

The Carcinogenicity of Formaldehyde

Annex 3

A study-by-study summary of the human epidemiological data mainly relied upon by the IARC Working Group in reaching its conclusion in relation to formaldehyde exposure and nasopharyngeal cancer

This annex provides a summary description of each study considered by the 2004 IARC Working Group to be critical in reaching its decision in relation to formaldehyde exposure and nasopharyngeal cancer. The studies have been summarised relatively succinctly, to aid clarity, and the summaries have focussed primarily on the findings of each study in relation to nasopharyngeal cancer.

The National Cancer Institute (NCI) Cohort

Hauptmann M, Lubin JH, Stewart PA, Hayes RB & Blair A (2004). Mortality from solid cancers among workers in formaldehyde industries. *American Journal of Epidemiology* 159: 1117-1130.

Hauptmann *et al* (2004) provides the latest update of the mortality experience of a cohort of US workers involved in the industrial manufacture and/or use of formaldehyde (the "NCI cohort"). This cohort was initially defined by Blair *et al* (1986), and an extended follow-up reported by the same group in 1990 (Blair *et al*, 1990). In the latest analysis, the cohort comprises 25 619 workers employed at ten US industrial plants involved in the production and/or use of formaldehyde. The workers in the cohort were those employed at these plants prior to January 1st 1966. In this most recent update, the mortality experience of the cohort is followed to 31st December 1994; this represents an additional 15 years of follow-up compared to the previous analyses. Median duration of follow-up was 35 years.

Exposure information (8-hour TWA and short-term peak) was estimated from knowledge of job titles and tasks, in conjunction with plant visits and monitoring data (the latter being available only for 8-hour TWA exposures). Exposure information was also obtained for formaldehyde particulates (e.g. paraformaldehyde or trioxane)

and other widely used chemicals, including some suspected carcinogens, at the plants. The exposure assessment covered the period up to 1980. Formaldehyde exposure was determined in terms of cumulative exposure (ppm-years), average exposure intensity (ppm), duration of exposure (years), highest peak exposure category (5 categories defined, including non-exposed) and exposure to formaldehyde-containing particulates (ever/never). Duration of exposure to each of 11 other specific substances (years) and duration of working as a chemist or laboratory technician (years) were also estimated, the latter because of the potential for exposure to various other chemicals. Exposures were calculated by using a 15-year lag interval to account for latency of solid cancers.

Standardized mortality ratios (SMRs; compared with the US population) and relative risks (RRs; Poisson regression with adjustment for calendar year, age, sex, race and pay category) were estimated. In the RR estimation, the low-exposure category was used as the reference wherever possible, to minimise any confounding in relation to socio-economic characteristics, which may differ between non-exposed and exposed workers. Where there were no deaths from the cancers of interest in the low exposure group, the non-exposed group was used as the reference.

In exposed workers, median duration in jobs involving formaldehyde exposure was 2 years (range 0-46 years), with median average intensity of exposure 0.3 ppm (0.01-4.25 ppm) and median cumulative exposure 0.6 ppm-years (0.0-107.4 ppm-years).

Overall mortality from all causes, all cancer and solid cancer was significantly decreased among all workers, both unexposed and exposed. Amongst exposed workers, the only statistically significant excess mortality among the diseases examined was seen for cancer of the nasopharynx (8 deaths¹, SMR 2.10; 95% CI:

¹ Note that on the basis of secondary sources other than death certificates, it was discovered that one nasopharyngeal cancer death (in an exposed worker) had been misclassified on the death certificate, and was actually an oropharyngeal cancer. For this subject, the death was classified as nasopharyngeal cancer for determination of the SMR (since the population reference rates are based on death certificates), but was correctly classified as an oropharyngeal cancer for estimation of RRs in the internal analyses.

1.05-4.21). Note, however, that when an exact confidence interval was calculated, it was not statistically significant (0.91-4.14). No other statistically significantly elevated SMRs were observed in exposed workers.

Examination of RRs for all solid cancers showed no consistent evidence for increasing risk with any measure of increasing formaldehyde exposure. Similarly, RRs for lung cancer mortality showed no association with formaldehyde exposure.

The authors specifically considered sites of direct contact with inhaled formaldehyde - nasopharynx, mouth, salivary gland, nasal cavity and larynx – as a single group (denoted upper respiratory tract). The RRs for this group showed a consistently increasing (but not statistically significant) trend with increasing average intensity of exposure and with peak exposure, but not with cumulative exposure or exposure duration (for which there was a non-significant negative trend). In relation to average intensity of exposure, compared with the low exposure reference group (>0-<0.5 ppm; RR=1.0), the RR increased to 2.21 in the high (\geq 1.0 ppm) exposure group. In terms of peak exposure, the RR was 1.65 in the high (\geq 4.0 ppm) exposure group compared with the low exposure reference group (>0-<2.0 ppm).

Although the 9 nasopharyngeal cancer deaths were included in the upper respiratory tract group, they were also analysed separately. Of these 9 deaths, 7 occurred in the exposed group (see footnote 1), and 2 in unexposed workers. Four exposed cases had cumulative exposures of <5.5 ppm-years, while the other three exposed cases had cumulative exposures of 12.5, 21.7 and 52.3 ppm-years. All exposed cases had maximum peak exposures of \geq 4.0 ppm. The RRs for nasopharyngeal cancer increased non-statistically significantly with increasing average intensity of exposure, with unexposed workers as the baseline. For peak exposures, the trend was statistically significant with unexposed workers as the baseline. For cumulative formaldehyde exposure, there was also a statistically significantly increasing RR with increasing category of formaldehyde exposure. For exposure duration there was an increasing trend that was not statistically significant. Adjustment for other exposures did not substantially change the observed associations. Also, alternative categorisations for peak exposure result, which ignored peaks in jobs of short duration or rare peaks, resulted in two- to seven-fold risks for nasopharyngeal cancer in the highest exposure category compared with the unexposed.

To summarise the trend results for nasopharyngeal cancer, among the exposed, the RR increased with all exposure measures except duration of exposure and was two- to four-fold for workers exposed to the highest levels of formaldehyde. None of the nasopharyngeal cancer cases were assessed as having been exposed to wood dust. No information was available on the presence of antibodies to Epstein-Barr virus, another major risk factor for nasopharyngeal cancer.

The study also had other limitations. Extension of the mortality from the previous analysis used the National Index Plus to determine vital status and subjects not identified as deceased from this source were assumed to be alive, although it is unlikely that missing deaths were related to formaldehyde exposure. Exposure misclassification is another potential problem, although the detailed exposure assessment in this study should minimise the misclassification for average and cumulative exposure, the possibility of misclassification is higher for peak exposures, although this would like have resulted in an bias of the trend results towards the null. The study had strengths in that follow-up was relatively long (up to 60 years), there was a detailed exposure assessment and control for possible confounders. Smoking was assessed as a possible confounder and was found not to be related to formaldehyde exposure.

It is interesting to note that 5 of the 9 nasopharyngeal cancer deaths occurred at one of the 10 plants – see summary of Marsh (2002).

Overall, this study provides some supporting evidence for an increasing risk of nasopharyngeal cancer associated with increasing exposure to formaldehyde.

Marsh GM, Youk AO, Buchanich JM, Cassidy LD, Lucas LJ, Esmen NA and Gathuru IM (2002). Pharyngeal cancer mortality among chemical plant workers exposed to formaldehyde. *Toxicology and Industrial Health* 18: 257-268.

As indicated above, five of the nine nasopharyngeal cancer deaths identified in the NCI cohort occurred in a single plant, a plastics production plant in Wallingford, CT. Cause-specific mortality of the workers at this plant was studied by Marsh *et al* (1994, 1996), to investigate the possible association between formaldehyde exposure and cancers of the upper respiratory tract, following the observations of excess cancers at these sites, in workers from this plant, reported by Blair *et al* (1986). Marsh *et al* (2002) provides the most recent update of the mortality experience of this Wallingford plant cohort, with follow-up of workers to 1998.

The Wallingford plant cohort comprises 7 359 workers, employed between 1941 and 1984, and thus the cohort includes almost twice as many workers as were included in the NCI cohort (where workers were included if they were first employed at the plant between 1941 and 1966). This most recent update follows the mortality experience of 7 328 workers at risk between 1945 and 1998. Exposure to formaldehyde to 1995 was estimated from information on sampling data and job descriptions, as well as on verbal descriptions of jobs and tasks by plant personnel, including the plant industrial hygienist. Exposure to particulates (product and non-product) and to pigment was also assessed.

SMRs were calculated with reference to the US population and the local population. The analyses focussed on nasopharyngeal cancer and other pharyngeal cancers, and SMRs by occupational exposure were calculated with and without considering co-exposures to particulates and pigments. Quantitative formaldehyde exposure measures included duration of exposure, average intensity of exposure and cumulative exposure. In addition, a nested case-control study was performed for the 22 cases of pharyngeal cancer, including the 7 cases of nasopharyngeal cancer. Each case was matched on race, sex, age and year of birth to four controls from the remaining members of the cohort.

The median average intensity of formaldehyde exposure for exposed workers as 0.14 ppm – the authors reported that this estimate was more than 10 times lower

than estimated in the NCI study. It is noteworthy that around half of the workers in the cohort (3 974 workers) had been employed for less than 1 year.

SMRs for all cancers were close to expected, compared with either US or local county rates. Statistically significantly elevated SMRs (based on US and/or county rates; following figures based on county rates) were found for cancers of the buccal cavity and pharynx (31 deaths, SMR 1.52; 95% CI 1.03-2.15), pharyngeal cancers (22 deaths, SMR 2.23; 1.40-3.38), nasopharyngeal cancer (7 deaths, SMR 5.00; 2.01-10.30), cancers of the respiratory system (278 deaths, SMR 1.22; 1.08-1.38), 'other specified sinus' (this category includes the ethmoid, frontal and sphenoidal sinuses) cancers (2 deaths, SMR 10.96; 1.33-39.58) and cancers of the bronchus, trachea and lung (262 deaths, SMR 1.21; 1.06-1.36).

The SMRs for all pharyngeal cancer and for nasopharyngeal cancer separately were examined in relation to selected measures of work history and formaldehyde exposure. For the 7 nasopharyngeal cancer cases, similar excesses were seen in the short term (<12 months employment) employees (4 deaths, SMR 5.35; 1.46-13.71) and long-term (>12 months) employees (3 deaths, SMR 4.59; 0.95-13.42). The excess seemed mainly concentrated in those workers first hired between 1947 and 1956 (6 deaths, SMR 8.13; 2.98-17.69) and seemed strongest among workers with 20-29 years since first exposure (3 deaths, SMR 8.72; 1.80-25.48). The nasopharyngeal cancer excess provides limited evidence for an association with duration of exposure, cumulative exposure or duration of exposure in jobs with >0.2 ppm or >0.7 ppm. These findings were not materially altered when adjusted for co-exposures to particulates or pigments.

Similarly, the results of the nested case-control study did not show any clear or consistent evidence for increased risk of pharyngeal cancer (expressed as odds ratios, OR) and measures of formaldehyde exposure. The only notable observation was some evidence for an increased risk of pharyngeal cancer with increasing duration of exposure to formaldehyde >0.2 ppm. Separate analyses were not presented for nasopharyngeal cancer.

Excesses of the size of those found for nasopharyngeal cancer in the Wallingford cohort are unlikely to be explained by bias or confounding. However, the excess

seems at best weakly associated with formaldehyde exposure. On balance, therefore, the evidence supporting a causal association between formaldehyde exposure and nasopharyngeal cancer from this study is outweighed by the evidence against.

The UK cohort

Coggon D, Harris EC, Poole J & Palmer KT (2003). Extended follow-up of a cohort of British chemical workers exposed to formaldehyde. *Journal of the National Cancer Institute*, **95**: 1608-1615.

A cohort of just over 14,000 workers from 6 factories in the UK where formaldehyde was used or produced and who had potential exposure to formaldehyde, was identified in the early 1980s (Acheson *et al*, 1984) and first updated in the 1990s (Gardner *et al*, 1993). Three of the factories were involved in the production of formaldehyde and its use on site for the manufacture of resins and adhesives; two were involved in the production of formalin, paraformaldehyde and alcohols; and the other was involved in the production of resins from imported formalin. The most recent analysis of this cohort of 14 014 workers is provided by Coggon *et al*, (2003), which extends the follow-up by 11 years (compared with Gardner *et al*, 1993), to 31st December 2000.

Exposure to formaldehyde was described quantitatively by one of five categories (background, low, moderate, high or unknown), based on occupational histories. No measurements of formaldehyde (personal or static sampling) were made before 1970, but from later measurements and workers' recall of irritant symptoms, estimates of time-weighted average exposure concentrations associated with each category were derived. Background exposure corresponded to time-weighted average concentrations of < 0.1 ppm; low exposure to 0.1-0.5 ppm; moderate exposure to 0.6-2 ppm; and high exposure corresponded to > 2 ppm. Within each factory, each job was allocated to the same exposure category for all time periods. In addition to formaldehyde, other hazardous materials were handled at some of the factories, but any exposures to these substances were stated to be relatively low.

In addition to analyses of mortality by underlying cause of death, cancer registrations and contributing causes of death listed on death certificates were checked for nasal and nasopharyngeal cancers.

Overall mortality was examined using SMRs based on national rates and some analyses included an adjustment to take account of local variations in mortality rates.

Overall mortality in the cohort was slightly higher than expected based on national death rates (SMR 1.04, 95% CI 1.02-1.07), as was mortality from all cancers (SMR 1.10, 95% CI 1.04-1.16), and mortality from non-malignant respiratory disease (SMR 1.12; 1.04-1.21). Mortality from pharyngeal cancer was similar to that expected (SMR 1.55; 0.87-2.56, 15 cases), as was the SMR for nose and nasal sinuses (SMR 0.87, 0.11 to 3.14, 2 cases). Among men who had had high exposure to formaldehyde, SMRs from all causes (1995 deaths; SMR 1.15, 95% CI 1.10-1.20) and SMRs from all cancers (621 deaths; SMR 1.31, 95% CI 1.21-1.42) were slightly higher than for the total cohort. The SMR was also higher for respiratory disease. For pharyngeal cancer the SMR in high exposed workers was 1.91 (0.70-4.17, 6 cases), although only one of these cases was nasopharyngeal cancer (2.0 expected) and the man concerned did not work in a high exposure job. There were no cases of nasal cancer in men with high exposure to formaldehyde; there were, however, two cases that were registered with nasal cancer but who died of other causes, and both of these men worked in high exposed jobs. In men who had never been recorded as working in a high exposure job, mortality from all causes and from all cancers was close to that expected (SMR 0.99 in each case).

Overall, therefore, this study provides no convincing evidence for an association between formaldehyde exposure and cancer in humans.

The US garment workers cohort

Pinkerton LE, Hein MJ & Stayner LT (2004). Mortality among a cohort of garment workers exposed to formaldehyde: an update. *Occupational and Environmental Medicine*, 61: 193-200.

A cohort of over 11,000 US workers at three garment manufacturing facilities was first reported on by Stayner *et al*, (1985, 1988). These facilities use formaldehyde in fabric treatment. Pinkerton *et al*, (2004) extended the follow-up of this cohort of workers by an additional 16 years to 31st December 1998.

Data on personal exposure levels for 549 randomly selected employees in five different departments, measured in 1981 and 1984, showed formaldehyde exposure to be similar across departments and plants, ranging from 0.09 – 0.2 ppm (8h TWA), with geometric mean concentration 0.15 ppm. Earlier exposures are thought to have been substantially higher. Work histories were not updated in the latest follow-up. It was assumed that exposure ceased in 1981 in 2 plants and in 1983 in the other, that is the point at which work histories were obtained for the original study. Consequently, duration of exposure was underestimated for 1230 (11.1%) members of the cohort.

Overall, mortality from all causes was lower than expected (SMR 0.92, 95% CI 0.88-0.96), as was mortality from all cancers (SMR 0.89, 95% CI 0.82-0.97). There was no excess of pharyngeal cancer (3 deaths; SMR 0.64, 95% CI 0.13-1.86). Two of the three cancers of the pharynx were cancers of the hypopharynx, the other was of an unspecified site within the pharynx. No nasal (0.16 expected) or nasopharyngeal (0.96 expected) cancers were observed.

Overall, this study is essentially uninformative about the possible association between formaldehyde and nasopharyngeal cancer.

Other studies

Hildesheim A, Dosemeci M, Chan CC, Chen CJ, Cheng YJ, Hsu MW et al (2001). Occupational exposure to wood, formaldehyde and solvents and risk of nasopharyngeal carcinoma. *Cancer Epidemiology, Biomarkers and Prevention*. 10: 1145-1153.

This study evaluated the link between occupational exposures to wood dust, formaldehyde and solvents and the development of nasopharyngeal cancer in Taiwan. Newly diagnosed nasopharyngeal cancer cases (n=375) were identified from two tertiary care hospitals between July 15, 1991 and December 31, 1994. Controls were individually matched by age (within 5 years), sex and district of residence to cases; a total of 327 (87% of those approached) eligible controls agreed to participate in the study.

Information was gathered (for cases, before treatment) on socio-demographic characteristics, adult and childhood diet, cigarette smoking and betel quid chewing, alcohol consumption, residential history, medical history and occupational history. For each subject, information on occupational history (for all jobs held for ≥ 1 year since the aged of 16), blind to case-control status, was used to estimate the following for wood dust, formaldehyde and organic solvents: years of exposure; average intensity of exposure; average probability of exposure; cumulative exposure; age at first exposure; and years since first exposure. Exposures were re-calculated after exclusion of exposures occurring in the 10 years preceding diagnosis (cases) or interview (controls). Jobs involving wood dust exposure were additionally classified based on whether exposure was likely to be hardwood alone, softwood alone, or both. Peripheral blood specimens were also collected to test for various anti-EBV antibodies known to be associated with nasopharyngeal cancer. Odds ratios (OR) were estimated using logistic regression with an adjustment for age, sex, education and other confounding factors.

Of the cases, 74 (20%) had been exposed to formaldehyde compared with 41 (13%) of the controls. An OR of 1.4 (95% CI 0.93-2.2) for nasopharyngeal cancer, after control for confounding factors, was calculated for individuals ever exposed to formaldehyde. There was some evidence of increasing OR with increasing years of

exposure to formaldehyde (OR = 1.3 and 1.6 for ≤ 10 years and > 10 years respectively, p-trend = 0.08). Compared with unexposed individuals, those exposed for > 20 years had an OR of 1.7 (95%CI 0.77-3.5), but the trend observed when more refined duration categories (no exposure, ≤ 10 , > 10 - 20 , and > 20 years of exposure) were examined was not quite significant (p-trend 0.09). There was little evidence of increasing risk with increasing duration of exposure in the 10 years preceding diagnosis/interview or with cumulative exposure (OR = 1.2 and 1.5 for > 10 years of exposure and ≥ 25 intensity years of exposure respectively). Stronger effects were seen in analyses of individuals with a high average intensity of exposure, but no clear dose response relationships were observed. In individuals with a high average intensity of exposure, ORs of 2.1, 95% CI 0.94-4.8 and 2.1, 95% CI 1.0-4.2 were estimated for exposure duration ≤ 10 and > 10 years respectively, compared with those unexposed. Similarly, individuals with a high average probability of exposure, ORs associated with ≤ 10 years and > 10 years of exposure were 2.6 (1.1-6.3) and 1.4 (0.75-3.0) respectively.

When analyses were restricted to cases and controls that tested positive for EBV antibodies (360 cases, 94 controls), a statistically significantly increased OR for nasopharyngeal cancer was observed for exposed compared with unexposed individuals (RR 2.7, 95% CI 1.2-6.2). There was no evidence for any clear dose-response patterns with increased duration or cumulative formaldehyde exposure. The observed associations were not materially affected by additional adjustment for wood dust or solvent exposure.

This study is limited in that the exposure were assessed on the basis of job title and thus in the absence of any direct information on exposures. Thus there remains a significant potential for exposure misclassification. Another potential problem is that the cases were hospital-based, but the controls were population-based, so there exists the possibility of some referral bias.

Overall, this study found a modest and non-significant association between duration of formaldehyde exposure and nasopharyngeal cancer risk, an effect apparently restricted to men.

Armstrong RW, Imrey PB, Lye MS, Armstrong MJ, Yu MC & Sani S (2000). Nasopharyngeal carcinoma in Malaysian Chinese: occupational exposures to particles, formaldehyde and heat. *International Journal of Epidemiology*, 29: 991-998.

In this study, 282 Malaysian Chinese with histologically confirmed nasopharyngeal (squamous cell) carcinoma were interviewed about occupational history, diet, alcohol consumption and tobacco use. An equal number of Malaysian Chinese controls, pair-matched to cases by age and sex, were also interviewed.

Data were collected from each participant during two 40-50 minute in-home, structured interviews on residential and occupational histories, as well as information on diet smoking and alcohol consumption. For each job in the occupational history, level of exposure to 20 inhalants especially formaldehyde (ever/never, low, medium, high) was assessed blind to case-control status with reference to kind of job, work performed, mode of contact (respiratory and/or cutaneous), respondent reporting of exposure to particular inhalants, years of exposure, frequency and duration. To account for possible long latency for nasopharyngeal cancer, cumulative exposures were restricted to each of five time frames: >1, 5, 10 15 and 20 years prior to nasopharyngeal cancer diagnosis. Participants were also classified by exposure categorised as: >10 years of exposure, >5 years of high level exposure and >20 years of low level exposure, at anytime in a subject's working life. All analyses were carried out using logistic regression.

No association was found between formaldehyde exposure and nasopharyngeal cancer when an adjustment was made for diet and smoking (OR 0.71; 95% CI 0.34-1.43). There was also no association for a ten-fold increase in exposure (OR = 0.88; 0.70-1.12). Thus this study conveys no suggestion that occupational exposure to formaldehyde confers a nasopharyngeal cancer risk.

Hansen J and Olsen JH (1995). Formaldehyde and cancer morbidity among male employees in Denmark. *Cancer Causes and Control*, 6: 354-360.

Men with cancer diagnosed in the period 1970-84 who were born between 1897 and 1964 were identified from the Danish Cancer Registry. Individual employment histories were obtained through comprehensive record linkage with the Danish Supplementary Pension Fund. Details of companies with a history of use of

formaldehyde were retrieved from the Danish Product Register. Thus male cancer patients whose longest work experience since 1964 had started at least 10 years before diagnosis were regarded as potentially exposed to formaldehyde. Patients were further classified as low-exposed (white-collar workers) and above baseline exposure to formaldehyde (blue-collar workers). No information was available from the Danish Product Register for potential exposure to wood dust. However, using the combined information on industry and job title, blue-collar workers who worked in wood and furniture companies and carpentry enterprises, and those whose job was a cabinet maker, joiner or carpenter, regardless of industry, were regarded as having concomitant exposure to wood dust.

Since only cancer cases were included in the data, the risks for cancer at specific sites were estimated using standardised proportionate incidence ratios (SPIRs). The SPIR approximates the standardised incidence ratio (SIR) when the cancer is rare (e.g. nasal and nasopharyngeal cancer).

Of the 91,182 patients with an employment history, 2041 had had their longest work experience at least 10 years before the date of diagnosis of cancer at one of the 265 companies at which formaldehyde was used or produced. The risk of nasopharyngeal cancer was not different to that expected SPIR 1.3 (0.3-3.2, 4 cases), although there was evidence of a raised risk for nasal cancer SPIR 2.3 (1.3-4.0, 13 cases). The latter risk was emphasised when attention was restricted to men exposed to formaldehyde in the absence of wood dust SPIR 3.0 (1.4-5.7, 9 cases). Note that 4 of the 13 nasal cancers in this study were also included in Olsen *et al* (1986).

Because of the relatively few number of nasopharyngeal cancers in this study, the study was essentially uninformative about nasopharyngeal cancer risk and exposure to formaldehyde.

Hayes RB, Blair A, Stewart PA, Herrick RF and Mahar H (1990). Mortality of US embalmers and funeral directors. *American Journal of Industrial Medicine*, 18: 641-652.

This proportionate mortality study investigated the causes of mortality in 4046 male US embalmers and funeral directors, who had died between 1975 and 1985. The

basis of the study was to further investigate mortality among professional workers exposed to formaldehyde. This summary focuses specifically on mortality arising from nasopharyngeal cancer.

No information on formaldehyde exposure was obtained. Proportionate Mortality Ratios (PMRs) were calculated with reference to the US population.

There was a non-statistically significant excess of nasopharyngeal cancer (4 deaths; PMR 2.16, 95% CI 0.59-5.54). This is broken down into a PMR of 1.89 (95 % CI 0.39-5.48) in whites (3 deaths, 1.6 expected) and 4.00 (95 % CI 0.10-22.29) in non-whites (1 death, 0.25 expected). Although this finding is not statistically significant, the authors report that the increase is consistent with findings in other studies of formaldehyde exposed workers. There were no deaths from sinonasal cancer (1.7 expected).

Overall, although this study shows a non-statistically significant excess of mortality in the study group, it is uncertain whether this can be linked to formaldehyde exposure.

Walrath J & Fraumeni JF (1983). Mortality patterns among embalmers. *International Journal of Cancer*, 31: 407-411.

This proportionate mortality study investigated causes of mortality in male embalmers licensed to practice in New York between 1902 and 1980, and known to have died between 1925 and 1980. Death certificates were received for 1263 subjects (1132 white and 79 non-white). No nasopharyngeal cancer deaths were reported within this group, and so this study is essentially uninformative with respect to nasopharyngeal risk from occupational exposure to formaldehyde.

Olsen JH & Asnaes S (1986). Formaldehyde and the risk of squamous cell carcinoma of the sinonasal cavities. *British Journal of Industrial Medicine*, 43: 769-774.

This case-control study supersedes that cited by IARC as Olsen *et al* (1984). It included 759 patients with histologically verified cancers of the nasal cavity (287 cases), paranasal sinuses (179 cases) and nasopharynx (179 cases), and 2495 cancer controls diagnosed in Denmark between 1970 and 1982. The controls were selected from patients with cancer of the colon, rectum, prostate and breast

diagnosed during the same period. For all subjects, it was determined (blinded to case/control status) via linkage to the Danish Supplementary Pension Fund whether or not they had been exposed to formaldehyde and/or wood dust. Further categorisation was made on the basis of whether exposed subjects had been exposed with certainty; had probably been exposed; or whether no information on exposure could be obtained.

After adjustment for exposure to wood dust, RRs of 2.3 (0.9-5.8) and 2.2 (0.7-7.2) were found for squamous cell carcinoma and for adenocarcinoma of the nasal cavity and paranasal sinuses respectively, in men ever exposed to formaldehyde compared with men never exposed. However, analysis of the risk of histologically specified carcinomas of the nasopharynx did not show any association with either formaldehyde or wood dust exposure.

Vaughan TL, Strader C, Davis S & Daling JR (1986). Formaldehyde and cancers of the pharynx, sinus and nasal cavity: II Residential exposures. *International journal of Cancer*, **38**: 685-688.

This study investigates associations between potential exposure to formaldehyde in the home and cancers of the pharynx, sinus and nasal cavity. Formaldehyde is a component in a wide range of domestic products, including cosmetics, textiles, and leather goods. However, in the USA, approximately half of the formaldehyde made goes into the production of resins used in the manufacture of particle board and plywood which have been used in many new homes, particularly mobile homes, and also into urea-formaldehyde foam insulation. A population-based case-control study was carried out in 13 counties of western Washington, USA. Cases were identified between 1979 - 1983 among persons aged between 20 - 74 years. They consisted of 205 cases of oro- and hypopharyngeal cancer, 27 cases of nasopharyngeal cancer and 53 cases of cancers of the sinus and nasal cavity. Controls (n = 552) were selected to be similar in age and sex to the cases and were identified via random digit dialling.

A structured telephone interview was carried out to determine the residential history of a subject since 1950, (including type of dwelling, use of urea-formaldehyde foam insulation and occurrence of home renovation or new construction using particle

board or plywood), in addition to their lifetime occupational history. Information on potential confounding factors was also collated, including smoking, alcohol consumption and demographic characteristics. ORs were estimated via multiple logistic regression modelling. In the analyses of nasopharyngeal cancer, the authors controlled for the confounding effects of smoking and ethnic origin.

The results for nasopharyngeal cancer show that 8/27 cases (29.6%) reported having lived in a mobile home since 1950 as compared to 82 controls (14.9%). Of these nasopharyngeal cancer cases, 4/8 (50%) reported a duration of residence of ≥ 10 years, compared with 18/82 (22%) of the controls. Thirty-seven percent of the nasopharyngeal cancer cases reported having resided in a dwelling with inside construction of plywood or particle board compared with 35.7% of the controls. Thirteen (2.4%) of the controls reported living in a residence with urea-formaldehyde foam insulation whereas none of nasopharyngeal cancer cases were potentially exposed to formaldehyde in this way.

A significant association between living in a mobile home for 10 years or more and risk of nasopharyngeal cancer was reported (OR 5.5, 95% CI 1.6-19.4). Living in a mobile home for 1-9 years produced an OR of 2.1 (95% CI 0.7-6.6) for risk of nasopharyngeal cancer. The authors also performed a trend analysis of time in mobile home against risk of nasopharyngeal cancer, which was statistically significant ($p = 0.006$ from the Wald test).

No associations or any indication of a trend were found between nasopharyngeal cancer (or any of the other cancer sites studied) and reported exposures to particle board and plywood.

The authors also investigated whether the nasopharyngeal cancer risk associated with living in a mobile home was modified by potential occupational exposures to formaldehyde. An exposure score was calculated as a weighted sum of years spent in formaldehyde-associated jobs (excluding 15 years before diagnosis), taking into account estimates of both likelihood and intensity of exposure. Subjects with scores of ≥ 5 were considered occupationally exposed. Compared to those subjects with neither occupational nor mobile home exposures, the adjusted ORs were: 1.7 (95% CI 0.5-5.7) for occupational exposures only; 2.8 (95% CI 1.0-7.9) for residential

exposures only; and 6.7 (95% CI 1.2-38.9) for both occupational and residential exposures.

The nasopharyngeal cancer risk was unchanged when living in a mobile home in the distant past was compared to living in one more recently, by exclusion of exposures occurring in the previous 15 years.

This study shows an association between living in a mobile home and nasopharyngeal cancer, but not with other cancers of the pharynx or sinonasal cancer, the risk increasing with number of years spent living in a mobile home. There is a potential for recall bias, in the large number of next of kin interviews carried out for the cases, but not for the controls. However, there was no association between nasopharyngeal cancer and exposure to urea-formaldehyde foam insulation, plywood or particle board, all of which are sources of formaldehyde exposure.

While the authors speculate that the positive association could be linked to formaldehyde exposure, they also acknowledge that there may be other factors associated with living in a mobile home and the risk of nasopharyngeal cancer.

Vaughan TL, Strader C, Davis S & Daling JR (1986). Formaldehyde and cancers of the pharynx, sinus and nasal cavity: I Occupational exposures. *International journal of Cancer*, **38**: 677-683.

This study utilised the same study population described above (Vaughan *et al*, 1986) but investigated whether occupational exposure to formaldehyde was associated with risk of oro- and hypopharyngeal cancer, nasopharyngeal cancer and cancers of the sinus and nasal cavity.

Occupational formaldehyde exposure was assessed by means of a job-exposure linkage system (occupation-industry-exposure estimate). Each unique job was classified into one of three categories: unlikely, possible or probable. Each job with probable exposure was then classified into two levels according to intensity of exposure. Finally, these estimates of likelihood and intensity were combined into a summary variable with four categories: high (probable exposure to high levels);

medium (probably exposure to low levels), low (possible exposure at any level), and background. Four methods of summarising an individual's occupational exposure to formaldehyde were used: maximum exposure category (background, low, medium, high); number of years exposed (0, 1-9, ≥ 10 years); exposure score for all jobs based on the weighted sum of the number of years in each job and the formaldehyde exposure level of each job (0-4, 5-9, 10-19 and ≥ 20); and exposure score taking into account an induction period, which excluded all jobs within 15 years of the diagnosis date (0-4, 5-9, 10-19 and ≥ 20). Estimates of risks were derived using ORs via a multiple logistic model.

Of the 27 nasopharyngeal cancer cases, 16 (59.3%) were in the background exposure group (compared with 69% of controls), 7 (25.9%) in the low exposure group (compared with 21.9% of controls), 4 (14.8%) in the medium exposure group (compared with 7.6% of controls) and no cases were reported with high exposure (compared with 1.4% of controls).

In terms of number of years exposed, 16 cases (59.3%) had < 1 year exposure (compared with 69.0% of controls), 8 cases (29.6%) had 1-9 years of exposure (compared with 23.0% of controls) and 3 cases (11.1%) with ≥ 10 years of exposure (compared with 8.0% of controls).

In terms of exposure score for all jobs, 21 cases (77.8%) had a score of 0-4 (compared with 84.1% of controls), 3 cases (11.1%) had a score of 5-9 (compared with 5.6% of controls), no cases had a score of 10-19 (compared with 5.1% of controls) and 3 cases (11.1%) had a score of ≥ 20 (compared with 5.3% of controls).

In terms of exposure score taking into account an induction period, 21 cases (77.8%) had a score of 0-4 (compared with 88.8 % of controls), 3 cases (11.1%) had a score of 5-9 (compared with 3.8% of controls), 1 case (3.7%) had a score of 10-19 (compared with 3.4% of controls) and 2 cases (7.4%) had a score of ≥ 20 (compared with 4.0% of controls).

There were more cases than controls with high exposure scores, but no clear trend with increasingly heavy exposure to formaldehyde.

As for the analysis of residential exposures, smoking and ethnic origin were taken account of in the logistic regression modelling. The risk estimates for all four of the high exposure categories for nasopharyngeal cancer were elevated but they did not reach statistical significance. However, in addition, the ORs for three of the intermediate exposure categories was intermediate in value between the reference category and the highest exposure category, and were thus consistent with a dose-response relationship. The risk estimates for increasing exposure score levels with an induction period accounted for were 1.7 (0.5-5.7) and 3.1 (0.4-10.0).

Overall, this study found no association between nasopharyngeal cancer and occupational exposure to formaldehyde. The study was limited by the uncertainty associated with assignment of formaldehyde exposures. As mentioned above, a large proportion of the interviews for cases, were with next-of-kin respondents. The small number of nasopharyngeal cancer cases limits the power of the study to reliably identify even moderate true elevations in risk.

Vaughan TL, Stewart PA, Teschke K, Lynch CF, Swanson GM, Lyon JL & Berwick M (2000). Occupational exposure to formaldehyde and wood dust and nasopharyngeal carcinoma. *Occupational and Environmental Medicine*, **57**: 376-384.

This population-based case control study was carried out at 5 cancer registries in the USA to investigate whether occupational exposures to formaldehyde or wood dust increase the risk of nasopharyngeal cancer. Cases (n=196) were identified as subjects aged 18 to 74 with a newly diagnosed nasopharyngeal cancer between 1987 and 1993, and controls (n=244) were frequency matched by age (5 year groups), sex and cancer registry, selected over the same period from the general population through random digit dialing. This report concentrated on the 196 cases with epithelial cancers, and these were classified into 3 different groups: epithelial not otherwise specified (n =24), undifferentiated or non-keratinising (n=54) and squamous cell (n=118). Information was collected from structured telephone interviews on demographic background, previous medical conditions and use of medication, family history of cancer, use of tobacco and alcohol products, and a lifetime history of occupational and chemical exposure.

Estimates of formaldehyde exposures were carried out on a job by job basis blinded to case or control status, for each subject by industrial hygienists. Estimates were based on published and unpublished literature, as well as personal experience. Each job held by a subject was assigned a probability of being exposed to formaldehyde as follows: definitely not or unlikely (<10%), possible ($\geq 10\%$ and <50%), probable ($\geq 50\%$ and <90%), and definite ($\geq 90\%$). The probability represented the percentage of people with a similar job profile (occupation, industry, dates of employment, etc) expected to be exposed to formaldehyde. Jobs with potential exposure were further assigned an estimated concentration of exposure representing an 8-hour time weighted average: low (<0.10 ppm), moderate (≥ 0.10 and <0.50 ppm), and high (≥ 0.50 ppm).

The following sets of variables for formaldehyde were calculated for each subject: ever exposed, maximum concentration exposed (three levels plus unexposed) over the lifetime, duration (years) exposed, and cumulative exposure. Duration and cumulative exposure was also calculated after excluding any exposures during the 10 years before the reference date - 1 year before diagnosis (cases) or ascertainment (controls). Odds ratios and 95% confidence intervals associated with potential occupational exposure to formaldehyde were calculated with logistic regression, in which the potential confounding effects of other risk factors, age, sex, race, cancer registry site, cigarette use, alcohol intake, and education were taken into account. Tests for trend were also carried out, after transformation to the log scale.

Of the 196 nasopharyngeal cancer cases, 79 had were classified as having been potentially exposed to formaldehyde (40.3%) compared with 79 controls (32.4%). After adjusting for confounders an OR of 1.3 (95% CI 0.8-2.1) for risk of nasopharyngeal cancer was calculated. The OR was modestly increased among those who had been exposed to higher concentrations (>5.0 ppm) but few subjects in this study had worked in such jobs.

There was some evidence of trend of increasing risk with increasing duration of work in jobs with potential exposure ($p=0.070$). A 2.1-fold (95% CI 1.0-4.5) increased risk of nasopharyngeal cancer is reported for those working for 18 years or more in jobs with the potential for formaldehyde exposure.

There was no evidence of an association with undifferentiated and non-keratinising tumours, whereas for differentiated squamous cell and epithelial not otherwise specified, significant trends in risk were found with increasing duration of work in jobs exposed to formaldehyde.

The OR associated with ever holding a job judged to involve possible, probable or definite exposure to formaldehyde was 1.6 (1.0-2.8). This association was stronger when analyses focused on jobs with higher probabilities of exposure to formaldehyde. Among subjects ever holding a job judged probably exposed (or higher) the OR was 2.1 (1.1-4.2). Of the 12 people who had ever held jobs considered definitely exposed, 10 were cases yielding an OR of 13.3 (3.4-70). These 10 cases held a total of 14 jobs with definite exposures and an additional 12 with probable or possible exposures.

Significant exposure-response relations were found between risk of nasopharyngeal cancer and duration of exposure to formaldehyde as well as cumulative exposure when jobs with possible or higher probability of exposure were considered. The OR associated with a duration >18 years of exposure was 2.7 (1.2-6.0), and with a cumulative exposure >1.10 ppm-year was 3.0 (1.3-6.6). When jobs with probable or definite probabilities were considered, the trends were less evident. However, when only jobs with definite exposures were examined highly significant ($p < 0.001$) trends in risk of nasopharyngeal cancer with increasing duration and cumulative exposure were found.

These analyses were also carried out taking into account a 10-year lag period. The individual and overall results were stated as being similar. The authors also found evidence that suggested that the association between nasopharyngeal cancer and potential exposure to formaldehyde was stronger among cigarette smokers. The ORs were essentially unaffected by adding exposure to wood dust to the models.

This study has some strengths. The association with formaldehyde was restricted to specific histological sub-types of nasopharyngeal cancer, consistent with other evidence. It is the largest case-control study that has focused on occupational exposures, and includes incident rather than fatal cancers. The study also has some limitations, including a lack of measurements for formaldehyde, and the possibility of

exposure misclassification, and the large proportion of proxies interviewed instead of the cases.

However, overall, this study supports the hypothesis that formaldehyde exposure increases nasopharyngeal cancer risk.

Roush GC, Walrath J, Stayner LT, Kaplan SA, Flannery JT & Blair A (1987). Nasopharyngeal cancer, sinonasal cancer and occupations related to formaldehyde: A case-control study. *Journal of the National Cancer Institute*, **79**: 1221-1224.

In this study based in Connecticut, USA, occupational information was obtained for 198 males with sinonasal cancer and 173 males with nasopharyngeal cancer from the local tumour registry who had died of any cause, over 41 years (1935-1975); and for 605 control subjects sampled without matching from death certificates over the same time period.

Exposures to formaldehyde were assigned blind to case-control status on the basis of job title/industry, specific employment and year of employment. Each subject and each job-industry combination were assigned a probability of exposure (unexposed, possibly exposed, probably exposed, definitely exposed) and level of exposure (0, low (< 1 ppm), high (\geq 1 ppm)). Only 10 study subjects were judged to have been to a high level of formaldehyde for most of their working lives (1 sinonasal cancer, 2 nasopharyngeal cancers and 7 controls).

Odds ratios for risk of nasopharyngeal cancer were calculated on the basis of the following 4 scenarios: (1) probably exposed to some level of formaldehyde for most working life; (2) probably exposed to some level for most of working life and probably exposed to some level 20 or more years prior to death; (3) probably exposed to some level for most of working life and probably exposed to high level in some year; or (4) probably exposed to some level for most of working life and probably exposed to high level 20 or more years prior to death.

Subjects were excluded from particular analyses when insufficient information was available to classify them with respect to formaldehyde exposure.

For scenarios 1, 2 and 3 the adjusted ORs for nasopharyngeal cancer were not statistically significantly increased (OR 1.0, 95% CI 0.6-1.7; OR 1.3 95% CI 0.7-2.4 and OR 1.4, 95% CI 0.6 3.1). A marginally statistically significant (two-sided p = 0.1) increase in risk was found with scenario 4 (OR 2.3, 95% CI 0.9-6.0) in which 7/113 nasopharyngeal cancer cases were observed in the exposed group compared 14/424 in controls. The OR increased to 4.0 (95% CI, 1.3-12.0) in this scenario in men dying aged 68 years or more.

The authors urge caution in interpreting their own results. The exposure index is based on indirect information, and non-occupational exposures to formaldehyde and other potentially causal agents (e.g. wood dust) were not assessed.

Overall, although this study suggests an association between nasopharyngeal cancer in older workers probably exposed to a higher levels of formaldehyde for 20 or more years prior to death, it does not eliminate other potential causal factors, and therefore provides minor support for a causal interpretation.

West S, Hildesheim A & Dosemeci M (1993). Non-viral risk factors for nasopharyngeal carcinoma in the Philippines: results from a case-control study. *International Journal of Cancer*, **55**: 722-727.

This study, conducted in the Philippines, was undertaken to investigate the aetiology of nasopharyngeal cancer in this population, as little was known about its potential risk factors. Incident nasopharyngeal cancer cases in 104, predominantly non-Chinese, subjects were matched for sex, age and neighbourhood with 104 hospital (100% response) and 101 community controls (77% response). Information was collected by personal interview on socio-demographic factors, adult diet, occupational history, cigarette smoking, use of betel nut, burning of anti-mosquito coils and use of herbal medicines.

Each occupation was classified blind to case-control status as likely or unlikely to involve exposure to any of the following: formaldehyde, solvents, wood dust, dust and pesticides. This information was then combined with a subject's complete occupational history to obtain the following exposure estimates: (1) overall duration

of exposure; (2) duration of exposure excluding exposure in the 10 years immediately preceding diagnosis (for cases) or interview (for controls); (3) number of years since first exposure; and (4) age at first exposure.

Odds ratios were calculated using conditional logistic regression to assess associations between risk factors and nasopharyngeal carcinoma.

The authors adjusted the ORs for formaldehyde exposure and nasopharyngeal cancer to take account of years since first exposure to dust and/or exhaust fumes.

After lagging exposures 10 years, those exposed to formaldehyde for 15 or more years were found to be at a non-significant 2.1-fold excess risk of developing nasopharyngeal cancer (0.70-6.2). More striking effects were observed when latency since first exposure and age at first exposure were examined. Subjects first exposed to formaldehyde before the age of 25 were at a 2.7-fold excess risk of developing nasopharyngeal cancer (1.1-6.6) and those first exposed 25 or more years preceding diagnosis or interview were at a 2.9-fold excess risk of developing nasopharyngeal cancer (1.1-7.6), effects that were independent of the association between exposure to other occupational exposures and nasopharyngeal cancer. When latency since first exposure was investigated more finely, the 5 cases who were first exposed to formaldehyde 35 or more years preceding diagnosis were found to be at a 5.6-fold greater risk of developing nasopharyngeal cancer than those never exposed to formaldehyde (0.58 to 52.9). A stronger effect was not observed however when only those individuals most likely to be exposed, or most likely to be exposed to high doses, were compared to unexposed subjects.

When exposures to formaldehyde and dust/exhaust were examined jointly, the two exposures appear to have independent effects on risk. Those first exposed to formaldehyde 25 or more years preceding diagnosis were at the highest risk, relative to those unexposed to both factors (OR=15.7, 2.7-91.2). Subjects first exposed to formaldehyde before the age of 25 were at 4.0-fold excess risk of disease (1.3-12.0).

Similar results were obtained when cases were compared separately to hospital and community controls.

Overall, therefore, this study observed a strong association between estimated formaldehyde exposure and nasopharyngeal cancer. However, as with the other case-control studies, exposures were estimated indirectly and occupational histories were obtained by interview rather than from records.