FORMALDEHYDE EPIDEMIOLOGY

OCTOBER 1986

TABLE OF CONTENTS

FORMALDEHYDE EPIDEMIOLOGY

This paper summarizes the epidemiologic evidence on formaldehyde as of October 1, 1986.[1/]

Introduction

Formaldehyde has been widely used in the workplace for more than ninety years, at levels substantially higher than those found in homes. Epidemiologic studies covering thousands of workers show no overall excess cancer risk among formaldehyde workers. In particular, there is no overall elevation of upper respiratory cancers, the type of cancers that might be expected based on rodent tests.[2/]

1/ The paper summarizes the major cohort and case-control studies which addressed formaldehyde exposure but is not all inclusive.

2/ Tests by the Chemical Industry Institute of Toxicology (CIIT) on rats exposed to formaldehyde gas for virtually a lifetime show a 44 percent incidence of nasal tumors in the rats at 14.3 ppm, 0.9 percent incidence (not statistically significant) at 5.6 ppm, and zero incidence at 2.0 ppm. The rats were exposed for six hours a day, five days a week, for up to two years (virtually a lifetime). In mice similarly exposed, CIIT found a 0.9 percent incidence (not statistically significant) at 14.3 ppm, and a zero incidence at 5.6 ppm and 2.0 ppm. A New York University study also showed nasal carcinomas in rats exposed to 14 ppm.

Formaldehyde is rapidly metabolized, and if formaldehyde were to cause cancer in man,[3/] it would be expected to cause cancer at the site of contact, not a remote site. As the NCTR Consensus Panel stated, "[t]he data now available lead the Risk Estimation Panel to believe that the

---

3/ The CIIT study shows that formaldehyde may cause cancer in rats at lifetime doses in the range of 14 ppm. The fact that humans are exposed to a chemical that is identified as a rodent carcinogen or potential carcinogen does not mean that the humans have an increased risk of contracting cancer. First, human beings simply cannot tolerate -- even for a few minutes -- exposure at the highly irritating 14.3 ppm level to which the rats were exposed.

Second, there is a very steep dose-response curve to the CIIT results. While formaldehyde apparently led to cancer in 44 percent of the rats at 14.3 ppm, there was no statistically significant incidence of cancer in rats at 5.6 ppm, and no incidence at 2 ppm.

Third, there is evidence of interspecies variation in the response to formaldehyde. There was no statistically significant incidence of cancer in mice at any dose. Other animal studies in hamsters, mice and monkeys have shown no adverse effects from low level formaldehyde exposure.

Fourth, in the CIIT tests, high "cytotoxic" doses of formaldehyde caused acute injury and death of cells in the rats' nasal cavities; surviving injured cells then rapidly divided to replace the dead cells. CIIT regards this cell death and attendant proliferation of new cells as most probably an essential precondition to the cancer observed. It is believed that formaldehyde acts on DNA during cell division, which occurs at an increased rate as a result of exposure to cytotoxic doses. In addition, at lower doses there are biological protective mechanisms (e.g., cell repair, detoxification, and the nasal mucociliary protective "blanket").

target sites of formaldehyde are not primarily distinct from the site of exposure."[4/]

This paper reviews epidemiology data on a possible association between formaldehyde and upper respiratory cancer, lung cancer, and remote sites such as the brain.

Summary

The epidemiologic data base on formaldehyde now comprises a collective cohort approaching 56,000 formaldehyde-exposed individuals. Formaldehyde is one of the most widely studied chemicals. The studies have observed no excess cancer overall (1,938 deaths observed versus 2,067 expected) and no excess nasal cancer. The numbers of observed and expected cancers in the cohorts studied to date are consistent with a null hypothesis: no association.

- The ratios of observed to expected numbers of total cancers for all studies combined were 0.90 for professional workers and 0.96 for industrial workers.
- For lung cancer: 0.91 for both groups.
- For nasal cancers: 0.36 for both groups.
- For buccal cavity and pharynx cancers: 0.99 for both groups.
- For brain cancer: slightly elevated for both groups combined (1.06), 1.77 for professional groups and 0.67 for industrial workers (both statistically significant).
- At other sites, the ratio of observed-to-expected was either below 1.0 (bladder, lymphomas and Hodgkin's disease, digestive, stomach, liver, pancreatic); or only slightly elevated (prostate, colon, kidney, lymphatic and hematopoietic leukemia.

4/ 58 Envir. Health Perspec. 323, 355 (1984); see also id. at 347.

Total Observed and Expected Deaths for
Professional and Industrial Cohorts by Site[5/]

Site	Professional		Industrial		Total	
	Obs./Exp.	Ratio	Obs./Exp.	Ratio	Obs./Exp.	Ratio
Nasal Passages	0/1.7	0	2/3.9	0.51	2/5.6	0.36
Buccal cavity and pharynx	20/23.8	0.84	29/27.5	1.05	49/51.3	0.96
Brain	40/22.6	1.77*	27/40.5	0.67*	67/63.1	1.06
Lymphatic and hematopoietic	83/68.2	1.22	94/107.6	0.87	177/175.8	1.01
Leukemia	41/29.6	1.39	37/43.0	0.86	78/72.6	1.07
Lung	188/264.2	0.71*	445/430.6	1.03	633/694.8	0.91*
Prostate	61/51.6	1.18	33/30.9	1.07	94/82.5	1.14
Bladder	25/27.7	0.90	17/17.7	0.96	42/45.4	0.93
Kidney	21/18.7	1.12	20/18.5	1.08	41/37.2	1.10
Digestive	221/266.6	0.83*	166/204.5	0.81*	387/471.1	0.82*
Stomach	29/53.6	0.54*	28/35.6	0.79	57/89.2	0.64*
Colon	87/64.3	1.35*	57/69.9	0.82	144/134.2	1.07
Liver	15/17.5	0.86	13/14.8	0.88	28/32.3	0.87
Pancreatic	54/44/2	1.22	28/39.8	0.70*	82/84.0	0.98
Lymphomas & Hodgkins /	42.38.1	1.10	57/64.6	0.88	99/102.7	0.96[6/]

*Significantly different from 1.00 at p-value .05

5/ Four studies (Liebling, Marsh, Tabershaw and Wong) appear to be included in the Blair (NCI) study (Industrial category) and therefore are not included in this table.

6/ It is not appropriate to compile a grant total of this table because this analysis examines several subsites both individually and in combination (e.g., leukemia/lymphomas/Hodgkins are subsites of lymphatic and hematopoietic; similarly, the digestive category includes several individual subsites).

Charts showing observed and expected ratios in each of the major cohort mortality studies, and odds ratios in the case control studies, organized by site and study, are attached as an Appendix.

a. Summary of Upper Respiratory Cancer Epidemiology Data

In retrospective cohort mortality studies to date, involving a collective cohort of 56,000 workers, there has been no excess nasal cancer. The observed-to-expected ratio is 0.36. The absence of elevated nasal cancer risk in the collective epidemiologic data base is significant given that there is an 80% concordance between the site of cancer in animals and man[7/] and that formaldehyde would likely be a contact carcinogen. In view of the ubiquitous use of formaldehyde, the rarity of nasal cancer in the United States is also reassuring.

Similarly, no overall excess in the category "pharynx and buccal cavity cancers" emerges from the retrospective cohort mortality studies.[8/] In two studies (National Cancer Institute and NIOSH), excesses were seen in certain anatomical

---

7/ L. Tomatis, "Evaluation of the Carcinogenicity of Chemicals: A Review of the Monograph Program of IARC," 38 Cancer Res. 887,881 (1978).

8/ In view of diagnostic difficulties, it is appropriate to combine the nasopharynx and buccal cavity subsites in the epidemiology analysis.

sites within this category based on small numbers of cases. However, the nasopharyngeal cancer excess seen in the NCI study appears to represent a "cluster" phenomenon at a single plant and is unlikely to be due to formaldehyde in view of the short duration of formaldehyde employment (2 of the 4 workers had only worked in formaldehyde operations for a few months). Moreover, three of the four had worked in metal plants. The buccal cavity excess found by Stayner et al. in the NIOSH study results from use of unconventional statistical analysis. The excess disappears if conventional probability analysis is utilized.

The case-control studies also show a negative pattern with respect to formaldehyde and upper respiratory cancer. Studies by Fayerweather, Hernberg, and Partanen show no association between nasal cancer and formaldehyde. Olsen's study shows no excess nasal risk from formaldehyde exposure in the European furniture industry when confounding wood dust exposure is eliminated. One of the two exposure assessments in Hayes' study of sinonasal cases in the Netherlands shows a statistically significant association between sinonasal cancer and formaldehyde exposure. However, the accuracy of the exposure assessment is questionable, a problem characteristic of case-control studies. Vaughan's recent studies of residential and occupational exposure found no association between sinonasal cancer and formaldehyde.

In his case-control study that investigated the possible association between workplace exposure to formaldehyde and sinonasal, nasopharyngeal and oropharyngeal cancer, Vaughan found "no significant association between occupational exposure and any of the cancer sites studied." In his companion residential study, he studied nine scenarios: three exposure situations (UFFI homes, new conventional homes containing particle board and plywood and manufactured homes) and three cancer sites (SNC, NPC and OHPC). There was "no association" between formaldehyde exposure and any of the cancer sites in the UFFI homes or new conventional homes. Nor was there any association with respect to residence in manufactured homes and sinonasal or oropharyngeal cancer.

The Vaughan study is being reported as if it were a positive study because in one of the nine residential exposure scenarios which they studied, i.e. manufactured homes, excess nasopharyngeal cancer was seen based on a handful of cases.[9/] As discussed further below, additional investigation would certainly be warranted before this excess is attributed to formaldehyde. Most of the nasopharyngeal cancer cases occurred in homes that are more than 25 years old where formaldehyde levels would likely have been similar to

---

9/ The statistically significant excess that occurs in the category of mobile home residents with more than 10 years of exposure is based on 4 cases.

those in conventional homes. Most of the observed cancers occurred in smokers. NPC has been associated with smoking, socioeconomic status and ethnic origin. Vaughan himself urges that "the association found with living in a mobile home must be interpreted with caution since it is based on a small number of cases and may be due to factors other than formaldehyde."

b. Summary of Lung Cancer Epidemiology Data

Overall, there is a deficit of lung cancer in the considerable collective cohort of industrial workers studied to date. Since lung cancer is not a rare cancer, the studies ought to have had the power necessary to show an excess if formaldehyde really posed a risk of lung cancer.

c. Summary of Brain Cancer Epidemiology Data

Brain cancer excesses appear in professional groups but there is a statistically significant deficit among industrial workers. As noted above, it is biologically implausible that formaldehyde would cause remote site cancers and the excess among professional groups may be due to social class/diagnostic bias or other exposures.

I. Upper Respiratory Cancer

A. Retrospective Cohort Mortality Studies

1. Nasal Cancer

Cohort studies identify a group of individuals with a particular exposure in the past and follow this group over time to ascertain their mortality experience. A number of large-scale cohort mortality studies have investigated an association between formaldehyde exposure and upper respiratory cancer. No nasal cancer excess has been found.

A study of 2,490 formaldehyde workers by Dr. Gary Marsh of the University of Pittsburgh found no nasal cancer and no dose-response relationship between formaldehyde exposure and respiratory or other cancer.[10/] Similarly, a study of 2,026 formaldehyde workers by Dr. Wong found no nasal cancer mortality, no excess upper respiratory cancer mortality, and no excess lung mortality.[11/] Two studies of morticians by

---

10/ Marsh, G., "Proportional Mortality Among Chemical Workers Exposed to Formaldehyde," 39 Brit. J. Ind. Med. 313 (1983). A follow-up study examined the same cohort for one overlapping year (1976) and four years forward. Liebling, T., et al. "Cancer Mortality Among Workers Exposed to Formaldehyde," 5 Amer. J. Ind. Med. 485 (1984).

11/ Wong, O. reprinted in, Formaldehyde Toxicity (Gibson, J., Edit.) Hemisphere Publishing Corp., New York (1983). A follow-up study of the Wong cohort was conducted with 58 additional cohort members. Tabershaw Associates, "Historical Prospective Mortality Study of Past and Present Employees of the Celanese Chemical and Plastics Plant Located in Bishop, Texas." Rockville, Maryland (1982).

Doctors Walrath and Fraumeni of the National Cancer Institute (1,132 from New York state[12/] and 1,109 from California[13/]) also disclosed no nasal cancer mortality or unusual level of respiratory cancer mortality. Dr. Levine's study of 1,477 morticians licensed over a 20-year period showed no deaths from nasal cancer, and upper respiratory cancer was less than expected.

Professor Acheson reported on a large-scale study of formaldehyde workers conducted by the British Medical Research Council's Environmental Epidemiology Unit.[14/] Records on 7,716 workers who entered the workforce before 1965 were traced through 1981. Exposure levels in the early years were high. Yet, there were fewer cancers than expected. There were no nasal cancer deaths, although one such death would have been expected, and no excess nasopharyngeal cancer.

12/ Walrath, et al., "Mortality Patterns Among Embalmers," 31 Int'l. J. Cancer, 407 (1983).

13/ Levine, et al., "Mortality of Ontario Undertakers," J. Occ. Med., 26:740 (1940).

14/ "Formaldehyde in the British Chemical Industry," Lancet, March 17, 1984, 611-616. The workforce experience did not show a significant increase in mortality from lung cancer at any of these factories when compared with the local male population. (There was an increase in lung cancer mortality at one of the six factories studied when compared to the male population of England and Wales as a whole, but not when compared to the local population.) No excesses for other cancer sites (e.g., skin, kidney, pancreas, brain) were found.

The National Cancer Institute (NCI) study by Blair, et al. observed no excess nasal cancer overall among 26,511 workers employed in various plants from 1938-1968 with a total follow-up of 600,000 person-years. (Two nasal cancers observed; 2.2 expected).15/

The NIOSH study by Stayner, et al. observed no excess nasal cancer (and no excess cancer overall) in a cohort of 11,030 female garment workers. (0 nasal cancers observed; 1.6 nasal cancers expected).16/

2. Pharyngeal and Buccal Cancer

a. NCI Study

The NCI report found a statistically significant increase in nasopharyngeal cancer based on a small number of deaths. Four of the five cases were clustered at a single plant. There are a number of reasons why, on the basis of current evidence, these excesses should not be attributed to formaldehyde exposure:

> (1) Four deaths due to nasopharyngeal cancer were clustered at a single American Cyanamid plant and the deaths occurred around the same time. According to American Cyanamid, two of

---

15/ "Mortality Among Industrial Workers Exposed to Formaldehyde," Journal of the National Cancer Institute, June, 1986.

16/ "Retrospective Cohort Mortality Study of Workers Exposed to Formaldehyde in the Garment Industry," May, 1986. This study follows a prior PMR (proportionate mortality) study by Stayner et al., 120 Ann. J. Epidemiology 458 (1984).

the four nasopharyngeal cases were in workers who had been employed only for a few months. The four workers' exposures were 3 months, 7 months, 5 years, and 20 years respectively. It is most unlikely that the two short-term cases could be due to formaldehyde.

(2) Three of the four cases had worked in metal plants in the area. In case-control studies of the nasopharynx, increased risks have been associated with exposure to metal manufacturing fumes, chemicals, and a variety of dusts. Review of the relevant local cancer rates shows an excess over the national rate for New Haven County, Connecticut--where the "cluster" plant is located--indicating that other local causes may account for the cluster cases.

(3) Other resin plants in the NCI study had similar formaldehyde exposures without nasopharyngeal cancer excesses. Absent the "cluster effect" at the Cyanamid plant, there would have been no excess of nasopharyngeal deaths in the NCI study. No nasopharyngeal cancer deaths were observed in the large cohort mortality studies by Acheson and Stayner.

b. NIOSH Study

The NIOSH (Stayner) study of apparel workers reported "a statistically significant excess in mortality from cancers of the buccal cavity (SMR=343)." An excess of buccal cavity cancer was found based on 6 cases (2 parotid gland, 1 oral mucosa, 1 floor of mouth, and 2 tonsils). The study cautions that "these findings are based on relatively small numbers and that confounding factors may still exist."[17/] In addition,

---

17/ "A Retrospective Cohort Mortality Study of Workers Exposed to Formaldehyde in the Garment Industry" May, 1986 at 2.

if the study had used more conventional analysis, the results would not have been statistically significant. As Dr. Philip Cole of the University of Alabama stated in hearing testimony before OSHA in May 1986:

> Stayner found 4 deaths attributable to the rubric "buccal cavity," with 1.2 expected. This led to an SMR of 343 with confidence limits of 118 and 786 and a p-value said to be less than 0.05. But Stayner has used unconventional criteria of statistical significance. When changed to the conventional 95% confidence range, the limits become 90 to 853--not significant; and the two-sided p-value becomes greater than 0.05, actually 0.07, again not significant.

In summary, the data from the retrospective cohort mortality studies with respect to nasopharyngeal and buccal cavity cancer, yields an observed-to-expected ratio of buccal cavity and pharynx cancers combined of 0.90 for the professional groups and 1.05 for the industrial workers. For both groups, the observed-to-expected ratio was 0.99.

3. Case-Control Studies

A case-control study compares potential risk factors among individuals who have specific disease (cases) with similar individuals who do not have the disease (controls). Several case-control studies have investigated an association between formaldehyde and upper respiratory cancer.

a. The Fayerweather Study

Fayerweather, et al. conducted a matched pairs case-control analysis of cancer deaths among chemical plant

employees who had worked with formaldehyde for at least five years.[18/] Cases were identified from active and pensioned male employees at eight DuPont plants. Exposure to formaldehyde for 481 cancer deaths and an equal number of controls was estimated from work histories. The authors adjusted for age, sex, pay class, plant site, and smoking history. There was no excess mortality among exposed workers and no excess nasal cancer. Odds ratios were not substantially elevated for buccal or pharyngeal cancer, or cancers of the brain, kidney, lung or hematopoietic system.[19/]

b. The Hernberg Study

Based on data from Finnish and Swedish national cancer registries and from Danish hospitals, Hernberg, et al.[20/] conducted a collaborative matched pair case-control analysis of nasal and sinonasal cancer. 167 cases were matched with controls. There were significant associations between nasal and sinonasal cancer and exposure to softwood dusts. Welding, flame-cutting, and soldering were significantly associated with

---

18/ "Case-control study of cancer deaths in DuPont workers with potential exposure to formaldehyde," Formaldehyde: Toxicology-Epidemiology-Mechanisms (Marcel Dekker, N.Y. 1983).

19/ Odds ratios for prostate and bladder cancer increased with an increase in the cumulative exposure index.

20/ "Nasal Cancer and Occupational Exposures," Scand. J. Work Envir. H. 9:208 (1983).

nasal cancer, as was chromium exposure. Occupations where formaldehyde exposure may have occurred showed no association with nasal cancer.

c. The Hayes Study

Hayes, et al. reported increased relative risk among formaldehyde-exposed workers in the Netherlands.[21/] This study was generally well-conducted; for example, detailed job, health, and smoking histories were obtained. However, as the author admits, "consideration must be given to the limitations of this study, particularly with regard to the definition of exposure to formaldehyde and the possibility of exposure to other carcinogens in these occupations."

There are indeed serious questions as to whether the individuals were even exposed to formaldehyde, the exposure levels and duration, and what other exposures they encountered in the workplace. These uncertainties result from procedural limitations for exposure determination. Two different exposure estimates were provided; they varied significantly, and only one assessment indicated a statistically significant elevation in risk. The other hygiene classification did not indicate elevation of risk. No actual workplace measurements were taken, and there were no interviews to ascertain historical

---

21/ "Tumors of the Nose and Nasal Sinuses," Dept. of Public Health and Social Medicine, Erasmus University Rotterdam (1984).

levels. Job classifications were very vague (e.g., "woodworkers") and apparently no analysis was made to determine whether exposures within the job category changed over time as processes changed.

d. The Olsen Study

Olsen studied 839 cases of sinonasal and nasopharyngeal cancer from the Danish Cancer Registry.[22/] He reported no increased risk of nasopharyngeal cancer, but he did conclude that there was a relative risk of 2.8 and 2.5 for sinonasal cancer for formaldehyde and wood dust exposed workers, respectively. When the results were corrected for wood dust, the relative risk associated with formaldehyde exposure was 1.6, which the authors concluded was not statistically significant.

As in the Hayes study, exposure analysis was problematic. There were no visits to the plants or personal interviews to confirm exposure and no determination of historical exposure levels to formaldehyde.[23/]

22/ "Occupational Formaldehyde Exposure and Increased Nasal Cancer risk in Man," 34 Int. J. Cancer, 639-644 (1984).

23/ For example, it is possible that many of the woodworkers, joiners, cabinet-makers, and cleaners in the food processing industry had no formaldehyde exposure. Individuals in other occupations such as hospital laboratory technicians, physicians, dentists, nurses, and boat builders may have had some formaldehyde exposure, but are unlikely to have been exposed on a continuing basis.

e. Vaughan Occupational Study

Vaughan, et al. (in press International Journal of Cancer), conducted a case-control study in 13 counties of western Washington State to determine if occupational formaldehyde exposure was related to cancer of the oro- and hypopharynx (OHPC), nasopharynx (NPC), or sinonasal (SNC) cavities.[24/] The study concludes that "[N]o significant associations were found between occupational formaldehyde exposure and any of the cancer sites under study." Relative risks were elevated for OHPC and NPC accounting for an induction period.

The authors acknowledge limitations inherent in the case-control study methodology, including incomplete information on exposures and the small number of cases. A large number of cases are from workers in the shipbuilding industry with exposure to metal fumes, known to be associated with the types of cancer involved in this study. The categorization of jobs is very general. There is no estimate of exposure levels to formaldehyde, or estimates of exposures to other chemicals or materials.[25/]

24/ "Formaldehyde and Cancers of the Pharynx, Sinus, and Nasal Cavity," in Press Internal Journal of Cancer, Dec. 1986.

25/ As pointed out by the Office of Science and Technology Policy, case-control studies have strengths and weaknesses. While case-control studies are an efficient

(Footnote Continued)

f. Vaughan Residential Study

In the residential study, "[n]o associations were found between any of the cancers and a history of exposure to new construction containing particle board and plywood, or to urea-formaldehyde foam insulation." With respect to manufactured homes, odds ratios for both OHPC and SNC were below one -- no association. SNC cases actually declined with length of exposure in mobile homes (from 5 cases after 1-9

25/ (Continued From Previous Page)

means of studying rare diseases, they have a number of shortcomings including uncertainties in exposure classification:

> Case-control studies provide a more efficient means of studying rare diseases, with fewer individuals needed for study as compared with the cohort approach; a shorter time period for study completion and generally lower costs as compared with the cohort method; an opportunity to evaluate simultaneously several causal hypotheses as well as interactions (the extent and manner in which two or more risk factors modify the strength of one another); and a capacity to evaluate the effects of common exposures as well as those rare exposures which may account for a large proportion of the cases. On the other hand, the case-control approach has some problems in directly estimating the risk associated with a particular exposure, except in special circumstances . . . in reducing certain biases (e.g., selection, historical recall) that affect the comparability of cases and controls; and in providing detailed and precise information on exposures occuring in the past.

50 Fed. Reg. 10372, 10422 (March 14, 1985).

years of exposure to zero cases with 10 or more years of exposure).

For nasopharynx cancer, the authors cited "a strong association between a history of having lived in a manufactured home and NPC." However, there is the significant caveat that "[t]he association found with living in a mobile home must be interpreted with caution since it is based on a small number of cases and may be due to factors other than formaldehyde." The authors recommend additional studies of indoor air pollutants. There are a number of question marks concerning an association between mobile home residence and nasopharyngeal cancer:

> -- The claimed association between living in a mobile home and increased risk of NPC is based on only 4 cases. Chance cannot be excluded. If one case is misclassified, the excess is no longer significant.
>
> -- It is hard to distinguish diagnostically between pharyngeal cancers. If NPC and OHPC are combined, there is virtually no difference in the number of cases in mobile homes and in controls.26/

26/ The authors indicate that twice as many NPC cases lived in a mobile home (29.6%) as compared to controls (14.9%). It is more relevant to compare the combined category of OHPC and NPC cases who have lived in a mobile home versus the number of such cases among the controls. If this computation is performed on the basis of the tables provided, 15.5% of NPC and OHPC cases lived in mobile homes versus 14.9% of controls -- no real difference. If all three categories of cancer (OHPC, NPC, and SNC) are examined, only 14.4% of all cancer cases lived in mobile homes versus 14.9% of controls. Thus, there are no excess cases among mobile home residents if OHPC and NPC cases are combined and if all three categories of cancer are combined.

-- NPC has been related to respiratory infections and smoking.[27/] Socioeconomic bias has been related to NPC.[28/] Occupational factors also need to be considered. We are currently seeking a copy of the complete study to ascertain the extent to which the authors made correction for such factors.

-- The 4 cases involving more than 10 years exposure were all pre-1965 mobile homes where formaldehyde exposure is not likely to be different than controls.[29/] Indeed, in 2 of the 4 homes, which were pre-1950 homes, formaldehyde may not have been the resin. Further factual investigation is underway.

-- There needs to be further analysis of controls to eliminate the possibility of control bias.

In conclusion, the spot excesses which Vaughan finds are in no way inconsistent with chance. Vaughan studied at least nine scenarios of residential exposure: (3 sites: OHPC, SNC and NPC; and 3 exposures: mobile home residence, UF-foam and conventional homes with particleboard/plywood). It would not be unusual for one of nine truly null relationships to appear to be statistically significant by chance alone. Indeed, there was one statistically significant decrease (association with SNC and

---

27/ U. Prasard "Nasopharyngeal Carcinoma in Man," Nasal Tumors in Animals and Man I:158-164 ed. Reznik and Stinson.

28/ Occupational Mortality, the Registrar General's Decennial Supplement for England and Wales at 46-48.

29/ George Myers, "Advances in Methods to Reduce Formaldehyde Emissions", September 1986, in publication for Proceedings on Conference on Composite Board products for Furniture and Cabinets, Figure 1.

residence in a mobile home as well as one significant increase -- NPC). The authors themselves caution that "the association found with living in a mobile home may not be due to formaldehyde."

g. Finnish Woodworkers Study

Partanen and Kauppinen, et al. conducted a case-referent study among Finnish woodworkers to investigate the associations between formaldehyde exposure and respiratory and related cancers.[30/] Exposure to formaldehyde was assessed with job-exposure matrices. The median of the time-weighted average concentration was about 1 ppm, and the mean duration of exposure was 10 years. There were no statistically significant excesses. No exposure-response relation was observed for the level, duration, or dose (ppm-years) of formaldehyde exposure. The authors state: "considering nasal cancers in particular, little epidemiologic evidence has been advanced so far indicating that formaldehyde is an etiologic factor for humans."

In sum, the case-control studies show a negative pattern with respect to formaldehyde and upper respiratory cancer.[31/]

30/ "Formaldehyde Exposure and Respiratory and Related Cancers: A Case Referent Study Among Finnish Woodworkers," Scand. J. Work. Environ. Health, 11 (1985) 409-415.

31/ In addition to the above-described case-control studies, Brinton et al. conducted two case-control studies

(Footnote Continued)

II. Lung Cancer

There is no overall excess of lung cancer in the epidemiologic studies. In professional groups, the ratio of observed-to-expected lung cancers is 0.71 (including two studies of embalmers (New York and California) by Walrath and Frumeni; Levine's study of embalmers; Stroup's study of anatomists and three separate studies of pathologists by Matanoski, Harrington and Shannon and Harrington and Oakes). For industrial groups, the observed-to-expected ratio is 1.03 based on the NCI, Acheson and NIOSH studies.

Overall lung cancer was not elevated in the NCI study. A significant elevation was observed in the NCI study among a subgroup of workers (white male 20-29 year latency)

31/ (Continued From Previous Page)

relating to cancer of the nasal cavities and sinuses. Brinton et al., Am. J. Epidemiology 119:896-906 (1984); Brit. J. Ind. Med., 42:469-474 (1985). In the first study, odds were elevated for certain industries but with respect to occupational formaldehyde exposure the odds ratio was below 1.0. A follow-up study, "Nasal Cancer in the Textile and Apparel Industry" reported that formaldehyde exposure in the textile industry not only did not elevate the risk of nasal cancer but "was actually associated with a non-significant decrease in risk."

Tola conducted a case-control study for cancer of the nose and nasal sinuses. Occupational risk was not elevated but leisure time knitting and sewing and chronic nasal disease was more common among female cases than among controls. No association with formaldehyde exposure was reported. Tola et al., Int. Arch. Occup. Environ. Health, 46:79 (1980).

when compared to national rates, but there was no excess when compared to local rates. Exhaustive analyses involving the entire NCI data set show that the observed lung cancers did not exhibit a dose-response relationship.[32/] Nor did the incidence of lung cancer increase with duration of employment.

The substantial collective cohort studied to date shows an observed-to-expected ratio of 0.91 (industrial and professional groups combined). This cancer is not rare, so the "power" of the studies is not a significant issue for lung cancer.

III. Remote Site Cancers

A. Brain Cancer

For industrial groups there is a statistically significant deficit of brain cancers. (Observed-to-expected ratio of 0.67). A significant excess (1.77) observed among professional groups may have resulted from diagnostic bias or other social class factors.[33/] As the NCTR Consensus Workshop concluded, due to its rapid metabolism, it is biologically implausible that formaldehyde causes remote site

---

32/ A slight excess in lung cancer was observed in the NIOSH study but there was no dose response relationship and the authors did not attribute the excess to formaldehyde.

33/ See R. Levine, Letter to the Editor, 62 Environ. Health Perspec. 465 (1985).

cancer.[34/] A CPSC briefing package prepared after a detailed investigation of formaldehyde carcinogenicity and textile exposure also concluded that remote site carcinogenesis is unlikely for formaldehyde.[35/] Moreover, anatomists and embalmers work with a variety of agents (e.g., embalming chemicals, viruses in body tissues, dyes), and both groups experience an exposure profile very different from most industrial workers.

The NCI and Stayner studies are reassuring with respect to lack of brain cancer risk. (The NCI study has an observed-to-expected ratio of 0.81, and the Stayner study has an observed-to-expected ratio of 0.71.) Given that the NCI and Stayner studies found no excess brain cancer, there is even less evidence that industrial workers are at increased risk of brain cancer from formaldehyde exposure.

B. Leukemia

The leukemia odds ratio is only slightly elevated and, like the brain cancer excess, it is biologically implausible that formaldehyde exposure would cause leukemia. The phenomenon of diagnostic/social class bias may also play a role in the slight excesses observed in the studies to date.

34/ See NCTR Consensus Workshop Report, 58 Environ. Health Perspec. 323-381, at 347 (1984).

35/ Cohn, "Dermal Application of Formaldehyde and Carcinogenesis," Tab A in CPSC Briefing Package, "Status Report on the Formaldehyde in Textiles Portion of Dyes and Finishes Project." (Dec. 30, 1983).

CONCLUSION

Formaldehyde is one of the most extensively studied chemicals in the epidemiology literature. The numerous epidemiology studies reported to date when viewed collectively do not demonstrate that formaldehyde enhances or increases background incidence of cancer. While sporadic excesses have appeared, no consistent biologically plausible pattern has emerged.

Observed and Expected Data By Site and Study

Site	Observed	Expected	Obs./Exp. Ratio
Nasal Passages			
Professional			
NY Embalmers (Walrath)	0	0.5	
CA Embalmers (Walrath)	0	0.6	
Anatomists (Stroup)	0	0.4	
Embalmers (Levine)	0	0.2	
Pathologists (Harrington & Shannon	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	0	0.0	
Industrial			
Blair	2	2.2	0.91
Acheson	0	1.1	
Stayner (1986)	0	.6	
TOTAL	2	5.6	0.36
Buccal cavity and pharynx			
Professional			
NY Embalmers (Walrath)	8	7.1	1.13
CA Embalmers (Walrath)	8	6.1	1.31
Anatomists (Stroup)	1	6.8	0.15*
Embalmers (Levine)	1	2.1	0.48
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	2	1.7	1.2
Industrial			
Blair	18	19.0	0.96
Acheson	5	4.6	1.09
Stayner (1986)	6	3.9	1.55
TOTAL	49	51.3	0.96
Brain			
Professional			
NY Embalmers (Walrath)	9	5.8	1.56
CA Embalmers (Walrath)	9	4.7	1.94*
Anatomists (Stroup)	10	3.7	2.70*
Embalmers (Levine)	3	2.6	1.15
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	4	1.2	3.31*
Pathologists (Matanoski)	5	4.6	1.09

Site	Observed	Expected	Obs./Exp. Ratio
Brain--continued			
Industrial			
Blair	17	21.0	0.81
Acheson	5	12.5	0.40*
Stayner (1986)	5	7.0	0.71
TOTAL	67	63.1	1.06
Lymphatic & hematopoietic			
Professional			
NY Embalmers (Walrath)	25	20.6	1.21
CA Embalmers (Walrath)	19	15.6	1.22
Anatomists (Stroup)	18	14.4	1.25
Embalmers (Levine)	8	6.5	1.24
Pathologists (Harrington & Shannon)	11	8.1	1.36
Pathologists (Harrington & Oakes)	2	3.0	0.67
Pathologists (Matanoski)	-	-	
Industrial			
Blair	56	61.5	0.91
Acheson	20	26.3	0.76
Stayner (1986)	18	19.8	0.91
TOTAL	177	175.8	1.01
Leukemia (only)			
Professional			
NY Embalmers (Walrath)	12	8.5	1.40
CA Embalmers (Walrath)	12	6.9	1.75*
Anatomists (Stroup)	10	6.7	1.48
Embalmers (Levine)	4	2.5	1.60
Pathologists (Harrington & Shannon)	2	3.1	0.65
Pathologists (Harrington & Oakes)	1	1.9	0.53
Pathologists (Matanoski)	-	-	
Industrial			
Blair	19	23.7	0.80
Acheson	9	11.4	0.79
Stayner (1986)	9	7.9	1.14
TOTAL	78	72.6	1.07
Lung			
Professional			
NY Embalmers (Walrath)	72	66.8	1.08
CA Embalmers (Walrath)	41	42.8	0.96
Anatomists (Stroup)	12	43.0	0.28*
Embalmers (Levine)	19	20.2	0.94

Site	Observed	Expected	Obs./Exp. Ratio
Lung--continued			
Pathologists (Harrington & Shannon)	23	48.0	0.48
Pathologists (Harrington & Oakes)	9	22.0	0.41*
Pathologists (Matanoski)	12	21.4	0.56
Industrial			
Blair	201	181.5	1.11
Acheson	205	215.0	0.95
Stayner (1986)	39	34.1	1.14
TOTAL	633	694.8	0.91*
Prostate			
Professional			
NY Embalmers (Walrath)	15	16.4	0.91
CA Embalmers (Walrath)	23	13.1	1.75*
Anatomists (Stroup)	20	18.7	1.07
Embalmers (Levine)	3	3.4	0.88
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	-	-	
Industrial			
Blair	33	29.0	1.15
Acheson	-	-	
Stayner (1986)	0	1.9	
TOTAL	94	82.5	1.14
Bladder			
Professional			
NY Embalmers (Walrath)	7	7.3	0.96
CA Embalmers (Walrath)	8	5.8	1.38
Anatomists (Stroup)	5	7.2	0.69
Embalmers (Levine)	1	2.0	0.50
Pathologists (Harrington & Shannon)	2	3.5	0.57
Pathologists (Harrington & Oakes)	2	1.9	1.07
Pathologists (Matanoski)	-	-	
Industrial			
Blair	14	15.0	0.96
Acheson	-	-	
Stayner (1986)	3	2.7	1.12
TOTAL	42	45.4	0.93

Site	Observed	Expected	Obs./Exp. Ratio
Kidney			
Professional			
NY Embalmers (Walrath)	8	5.4	1.54
CA Embalemrs (Walrath)	4	4.0	1.00
Anatomists (Stroup)	1	4.0	0.25
Embalmers (Levine)	1	1.7	0.59
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	7	3.6	1.94
Industrial			
Blair	18	15.0	1.20
Acheson	-	-	
Stayner (1986)	2	3.5	0.55
TOTAL	41	37.2	1.10
Digestive			
Professional			
NY Embalmers (Walrath)	68	65.2	1.04
CA Embalmers (Walrath)	69	57.0	1.21
Anatomists (Stroup)	38	72.0	0.53*
Embalmers (Levine)	17	22.6	0.75
Pathologists (Harrington & Shannon)	21	34.3	0.61*
Pathologists (Harrington & Oakes)	8	15.5	0.51*
Pathologists (Matanoski)	-	-	
Industrial			
Blair	136	153.0	0.89
Acheson	-	-	
Stayner (1986)	30	51.5	0.58*
TOTAL	387	471.1	0.82
Stomach			
Professional			
NY Embalmers (Walrath)	12	13.4	0.90
CA Embalmers (Walrath)	12	15.1	0.79
Anatomists (Stroup)	2	19.3	0.10
Embalmers (Levine)	3	5.8	0.52
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	-	-	
Industrial			
Blair	42	48.0	0.87
Acheson	-	-	
Stayner (1986)	15	21.9	0.82

Site	Observed	Expected	Obs./Exp. Ratio
Stomach--continued			
TOTAL	86	123.5	0.70
Colon			
Professional			
NY Embalmers (Walrath)	29	20.3	1.43*
CA Embalmers (Walrath)	30	16.0	1.87*
Anatomists (Stroup	20	18.5	1.08
Embalmers (Levine)	8	9.5	0.85
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	-	-	
Industrial			
Blair	42	48.0	0.87
Acheson	-	-	
Stayner (1986)	15	21.9	0.82
TOTAL	144	134.2	1.07
Liver			
Professional			
NY Embalmers (Walrath)	5	4.7	1.06
CA Embalmers (Walrath)	4	4.7	0.85
Anatomists (Stroup)	1	5.7	0.18
Embalmers (Levine)	1	0.6	1.67
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	4	1.8	0.86
Industrial			
Blair	11	11.0	1.00
Acheson	-	-	
Stayner (1986)	2	3.8	0.52
TOTAL	28	32.3	0.87
Pancreatic			
Professional			
NY Embalmers (Walrath)	13	12.3	1.05
CA Embalmers (Walrath)	12	8.9	1.35
Anatomists (Stroup)	11	9.8	1.12
Embalmers (Levine)	4	3.9	1.03
Pathologists (Harrington & Shannon)	-	-	
Pathologists (Harrington & Oakes)	-	-	
Pathologists (Matanoski)	14	9.3	1.51

Site	Observed	Expected	Obs./Exp. Ratio
Pancreatic-- contintued			
Industrial			
Blair	23	30.3	0.76
Acheson	-	-	
Stayner (1986)	5	9.5	0.52
TOTAL	82	84.0	0.98
Lymphomas & Hodgkin's Disease			
Professional			
NY Embalmers (Walrath)	11	9.6	1.15
CA Embalmers (Walrath)	7	8.7	0.80
Anatomists (Stroup)	8	7.7	1.04
Embalmers (Levine)	4	4.0	1.00
Pathologists (Harrington & Shannon)	9	5.0	1.80
Pathologists (Harrington & Oakes)	1	1.9	0.54
Pathologists (Matanoski)	2	1.2	1.73
Industrial			
Blair	37	37.8	0.98
Acheson	11	14.9	0.74
Stayner (1986)	9	11.9	0.76
TOTAL	99	102.7	0.96

*Significantly different from 1.00 at $p < .05$

Four studies (Liebling, Marsh, Tabershaw, and Wong) would appear to be included in the Blair (Industrial) study and therefore are not included in this table.

Total Observed and Expected Deaths for
Professional and Industrial Cohorts by Site[5]

Site	Professional		Industrial		Tota	
	Obs./Exp.	Ratio	Obs./Exp.	Ratio	Obs./Exp	Ratio
Nasal Passages	0/1.7	0	2/3.9	0.51	2/5.6	[illegible]
Buccal cavity and pharynx	20/23.8	0.84	29/27.5	1.05	49/51.	[illegible]
Brain	40/22.6	1.77*	27/40.5	0.67*	67/63.	[illegible]
Lymphatic and hematopoietic	83/68.2	1.22	94/107.6	0.87	177/17[illegible]	[illegible]
Leukemia	41/29.6	1.39	37/43.0	0.86	78/72.[illegible]	[illegible]
Lung	188/264.2	0.71*	445/430.6	1.03	633/69[illegible]	[illegible]*
Prostate	61/51.6	1.18	33/30.9	1.07	94/82.[illegible]	[illegible]
Bladder	25/27.7	0.90	17/17.7	0.96	42/45.[illegible]	[illegible]
Kidney	21/18.7	1.12	20/18.5	1.08	41/37.[illegible]	[illegible]
Digestive	221/266.6	0.83*	166/204.5	0.81*	387/47[illegible]	[illegible]*
Stomach	29/53.6	0.54*	28/35.6	0.79	57/89.[illegible]	[illegible]*
Colon	87/64.3	1.35*	57/69.9	0.82	144/13[illegible]	[illegible]
Liver	15/17.5	0.86	13/14.8	0.88	28/32.[illegible]	[illegible]
Pancreatic	54/44/2	1.22	28/39.8	0.70*	82/84.[illegible]	[illegible]
Lymphomas & Hodgkins	42.38.1	1.10	57/64.6	0.88	99/102.	[illegible][6]

*Significantly different from 1.00 at p-value .05

5/ Four studies (Liebling, Marsh, Tabershaw and Wong) [illegible] to be included in the Blair (NCI) study (Industrial category) and therefore are not included in this table.

6/ It is not appropriate to compile a grant total of this table because this analysis examines several subsites both individually and in combination (e.g., leukemia/lymphomas/Hodgkins are subsites of lymphatic and hematopoietic; similarly, the digestive category includes several individual subsites).

Observed and Expected Numbers of Total Cancers by Study[1/]

Professional	Observed	Expected	Obs./Exp. Ratio
NY Embalmers (Walrath)	243	218.9	1.56
CA Embalmers (Walrath)	205	169.6	1.21*
Anatomists (Stroup)	120	187.9	0.64*
Embalmers (Levine)	58	66.7	0.87
Pathologists (Harrington & Shannon)	69	111.7	0.62*
Pathologists (Harrington & Oakes)	32	52.3	0.61*
TOTAL PROFESSIONAL	727	807.1	0.90*
Industrial			
Blair	570	566.0	1.01
Acheson	455	468.0	0.97
Stayner (1986)	186	226.1	0.82*
TOTAL INDUSTRIAL	1211	1260.1	0.96
TOTAL BOTH GROUPS	1938	2067.2	0.94*

*Significantly different from 1.00 at p .05.

1/ Four studies (Liebling, Marsh, Tabershaw and Wong) would appear to be included in the Blair (Industrial) study and therefore are not included in this table.

Information Relevant to Analysis of Formaldehyde Studies

Cohort Studies

Professional	Population Studied	Other Factors
NY Embalmers (Walrath)	1109 White Males (PMR)	Professional studies show no excess upper respiratory cancer; brain cancer excesses may reflect socioeconomic bias or other exposures.
CA Embalmers (Walrath)	1132 White Males (PMR)	
Anatomists (Stroup)	Cohort of 2,239 men	
Embalmers (Levine)	Cohort of 1,477 men	
Pathologists (Harrington & Shannon)	Cohort of 2,079 male pathologists and 12,944 laboratory technicians (England, Wales and Scotland)	
Pathologists (Harrington & Oakes)	Cohort of 2,307 male pathologists (United Kingdom) (413 women excluded).	
Pathologists (Matanoski)	381 males in American Association of Bacteriologists and 181 deaths in American Society for Experimental Pathology (PMR).	

Industrial

Blair	Cohort of 26,561 men in 10 plants. Analysis limited to 16,962 exposed white males.	NPC cluster not observed at other plants; 2 of 4 workers had only brief exposure; previous employment of cases and resin composition need to be considered.
Acheson	Cohort of 7,680 men (mortality rates of England and Wales)	No excess nasal cancer.

Stayner	Cohort of 11,030 garment workers.	No excess nasal cancer; excess buccal disappears if conventional statistical analysis is used.
Case Control Studies		
Olsen	839 cases from the Danish cancer registry	No nasal cancer excess after correction for other confounding exposures.
Hayes	188 nasal and sinonasal cancer cases in the Netherlands 1978-1981.	Uncertainty of exposure assessment; only one exposure assessment is statistically significant.
Vaughan - occupational - residential	285 incident cases in western Washington of pharyngeal cancer (1980-1983) and sinonasal cancer (1979-1983)	Socioeconomic bias, small number of cases; uncertainty over levels in the homes and other exposures.
Partanen	57 cases from the Finnish cancer registry 1957-1980.	No nasal cancer excess found.

ODDS RATIOS FOR CASE CONTROL STUDIES

Site	Cases	Controls	Odds Ratio
Sinonasal			
Fayerweather	0	481	-
Brinton-Formaldehyde	2	290	0.35
Olsen-uncorrected	839	2465	2.8*
Olsen-corrected for sawdust exposure	839	2465	1.6
Hayes-Low Wood Dust			
Southampton	63	161	2.5*
Montreal	63	161	1.6
Hayes-High Wood Dust			
Southampton	28	34	1.9
Montreal	28	34	-
Vaughan-Occupational			
Low Exposure	9	121	0.8
Medium/High Exposure	3	50	0.3
Vaughan-Residential/Mobile Home			
1-9 Years	5	64	0.6
10+ Years	0	18	-
Vaughan-Residential/Particleboard			
1-9 Years	13	100	1.8
10+ Years	12	97	1.5
Oro- and Hypopharynx			
Vaughan-Occupational			
Low Exposure	41	121	0.8
Medium Exposure	13	42	0.8
High Exposure	4	8	0.6
Vaughan-Residential/Mobile Homes			
1-9 Years	21	64	0.9
10+ Years	7	18	0.8
Vaughan-Residential/Particleboard			
1-9 Years	40	100	1.1
10+ Years	28	97	0.8

Site	Cases	Controls	Odds Ratio
Nasopharyngeal			
Vaughan-Occupational			
Low Exposure	7	121	1.2
Medium/High Exposure	4	50	1.4
Vaughan-Residential/Mobile Homes			
1-9 Years	4	64	2.1
10+ Years	4	18	5.5*
Vaughan-Residential/Particleboard			
1-9 Years	6	100	1.4
10+ Years	4	97	0.6
Respiratory			
Partanen-Formaldehyde			
No minimum latency	13	171	1.44/1.33**
10 Year minimum latency	8	171	1.27/1.60**
Partanen-Formaldehyde, Peak Exposure			
No minimum latency	5	171	1.26/0.92**
10 Year minimum latency	4	171	1.05/0.65**
Partanen-Formaldehyde Containing Wood Dust			
No minimum latency	10	171	1.22/1.24**
10 Year minimum latency	5	171	0.82/1.14**
Lung			
Fayerweather	181	481	0.74
Brain			
Fayerweather	12	481	0.45

*Statistically significant excess.

**Odds ratio estimate adjusted for survival status and cigarette smoking.