non-experimental studies have typically involved the examination of nasal and buccal cells and blood lymphocytes of occupationally exposed workers and unexposed control subjects who volunteered (Table 1).

### 2.1.1 Cytologic Studies

Edling *et al* (1987) biopsied the nasal mucosa of 38 laminate processing workers exposed to formaldehyde and 25 unexposed controls. Age and smoking habits were similar between the groups. The range of exposure to formaldehyde was 0.5-1.1 mg/m$^3$ (0.4 to 0.9 ppm)[1]. The exposed workers had been employed in the plant for an average of 10.5 years. A histologic score (0-8) for changes in nasal mucosa, from normal (0) to keratosis (4) to carcinoma (8), was assigned to each specimen after blind review by a pathologist. The average histologic score was higher among the exposed (2.8) than among the non-exposed (1.8) ($p<0.05$). The score did not increase with duration of exposure. As the study was voluntary, the authors raise the issue of a selection bias caused by workers with upper airways symptoms volunteering. Information on concurrent or recent upper respiratory infections was not collected. In an extension of their study, Edling *et al* (1988) added workers from two particle board plants to their study. This study primarily expanded the number of exposed workers from 38 to 75 and used the same histologic scoring index and controls as earlier. The average histologic score among the exposed workers was 2.9 compared with 1.8 among the non-exposed subjects ($p<0.05$). There was no relation between length of exposure and histologic response. Ten men with more than 20 years of exposure had an average histologic score lower than the overall mean score among all exposed workers (2.5 vs. 2.9).

Berke (1987) studied 42 exposed workers from a phenol-formaldehyde plant and 38 non-exposed controls for clinical and cytologic abnormalities of the nasal cavity. Exposure to formaldehyde ranged from 0.02-2.0 ppm, with occasional peaks up to 9 ppm. He found no differences between the groups for polyps, blocked airway, erythema, oedema or fissures of the nasal cavity. The cytologic examination of nasal swabs revealed no differences between the exposed and non-exposed workers. Atypical squamous metaplasia seen in the workers was a function of age and unrelated to formaldehyde. Holmstrom *et al* (1989) examined nasal tissue specimens from 70

[1] All measurements of concentration in this report are given as originally quoted by the authors and if appropriate are converted to ppm for ease of comparison. The converted figures are given in parenthesis.

Table 1. Cytologic and Cytogenetic Studies of Formaldehyde-Exposed Workers

| Authors | Country | Industry | Exposure Levels (ppm) | Exposed | Controls | Tissue | Results |
|---|---|---|---|---|---|---|---|
| Fleig *et al*, 1982 | Germany | Formaldehyde manufacturing | 5 <1971<br>1 >1970 | 15 | 15 | Lymphocytes | No significant difference in chromosome aberrations between exposed workers and controls |
| Thomson *et al*, 1984 | UK | Pathology workers | 1.8-3.9 | 6 | 5 | Lymphocytes | No significant difference in chromosome aberrations between exposed workers and controls |
| Bauchinger and Schmid, 1985 | Germany | Paper factory workers | 1 - 3 | 20 | 20 | Lymphocytes | Significant difference in some cytogenetic measures but not in SCE |
| Yager *et al*, 1986 | USA | Anatomy students | 1.2 | 8 | - | Lymphocytes | Small but significant increase in SCE |
| Edling *et al*, 1987 | Sweden | Particle board factory | 0.4 - 0.9 | 38 | 25 | Nasal | Significant difference on histology index but no relation to dose or duration |
| Edling *et al*, 1988 | Sweden | Particle board factory | 0.08 - 1.0 | 75 | 25 | Nasal | Significant difference on histology index but no relation to dose or duration |
| Berke, 1987 | USA | Formaldehyde manufacturing | 0.02 - 2 | 42 | 38 | Nasal | No relation to clinical or cytologic results |
| Holmstrom *et al*, 1989 | USA | Resins manufacturing | 0.04 - 0.4 (laminate)<br>0.17- 0.25 (furniture) | 62 | 32 | Nasal | Significant difference on histology index, but no relation to dose or duration. |
| Boysen *et al*, 1990 | Norway | Formaldehyde | 0.5 - >2.0 | 37 | 37 | Nasal | No significant difference between groups on histology index |
| Ballarin *et al*, 1992 | Italy | Plywood factory | 0.08 - 0.3 | 15 | 15 | Nasal | Significantly increased frequency of micronuclei among exposed, but no dose-response effect |
| Norppa *et al*, 1992 | Finland | Plywood factory | 0.1 - 0.3 | 28 | 34 | Buccal | Increased micronuclei in buccal cells but not in blood lymphocytes. No relation to level of exposure. |
| Suruda *et al*, 1993 | USA | Mortuary students | 0.15 - 4.3 | 29 | - | Lymphocytes<br>Nasal Buccal | Significantly increased micronuclei from buccal area cells and blood lymphocytes, but not from nasal cells. Results for men and women differ. Numerous other internal inconsistencies. |

workers exposed to formaldehyde in a laminate plant, 62 workers exposed to both formaldehyde and wood dust in furniture making plants, and 32 control subjects from government offices. Nasal biopsies were taken from the medial or inferior aspect of the middle turbinate and posterior to the anterior border of the turbinate. A histologic score (0-8), as used by Edling *et al* (1987), was assigned to each specimen by a pathologist blind to exposure status. Formaldehyde exposure ranged from 0.05 to 0.5 mg/m$^3$ (0.04 to 0.4 ppm) for the laminate plants and from 0.2 to 0.3 mg/m$^3$ (0.17 to 0.25 ppm) for the furniture plants. Exposure to wood dust in the furniture plants ranged from 1 to 2 mg/m$^3$. The mean histologic index score was 2.16 among laminate plant workers, 2.07 among furniture workers, and 1.56 among the controls. The difference between the laminate plant workers and the controls was statistically significant ($p<0.05$); the difference between the furniture workers and controls was not. There was no relation between formaldehyde exposure level or duration of employment and the histologic index score.

Boysen *et al* (1990) examined the nasal mucosa of 37 volunteer formaldehyde-exposed workers and 37 non-exposed control subjects (mostly office workers). Exposure ranged from 0.5 to >2 ppm. Biopsy specimens were taken from the anterior curvature of the middle turbinate of the nasal cavity. There was no significant difference between the exposed and non-exposed workers based on a histological score, even though the control workers were, on average, two years older and histologic changes increase with age. There were 3 exposed subjects with nasal epithelial dysplasia but two of the three were also exposed to wood dust, confounding the observations. The potential bias of using volunteers is not addressed by the authors. Symptomatic subjects may more readily volunteer for the study. Moreover, with 37 subjects in each group it is not clear how statistical adjustments in the analysis could be meaningfully done for age, cigarette smoking, past occupational history and past and present nasal disease.

### 2.1.2 Cytogenetic Studies

Fleig *et al* (1982) examined the lymphocytes from peripheral blood of 15 exposed and 15 non-exposed workers in a formaldehyde manufacturing and resins processing plant. The average number of years of formaldehyde exposure was 28. Data on potential confounding variables such as cigarette smoking, x-ray exposure, recent viral diseases, vaccinations, drug use, and alcohol intake were collected on the volunteers, although not used in the analysis. Exposure levels did not exceed 5 ppm before 1971 and 1 ppm after 1970. No excess in chromosomal aberrations was noted between the exposed and control groups (3.07 vs. 3.33). There was no relationship between chromosomal abnormalities and the level of formaldehyde exposure.

Thomson *et al* (1984) studied chromosomal aberrations and sister-chromatid exchange (SCE) frequencies in peripheral lymphocytes of pathology laboratory workers (6 exposed, 5 not exposed). Depending on the job, average exposure levels ranged from 2.26 mg/m$^3$ to 4.73 mg/m$^3$ (1.8 - 3.9 ppm), with peaks in excess of 11 mg/m$^3$ (9.1 ppm). No significant differences were noted between the two groups of workers for chromosomal aberrations or SCE. Even subjects with the highest levels of exposure (peaks >11 mg/m$^3$; (9.1 ppm)) showed no measurable increase in frequencies of abnormalities.

A study of 20 formaldehyde-exposed paper manufacturing workers and 20 controls examined chromosomal aberrations and SCE in peripheral lymphocytes (Bauchinger and Schmid, 1985). The authors reported a statistically significant increase of dicentrics (0.0013 vs. 0.0005) or dicentric and ring chromosomes (0.0003 vs. 0.0001), although there was no difference in structural aberrations (0.87 vs. 0.86) or SCE (8.87 vs. 9.53). The statistical methods and the relevance of the types of aberrations examined in this study have been called into question (Englehardt *et al*, 1987; IPCS, 1989). Yager and colleagues (1986) examined SCE rates in peripheral lymphocytes of 8 non-smoking students before and after a 10-week anatomy course. The course was held twice per week. The mean formaldehyde level in the laboratory was 1.5 mg/m$^3$ (1.2 ppm). Information on caffeine and alcohol intake, recent immunizations and chemical exposures at home was collected, although none of these data was used in the analysis. A small but statistically significant increase was reported for SCE after start of the class (6.39 vs. 7.20). The students were also exposed to other chemicals including phenol, which can induce SCE.

Ballarin *et al* (1992) in a study of 15 non-smoking formaldehyde-exposed plywood factory workers and 15 non-exposed hospital and university office workers reported a significantly greater frequency of micronucleated nasal cells among the exposed subjects, although there was no dose response between exposure and micronuclei. Formaldehyde levels ranged from 0.1 mg/m$^3$ to 0.39 mg/m$^3$ (0.08 to 0.32 ppm). Wood dust ranged from 0.23 mg/m$^3$ to 0.73 mg/m$^3$. No information is given on how the workers were recruited and a volunteer bias may be operating in which exposed subjects with symptoms are more likely to participate. Although the authors admit that concomitant exposure to wood dust may confound the association with formaldehyde, no attention was given to potential confounding factors such as upper respiratory infections (colds), allergies, and the use of nasal inhalants. There may be a socioeconomic status (SES) difference between exposed plywood factory workers and the control subjects which in turn may relate to differences in background exposure to nasal irritants. There was considerable exposure to glues among the exposed subjects and their effects on micronuclei are unknown. The issue of former smokers among the plywood factory workers is also ignored. The proportion of ex-smokers is likely to be higher in the plywood factory workers than the controls who were employed in clerical positions.

In another study of buccal micronuclei Norppa *et al* (1992) examined 28 exposed workers and 34 control subjects. The exposed workers were recruited in an unknown manner from plywood, chipboard and fibreglass factories. Both buccal mucosal cells and peripheral blood lymphocytes were collected, although the manner is not described. Formaldehyde exposure ranged from 0.1 to 0.3 ppm. The exposed workers showed more micronucleated buccal cells than the controls. There was no relationship between the number of micronuclei and the level of formaldehyde exposure. Likewise there was no relationship between formaldehyde and micronucleated cells in blood lymphocytes. Due to the nature of this publication (an abstract), descriptions of the control group on age and gender matching, method used for obtaining the buccal cells, whether slide reviewers were blinded to exposure status, prevalence of present or past smoking habits, wood dust exposure levels, oral hygiene conditions, alcohol consumption, colds, allergies, etc., is lacking. Without information on these factors any interpretation of this study is limited.

In the most recent investigation, Suruda *et al* (1993) studied 29 mortician students as they were about to start their training. The authors measured a number of variables before and after the 85-day training period. Cells with micronuclei in the nasal and buccal cavities and in the blood lymphocytes were counted along with estimates of SCE both before and after the embalming course. Exposure to formaldehyde ranged from 0.15 to 4.3 ppm with a mean exposure of 1.4 ppm. Peak exposures up to 6.6 ppm occurred. The number of micronuclei in the buccal cells appeared to be related to exposure to formaldehyde in men but not women. There was no association between exposure and micronuclei in nasal cells. A statistically significant increase, however, in micronucleated lymphocytes was reported ($p<0.05$). This was unexpected by the authors as formaldehyde is unlikely to influence sites remote from the respiratory tract (IPCS, 1989), and thus suggests that the higher frequency of buccal micronuclei among exposed males may be unrelated to formaldehyde. SCE were lower after formaldehyde exposure than before. The authors conclude that there is no evidence of a direct mechanism for carcinogenesis. Although this study was carefully performed a number of shortcomings exist. For pre-exposure buccal cells, there were no micronuclei in any of the male samples and none in 5 out of 7 female samples. Some micronuclei would be expected, thus calling into question the suitability of the control (Titenko-Holland *et al*, 1994). With only 29 subjects it is not clear how the authors can statistically adjust (model) for the effects of age, gender and cigarette smoking. There was no mention of evaluation for past or current allergies or upper respiratory tract infections. The role of hepatitis vaccination is ignored, although 48% of the subjects were so treated. The effect of hepatitis vaccination on micronuclei is not known.

## 2.2 Evaluation of Biologic Marker Studies

All the cytologic and cytogenetic studies of formaldehyde exposure among occupationally exposed populations were non-experimental in design. There was no randomized assignment of exposure to formaldehyde. As a result, the issues of bias, confounding and chance must be examined before a sound interpretation of any non-experimental study can be reached (Doll, 1985; IARC, 1987). Each study examined in this section suffered from bias and confounding, and all were too small to properly evaluate confounding factors or chance. The principles by which a causal association is evaluated in non-experimental studies are: strength of the association, consistency across studies, dose-response effect, temporality, and biologic coherence and plausibility (Hill, 1965; Rothman, 1986). These criteria are not met in the cytologic and cytogenetic studies of formaldehyde-exposed workers. The positive findings were modest in regard to the strength of the association. The results were not consistent across studies and often inconsistent within studies. None showed evidence of a dose-response effect.

In short, there appears to be no cytogenetic study published to date that provides adequate data to allow for a conclusion about the effects of formaldehyde exposure on the human chromosome *in vivo*. Deficiencies in control of bias and confounding limit each study, while small sample size prohibits adequate and robust evaluation of any potential effect of formaldehyde.

Observations on the frequency of micronuclei to study the effects of potential carcinogens is a new area of research with many unanswered questions. The relationship between the induction of micronuclei and human cancer risk is unknown (Vine, 1990). Micronuclei frequency is increased by age, gender (females have higher frequency), cigarette smoking, alcohol, viruses, chemicals and diet (low levels of folic acid and vitamin $B_{12}$ ) (Vine, 1990). Proper control for these confounding factors will necessitate large-scale, well-executed studies, with complete and detailed analysis. Until these issues are resolved results of micronuclei studies of formaldehyde workers will remain of limited usefulness.

In the studies reported, the incidence of micronuclei was estimated in buccal cells which are not the targets for carcinogenic effects of formaldehyde. Likewise the nasal cells are taken from a region of the nasal cavity not affected in rats. Hence the results can only be interpreted in terms of whether formaldehyde induces cellular changes in somatic cells. It would not be surprising if formaldehyde, an irritant gas, induced cytological changes in superficial mucosal epithelial cells. However, the studies of Edling *et al* (1987) and Berke (1987) only provided equivocal evidence of cytologic changes. An increase in the frequency of micronuclei could be interpreted as evidence of genotoxicity in the affected cells, but once again the evidence is equivocal.