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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 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) 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 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.

SECTION 3. EPIDEMIOLOGY

Since the early 1980s there have been a large number of epidemiologic studies of formaldehyde and cancer risk and several reviews of the subject (Higginson *et al*, 1988; Purchase and Paddle, 1989; IPCS, 1989; Blair *et al*, 1990; Partanen, 1993; McLaughlin, 1994). For purpose of this review, the studies will be divided into 3 groups: cohort studies of formaldehyde industry workers, studies of professionals, and case-control studies. These categories have been chosen as they reflect a declining precision in the ascertainment and likelihood of exposure to formaldehyde.

Formaldehyde industry workers are those subjects with the most certain exposure and likely to have relatively high and sustained levels of exposure compared with other workers. Professionals such as pathologists, anatomists, and morticians are also almost certainly exposed to formaldehyde, perhaps at relatively high levels for short periods of time. For the most part, the case-control studies provide the weakest evidence of exposure; in almost all such studies there is no direct exposure measurement and putative formaldehyde exposure is inferred from job titles, some of which (such as carpenters) are so broad that the possibility of formaldehyde exposure is quite uncertain.

3.1 Cohort Studies of Formaldehyde Industry Workers

The most informative studies on the hypothesis of formaldehyde and cancer risk are the cohort studies of industry workers, since workers have been exposed to known amounts of formaldehyde and have been under observation for long periods of time to allow for sufficient latency for cancer to occur. Studies of industry workers are listed in Table 2.

The two principal cohort studies of formaldehyde industry workers are the 10 plant industry-wide study in the U.S. (Blair *et al*, 1986) and the 6 plant industry-wide study in the U.K. (Gardner *et al*, 1993). The U.S. study was a large (26,561) nationwide investigation, which included plants reported on previously by other researchers (Marsh, 1982; Fayerweather *et al*, 1983; Wong, 1983; Liebling *et al*, 1984) and as a result these earlier studies are not further reviewed here. The U.S. cohort was defined as all workers first employed before 1 January 1966 and followed until 1 January, 1980 for vital status. All death certificates were reviewed and coded by a study nosologist and there was no minimum employment period for cohort membership. A complex job-exposure matrix was developed for 6,700 job titles. The matrix took into consideration job, work area, and calendar year. Exposure information was gathered by walk-through surveys in each plant, review of monitoring data, and operational changes over time. The matrix was reviewed by industrial hygienists from the participating plants. The mortality experience of the workers was compared with

Table 2. Cohort Studies of Formaldehyde Industry Workers

Authors	Country	Subjects	Study Design	Site	Risk Ratio	(95% CI)
Blair *et al*, 1986	USA	26,561	Retrospective cohort mortality study	All cancer	101	(93-109)
				Nasal	91	(11-328)
				Nasopharynx	300	(109-653)
				Oral/Pharynx	96	(57-152)
				Lung	112	(97-128)
				Brain	81	(47-130)
				Leukaemia	80	(48-124)
Bertazzi *et al*, 1986, 1989	Italy	1,332	Retrospective cohort mortality study	All cancers	106	(76-143)
				NasalNasopharynx	0 vs 0.03	
				Oral/Pharynx	(NR)	
				Lung	(NR)	
				Brain	186	(110-293)
				Haematologic neoplasms	(NR) 154	(50-359)
Edling *et al*, 1987	Sweden	521	Retrospective cohort mortality and incidence study	All cancers (mortality data)	0.99	(0.8-1.2)
				Nasal	(NR)	
				Nasopharynx	(NR)	
				Oral/Pharynx	(NR)	
				Lung	0.57	(0.1-2.1)
				Brain	(NR)	
				Leukaemia	(NR)	
Stayner *et al*, 1988	USA	11,030	Retrospective cohort mortality study	All cancers	82	(73-93)[1]
				Nasal	0	Observed
				Nasopharynx	0	Observed
				Oral/Pharynx	155	(68-307)
				Lung	114	(86-149)
				Brain	71	(28-149)
				Leukaemia	114	(60-200)
Gardner *et al*, 1993	UK	14,017	Retrospective cohort mortality study	All cancers		
				<1965	114	(106-122)
				>1964	97	(81-115)
				Nasal	1 vs 1.74	
				Nasopharynx	0 vs 1.3	
				Oral/Pharynx		
				<1965	125	(64-218)
				>1964	1 vs 2.1	
				Lung		
				<1965	112	(100-124)
				>1964	113	(85-147)
				Brain		
				<1965	92	(52-149)
				>1964	89	(29-207)
				Leukaemia		
				<1965	90	(50-148)
				>1964	91	(25-232)
Andjelkovich *et al*, 1994	USA	3,929	Retrospective cohort mortality study	All cancers	93	(86-101)
				Nasal	0	Observed
				Nasopharynx (non-exposed worker)	1	Observed
				Oral/pharynx	131	(48-286)
				Lung	120	(89-158)
				Brain	62	(7-223)
				Leukaemia	43	(5-157)

NR not reported
1 90% CI

the U.S. population and for some cancer sites local mortality rates were used. Although black men and white women were included in the analysis, their numbers were small, hence, this review will report on results for white men only. There was no overall cancer excess in the U.S. cohort (Standardized Mortality Ratio (SMR) = 101, 95% Confidence Interval (CI): 93-109). Nasal cancer, the major *a priori* site at the time of the study, showed no excess risk (2 observed vs. 2.2 expected). Because of earlier reports on medical professionals and morticians other cancer sites were also under *a priori* suspicion of a link to formaldehyde, namely, buccal cavity and pharynx (SMR= 96, 95% CI: 57-152), brain (SMR=81, 95% CI: 47-130), and leukaemia (SMR=80, 95% CI 47-130). Lung cancer was slightly but not significantly above expectation (SMR=112, 95% CI: 97-128), and was not correlated with intensity or duration of exposure, cumulative exposure, or peak exposure.

Although mortality for buccal cavity and pharynx cancer was not elevated (SMR=96), when the numerous subsites within the mouth and pharynx were examined, an excess risk for nasopharyngeal cancer (NPC) was seen (7 observed vs. 2.2 expected). This was unexpected and was the first report in the literature associating NPC with exposure to formaldehyde. Of the 7 NPCs, 6 were associated with exposure to formaldehyde (SMR=300). There was a suggestive non-significant trend with cumulative exposure (Blair *et al*, 1986, 1987). However, for the other sites of the pharynx (shown in Table 5 of Blair *et al*, 1986) there was an inverse association with level of exposure: SMR=210 for $\leq$0.5 ppm-yr; SMR=30 for 0.51-5.5 ppm-yr; and SMR=0 (0 observed vs. 2.1 expected) for > 5.5 ppm-yr, suggesting a protective effect for other areas of the pharynx. Another anomaly of the subgroup analysis is the fact that only 1 unspecified oral/pharyngeal cancer death was found in the formaldehyde cohort vs. 4.4 expected, suggesting that classification of causes of death in the cohort members may differ from that used nationally and raising the possibility of misclassification, a serious problem when examining subsites within the oral cavity and pharynx, particularly when using death certificates (Percy *et al*, 1990). Correction for the differences in diagnostic criteria used in the general population and in occupational cohorts reduced the significance of the excess risk of NPC (Purchase and Paddle, 1989).

A further deficit of the Blair study was the absence of validation of the NPC deaths in the U.S. study by the investigators. Four of the 6 exposed NPC cases occurred in one plant in Connecticut (Blair *et al*, 1987; Collins *et al*, 1987). Recently, a validation study of the 4 NPC deaths which occurred in the Connecticut plant was performed. Of the 4 NPC cases one has been determined through Connecticut Cancer Registry records to have cancer of the *tonsillar fossa* and not NPC (Lucas, 1994). This worker also had a history of cirrhosis of the liver and chronic bronchitis, suggesting heavy alcohol intake and cigarette smoking, both known causal factors in the etiology of oral/pharyngeal cancer (Blot *et al*, 1988). Also, of the 4 NPC cases from the Connecticut plant, the

misdiagnosed worker was the one who had the longest period of exposure, 18 years. Removal of this worker greatly weakens the trend reported by Blair *et al* of rising NPC risk with rising formaldehyde exposure. Two of the remaining three confirmed NPC cases had less than one year of employment: one was employed for 8 months, the other for 7 months (Collins *et al*, 1987; Lucas, 1994). Further, a recent analysis of the U.S. formaldehyde cohort found that although short-term workers had a higher total cancer risk, their exposure to formaldehyde was not greater than long-term workers (Stewart *et al*, 1992). In summary, this large-scale study provides no clear evidence of a link between formaldehyde and NPC or any other cancer.

The other principal study of formaldehyde industry workers is a 6 plant study in the U.K. involving 14,017 workers (Gardner *et al*, 1993). The workers were stratified into 2 groups; those first employed before 1965 (7,660) and those first employed after 1964 (6,357). This report is an extension of an earlier report by Acheson *et al* (1984). The stratification into 2 groups was done to allow for comparison with the Acheson *et al* report. Both mortality and incidence data were used to identify cancer among cohort members. Local mortality rates were also used to adjust for varying mortality rates by region. All workers were followed up to December 31, 1989. There was one death from nasal cancer vs. 1.74 expected. No non-fatal nasal cancers were observed. The worker with nasal cancer was from the low exposure category (0.1-0.5 ppm) and exposed for 5 years. There were no deaths from NPC (vs. 1.3 expected) and no non-fatal NPC cancers. The ability to check for incidence of these rare but not highly fatal cancers like nasal cancer and NPC is an advantage in this study. The 5-year survival rate for nasal cancer is 58% and 41% for NPC (Miller *et al*, 1993). There was a slight non-significant excess risk of oral/pharyngeal cancer (SMR=110, 95% CI: 59-189). There were 21 brain cancer deaths vs. 23 expected and there were 19 leukaemia deaths vs. 21.2 expected. Hence, *a priori* sites (nasal, NPC, oral/pharynx, brain and leukaemia) were not in excess among these British formaldehyde workers. For lung cancer there was a slight and marginally significant SMR of 112 (100-124) for workers employed before 1965, while those employed after 1964 had a similar risk but it was not statistically significant (SMR=113, 95% CI: 85-147). The excess in the earlier hired group comes almost entirely from one company where 62% of all lung cancer deaths occurred (SMR=121, 95% CI: 105-138). Further examination of risk at this plant showed no clear relation with degree of exposure, duration of employment, latency or cumulative dose. There was no adjustment for the effect of cigarette smoking and with an excess risk of only 12% the confounding effect of smoking cannot be ignored. In fact, for non-malignant respiratory diseases among workers hired before 1965, this plant had a highly significant SMR of 142 (95% CI: 124-161), suggesting that cigarette smoking may be in excess, since non-malignant respiratory diseases were unrelated to formaldehyde exposure. Further, known lung carcinogens, such as asbestos and hexavelant chromium, were used at this plant.

In the U.K. study, it is noteworthy that 35% of the workers first hired before 1965 and 21% of those hired after 1964 were categorized as being in the high formaldehyde exposure (>2 ppm) group. This is a much larger percentage of workers than seen in the U.S. study, where the comparable group was 3%. Therefore, if formaldehyde were a human carcinogen, a clear carcinogenic effect would be expected in the U.K. study. None was observed.

In a small cohort study of formaldehyde workers in an Italian resin plant, Bertazzi *et al* (1986) studied the mortality of 1,332 resin workers from 1959 through December, 1980. To be included in the study the workers must have been employed at least 30 days. National and local rates were used to calculate expected numbers of deaths. Since SMR were much higher using national rates, the authors restricted the analysis to the use of local rates. Besides formaldehyde resins, styrene- and epoxy-based resins were also made. No nasal cancers or NPC were reported. SMR on oral/pharyngeal cancer, brain cancer or leukaemia were not presented. A SMR for haematologic cancers (SMR=154, 95% CI: 50-359, 5 deaths) was presented but not further clarified or discussed. A statistically significant SMR of 186 for lung cancer (95% CI: 110-293) was seen among the resin workers in total, but when analysed by type of exposure, the formaldehyde group (SMR=136, 95% CI: 44-318) was at lower risk than those with "other exposure" (SMR=148, 95% CI: 54-322) and "unknown exposure" (SMR=358, 95% CI: 143-738). For the formaldehyde group there was no relation between risk of lung cancer and duration of employment or latency. In an update to this cohort, overall lung cancer mortality was no longer in excess (24 observed vs. 23.9 expected) (Bertazzi *et al*, 1989).

A small study of 521 Swedish abrasive workers who used formaldehyde resins as a binder reported no excess of cancer incidence or mortality (Edling *et al*, 1987). No nasal cancers were reported and one nasopharyngeal cancer was observed (expected number not provided).

In a relatively large cohort study of 11,030 female textile workers who used formaldehyde resins to reduce creasing in shirts, the National Institute for Occupational Safety and Health (NIOSH) studied the mortality experience of female employees from 1955-59 to December, 1982 (Stayner *et al*, 1988). Workers had to have been employed for at least 3 months before being eligible for the cohort. Three plants were studied, one started use of formaldehyde in 1955, the other two in 1959. Expected numbers of deaths were calculated using U.S. and State rates. Ninety percent confidence intervals were used rather than the standard 95% interval and accordingly a one-sided rather than a two-sided p-value was also used to evaluate statistical significance. The authors observed no deaths from nasal cancer or NPC. The SMR for brain cancer was 71 (90% CI: 28-149) and for leukaemia was 114 (90% CI: 60-200). There was a non-significant elevation in lung cancer mortality (SMR=114, 90% CI: 86-149), but this was a result, according to the authors, of an

elevated risk among short-term workers where exposure to formaldehyde was recent and much lower than in the past. The potential for asbestos exposure among textile workers was not assessed in this study. The main finding of this well-conducted study was a statistically significant elevation of buccal cavity cancer, 4 observed vs. 1.2 expected (SMR=343, 90% CI: 118-786). However, if a conventional 95% CI is calculated, the SMR is no longer significant (95% CI: 93-877); p>0.05) (Bailar and Ederer, 1964). Moreover, two of these 4 deaths occurred among white women from the rural south, where snuff dipping is a common practice. One of the women was a snuff dipper and died from oral mucosa cancer and another smoked cigarettes. Snuff dipping is a proven oral carcinogen and long-term use increases the risk of oral mucosa cancer almost 50 fold (Winn *et al*, 1981; Surgeon General, 1986). There was no excess of pharyngeal cancer deaths among workers: 2 observed vs. 1.8 expected.

A recent mortality study of a subcohort of 3,929 workers in an automotive iron foundry in the U.S. with exposure to formaldehyde found no relation to cancer risk (Andjelkovich *et al*, 1994). There were no deaths reported from nasal cancer, and one death from NPC, but this was of a non-exposed worker.

3.2 Evaluation of Cohort Studies

Overall, the cohort studies of formaldehyde industry workers have provided scant evidence to link formaldehyde exposure with human cancer risk. Because of the certainty of exposure to formaldehyde, these studies do not have the problem found in other epidemiologic investigations, such as case-control studies, which use hypothetical exposure estimates. The workers were in the formaldehyde industry itself or used formaldehyde in a manufacturing process. The cohort studies of formaldehyde industry workers provide no evidence to support the animal findings of an excess risk of nasal cancer. The excess of NPC, reported in one study, can no longer be considered evidence of a true association. This *post hoc* finding suffered from misdiagnosis and multiple subgroup comparison bias. Subdivision of the many sites within the oral cavity and pharynx increased the chance of finding a spurious result.

From the epidemiologic studies most likely to uncover a cancer risk, namely cohort studies of formaldehyde industry workers, no convincing evidence of a cancer problem has been observed.

3.3 Professional Groups Exposed to Formaldehyde

For more than 100 years, professionals such as pathologists, anatomists, and embalmers have used formaldehyde as part of their routine activities. They also come into contact with a wide

variety of other chemicals and agents. The 10 studies of professionals that will be reviewed are listed (Table 3).

Harrington and Shannon (1975) examined the mortality experience of 2,079 British pathologists and 12,944 medical laboratory assistants. The pathologists were studied for the period 1955 to 1973, while the technicians were studied for the period 1963 to 1973. No deaths from nasal cancer, oral/pharyngeal cancer, NPC or brain cancer were reported in either cohort. Lung cancer risk was quite low among both the pathologists (11 observed vs. 27.9 expected; SMR=39, 95% CI: 20-70) and the technicians (13 vs. 22.2; SMR=59, 95% CI 30-100). Besides a large excess of suicides in both groups, the only cancer with increased risk was that of lymphoma and haematoma (8 vs. 4; SMR=200, 95% CI 86-394). As can be seen by an examination of the 95% confidence intervals, the result is not significantly higher than expectation. This rubric of diseases included leukaemia (1 vs. 1.6) and Hodgkin's disease (1 vs. 0.7), which were not in excess. The authors suggest that the excess was derived from "lymphomata", multiple myeloma, and polycythemia vera, although actual numbers were not presented. In a later study, Harrington and Oakes (1984) extended the follow up of the pathologists from 1974 through 1980. No deaths from nasal cancer, oral/pharyngeal cancer or NPC were reported. There were still significantly fewer lung cancer deaths than expected (9 vs. 22.0; SMR=41, 90% CI: 21-71). There was an excess of brain cancer deaths (4 vs. 1.2) for a SMR of 331, which the authors report as statistically significant because of use of 90% CIs. If the more standard 95% CIs were calculated, the brain cancer SMR would not be statistically significant (SMR=331, 95% CI: 90-847). In contrast to the earlier report, there was no excess of deaths from lymphatic and haematopoietic cancers (9 vs. 11.7); although suicides were again significantly elevated (7 vs. 2.0). A further follow-up of these pathologists through 1986 was performed (Hall et al, 1991). No cases of nasal or nasopharyngeal cancer were reported; and no cancer sites were observed to be significantly in excess of expected.

Walrath and Fraumeni (1983) reported on the mortality experience of 1,132 New York State embalmers licensed to practice between 1902 and 1980 and known to have died between 1925 and 1980. They used proportional mortality analysis which compares the proportion of causes of death in the study group to the proportion found in the comparison group. The comparison group in this study was U.S. white males who died between 1925 and 1980. Statistical significance was evaluated using a chi-square test, although it is not clear if a one-sided or two-sided p-value was used in the paper. No nasal cancers or NPC were reported. There were 8 deaths from oral and pharyngeal cancer compared with 7.1 expected. For lung cancer, there were 72 deaths vs. 66.8 expected (Proportional Mortality Ratio [PMR]=108). There were 9 deaths from brain cancer compared with 5.8 expected (PMR=156, $p>0.05$); and 12 leukaemia deaths compared with 8.5 expected (PMR=140, $p>0.05$). The authors also calculate proportional cancer mortality ratios

Table 3 Studies of Professionals

Author	Country	Profession	Subjects	Study Design	Site	Risk Ratio (95% CI)	
Harrington and Shannon, 1975	UK	Pathologists, Laboratory Technicians	2,079 12,944	Retrospective cohort mortality study		Pathologists	Technicians
					All cancers	0.60 (0.4-0.8)	0.62 (0.4-0.9)
					Nasal	(NR)[1]	(NR)
					Nasopharynx	(NR)	(NR)
					Oral/Pharynx	(NR)	(NR)
					Lung	0.39 (0.2-0.7)	0.59 (0.3-1.0)
					Brain	(NR)	(NR)
					Leukaemia	1 vs 1.6	1 vs 2.2
Walrath and Fraumeni, 1983	USA	Embalmers, Funeral Directors	1,132	Proportional mortality study	All cancers	111	(97-126)
					Nasal	(NR)	
					Nasopharynx	(NR)	
					Oral/Pharynx	113	(49-222)
					Lung	108	(85-136)
					Brain	156	(72-296)
					Leukaemia	140	(72-244)
Walrath and Fraumeni, 1984	USA	Embalmers	1,007	Proportional mortality study	All cancers	121	(105-139)
					Nasal	0 vs 0.6	
					Nasopharynx	(NR)	
					Oral/Pharynx	131	(56-258)
					Lung	96	(69-130)
					Brain	194	(89-368)
					Leukaemia	175	(90-305)
Harrington and Oakes, 1984	UK	Pathologists	2,307	Retrospective cohort mortality study	All cancers	61	(42-86)
					Nasal	(NR)	
					Nasopharynx	(NR)	
					Oral/Pharynx	(NR)	
					Lung	41	(21-70)
					Brain	331	(90-847)
					Leukaemia	1 vs 1.1	
Levine *et al*, 1984	Canada	Undertakers	1,477	Retrospective cohort mortality study	All cancers	87	(66-112)
					Nasal	0 vs 0.2	
					Nasopharynx	(NR)	
					Oral/Pharynx	1 vs 2.1	
					Lung	94	(57-147)
					Brain	115	(23-336)
					Leukaemia	160	(44-409)
Stroup *et al*, 1986	USA	Anatomists	2,317	Retrospective cohort mortality study	All cancers	64	(53-76)
					Nasal	0 vs 0.5	
					Nasopharynx	(NR)	
					Oral/Pharynx	1 vs 6.8	
					Lung	30	(10-50)
					Brain	270	(130-500)
					Leukaemia	150	(70-270)
Logue *et al*, 1986	USA	Pathologists	5,585	Retrospective cohort mortality study	All cancers	(NR)	
					Nasal	(NR)	
					Nasopharynx	(NR)	
					Oral/pharynx	0.71	(NR)
					Lung	0.24	(NR)
					Brain	(NR)	
					Leukaemia	1.1	(NR)

NR = not reported

Table 3 Studies of Professionals (cont.)

Author	Country	Profession	Subjects	Study Design	Site	Risk Ratio	(95% CI)
Hayes *et al*, 1991	USA	Embalmers, Funeral Directors	4,046	Proportional mortality study	All cancers	107	(100-114)
					Nasal	0 vs 1.7	
					Nasopharynx	216	(59-554)
					Oral/Pharynx	120	(81-171)
					Lung	95	(85-106)
					Brain	123	(80-184)
					Lymphatic & Haematopoietic	139	(115-167)
Matanoski, 1991	USA	Pathologists	6,411	Retrospective cohort mortality study	All cancers	78	(71-85)
					Nasal	(NR)	
					Nasopharynx	(NR)	
					Hypopharynx	470	(97-1,370)
					Oral/Pharynx	52	(28-89)
					Lung	56	(44-70)
					Brain	134	(71-229)
					Leukaemia	135	(92-192)
Hall *et al*, 1991	UK	Pathologists	4,512	Retrospective cohort mortality study	All cancers	45	(34-59)
					Nasal	(NR)	
					Nasopharynx	(NR)	
					Oral/pharynx	(NR)	
					Lung	19	(9-36)
					Brain	218	(80-475)
					Leukaemia	152	(41-389)

NR = not reported

(PCMR) for the cancer sites, which are superior to the PMR method, since the relative proportions of deaths are restricted only to cancers and thereby limit sources of variation in proportions of death (Checkoway *et al*, 1989). PCMR calculations reduced the magnitude of the PMR for brain cancer and leukaemia to 138 from 156 and to 119 from 140, respectively. Statistically significant PMR were observed for colon cancer (PMR=143) and skin cancer (PMR=221), but when PCMR were calculated these sites were no longer statistically significant: PCMR for colon cancer=130; PCMR for skin cancer=184. Moreover, if 95% confidence intervals were calculated for colon cancer (PMR=143, 95% CI: 96-205) and for skin cancer (PMR=221, 95% CI: 95-435), it can be seen that the CIs include unity and would not be statistically significant using a two-tailed test. When PMR were examined by job titles (embalmers only or both embalmers and funeral directors) the mortality ratios were higher for embalmers. This was thought to reflect greater exposure. In another study, Walrath and Fraumeni (1984) reported on the proportional mortality of 1,007 white male embalmers licensed to practice in California. The study period started in 1925 and lasted through 1980. Both PMR and PCMR were calculated using U.S. white males for comparison. No nasal cancer deaths occurred in this cohort of embalmers and no NPC deaths were reported. Eight oral and pharyngeal cancer deaths occurred vs. 6.1 expected (PMR=131; PCMR=99). There were 41 lung cancer deaths compared with 42.9 expected PMR=96; PCMR=87). Nine deaths from brain cancer were

seen vs. 4.7 expected (PMR=194), which was reported as statistically significant ($p<0.05$). However, the 95% CI of 89-368 is not consistent with such an interpretation, indicating a one-tailed test was used. Moreover, the PCMR for brain cancer of 168 was reduced from the PMR of 194 and was not statistically significant. Leukaemia deaths were also considered to be significantly greater than expected (12 observed vs. 6.9 expected, PMR=175) but the 95% CI (90=305) for the leukaemia PMR does not support this inference. Neither does the lower PCMR of 140 from 175 for leukaemia. As in the study of the New York state embalmers, the PMR for colon cancer was significantly raised at 187 (30 vs. 16.0), but when a PCMR was calculated the excess was no longer significantly elevated (PCMR=144). An unexpected excess was seen for deaths from prostate cancer (23 vs. 13.1; PMR=175, $p<0.05$), but the PCMR of 126 for this cancer was not significantly elevated.

A retrospective cohort mortality study of 1,477 Ontario morticians by Levine *et al* (1984) examined mortality for the period 1950 through 1977. Mortality rates for Ontario during this period were used to calculate expected numbers of deaths. There were no nasal or NPC deaths in the cohort. One death from oral and pharyngeal cancer was observed compared with 2.1 expected. Nineteen lung cancer deaths were seen vs. 20.2 expected (SMR=94). Three brain cancer deaths were reported compared with 2.6 expected. For leukaemia, 8 deaths were reported vs. 6.5 expected (SMR=124). Separate results were not presented for colon cancer, but the SMR was 85 for deaths from small and large intestine and rectum combined (8 observed vs. 9.5 expected). Prostate cancer was not elevated (SMR=88). The most striking cause of death in this cohort of Ontario morticians was cirrhosis of the liver (SMR=238, $p\leq0.001$, based on 18 deaths vs. 7.6 expected). Cirrhosis of the liver was not elevated in the studies of Harrington and Shannon (1975) and Harrington and Oakes (1984), but the PMR studies of Walrath and Fraumeni (1983, 1984) did show some elevations.

In 1986, Stroup *et al* published a retrospective cohort mortality study of 2,317 U.S. male anatomists. The mortality follow up was for the period 1925 through 1979. Their mortality experience was compared with that of U.S. males for the period 1925 through 1979, and for certain cancer sites rates of U.S. psychiatrists for the period 1900 through 1969 were used. In this cohort of anatomists overall cancer mortality was remarkably low (SMR=64, 95% CI: 53-76). There were no deaths from nasal cancer or NPC. In fact, there was only one death from all oral and pharyngeal cancers combined compared with 6.8 expected (SMR=20, 95% CI: 0-80). For lung cancer, 13 deaths were observed compared with 43.1 expected (SMR=30, 95% CI: 10-50). There were no excesses for colon cancer (SMR=110, 95% CI: 70-170) or prostate cancer (SMR=100, 95% CI: 60-160). Leukaemia showed some increases with an SMR of 150 (95% CI: 70-270). One cancer site was significantly elevated indicating brain cancer with a SMR of 270 (95% CI: 130-500). When U.S. psychiatrists were used as the comparison population, the SMR increased to 600 (95% CI: 230-

1560), while the SMR for leukaemia went from 150 to 80 (95% CI: 20-290). The authors, however, make a point of noting that this excess risk for brain cancer does not necessarily implicate formaldehyde, as anatomists are exposed to a large number of other agents.

Logue *et al* (1986) studied the mortality experience of U.S. pathologists and radiologists using death rates of U.S. white males for comparison. There was no excess cancer mortality among pathologists or radiologists relative to U.S. white males. When these two professional groups were compared to each other using age-adjusted mortality rates, their cancer rates were similar.

Hayes *et al* (1990) executed a large-scale proportional mortality study of U.S. embalmers and funeral directors for the period 1975 through 1985. This study did not include the deaths from the two earlier studies of Walrath and Fraumeni (1983, 1984). There were 3,649 deaths among white and 397 among non-white embalmers and funeral directors. No nasal cancer deaths were observed compared with 1.7 expected. Four NPC were seen vs. 1.85 expected (PMR=216, 95% CI: 59-554), which is compatible with chance. For oral and pharyngeal cancer deaths, 30 were seen vs. 25 expected (PMR=120, 95% CI: 81-171). There was no excess of lung cancer deaths (308 vs. 324.5, PMR=95, 95% CI: 85-106). For brain cancer deaths, 24 were observed vs. 19.4 expected (PMR=123, 95% CI: 80-184). The authors calculated a PCMR for brain cancer of 109. A significantly high proportion of lymphatic and haematopoietic malignancies was reported (PMR=139, 95% CI: 115-167), mostly as a result of an excess of deaths from myeloid leukaemia (PMR=157, 95% CI: 101-234) and "other and unspecified leukaemias" (PMR=228, 95% CI: 139-352). The lymphatic and haematopoietic PMR was higher for funeral directors (PMR=156, 95% CI: 123-194) than for embalmers (PMR=123, 95% CI: 78-185), a finding inconsistent with assumptions made in earlier analyses of these professionals that embalmers have greater exposure than funeral directors (Walrath and Fraumeni, 1983). This inconsistency by job type is ignored by the authors.

The largest study of professionals to date has been of 6,411 male U.S. pathologists followed for vital status from 1925 to 1978 (Matanoski, 1991). (The overlap between this study population and that of Logue *et al* (1986) is unknown. However, the present study is larger and more thoroughly analysed.) For comparison, the mortality rates of U.S. white males and U.S. male psychiatrists were used. As in all other cohort mortality studies of professionals, there was no excess of total cancers (SMR=78, 95% CI: 71-85). In fact of the 7 cohort mortality reports on professionals, 6 have significantly reduced SMR for total cancer (Harrington and Shannon, 1975; Harrington and Oakes, 1984; Stroup *et al*, 1986; Logue *et al*, 1986; Matanoski, 1991; Hall *et al*, 1991). There were no nasal or NPC deaths reported. There were significantly fewer oral/pharyngeal cancer deaths than expected (13 vs. 25, SMR=52; 95% CI: 28-89). Stomach cancer deaths were also significantly reduced (31 vs. 83.8, SMR=37, 95% CI: 25-53). Lung cancer occurred at almost half the expected

rate (77 vs. 137.5, SMR=56, 95% CI: 44-70). There were no excesses of colon cancer (SMR=94, 95% CI: 72-120) or prostate cancer (SMR=80, 95% CI: 61-102). A non-significant increase in brain cancer was seen (SMR=134, 95% CI: 71-229). When psychiatrists were used for comparison, there was little difference (SMR=141, 95% CI: 81-261). There were elevated but non-significant SMRs for some lymphatic-haematopoietic malignancies: lymphosarcoma (SMR=131, 95% CI: 66-235), leukaemia (SMR=135, 95% CI: 92-192), and "other lymphatic" (SMR=154, 95% CI: 114-238) cancer, but a deficit of Hodgkin's disease (SMR=36, 95% CI: 4-131). Pancreatic cancer mortality was significantly elevated (SMR=139, 95% CI: 102-185). Comparison with U.S. psychiatrists changed the pancreatic cancer SMR little (SMR=141, 95% CI: 104-188).

Perhaps the most interesting result in this cohort of pathologists was the elevated SMR for hypopharyngeal cancer (not NPC as reported in the review by Partanen *et al*, 1993), (3 vs. 0.64, SMR=470, 95% CI: 97-1370), particularly since total oral/pharyngeal cancer deaths were significantly reduced (SMR=52, 95% CI: 28-89). If the 3 hypopharyngeal cancers and their expected numbers were removed from the total oral/pharyngeal cancer deaths, the SMR would be even lower than the already significantly reduced SMR of 52. Such a result suggests (as in Blair *et al*, 1986, 1987) that the hypopharyngeal cancer finding is a chance event resulting from multiple subgroup comparisons of the numerous sites of the oral/pharyngeal cavity. In fact, Matanoski did not consider the elevated SMR for hypopharyngeal cancer deaths as evidence of a formaldehyde effect.

3.4 Evaluation of Cohort Studies

The studies of professionals provide a profile of cancer risk that does not support formaldehyde as a cause of human cancer. Malignancies of the upper and lower respiratory tract, the primary areas of contact of formaldehyde are almost uniformly below expectation. Those cancers found to be increased in some of the professional groups, such as cancers of the colon, brain, and leukaemia, are not found in excess in the studies of formaldehyde industry workers. Because of the rapid metabolism of formaldehyde at tissue contact, sites distal from exposure are unlikely to be related to formaldehyde (IPCS, 1989). Moreover, there is no animal evidence of cancer risk at distal sites.

3.5 Case-Control Studies

There are a large number of case-control studies that have attempted to evaluate cancer risk and formaldehyde exposure (Table 4). They include a number of cancer types, but most involve sites of the upper or lower respiratory tract. Some studies have been case-control investigations within a cohort of formaldehyde industry workers (Fayerweather *et al*, 1983; Bond *et al*, 1985; Partanen *et*

al, 1990, 1993; Andjelkovich *et al*, 1994), while the remainder have been community-based case-control studies using death certificates, hospitals or cancer registries for cancer cases and numerous sources for control subjects.

A number of the case-control studies have found no relationship with formaldehyde exposure and will not be reviewed in this chapter, although their overall results can be found in Table 4 (Fayerweather *et al,* 1983; Brinton *et al*, 1984; Bond *et al*, 1986; Gerin *et al,* 1989; Partanen *et al*, 1990; Wortley *et al*, 1992; Luce *et al*, 1993; Partanen *et al*, 1993; Andjelkovich *et al*, 1994). It should be noted that all nested case-control studies of formaldehyde workers, where exposure to formaldehyde is likely and not hypothetical, no links with increased cancer risk were observed (Fayerweather *et al*, 1983; Bond *et al*, 1985; Partanen *et al*, 1990; 1993; Andjelkovich *et al*, 1994). The remaining studies (all community based) that report a positive association will be examined in detail (Coggon *et al*, 1984; Olsen *et al,* 1984; Olsen and Asnaes, 1986, Vaughn *et al*, 1986a, b; Hayes *et al*, 1986; Roush *et al*, 1987; Merletti *et al*, 1991; West *et al*, 1993). None of the studies reporting a positive association included actual measurements of formaldehyde exposure among cases or controls, but instead relied on surrogate measures (especially job title) to assess whether or not the subject may have been exposed.

A death certificate-based case-control analysis of 598 lung and 287 bladder cancers and 1,758 matched controls in England and Wales was done by Coggon *et al* (1984) for the study period 1975 through 1979. Occupation as listed on the death certificate was abstracted, and a job-exposure matrix developed using these data for a large number of agents, including formaldehyde. It is not clear if the industrial hygienist who made the exposure assignments was blinded to case-control status. Lung cancer was significantly associated with any exposure to asbestos, cutting oils, diesel fumes, solder, and formaldehyde (Odds Ratio [OR]=1.5, 95% CI: 1.2-1.8). When the analysis was further refined by examining risk among those most likely to be exposed to formaldehyde, the excess risk was eliminated (OR=0.9, 95% CI: 0.6-1.4), as were the significantly elevated OR for other exposures when a similar restriction was made, except for asbestos, which increased (OR=1.9, 95% CI: 1.2-2.9). The first OR calculation for formaldehyde used any job assumed to have formaldehyde exposure, which according to the authors, included a large number of jobs with known asbestos exposure and with a high prevalence of smokers. To quote the authors: "The association between lung cancer and occupations involving possible exposure to formaldehyde is impressive ($p<0.001$), but the absence of risk in jobs with high exposure is against a direct causal mechanism. Much of the excess lung cancer in the low-exposure group of occupations occurred in jobs also associated with other exposures known to cause lung cancer, for example, pipe fitters (asbestos), construction workers (asbestos), and lorry drivers (smoking)." Yet with these caveats in mind, the results of this study have been used in meta-analyses of formaldehyde and lung cancer

Table 4 Case-Control Studies

Author	Country	Cancer Type	Cases	Controls	Study Design	Site	Risk Ratio	(95% CI)
Fayerweather *et al*, 1983	USA	Multiple sites	481	481	Nested case-control study	Continuous exposure		
						All cancers	1.19	(NR)
						Oral cavity	0 cases, 0 controls	
						Oesophagus	1.00	(NR)
						Stomach	1.00	(NR)
						Liver, gallbladder, bile duct	0 cases, 0 controls	
						Bladder	5.25	(NR)
						Melanoma	1 case, 0 control	
						Lung	1.21	(NR)
Brinton *et al*, 1984	USA	Nasal	160	190	Hospital-based study	Ever exposed	0.35	(0.1-1.8)
Coggon *et al*, 1984	UK	Lung, bladder	598 587	1180	Death-certificate based study	Ever exposed		
						Lung	1.5	(1.2-1.8)
						Bladder	1.0	(0.7-1.3)
						Heavy exposure		
						Lung	0.9	(0.6-1.4)
						Bladder	1.5	(0.9-2.5)
Olsen *et al*, 1984	Denmark	Nasal nasopharyngeal	488 266	2465	Linked-registry study with cancer controls	Ever exposed		
						Nasal-men	2.8	(1.8-4.3)
						Nasal-women	2.8	(0.5-14.3)
						Nasopharynx-men	0.7	(0.3-1.7)
						Nasopharynx-women	2.6	(0.3-21.9)
						Exposed >10 yrs previously (nasal)		
							3.1	(1.8-5.3)
							1.6	(0.7-3.6)
							Adjusted for wood dust	
Vaughn *et al*, 1986a, b	USA	Nasal nasopharyngeal other pharynx	53 27 205	552	Population-based study	1984a-Medium or high occupational exposure		
						Nasal	0.3	(0-1.3)
						Nasopharynx	1.4	(0.4-4.7)
						Other pharynx	0.6	(0.1-2.7)
						1984b-Mobile home residence >10 yrs		
						Nasal	0.6	(0.2-1.7)
						Nasopharynx	5.5	(1.6-19.4)
						Other pharynx	0.8	(0.2-2.7)
Bond *et al*, 1986	USA	Lung	308	308 dec. 308 living	Nested case-control study	Ever exposed	0.62	(0.29-1.34)
Hayes *et al*, 1986	USA	Nasal	91	195	Next-of-kin interviews for 30% of cases and 12% of controls	Ever exposed (low wood dust)		
						Assessment A	2.5	(1.2-5.0)[1]
						Assessment B	1.6	(0.9-2.8)[1]

NR not reported
1 90% CI

Table 4 Case-Control Studies (cont.)

Author	Country	Cancer Type	Cases	Controls	Study Design	Site	Risk Ratio	(95% CI)
Olsen and Asnaes, 1986	Denmark	Nasal nasopharyngeal	466 293	2465	Linked-registry study with cancer controls	Ever Exposed Squamous cell carcinoma Adenocarcinoma Authors state no association with histologically verified nasopharyngeal cancer (no risk ratios reported)	 2.3 2.2	 (0.9-5.8) (0.7-7.2)
Roush *et al*, 1987	USA	Nasal nasopharyngeal	198 173	605	Cases from cancer registry, controls from death certificates	Probably exposed Nasal Nasopharynx Probably exposed to high level >20 years before death Nasal Nasopharynx	 0.8 1.0 1.5 2.3	 (0.5-1.3) (0.6-1.7) (0.6-3.9) (0.9-6.0)
Gerin *et al*, 1989	Canada	Multiple sites	5,311	~2,500	Cancer controls and population controls	Ever exposed Oesophagus Stomach Colorectal Liver Pancreas Lung Prostate Bladder Kidney Melanoma Non-Hodgkin's lymphoma Hodgkin's lymphoma	 1.0 1.1 0.9 1.0 0.7 0.8 1.1 1.2 1.0 1.0 0.9 0.5	 (0.6-1.6) (0.8-1.5) (0.7-1.1) (0.5-1.9) (0.4-1.2) (0.6-1.0) (0.8-1.4) (0.9-1.5) (0.7-1.4) (0.6-1.7) (0.6-1.3) (0.2-1.2)
Partanen *et al*, 1990	Finland	Nasal, oral/pharyngeal, larynx, lung	1 5 12 118	408	Nested case-control study	Ever exposed Exposed with 10 year latency 	 0.69 0.89	 (0.21-2.24)[1] (0.26-3.00)[1]
Merletti *et al*, 1991	Italy	Oral/ pharynx	86	373	Population-based study	Ever exposed Probable or definite exposure 	 1.6 1.8	 (0.9-2.8) (0.6-5.5)
Wortley *et al*, 1992	USA	Larynx	235	547	Population-based study	Exposure Low Medium High	 1.0 1.0 2.0	 (0.6-1.7) (0.4-2.1) (0.2-19.5)
Partanen *et al*, 1993	Finland	Hodgkin's disease Non-Hodgkin's lymphoma leukaemia	4 8 12	152	Nested case-control study	Ever exposed	 2.27	 (0.64-7.98)

NR not reported
1 90% CI

Table 4 Case-Control Studies (cont.)

Author	Country	Cancer Type	Cases	Controls	Study Design	Site	Risk Ratio	(95% CI)
Luce *et al*, 1993	France	Nasal	207	409	Hospital-based study	Possible exposure	0.96	(0.38-2.42)
						>20 years exposure	0.68	(0.27-1.75)
West *et al*, 1993	Philipp-ines	Nasal nasophar-yngeal	104	104 hospital, 101 neigh-bourhood	Population-based study	Duration of exposure		
						<15 years	2.7	(1.1-6.6)
						≥15 years	1.2	(0.48-32)
Andjelkovich *et al*, 1994	USA	Lung cancer	220	2220	Nested case-control study	Lag period		
						0 years	1.31	(0.83-2.07)
						10 years	0.95	(0.57-1.57)
						15 years	0.85	(0.50-1.45)
						20 years	0.84	(0.44-1.60)

NR not reported

(Blair *et al*, 1990; Partanen *et al*, 1993). It should be noted that exclusion of the 296 presumed formaldehyde-exposed lung cancers (the largest number of lung cancers of any formaldehyde study) and their 197 expected deaths would eliminate the slight excess risk of lung cancer reported in meta-analyses of "industrial workers".

In 1984, Olsen *et al* published a record linkage-based study of 488 sinonasal (SNC) and 266 nasopharyngeal (NPC) cancers and 2,465 cancer controls. Thirty-three percent of the cases were women. Cases and controls were diagnosed between 1970 and 1982 in Denmark. Using a 10-digit identification number unique to each Danish citizen, the authors linked the cases and controls to the Danish Pension Fund Registry (DPFR) and the Central Population Registry (CPR) to obtain historical occupational information (DPFR, 1970-1979) and more limited current employment data (CPR, 1980-1982). The job and industry codes found in these registries were used as the basis of a job-exposure matrix for formaldehyde and a number of other agents. Three industrial hygienists were used, blind to case and control status. NPC was unrelated to hypothetical formaldehyde exposure among men (OR=0.7, 95% CI: 0.3-1.7), while among women a non-significant elevation was seen (OR=2.6, 95% CI: 0.3-21.9). For women, none of the 12 exposures examined in the study was associated with a significantly increased risk of SNC or NPC. For men, putative exposure to formaldehyde was associated with a statistically significant OR for SNC of 2.8 (95% CI: 1.8-4.3), as was exposure to wood dust (OR=2.5, 95% CI: 1.7-3.7), metal work (OR=1.4, 95% CI: 1.0-1.5), and employment in paint, lacquer and glue manufacturing (OR=2.1, 95% CI: 1.4-3.0). Because some jobs were classified as having both wood dust and formaldehyde exposure, adjusted OR were calculated. When adjusted for wood dust, the significant OR of 2.8 for formaldehyde was

reduced to a non-significant OR of 1.6 (95% CI: 0.7-3.67). When adjusted for formaldehyde, the OR of SNC for wood dust was reduced but still significant (OR=2.1, 95% CI: 1.2-3.7). In a later analysis of the same data, Olsen and Asnaes (1986) examined SNC and NPC risk by cell type. Although they used the same data set, there are some discrepancies between the 1984 and 1986 analyses on the number of SNC (466 vs. 488 in 1984) and of NPC (293 vs. 266 in 1984), which the authors do not address. The number of controls remained the same at 2,465. There was no statistically significant association between formaldehyde exposure and risk of squamous cell SNC (OR=2.3, 95% CI: 0.9-5.8) or adenocarcinomas (OR=2.2, 95% CI: 0.7-2.2). A latency analysis did not materially change the results. Of the 13 squamous cell SNC, 9 were also exposed to wood dust. The wood dust OR for adenocarcinoma of the nasal cavity and sinuses was 16.3 (95% CI: 5.2-50.9). A latency analysis excluding the first 10 years since exposure to wood dust increased the OR to 30.4 (95% CI: 8.9-103.9). Histologically specified NPC showed no association with either formaldehyde or wood dust exposure. Hence, this further analysis of the Danish data by cell type demonstrated a strong relationship between adenocarcinoma of the nasal cavity and sinuses and putative exposure to wood dust. No relationship was seen for formaldehyde exposure and SNC by cell type or for NPC. In both studies there was a failure to adjust for cigarette smoking, which is a risk factor for SNC (Zheng *et al*, 1993).

In a small case-control study of 91 SNC and 195 controls in the Netherlands, Hayes *et al* (1986) examined hypothetical formaldehyde exposure and nasal cancer risk. The cases were ascertained during the period 1978 through 1981 from 6 institutions that treat head and neck tumours. There were two types of controls: living controls selected from male residents of the Netherlands in 1982 and deceased controls selected from deaths among men in 1980. The latter control group was chosen because some of the cases died before interview. Next-of-kin interviews were obtained for 27 (30%) of the 91 cases and 23 (12%) of the 195 controls. Analysis was by cell type and 90% CIs and one-sided p-values were used. This study also employed a job-exposure matrix for possible exposure to formaldehyde and wood dust independently developed and applied by two industrial hygienists (assessors A and B), blinded to case and control status. The matrix was derived from employment information obtained during the interview with the subject himself or his next of kin. The OR for formaldehyde exposure among workers with low dust exposure were 2.5 (90% CI: 1.2-5.0) and 1.6 (90% CI: 0.9-2.8) for assessors A and B, respectively. When the risk estimate for assessor A was adjusted for cigarette smoking it was reduced to 2.2 (90% CI: 1.1-4.6) but was not statistically significant if a 95% CI was used (95% CI: 0.9-5.2). The OR were lower among high dust exposed subjects. When putative formaldehyde exposure was examined by cell type, the OR for squamous cell nasal cancer among low dust exposed subjects as judged by assessor A was 3.0 (90% CI: 1.3-6.4) and 1.9 (90% CI: 1.0-3.6) by assessor B. The squamous cell cancer results were not adjusted for cigarette smoking, which is likely to be more strongly related to smoking than

adenocarcinoma of the nasal cavity and sinuses (Zheng *et al*, 1993). Other concerns with the study include a major discrepancy for putative formaldehyde exposure between assessors A and B. Assessor A considered 23% of the subjects to have at least some exposure, while assessor B classified 44% of the study subjects exposed. The source of the discrepancy was never clarified nor was a third assessor brought in to resolve the differences, which is common practice. Another concern not addressed by the authors is the next-of-kin interviews. There was no adjustment for these data and results may change with such adjustment. At the very least, the results should also have been presented with the next-of-kin data removed. Finally, the jobs classified as formaldehyde-exposed among low dust exposed subjects when examined closely are unconvincing as actual sources of formaldehyde exposure. As a result of these concerns, the data from this study are not persuasive of an association between formaldehyde and nasal cancer.

Vaughn *et al* (1986a) reported findings of an occupational matrix analysis of data from a case-control study of 205 oro- and hypopharyngeal cancer cases (OHPC), 27 NPC, 53 SNC and 552 controls. It was a population-based study in 13 counties of Western Washington State. Cases were between 20 and 74 years of age at diagnosis during the study period of 1979 through 1983. Controls were chosen using a random digit dialling method. Fifty percent of the cases were deceased, hence interviews for these subjects were with next of kin. All controls, however, were alive. The telephone interview included questions on smoking and alcohol habits, medical, residential and occupational histories. A job-exposure matrix was developed for formaldehyde, based on the job and industry titles obtained in the interview. The authors analysed hypothetical occupational exposure to formaldehyde 4 ways: maximum exposure levels; number of years exposed; exposure score; and exposure score excluding jobs held within the last 15 years. There were no significantly raised OR for any of these measures for OHPC, NPC, or SNC. To quote the first sentence of the discussion section: "This study found no association between pharyngeal or sinonasal cancer and occupational formaldehyde exposure beyond that which could be readily attributed to chance." However, in a companion paper, a residential exposure analysis is presented using the same study data (Vaughn *et al*, 1986b). The authors report an OR for NPC of 2.8 (95% CI: 1.0-7.9) for living in a mobile home. The OR increased to 5.5 (95% CI: 1.6-19.4) for those living 10 or more years in a mobile home. However, no association was seen for OHPC or SNC with mobile home living. There are a number of issues that go unaddressed in this analysis. First, there is no adjustment for education or any other SES variable. In the U.S., long-term mobile home living is associated with low SES. People living in mobile homes are likely to have a markedly different lifestyle from those living in more typical residences. The potential SES problem is aggravated by the use of telephone controls. For comparability, only cases with telephones should have been used in the analysis as telephone coverage is related to SES (Wacholder *et al*, 1992). Second, the authors state they adjusted results for cigarette smoking (5 categories) and ethnic background (4

categories), but with 27 NPC cases this would be difficult to do in a statistically meaningful way. Third, one of the ethnic groups they adjust for are Asians. NPC is a very rare tumour among whites in the U.S. (Nam *et al*, 1992), but common in China and other Asian countries, and among Asians in the U.S. (Burt *et al*, 1992). The Seattle area where the study was done has a relatively large Asian community. In the U.S., the incidence rate of NPC among Chinese men is 26 times higher (13.9 per 100,000) than that observed among white men (0.53 per 100,000) (Burt *et al*, 1992). Because of the high background incidence of NPC among Asians vis-a-vis whites in the U.S., results should have been presented separately for Asian subjects to test for risk difference by ethnicity, or at least with Asians excluded to see if that affected risk estimates. The authors did exclude the next-of-kin data in one part of their analysis, which rendered the OR for mobile home living non-significant (OR=2.8, 95% CI: 0.9-8.8). Finally, there was no age adjustment in the NPC analysis and the age distribution (presented in the occupational paper (Vaughn *et al*, 1989a, Table 3.2) suggests a clear imbalance with the cases older than the controls: age 20-49, 12% cases vs. 20% controls; age 50-59, 26% cases vs. 30% controls; and age 60-74, 62% cases vs. 50% controls. In summary , this small study has too many shortcomings to reasonably conclude that a link between mobile home living (or formaldehyde) and NPC risk has been established.

Roush *et al* (1987) performed a case-control study in Connecticut of NPC and SNC and hypothetical exposure to formaldehyde. Cases were men with NPC (173) and SNC (198) selected from the Connecticut Tumour Registry who died between 1935 and 1975, and the controls (605) were men who died in the State during the same time period. There were no interviews. Occupational data were abstracted from annual town directories which provided information on the inhabitants' employment. The authors state that employment information on death certificates was used, although it is unclear exactly how this was done, as the analysis uses time and duration-related employment variables that cannot be obtained from a death certificate. The employment information was classified by an occupational hygienist as to the likelihood of exposure to formaldehyde, blinded to case or control status. The relation to hypothetical formaldehyde exposure was examined in 4 ways: (I) probably exposed to some level for most of working life; (II) probably exposed to some levels for most of working life and probably exposed to some levels at 20+ years prior to death; (III) probably exposed to some levels for most of working life and probably exposed to high level in some year; and (IV) probably exposed to some level for most of working life and probably exposed to high level at 20+ years prior to death. There was no association with these 4 measures and risk of SNC. There was no association with these measures and risk of NPC, except for a non-significant OR of 2.3 (95% CI: 0.9-6.0) for measure IV. However, parts of the analysis are not clear. Table 1 in the paper presents information indicating that 47% of SNC and 56% of NPC and 46% of controls had information from the town directories on "3+ industries and 3+ jobs". This would suggest there is considerable missing information, particularly when trying to categorise

subjects into groups II and IV which use 20+ years prior to death as part of their definition. Whether this missing information is by case or control status is unclear. The numbers of SNC and NPC and controls in Table 2 appear greater than what would be expected given the low rates of extended job information shown in Table 1. Moreover, it is not clear who is included in these town directories and no data are presented on the validity of the employment information. Finally, the study included the NPC cases from the Connecticut component of the U.S. cohort study (Blair *et al*, 1986), and hence is not a strictly independent observation. In short, the concerns over the methods used in this study limit its usefulness in assessing any potential carcinogenicity of formaldehyde in man.

A small population-based case-control study of occupation and oral cavity and oropharynx cancer was completed in Turin, Italy by Merletti *et al* (1991). There were 86 cases and 373 controls. Personal interviews were obtained for 83% of the ascertained cases but only 55% of the controls. Lifestyle and occupational information was collected during the interview. The occupational data were coded and a job-exposure matrix was developed. Besides formaldehyde, 15 other exposures were evaluated. The authors found a non-significant OR of 1.6 (95% CI: 0.9-2.8) associated with any putative exposure to formaldehyde and an OR of 1.8 (95% CI: 0.6-5.5) associated with probable or "definite" hypothetical exposure to formaldehyde. Further analyses revealed no dose-response relationship and no relation to duration of exposure. The authors, however, claim their results are evidence of an association between formaldehyde exposure and risk oral/pharyngeal cancer. Yet, with 86 cases any meaningful statistical adjustment is difficult to achieve for age (3 categories), education (3 categories), birthplace (3 categories), tobacco (4 categories), and alcohol (3 categories). Residual confounding by tobacco and alcohol is the likely reason for the association with formaldehyde since cigarette smoking and alcohol account for the vast majority of oral/pharyngeal tumours (Blot *et al*, 1988). It should be pointed out that the authors admit to the problem of residual confounding by tobacco and alcohol. Another serous flaw is the low response rate among the controls (55%). Almost half of the identified controls did not participate in the study. The authors state that controls who did participate were more educated and younger than those who did not. Better education and younger age among the controls are probably inversely correlated with formaldehyde exposure.

The most recent case-control study to report an association between hypothetical exposure to formaldehyde and cancer risk was an investigation of NPC in the Philippines (West *et al*, 1993). There were 104 NPC cases and 205 controls (104 hospital controls and 101 community controls). One nurse interviewed all subjects. The interview included questions on sociodemographic factors, diet, occupational history, cigarette smoking, and use of herbal medicines, betel nut, and anti-mosquito coils. Cases had to have resided on the island of Luzon for at least 6 months. No such

requirement was in effect for the controls. The ascertainment or study period is not given, nor is it provided in an earlier publication from this investigation (Hildesheim *et al*, 1992). A job-exposure matrix was developed based on job information provided in the interview. There was no association between duration of putative exposure to formaldehyde and NPC risk. Risk was not related to duration of exposure at <15 years or >15 years. Use of a 10-year lag failed to show a statically significant link with formaldehyde. Only hypothetical exposure 25 or more years before diagnosis was associated with a significantly elevated risk (OR=2.9, 95% CI: 1.1-7.6) or being less than 25 years of age at first exposure (OR=2.7, 95% CI: 1.1-6.6). Presumably, these are the same individuals since the median age at diagnosis was 46. There were a number of other exposures equally or more strongly associated with NPC risk in the Philippines: exposure to dust and/or exhaust fumes 35 or more years since first exposure (OR=5.5, 95% CI: 1.9-16.0) or being less than 20 years of age at first exposure (OR=5.0, 95% CI: 2.4-10.4); high intake of fresh fish (OR=2.7, 95% CI: 1.2-6.1); daily exposure to anti-mosquito coils (OR=7.8, 95% CI: 2.7-22.8); and use of herbal medicines (OR=2.7, 95% CI: 1.4-5.2). In fact, there are so many striking findings that the possibility of interviewer bias should be considered, as there was only one interviewer and there is no description of any attempt to blind as to study hypotheses or case/control status. The cases and controls were not comparable on residency requirements, with the case having a 6-month requirement and the controls none. Although the time period is not long, such a discrepancy may affect occupational differences between cases and controls; at a minimum it makes them non-comparable on this and possibly other factors (Wacholder *et al*, 1992). In the final model when the authors adjust for all the statistically significant variables, the strongest association is still daily exposure to anti-mosquito coils (OR=5.9, 95% CI: 1.7-20.1). Moreover, in the final model, the authors fail to include a striking association with the Epstein-Barr virus (EBV) reported in an earlier paper (Hildersheim *et al*, 1992). EVB has been linked to NPC risk in a number of studies and thought by some researchers to be causally related to NPC (Hildesheim and Levine, 1993). OR ranging from 6.5 to 73.8 were reported for various anti-EBV antibody types. Another interesting aspect of this study is the appendix which illustrates the exposure scoring used by the authors. Of the 52 jobs listed, only one, a carpenter, is considered to have a "highly likely and/or likely to be high dose" for formaldehyde. Consequently, the findings on formaldehyde exposure in this study were derived from jobs that the authors considered to be of relatively low likelihood of actual formaldehyde exposure.

3.6 Evaluation of Case-Control Studies

The case-control studies provide the least convincing epidemiologic evidence because information on exposure is the weakest of the three categories of studies under review. Cohort studies of industry workers and studies of professionals at least have the benefit of likely if not certain

exposure. Among the case-control studies, the only investigations with some degree of certainty of exposure were the case-control studies within occupational cohorts, and these have been negative (Fayerweather *et al*, 1984; Bond *et al*, 1986; Partanen *et al*, 1990, 1993; Andjelkovich *et al*, 1994). The studies with suggestively positive results have all been community-based and used job-exposure matrices which are basically grounded in unverified assumptions. Furthermore, the studies reviewed in this section have failed to fully eliminate bias, confounding, and chance as likely explanations of the findings. The lack of consistency across studies, the absence of sound exposure information, and concerns over methods result in the case-control studies providing little clarification of any potential association between formaldehyde and cancer risk.

3.7 Evaluation of Epidemiologic Data

When evaluating epidemiologic evidence for a causal association, bias, confounding and chance must be ruled out as competing explanations (Doll, 1985; IARC, 1987). For those studies with positive associations between formaldehyde and cancer risk reviewed in this document, it is not presently possible to rule out sufficiently these three concerns which affect all epidemiologic research. Further, if the causal criteria used by epidemiologists of strength of association, consistency of results, dose-response effect, temporality, and biologic coherence and plausibility were applied to the studies under review, few would meet more than one or two criteria (Hill, 1965; Rothman, 1986). Neither singly nor in combination do the studies provide clear and convincing evidence that exposure to formaldehyde can increase the risk of cancer in man.

SECTION 4. CONCLUSIONS

Formaldehyde is a naturally occurring chemical found in all mammalian cells. It is metabolised rapidly and does not accumulate in the body. It has been used by man for more than 100 years in a large number of activities. Formaldehyde is a rat carcinogen when exposure is at levels high enough to cause cell damage. Its carcinogenic effect in mice is weak, and absent in other animal species. No tumours in rats or mice have been found beyond the initial site of contact with formaldehyde. *In vitro* results indicate genotoxic potential, while *in vivo* tests are conflicting. The results of the cytological and cytogenetic studies of formaldehyde exposure in man are mixed. In some studies, buccal cell micronuclei appear associated with formaldehyde exposure, among men more than women, while in other studies, nasal cell specimens and micronuclei are unrelated to exposure. The size, design and sophistication of these studies must improve before they can provide reliable information. Moreover, the relationship between increased micronuclei and human cancer risk is unknown and needs clarification before etiologic inferences can be drawn. Epidemiologic studies of cancer risk and formaldehyde have shown no convincing evidence of a relationship. In studies of formaldehyde industry workers, where exposure is reasonably certain and often quantified, no cancer risk has been unambiguously demonstrated. Professionals such as pathologists, anatomists and morticians, who likely use formaldehyde as part of routine activities, have not been linked with cancers of the upper or lower respiratory tract, the areas of contact with formaldehyde. Excess risks for cancers of the brain, colon, and leukaemia found in some studies of professionals are not supported by results of formaldehyde industry workers. Case-control studies within occupational groups exposed to formaldehyde report no association with an increased risk of cancer. Community-based case-control studies, where exposure to formaldehyde is least likely, have not eliminated bias, confounding, and chance as the most likely explanations of reported associations.

In summary, epidemiologic studies of formaldehyde industry workers, professionals who use formaldehyde, and numerous case-control investigations have failed to establish a relationship between formaldehyde exposure and increased cancer risk. The conclusions are at variance with the recent IARC decision keeping formaldehyde classified as 2A (IARC, 1995). The strength of the human evidence reviewed above does not warrant such a rating.

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