

Formaldehyde exposure and respiratory cancer — a meta-analysis of the epidemiologic evidence

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PARTANEN T. Formaldehyde exposure and respiratory cancer — a meta-analysis of the epidemiologic evidence. *Scand J Work Environ Health* 1993;19:8–15. A recent meta-analysis by Blair and his co-workers stimulated the undertaking of a reanalysis of the epidemiologic evidence of an association between formaldehyde and respiratory cancer. Emphasis was placed on extracting the maximal amount of relevant data from the source studies. In close agreement with the original analysis, the aggregated evidence did not indicate an excess risk or an exposure-response gradient for lung cancer. An exposure-response gradient was seen for both sinonasal and nasopharyngeal cancers. The risk for substantial exposure was significantly elevated (odds ratio 1.7 for sinonasal and 2.7 for nasopharyngeal cancer). It is suggested that at least substantial levels of occupational exposure to formaldehyde are associated with a risk of these cancers. The excess risk would be of the order of 100% or more over background rates.

Key terms: lung, nasal, nasopharynx, pharynx, review.

A recent review in the *Scandinavian Journal of Work, Environment & Health* by Blair and his co-workers (1) consolidated the results of over 30 epidemiologic studies on formaldehyde exposure and cancer. A causal role for formaldehyde was considered the most credible for cancers of the nasopharynx and, to a less extent, nose, nasal cavities, and sinuses, but not the lung. The effects on the aggregated results of the substitution and rederivation of some of the data extracted from the studies are scrutinized in the present reanalysis. The substitutions and rederivations of input were based on considerations of the maximal amount of information and maximal relevance.

Methods

The source studies for the present reanalysis were, with some updating, very much the same as in the original meta-analysis (1). The overlaps between some of the studies in the data were removed according to reference 1. To retain comparability, the statistical treatment of input from the studies was — with an important addition pertaining to the upper respiratory sites — kept the same as in the original analysis (1). Thus the observed (O) and expected (E) frequencies² were summed over the studies in the

broad category of any formaldehyde exposure exceeding background level and in the graded categories of low-medium and substantial exposure. In several studies, graded categories of exposure were supplied, variably delineated in each study via exposure probability, intensity, duration, cumulated exposure, or some other related indicator of the authors' choice. The aggregate risk ratios (RR) were estimated as aggregated observed-to-expected ratios, and the 95% confidence limits were set for the RR values by the Poisson model (2).

The upper respiratory sites were considered in the subcategories of (i) nasal cavity and sinuses, (ii) nasopharynx, and (iii) others (oropharynx, hypopharynx, lip, tongue, salivary glands, and mouth). The data for these sites derived overwhelmingly from case-referent studies with imprecise expected frequencies of exposed cases. These data were therefore aggregated via the more appropriate log-Gaussian, fixed-effects model for risk ratios (3), in addition to the Poisson format. The procedure, in essence, combined the estimates of the log RR values (or log odds ratios) by weighting each by the inverse of its variance. The confidence limits of an aggregated RR were then computed on the assumption of a Gaussian distribution of the log of the estimate of the aggregated RR. The required component RR values and the variances of the log RR values were extracted from the study reports. In some reports, estimated standard errors of the log RR values were readily provided; in others they were recovered from the reported confidence limits. In the few standardized mortality ratio (SMR) studies addressing upper respiratory sites, the variance of the RR (of the SMR, that is) was taken as the inverse of the observed frequency. These and other procedures have been de-

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² In studies in which expected frequencies were not readily available, the expected values were derived by dividing the appropriate observed values by the appropriate risk ratios or odds ratios.

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scribed by Greenland (4). A chi-squared test for homogeneity of the component RR values (3) was applied.

Input values

The main difference between the original analysis (1) and the reanalysis was the selection of the input values. Extraction of the maximal amount of relevant data from the different studies was pursued. Thus some individual realizations of input parameters chosen by Blair et al (1) were replaced by what were considered slightly more appropriate ones. The general principle was, in the qualitative analysis, to contrast the risk connected with formaldehyde exposure that exceeded background exposure to that associated with background exposure ("unexposed" subjects). The predetection latency period was accounted for when lagged inputs (RR or OR values referring to a period of more than 10 years after the onset of exposure) could be extracted. In the quantitative setting, similarly, the aggregated exposure-response analyses were based on lagged input values, if these values could be derived. In addition, confounder-adjusted values were extracted whenever available.

The substitutions made in the inputs for lung cancer appear in table 1, and the inputs that were accepted as such are readily found in reference 1. The complete inputs for the cancers of the upper respiratory sites are given in tables 3, 4, and 5 in the Results section. All of the changes are explained in the following text.

In Harrington & Shannon's mortality study of British pathologists (5), the figures of lung cancer for men in England and Wales were replaced by those for both genders in England, Wales, and Scotland in order to exploit fully the information provided in the report.

In the report by Harrington & Oakes (6), on a later follow-up of British pathologists, the mortality figures for lung cancer among both genders were preferred instead of those of men only; this was numerically a minor adjustment.

In place of unlagged values for lung cancer, lagged equivalents were extracted from the reports of Blair et al (7) on United States (US) workers producing and using formaldehyde, Bond et al (8) on Dow Chemical (Texas) workers, and Stayner et al (9) on US garment workers exposed to formaldehyde. For the exposure-response analyses in the large mortality study by Blair et al (7), low-medium formaldehyde exposure referred to any nonzero exposure up to 5.5 ppm-years, and any exposure exceeding 5.5 ppm-years was considered substantial.

Logue et al (10) contrasted the mortality of US pathologists with that of radiologists. The observed and expected values for lung cancer missing in reference 1 were replaced in the reanalysis with recalculated figures. Since 91 malignant neoplasms were recorded in the follow-up of the pathologists, with

reported death rates of 1.37/10³ years for all cancers and 0.21/10³ years (SMR 0.24) for respiratory cancers, the observed number of respiratory cancers (as a proxy for lung cancer) was calculated as (0.21/1.37) · 91 = 14, and the expected number as 14/0.24 = 58.

From the mortality study by Acheson et al (11, 12) on British chemical workers, nil, background, and unknown exposures to formaldehyde were excluded from the category of exposed workers.

The input for lung cancer from a Swedish national record linkage study by Malke & Weiner (13) in the original meta-analysis (1) presumably included, among others, all physicians, all biologists, most if not all textile workers, garment shop assistants, and paper and cardboard production workers as occupationally exposed to formaldehyde. In the reanalysis, data for fiber workers in plywood and fiberwood factories only were included.

The recent updating of the data on Finnish woodworkers by Partanen et al (14) provided, for the qualitative analysis, OR values for lung cancer, with adjustment for age, smoking, and vital status at the time of data collection.

In the case-referent study of sinonasal cancer conducted by Hayes et al (15) in The Netherlands, independent reconstruction of individual exposure histories from interview data was accomplished by two hygienists. Blair et al (1) used the assessment of one of the two. In the reanalysis, mean frequencies were calculated between the two hygienists in the cells of a three-dimensional arrangement spanned by wood dust (two categories), maximal formaldehyde level (three categories), and case-referent status, from the frequencies in table III in reference 15. The OR values adjusted for wood dust and their standard errors (on the log scale) for any, low-medium, and substantial exposure to formaldehyde were then calcu-

Table 1. Changes in input between the original analysis (1) and the reanalysis with respect to lung cancer.^a [O = observed frequency, E = expected frequency, RR = risk ratio (O/E)]

Reference	Original values (1)			Reanalysis		
	O	E	RR	O	E	RR
<i>Any exposure</i>						
Harrington & Shannon (5)	8	24.2	0.3	11	27.9	0.4
Harrington & Oakes (6)	9	22.0	0.4	9	22.7	0.4
Logue et al (10)	..	..	0.2	14	58	0.2
Acheson et al (11, 12)	205	215	1.0	162	160	1.0
Malke & Weiner (13)	214	183	1.2	6	6.7	0.9
Partanen et al (14)	13	9.8	1.3	7	7.9	0.9
Blair et al (7)	201	182	1.1	146	109	1.4
Bond et al (8)	9	27.0	0.6	4	12.9	0.3
Stayner et al (9)	39	34.1	1.1	8	9.2	0.9
<i>Low-medium exposure</i>						
Acheson et al (11, 12)	39	42	0.9	53	63	0.8
Partanen et al (14) ^b	10	6.6	1.5	11	4.7	2.3
Blair et al (7)	88	72	1.2	102	75	1.4
<i>Substantial exposure</i>						
Partanen et al (14) ^b	3	2.2	1.4	3	8.6	0.4
Blair et al (7)	62	56	1.1	44	33	1.3

^a Input values that were not changed can be found in reference 1 and they have not been reproduced here.

^b Respiratory cancers.

lated with the Mantel-Haenszel procedure (16), and the expected numbers needed in the Poisson analysis were derived as O/OR.

Vaughan et al (17) conducted a case-referent study on sinonasal, nasopharyngeal, and oro- and hypopharyngeal cancers in west Washington in the United States. For the low-medium and substantial exposure categories in the reanalysis, 15-year lagged OR values derived through a job-exposure matrix from telephone interview data were available. The figures were readily adjusted for age, gender, cigarette smoking, and alcohol consumption by incorporation of these covariates into a multiple logistic regression model. The graded exposure levels were based on a multiplicative function of maximal exposure level and number of years exposed. For the qualitative analysis, exposure levels over background were collapsed into "any" exposure to formaldehyde, and no adjustment or lagging seemed to be possible for the reported figures.

Vaughan et al (18) also studied residential exposures to formaldehyde from mobile homes and other structures. Numbers referring to living in mobile homes, lagged by 15 years, were selected for the reanalysis. Figures for "any exposure" were drawn from the category of ">1 year in mobile home," adjusted for cigarette smoking, alcohol consumption, gender, and age for sinonasal cancer and for race and cigarette smoking, and lagged by 15 years, for nasopharyngeal cancer.

From the population-based case-referent study of sinonasal and nasopharyngeal cancers in Connecticut by Roush et al (19), figures adjusted for age at death, year of death, and quality of occupational information were extracted. The low-medium category of formaldehyde exposure was taken to equal "probably exposed to some level for most of the worker's worklife and probably exposed to some level for ≥ 20 years prior to death," and the substantial level was "probably exposed to some level for most of the worker's worklife and probably exposed to a high level for ≥ 20 years prior to death." The latter category was included in the former one in the

present analysis because of the way the results were presented in reference 19. The low-medium category therefore served also as the "any" category.

A Danish case-referent study of sinonasal cancer by Olsen et al (20) provided 10-year lagged figures for formaldehyde exposure after adjustment for wood dust exposure.

Three studies missing in the original analysis (1) were included. From a case-referent study of sinonasal cancer by Brinton et al (21), gender-adjusted figures for formaldehyde exposure were available. Another case-referent study by Gallagher et al (22) on cancers of the oral cavity and oropharynx provided adjusted figures for "any," as well as "probable or definite" exposure, the latter being used as input for the "substantial" category of exposure. Merletti et al (23) published their case-referent study on cancer of the oral cavity and oropharynx after the original meta-analysis (1). They provided OR values adjusted for age, education, area of birth in Italy, tobacco smoking, and alcohol consumption. The "any" exposure category served as both "any" and "low-medium" exposure categories in the present analysis, as no separate "low-medium" category was provided by the authors. "Probable or definite" exposure, (ie, exposure very probably or definitely higher than that of the general population) was selected for "substantial" exposure.

A recent report of a record-linkage study of occupational factors for nasopharyngeal cancer in Sweden by Malmer et al (24) addressed, among other issues, formaldehyde. A standardized incidence ratio of 3.9, based on four exposed cases, was computed for fiberboard workers. However, no cases were reported among veneer and plywood workers, and an adequate input could not be extracted from the report. The study was therefore not considered in the present reanalysis.

Results

Lung

The results of the qualitative analysis of lung cancer are shown in table 2. Only the Poisson model was applied.

Practitioners of relevant medical specialties (pathology, anatomy, forensic medicine) displayed a markedly and significantly depressed risk of lung cancer (aggregated RR = 0.3 in the original analysis and upon reanalysis) (table 2). The aggregated RR for funeral directors, embalmers, and undertakers³ was 1.0 in both analyses, and, in close agreement

Table 2. Aggregated risk of lung cancer for different professional and occupational groups — Poisson model. [O = observed frequency, E = expected frequency, RR = risk ratio (O/E), 95% CI = 95% confidence interval]

Group	O	E	RR	95% CI
Anatomists, pathologists, forensic medicine specialists				
Blair et al (1) ^a	29	89.3	0.33	0.22—0.47
Reanalysis	54	159.7	0.34	0.26—0.44
Funeral directors, embalmers, undertakers, drug users				
Blair et al (1) ^a	490	520.4	0.94	0.86—1.03
Reanalysis	474	486.4	0.98	0.89—1.07
Industrial workers				
Blair et al (1) ^a	1181	1096.8	1.08	1.08—1.14
Reanalysis	833	751.6	1.11	1.03—1.19

^a Confidence limits recalculated by the present author; see reference 2.

³ In lack of a better category, people using formaldehyde solution (formalin) for medicinal purposes in the study of Friedman & Ury (25) were placed here. The authors motivated their scrutiny of lung cancer and formalin with the statement "since its vapor has been found to induce squamous cell carcinomas in the nasal cavity of rats . . . [p 172]" (25).

Table 3. Log-Gaussian^a and Poisson^b meta-analyses for formaldehyde exposure and sinonasal cancer. (O = observed frequency, E = expected frequency, RR = risk ratio, SE = standard error, 95% CI = 95% confidence interval)

Reference	Level or duration of exposure											
	Any				Low-medium				Substantial			
	O	E	RR	SE (lnRR)	O	E	RR	SE (lnRR)	O	E	RR	SE (lnRR)
Haynes et al (15)	40	23.4	1.71	0.291	12	8.2	1.46	0.414	28	14.9	1.88	0.339
Vaughan et al (17)	5	6.1	0.82	0.485	4	4.0	1.00	0.579	.	.	.	.
Vaughan et al (18)	5	8.3	0.60	0.546	.	.	.	.	.	.	.	.
Blair et al (7)	2	2.2	0.90	0.707	1	2.0	0.50	1.000	1	1.0	1.00	1.000
Roush et al (19) ^c	16	16.0	1.00	0.327	16	16.0	1.00	0.327	7	4.7	1.50	0.477
Harrington & Oakes (6)	—	0.1	.	.	.	.	.	.	.	.	.	.
Gallagher et al (22)	1	0.0	.	.	.	.	.	.	.	.	.	.
Hayes et al (26)	—	1.7	.	.	.	.	.	.	.	.	.	.
Acheson et al (11, 12)	—	1.1	.	.	.	.	.	.	.	.	.	.
Olsen et al (20)	23	14.4	1.60	0.418	.	.	.	.	.	.	.	.
Malker & Weiner (13)	—	0.2	.	.	.	.	.	.	.	.	.	.
Brinton et al (21)	2	5.7	0.35	0.717	.	.	.	.	.	.	.	.
All	93	77.9	.	0.161	33	30.2	.	0.249	36	20.6	.	0.266
RR (95% CI)												
Log-Gauss ^a	1.11	(0.81—1.53)			1.10	(0.67—1.79)			1.68	(1.00—2.82)		
Poisson ^b	1.19	(0.96—1.46)			1.09	(0.74—1.55)			1.75	(1.21—2.43)		
Blair et al (1) ^d	1.07	(0.82—1.38)			0.82	(0.58—1.12)			1.07	(0.72—1.53)		
Heterogeneity ^a												
X ²		7.49				1.20				0.44		
df		6				3				2		
P		0.28				0.75				0.81		

^a See the Methods section, reference 3, and reference 4.^b See the Methods section.^c Because of the way the results were presented in reference 19, the low-medium category consists of all of the exposure categories.^d Original aggregated risk ratios by Blair et al (1); the confidence limits were recalculated by the present author.^e See reference 3.**Table 4.** Log-Gaussian^a and Poisson^b meta-analyses for formaldehyde exposure and nasopharyngeal cancer. (O = observed frequency, E = expected frequency, RR = risk ratio, SE = standard error, 95% CI = 95% confidence interval)

Reference	Level or duration of exposure											
	Any				Low-medium				Substantial			
	O	E	RR	SE (lnRR)	O	E	RR	SE (lnRR)	O	E	RR	SE (lnRR)
Vaughan et al (17)	6	2.7	2.26	0.470	4	2.4	1.67	0.621	2	1.0	2.11	0.821
Vaughan et al (18)	3	1.0	3.00	0.673	.	.	.	.	.	.	.	.
Blair et al (7)	6	2.0	3.00	0.408	2	0.5	4.00	0.707	2	0.3	6.67	0.707
Roush et al (19) ^c	17	13.1	1.30	0.314	17	13.1	1.30	0.314	7	3.0	2.33	0.484
Hayes et al (26)	4	1.9	2.16	0.500	.	.	.	.	.	.	.	.
All	36	20.7	.	0.193	23	16.0	.	0.261	11	4.3	.	0.359
RR (95% CI)												
Log-Gauss ^a	2.00	(1.36—2.90)			1.59	(0.95—2.65)			2.74	(1.36—5.55)		
Poisson ^b	1.74	(1.21—2.41)			1.44	(0.91—2.16)			2.59	(1.29—5.36)		
Blair et al (1) ^d	1.22	(0.83—1.73)			1.10	(0.74—1.57)			2.06	(1.10—3.52)		
Heterogeneity ^a												
X ²		3.33				2.13				2.64		
df		4				2				2		
P		0.51				0.31				0.27		

^a See the Methods section, reference 3, and reference 4.^b See the Methods section.^c Because of the way the results were presented in reference 19, the low-medium category consists of all of the exposure categories.^d Original aggregated risk ratios by Blair et al (1); the confidence limits were recalculated by the present author.^e See reference 3.

with the original analysis, an RR of 1.1 [95% confidence interval (95% CI) 1.0—1.2] was found for industrial workers.

A quantitative analysis for lung cancer was performed for industrial workers only, as at least some

of the figures for professionals were confounded by social class. The aggregated RR was 1.2 (518 observed, 425 expected, 90% CI 1.1—1.3) for low-medium exposure and 1.1 (233 observed, 216 expected, 95% CI 0.95—1.2) for substantial exposure.

Table 5. Log-Gaussian^a and Poisson^b meta-analyses for formaldehyde exposure and cancers of the oropharynx, lip, tongue, salivary glands, and mouth. (O = observed frequency, E = expected frequency, RR = risk ratio, SE = standard error, 95% CI = 95% confidence interval)

Reference	Level or duration of exposure											
	Any				Low-medium				Substantial			
	O	E	RR	SE (lnRR)	O	E	RR	SE (lnRR)	O	E	RR	SE (lnRR)
Vaughan (17) ^c	31	22.0	1.41	0.235	16	17.8	0.90	0.384	15	11.5	1.30	0.419
Blair et al (7) ^d	13	18.9	0.69	0.277	11	14.9	0.74	0.302	2	4.9	0.41	0.707
Merletti (23) ^e	25	15.6	1.60	0.290	25	15.6	1.60	0.290	6	3.3	1.80	0.565
All	69	56.5		0.153	52	48.3		0.183	23	19.7		0.304
RR (95% CI)												
Log-Gauss ^a		1.18	(0.87—1.59)			1.05	(0.74—1.51)			1.15	(0.64—2.09)	
Poisson ^b		1.22	(0.95—1.54)			1.08	(0.80—1.42)			1.16	(0.74—1.75)	
Heterogeneity ^f												
X ²		5.46				3.64				2.84		
df		2				2				2		
P		0.065				0.16				0.24		

^a See the Methods section, reference 3, and reference 4.^b See the Methods section.^c Cancers of the oropharynx and hypopharynx.^d Cancers of the lip, tongue, salivary glands, gum, floor and other oral sites, oropharynx, hypopharynx, and other pharynx (except nasopharynx). Aggregated from table 5 of reference 7.^e Cancers of the oral cavity and oropharynx. Because of the way the results were presented in reference 23, the low-medium category consists of all of the exposure categories.^f See reference 3.

Upper respiratory sites

The complete input data and results of the log-Gaussian and Poisson meta-analyses for sinonasal, nasopharyngeal, and other sites of upper respiratory cancers are shown in tables 3, 4, and 5. In the reanalysis of both sinonasal and nasopharyngeal cancers (tables 3 and 4), a significant increase was associated with the "substantial" exposure category (RR 1.7 for sinonasal cancers and 2.7 for nasopharyngeal cancers). Neither an increased risk nor an exposure-response relation was suggested by the aggregated data for the combined category of oropharynx, hypopharynx, lip, tongue, salivary glands, and mouth (table 5).

Discussion

Some of the central problems of epidemiologic meta-analyses were encountered in this reanalysis. Thus the choice of the observed and expected frequencies, or the RR values and their variances, from the various studies may have suffered from subjectivity in a single-author exercise. A weighting of the component inputs by study quality was not formally attempted (but the choice of inputs was given some thought), and the source data were weighted by precision only. Some heterogeneity and inconsistency was unavoidable among the inputs from the different studies, particularly for lung cancer. All input was based on published — and most of it peer-reviewed — results. The procedure was double-edged in that some data could have been missing, but, if the missing data were available, their relevance and quality might have been difficult to judge.

Considering the statistical procedures, the Poisson model resulted in narrower confidence limits than did the log-Gaussian risk ratio model. Strictly taken, the Poisson model is incorrect when the expected frequencies contain error, which is essentially the case when the expected values are based on relatively small numbers of reference subjects. In particular, when aggregating results of a few small-sized case-referent studies, the Poisson formula may create a deceptive illusion of precision, and the log-Gaussian risk ratio model is preferable. The changes in the point estimates of the RR values between the original and the reanalysis were not however materially affected by the model; the changes in the input values were decisive.

Despite a fair number of changes in the input values, the results of the reanalysis agreed generally well with those of the original analysis (1). Thus, in light of epidemiologic evidence, it does remain unlikely that workplace exposures to formaldehyde pose any substantial lung cancer hazard among humans. The exposure-response gradient for lung cancer was slightly inverse, if any. The statistical significance on the Poisson model of RR = 1.2 for industrial workers derived from large numbers. Some persistent confounding (eg, from smoking) may have accounted for the increase, but a weak true effect of formaldehyde could not be absolutely excluded. The deficit observed among anatomists, pathologists, and specialists in forensic medicine was confounded by social class and had nothing to do with formaldehyde.

The aggregated data for the mixed category of cancers of the oropharynx, hypopharynx, lip, tongue, salivary glands, and mouth was not indicative of any

association with formaldehyde exposure. The data derived from three studies only, and the inputs were somewhat heterogeneous, the RR values from the component studies ranging from 0.4 to 1.8.

Upon reanalysis, and in slight contrast to the original analysis (1), sinonasal cancers did reveal an exposure-response gradient in the sense that the risk in the category of substantial exposure was significantly elevated ($RR = 1.7$ in the log-Gaussian model). Such a gradient was observed only for nasopharyngeal cancers in the original analysis (1). The rederivation of the input seemed to sharpen the gradients slightly for both sites, as compared with the results of the original analysis (1). On this evidence, the two contiguous sites appear to be the most likely targets for the carcinogenic action of formaldehyde in humans.

Confounding by wood dust is a concern, particularly when nasal cancer is considered, and it might be argued that some of the postulated nasal carcinogenicity might be due to some constituent of wood particulates other than formaldehyde. In two (15, 20) of the four studies that quantitatively contributed the most to the reanalysis of sinonasal cancer, however, exposure to wood dust was controlled for. In the one that addressed exposure-response for formaldehyde (15), a positive gradient was observed, and in the one that did not (20) a significant overall excess risk was found. Hayes et al (15) made a further note that formaldehyde exposure in their study was linked with squamous cell carcinoma, a finding consistent with data on rodents (27), while wood dust was the most strongly associated with nasal adenocarcinoma, as could be expected, particularly with hardwood dust, from extensive epidemiologic data (28, 29).

The aggregated exposure-response gradients for nasal and nasopharyngeal cancers were probably understated because the graded categories (low-medium and substantial) reflected the full variety of conceptions and definitions adopted in the different studies. An unknown degree of misclassification between exposure categories resulted from this heterogeneity. In some studies, job-exposure-matrix-type translation of job titles into exposure levels probably compounded the misclassification rates. If, on the other hand, publication bias or a file-drawer phenomenon (3) was operating, it would probably have had a positively biasing effect also on the exposure-response gradients. In light of the considerable industrial and economic importance of formaldehyde, however, the assumption may be defensible that also nonpositive high-quality studies on formaldehyde and cancer tend to get submitted and published.

Some further epidemiologic data, independent of the input used in this report, may enhance the nasal-nasopharyngeal hypothesis. Matanoski (30) has reported a 4.7-fold increase in nasopharyngeal and pharyngeal cancers (and also an excess risk of pancreatic and brain cancers and leukemia) among pathologists, as compared with psychiatrists. The author, however, suspended judgment as to the role of

formaldehyde, since there were other chemical exposures encountered by the pathologists. This study was not included in the formal reanalysis. Similarly, the data suggesting an elevated risk of nasopharyngeal cancer associated with formaldehyde exposure, reported in Sweden (24), were excluded, as the assessment of formaldehyde exposure was somewhat unclear in that particular study.

If the nose-nasopharynx hypothesis gains credibility, then rats and humans will come closer to each other in that the carcinogenic action of formaldehyde would affect both around an immediate target, which for rodents is the anterior mucosa of the nasal cavity and which for humans, for anatomic and physiological reasons, is both the anterior mucosa of the nasal cavity and contiguous sites such as the nasopharynx. It is also worthwhile to acknowledge that — in contrast to the animal cancer tests in which chemicals are administered at the maximal tolerated dose (31) — some of the levels of formaldehyde exposure scheduled in the animal carcinogenicity tests (27, 32–34) that induced tumors in nasal passages of rats were in the range of realistic workplace exposures. Extrapolation between species poses problems, however, as usual. Both the disposition of formaldehyde and, possibly, the tumorigenic response seem to be species dependent among rodents alone, as no carcinogenicity was demonstrated in hamsters (35) in an exposure scenario comparable with that of the rat experiments; and the effects on mice were much less pronounced than those on rats (33). The latter finding has been explained simply by the fact that, when exposed to formaldehyde, the mouse reduces its breathing volume substantially more than the rat, and therefore also lowers the amount of exposure (36).

The biological plausibility of the nasal-nasopharyngeal hypothesis is enhanced by the fact that formaldehyde, as a reactive compound, is rapidly and extensively metabolized to formate. Formaldehyde has genotoxic, typically cross-linking properties (37, 38). It is notable that reactions of formaldehyde with cellular deoxyribonucleic acid take place in the turbinates and anterior nasal mucosa in rodents, and in monkeys also in the nasopharynx, larynx, trachea, and carina (39). The sinuses however seem to remain unaffected in monkeys (39), a finding which may be relevant with respect to humans. In recent studies, micronuclei were found to occur more frequently in the epithelial cells of the buccal cavity (40) and nasal mucosa (41) in workers exposed to formaldehyde than in unexposed subjects.

With some relevance to respiratory cancers, the epidemiologic evidence on formaldehyde and non-respiratory cancers is insufficient and inconsistent (1). Elevated risk for cancers of some nonrespiratory sites remains a possibility. After the original meta-analysis, a short report (42) was published showing significant excesses of follicular non-Hodgkin's lymphoma and acute myeloid leukemia among Iowa and

Minnesota embalmers and funeral directors. In an animal bioassay (43), leukemia and gastrointestinal tumors were induced by the administration of formaldehyde in drinking water, a finding suggesting that the ingestion of formaldehyde, for example, in drinking water, might be associated with a carcinogenic hazard.

In summary, the current epidemiologic evidence is about sufficient for the conclusion that at least substantial occupational formaldehyde exposures are carcinogenic, and the risk is the most likely to concentrate on the nasal cavities and nasopharynx, but probably not the lung. The increase in the risk would be, considering the predominant downward confounding in the epidemiologic studies, 100% or more over the background incidence. The excess absolute cancer burden may remain somewhat limited, however, if the bronchi and the lungs — for which the background incidence is much higher — remain unaffected. This possibility seems likely, considering the current biological, experimental, and epidemiologic evidence.

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