FORMALDEHYDE (Group 2A)

A. Evidence for carcinogenicity to humans (*limited*)

A number of epidemiological studies using different designs have been completed on persons in a variety of occupations with potential exposure to formaldehyde[1-24]. Cancers that occurred in excess in more than one study are: Hodgkin's disease, leukaemia, and cancers of the buccal cavity and pharynx (particularly nasopharynx), lung, nose, prostate, bladder, brain, colon, skin and kidney[1]. The studies reported are not entirely independent; the plant studied by Liebling *et al.*[2] and Marsh[1,3] is also included in the study by Blair *et al.*[4]; the case-control study of Fayerweather *et al.*[5] includes some subjects who were later studied by Blair *et al.*[4]. Detailed estimates of formaldehyde exposure levels were made in the studies of British chemical workers[6], US formaldehyde producers and users[4], Finnish wood workers[7] and US chemical workers[5], and for the case-control studies of Vaughan *et al.*[8,9] and Hayes *et al.*[10].

In the study of US producers and users of formaldehyde, 11% of the subjects were not exposed, 12% had an estimated time-weighted average (TWA) exposure of <0.1 ppm (<0.12 mg/m^3), 34% a TWA of 0.1-<0.5 ppm (0.12-<0.6 mg/m^3), 40% a TWA of 0.5-<2 ppm

(0.6-<2.4 mg/m^3) and 4% a TWA of >2.0 ppm (>2.4 mg/m^3)[4]. On the basis of the job held that incurred the highest level of exposure, the distribution among British chemical workers was: nil/background, <0.1 ppm (<0.12 mg/m^3), 25%; 0.1-0.5 ppm (0.12-0.6 mg/m^3), 24%; 0.6-2.0 ppm (0.7-2.4 mg/m^3), 9%; >2.0 ppm (>2.4 mg/m^3), 35%; and unknown, 6%[6].

Excesses of cancers of the buccal cavity and pharynx have been reported in five studies[2,8,11-13], with a statistically significant excess for cancer of the buccal cavity based on three deaths[11] in one study and statistically significant excesses for cancer at both sites in another study, based on two deaths[2]. Interpretation of the results of the last study is difficult because the deaths were not obtained systematically from the entire workforce, but rather were ascertained from worker reports and obituaries. The occurrence of cancer of the nasopharynx was elevated in a cohort study of industrial workers[4] and in case-control studies[8,9,14]. Among industrial workers exposed to formaldehyde-containing particulates, standardized mortality rates (SMRs) for nasopharyngeal cancer rose with cumulative exposure to formaldehyde: 192 (one death) for <0.5 ppm(<0.6 mg/m^3)-years, 403 (two deaths) for 0.5-<5.5 ppm(0.6-<6.7 mg/m^3)-years and 746 (two deaths) for >5.5 ppm(>6.7 mg/m^3)-years. There was a similar trend with duration of exposure to formaldehyde, and all five cases held jobs in which hourly exposures exceeded 4.0 ppm formaldehyde[15]. A rising relative risk (RR) for nasopharyngeal cancer was seen by type of exposure to formaldehyde: 1.7 for occupation alone, 2.8 for living in mobile homes and 6.7 for both occupational and mobile-home exposures. These risks were unaffected by potentially confounding factors such as smoking, alcohol use and socioeconomic status[8,9]. An excess of nasopharyngeal cancer was reported in one study among women (RR, 2.6) exposed to formaldehyde, but not among men (RR, 0.7)[14]. Several other studies showed no excess[5,6,11,16], but no death from this tumour was reported in any of these studies.

Sinonasal cancer was associated with employment in jobs in which there is potential contact with formaldehyde in case-control studies in Denmark (RR, 2.8 in men and women)[14,17] and in the Netherlands (RR, 2.5 and 1.9 from two independent classifications of exposure)[10]. Risk for this tumour increased with level of exposure in the Netherlands[10] and with duration of exposure in Denmark[14]. Excess risks persisted in both studies when analyses were restricted to persons without exposure to wood dust (an established risk factor for this tumour, see p. 380), although they were no longer statistically significant. In one of the studies[10], the excess of sinonasal cancer from exposure to formaldehyde was found to be limited primarily to squamous-cell carcinoma, further differentiating the formaldehyde-associated excess from that caused by wood dust, with which adenocarcinoma predominates. In another of the studies[17], however, the excess was not confined to squamous-cell carcinoma. No excess of sinonasal cancer was found in industrial workers (SMR, 91), but only two deaths occurred[4]. Sinonasal cancer was not associated with occupational or residential exposure to formaldehyde in another study[8,9]. None of the other studies reported any death from sinonasal cancer. The RRs for sinonasal cancer in the studies of Hayes[10] and Vaughan[8,9] were adjusted for smoking habits.

Slight excesses in the occurrence of lung cancer have been noted in several studies[2,4,7,12,18,19]. These excesses have shown no consistent pattern with increasing level or duration of exposure to formaldehyde. A statistically significant excess (SMR, 132) was reported among wage workers 20 or more years after first exposure. The risk of lung cancer did not increase among this, or any other group, with either level or duration of exposure[4]. In the UK, the risk of lung cancer rose with level of exposure in one factory from an SMR of 58 among those with low exposure to an SMR of 118 among those with high exposure[6]. No such pattern was seen, however, for the other factories[6], nor was risk associated with cumulative exposure[20]. In a case-control study of respiratory cancer among Finnish plywood and particle-board workers, an odds ratio of 1.6 (adjusted for smoking) was found after ten years of latency. RRs, however, decreased with level and duration of exposure to formaldehyde[7]. In a cohort mortality study of 1332 workers in a formaldehyde-resin plant in Italy, there was an overall excess of lung cancer (SMR, 186). The excess occurred among those not exposed to formaldehyde (SMR, 148) as well as among those exposed (SMR, 136), with the greatest excess among those with uncertain exposure (SMR, 358). Lung cancer mortality was not clearly associated with duration of exposure[19].

Studies of professional groups have shown rather consistent deficits of lung cancer. None of these studies, however, included information on smoking, and the lower prevalence of tobacco use in these groups would probably lead to such deficits. No excess occurrence of lung cancer was noted among Danish physicians[21] or among persons exposed to formaldehyde at a US chemical production facility[22].

Mortality from leukaemia and/or cancer of the brain has been found consistently to be elevated in studies of professional groups[1,12,13,16,23,24]. Except for a very slight excess of leukaemia reported in one study[5] (which was not statistically significant), excesses of these tumours have not been found among industrial workers exposed to formaldehyde. Among professionals, gliomas were the predominant cell type of brain cancer, and the leukaemias were predominantly of the myeloid type. The absence of excesses for these cancers among industrial workers, however, argues against a role of formaldehyde.

Mortality from prostatic cancer has been found to be elevated among professionals[13] and among industrial workers[4,5], but the excess was statistically significant only among embalmers[13]. This tumour has shown a dose-response gradient in both studies of industrial workers, although the test for trend in the study of Blair[4] was not statistically significant.

Slight excesses of mortality from bladder cancer have been reported among professionals[13,23] and among industrial workers[5]. No such excess occurred, however, in the other large industrial cohorts, and none of the excesses was statistically significant. Significant excesses of colon cancer were noted among professionals[12,13] and among industrial workers[2]; nonsignificant elevations have also been reported[11,16]. A significant excess mortality from cancer of the skin was reported among New York embalmers (proportionate mortality ratio, 221)[12], and a slight excess was noted among industrial workers (based on two deaths)[11]. Excesses of Hodgkin's disease were seen among white industrial workers in

two studies, based on 14 deaths (SMR, 142)[4] and on one death[11]. The risk of Hodgkin's disease rose with level of formaldehyde exposure among wage and salaried workers alike, although each stratum had small numbers[4].

Although excess occurrence of a number of cancers has been reported, the evidence for a possible involvement of formaldehyde is strongest for nasal and nasopharyngeal cancer. The occurrence of these cancers showed an exposure-response gradient in more than one study, but the numbers of exposed cases were often small and some studies did not show excesses. The nose and nasopharynx could come into direct contact with formaldehyde through inhalation. Excess mortality from leukaemia and cancer of the brain was generally not seen among industrial workers, which suggests that the excesses for these cancers among professionals is due to factors other than formaldehyde. The slight excesses of cancer of the lung noted in several studies generally did not display the patterns of increasing risk with various measures of exposure (i.e., latency, duration, level or cumulative) usually seen for occupational carcinogens. No other cancer showed a consistent excess across the various studies.

B. Evidence for carcinogenicity to animals (*sufficient*)

Formaldehyde was tested for carcinogenicity by inhalation in two strains of rats and in one strain of mice. Significant increases in the incidence of squamous-cell carcinomas of the nasal cavity were induced in both strains of rats but not in mice[1,25]. A slight increase in the incidence of nasal cavity polypoid adenomas was also observed in male rats[25]. The tumours in the nasal cavity of rats were localized precisely: in the anterior portion of the lateral aspect of the nasoturbinate and adjacent lateral wall[26]. Experiments in which rats were exposed to both hydrogen chloride and formaldehyde showed that the carcinogenic response to formaldehyde does not result from the presence of bis(chloromethyl)ether (see p. 131), which is formed from the mixture of gases[27]. Another study in mice and one in hamsters by inhalation, one in rats by subcutaneous administration and one in rabbits by exposure in oral tanks were considered inadequate for evaluation[1,28].

C. Other relevant data

In single studies of persons exposed to formaldehyde, increases in the frequencies of chromosomal aberrations and sister chromatid exchanges in peripheral lymphocytes have been reported, but negative results have also been published. The interpretation of both the positive and negative studies is difficult due to the small number of subjects studied and inconsistencies in the findings[29].

No increase in the frequency of micronuclei or chromosomal aberrations was observed in rodents treated with formaldehyde *in vivo*; assays for dominant lethal mutations and DNA damage gave inconclusive results. Formaldehyde induced sperm-head anomalies in rats. It induced DNA-protein cross-links, unscheduled DNA synthesis, chromosomal aberrations, sister chromatid exchanges and mutation in human cells *in vitro*. It induced transformation of mouse C3H 10T1/2 cells and chromosomal aberrations, sister chromatid

exchanges, DNA strand breaks and DNA-protein cross-links in rodent cells *in vitro*. In *Drosophila*, administration of formaldehyde in the diet induced lethal and visible mutations, deficiencies, duplications, inversions and translocations and crossing-over in spermatogonia. It induced mutation, gene conversion, DNA strand breaks and DNA-protein cross-links in fungi and mutation and DNA damage in bacteria[29].

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