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VIA OVERNIGHT DELIVERY

Dr. Mary S. Wolfe
Executive Secretary
NTP Board of Scientific Counselors
NIEHS
111 TW Alexander Drive
Room A329
Building 101, South Campus
Research Triangle Park, NC 27709

Re: NTP Board of Scientific Counselors' Meeting; Review of Nominations for Listing in the 10th Report on Carcinogens, 65 Fed. Reg. 61352 (Oct. 17, 2000)

Dear Dr. Wolfe:

The Inter-industry Wood Dust Coordinating Committee requests an opportunity for Dr. William J. Blot to make an oral presentation at the December 13-15, 2000, meeting of the Report on Carcinogens (RoC) Subcommittee. Dr. Blot is an epidemiologist (formerly with National Cancer Institute) who has published on wood dust. His address is International Epidemiology Institute, Ltd., 1455 Research Blvd., Suite 550, Rockville, MD 20850. His telephone, fax, and e-mail addresses are: (telephone) 301/517-4060, (fax) 301/517-4063, (e-mail) blotw@cs.com. A copy of Dr. Blot's Statement and Curriculum Vitae are attached.

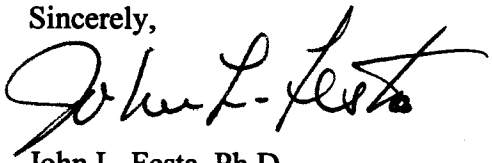
In his Statement, as in his prior peer-reviewed publication which is attached, Dr. Blot highlights the disparity in the epidemiologic findings on wood dust in Europe versus North America. "Whereas there is consistent evidence of a large increased risk of nasal adenocarcinomas among multiple groups of wood dust exposed workers in Europe, there is no corresponding clustering of this cancer among wood workers in North America." The sharp divergence in the findings between Europe and North America is highly relevant to the NTP's consideration of wood dust. In similar circumstances, the NTP has declined to list on the basis of disparities in geographical and other factors, focusing evaluation of the evidence on conditions applicable to current U.S. workers. Specifically,

> [NTP has] recognize[d] that certain aspects of occupational exposures may differ in parts of the world or may have changed over time. In addition, the manufacturing processes and operations reviewed by IARC in their determinations may differ greatly from what has been or is currently used in the United States.
> (9th RoC Report, Appendix A)

This language was relied upon in the determination not to list boot and shoe manufacture and repair in the 9th RoC Report, notwithstanding its IARC classification as a Category 1 "Known Human Carcinogen." By the same token, it is inappropriate to list wood dust in a report addressing U.S. exposures.

We would appreciate your distributing this cover letter and the attached statement to the members of the Subcommittee for their review before the meeting. Please call if there are any questions.

Sincerely,



John L. Festa, Ph.D.
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Attachments

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Statement of William J. Blot, Ph.D.

On the NTP Draft Tenth Report on Carcinogens

Background Document for Wood Dust

Prepared at the request of the Inter-Industry

Wood Dust Coordinating Committee

December 1, 2000

I have been asked by the Inter-Industry Wood Dust Coordinating Committee to provide comments on the scientific evidence on the risk of cancer associated with wood dust exposure in the United States. Wood dust has been designated as a Group 1 recognized human carcinogen by the International Agency for Research on Cancer (IARC) because of the excessive risk of nasal adenocarcinoma among wood dust exposed workers observed in a number of epidemiologic studies, primarily among European hardwood furniture and cabinet makers first exposed prior to 1950. As it considers listing wood dust in the Tenth Report on Carcinogens (10th RoC), the NTP should be aware, however, that there is a striking difference in the epidemiologic data on this issue between the United States and Europe. Whereas there is consistent evidence of a large increased risk of nasal adenocarcinoma among multiple groups of wood dust exposed workers in Europe, there is no corresponding clustering of this cancer among wood workers in North America.

The Draft 10th RoC for Wood Dust does not fully acknowledge the large difference in nasal cancer findings between continents. Indeed, in the introductory summary section entitled Carcinogenicity, the text states: "Risks were highest for adenocarcinoma, particularly among European populations. Studies of U.S. populations also showed similar significant positive associations." As shown below, this statement is incorrect.

Epidemiologic studies evaluating nasal cancer in association with wood dust exposure have been of two types, cohort studies tracking exposed workers and case-control studies assessing occupation among nasal cancer cases. In 1997 my colleagues and I published an article in the Journal of Occupational and Environmental Medicine (JOEM) summarizing the cohort and case-control data on nasal cancer among wood dust exposed populations (a reprint is attached). We described the sizeable increased risk of nasal adenocarcinoma among European woodworkers, dating initially from the late 1960s among workers exposed prior to World War II in the furniture making center of High Wycombe, England. Subsequent reports from elsewhere in Europe confirmed the association of elevated risk of nasal cancer among workers heavily exposed to wood dust, in each situation noting that the association was specific for adenocarcinoma. In meta-analytic reviews of the totality of available evidence by the 1990s, it was shown that woodworkers had a greater than 13-fold increase in nasal adenocarcinoma but no excess at all of squamous cell cancer.

In sharp contrast, there has been no similar excess in North America. Indeed, among several cohort studies tracking cancer among wood dust exposed groups, the number of nasal cancers observed has been approximately equal that expected based on general population rates. The results of the cohort studies, including a new investigation of American workers published since our report, are presented in Table 1. Although the

studies cited in Table 1 individually had few nasal cancers, cumulatively they had ample statistical power to detect the large increases in risk seen in Europe had they existed in the United States.

In North American case-control studies examining the issue, results have been mixed. A number have reported mildly positive associations, occasionally statistically significant, between nasal cancer (either adenocarcinoma or squamous cell cancer) and wood working occupations, but none of the few positive studies indicated excesses anywhere near what has been observed in Europe. In our JOEM review we listed 10 case-control studies conducted in North America: six were based on examining death certificate or medical record statements on occupation; and four were more detailed, obtaining occupational histories as well as information on risk factors from interviews using structured questionnaires. The six death certificate/medical records studies reported relative risks of nasal cancer associated with wood-related jobs ranging from 1.0 to 4.4, with the highest values tending to occur in the smallest and the lowest values in the largest studies. Table 2 lists results from the four more detailed case-control studies, plus two additional interview studies published since the review. As indicated, there is little consistent evidence of an increased risk in these more informative studies, and no hint of any of the large excesses seen in Europe.

The Draft 10th RoC Report tends to downplay this substantial geographic difference in epidemiologic findings. It dismisses the cohort studies as too small and suggests that the case-control studies were consistently positive. It highlights one of the case-control studies (Brinton et al, 1984) as showing a much stronger excess of adenocarcinoma than squamous cell cancer of the nasal sinuses and cavities. This study, of which I was a co-author, found an excess risk of nasal adenocarcinoma among furniture workers, but a deficit of squamous cell cancer, with a total relative risk of nasal cancer (all types combined) among furniture workers of 0.8, i.e., no overall increase in nasal cancer among the workers. Since it is highly unlikely that wood dust would be a cause of one type of nasal cancer but be an inhibitor of another type, caution is needed in interpreting the findings for either cell type.

In summary, I believe the draft documentation presents an incomplete picture of the evidence on nasal cancer in relation to wood dust exposure, and does not provide the justification for a proposed 10th RoC listing of wood dust *applicable to the situation in the United States*. If the only data available were from North America, in my view it is doubtful that the IARC would have classified wood dust as known human carcinogen.

The Draft report also discusses the epidemiologic evidence linking wood dust exposure with several other types of cancer. The Draft notes that some positive associations have

been reported, but also notes that there has not been consistency across studies and thus the only established relationship between wood dust and cancer is for nasal cancer. This was also the position of the IARC, with data arising since the IARC report continuing to indicate no general cancer hazard among wood workers.

The intent of a proposed NTP listing of wood dust in the 10th RoC is presumably to warn of a possible carcinogenic hazard of wood dust exposure in the United States. Because of the wide disparity between American and European epidemiologic findings on nasal cancer, such a warning is not as simple and uncomplicated as it might appear. Indeed, the warning is not needed for Americans since a nasal cancer excess has not been demonstrated for wood dust exposures in the United States. Issuing a warning when, based on the American experience, one may not be needed seems unlikely to be a beneficial course of action and could have adverse economic or social effects without any net gain in public safety or health.

Table 1. Nasal Cancer in North American Cohort Studies of Wood-dust Exposed Workers

First author (year)	Industry	No. of Workers	No. of nasal cancers Observed	Expected
Stellman (1984) [1]	Wood workers	10,322	2	1.0
Miller (1989, 1994) [1]	Furniture	34,801	2	2.5
Robinson (1990) [1]	Plywood	2,283	0	0.4
Roscoe (1992) [1]	Model makers	2,294	0	0.3
Stellman (1998)	Wood dust exposed	33,858	1	1.0
TOTAL			5	5.2

[1] see Blot et al. (1997)

Table 2. North American case-control interview studies of nasal cancer in relation to wood dust exposure

First author (year)	Industry	No. of exposed cases	RR	95% CI
Brinton (1984) [1]	Furniture	8	0.8	0.3-2.0
	Lumber	26	1.4	0.7-2.6
	Carpentry	13	1.5	0.6-3.4
Vaughan (1991) [1]	Wood-related	7	2.4	0.8-6.7
Mack (1995) [1]	Wood-related	1	0.2	0.0-1.5
Zheng (1993) [1]	Wood-related	8	1.7	0.6-4.3
Teschke (1997)	Wood dust exposed	6+	0.7	0.3-1.6
Mirabelli (2000)	Wood dust exposed	11	1.0	0.5-2.0

[1] see Blot et al. (1997)

References

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Wood Dust and Nasal Cancer Risk

A Review of the Evidence from North America

William J. Blot, PhD
Wong-Ho Chow, PhD
Joseph K. McLaughlin, PhD

In this article, biomedical literature assessing risks of nasal cancer and nonmalignant nasal pathology among woodworkers in North America is reviewed in detail and contrasted with experience from Europe and elsewhere. Exceptionally high rates of nasal adenocarcinoma have occurred among European hardwood furniture workers, but the epidemiologic evidence documents a disparity in findings between North America and Europe. Cohort studies of American wood-dust–exposed groups do not reveal excesses of nasal cancer, and wood-dust associations from US and Canadian case-control studies of nasal cancer tend not to be strong and differ across studies. Quantitative wood-dust exposure data are generally unavailable, but general dose information in European studies suggests that the excess risk of nasal cancer is associated with high levels of exposure. There is also an inconsistent association between wood-dust exposure per se and mucostasis or nasal histologic changes, and the mucostasis/metaplasia/dysplasia route to nasal cancer is still an unverified hypothesis. Considering the totality of evidence on the risk of cancer in exposed workers, it appears that wood-dust–related nasal adenocarcinoma essentially can be eliminated in Europe and its occurrence prevented in the United States if wood-dust exposures do not exceed an 8-hour time-weighted average 5 mg/m^3 standard.

In this review of the biomedical literature assessing risks of nasal cancer associated with occupational exposures to wood dust, we focus on studies of exposed workers in North America, although data from Europe and elsewhere are described and contrasted with the American experience. This review is intended to supplement rather than duplicate the recent International Agency for Research on Cancer monograph,[1] which concluded that there was sufficient evidence to classify wood dust as carcinogenic to humans (a Group 1 designation) based upon observed excesses of nasal adenocarcinoma in groups heavily exposed to predominantly hardwood dust. Our review assesses the extent to which North American data fit the international pattern, and may serve as an aid in evaluating wood-dust–exposure standards for American workers. Also reviewed are studies that have assessed the relationship between wood-dust exposure and nonmalignant nasal pathology and conditions thought to predispose to nasal cancer. Studies in experimental animals were not considered, because there are insufficient animal data for evaluating wood-dust carcinogenicity.

Cohort Studies

The association between nasal adenocarcinoma and wood-dust exposure first became apparent from a clustering of this rare cancer in High Wycombe, a furniture-making center in central England.[2] Among some groups of cabinetmakers in this area working primarily with beech, oak, and other hardwoods, rates of nasal

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TABLE 1
Cohort Studies Assessing Mortality from Nasal Cancer Among North American Workers Exposed to Wood Dust

First Author, Year	Industry	Number of Workers	Follow-up Period	Number of Nasal Cancers	
				Observed	Expected
Stellman, 1984[9]	Woodworkers	10,322	1959 to 1972	2	1.0
Miller, 1989, 1994[7,8]	Furniture	34,801	1946 to 1983	2	2.5
	Wood furniture	12,158	1946 to 1983	1	0.9*
Blair, 1986[12†]	Plywood	2,309	1951 to 1979	0	Unknown‡
Robinson, 1990[10]	Plywood	2,283	1945 to 1977	0	0.4
Roscoe, 1992[11]	Automobile model makers	2,294	1940 to 1984	0	0.3*

* Estimated value (expected number not presented by authors).
† As reported by Demers et al 1995.[13]
‡ No expected number was given separately for this cohort.

cancer were thought to nearly equal rates of lung cancer, the most common cancer in the British general population (rates of lung cancer were not elevated, however, among furniture makers).[2–5] Since these initial reports, numerous other studies have demonstrated elevated risks of nasal adenocarcinoma among workers in woodworking jobs, primarily those involved in furniture manufacturing.

A number of cohort studies have been conducted among workers with jobs with potential for wood-dust exposure. The largest include a 5-year follow-up of approximately 40,000 members of a Danish carpenter and cabinet makers' union[6] and an up to 42-year follow-up of 5100 British furniture workers, including workers in High Wycombe.[5] No increased risk of total cancer (all sites combined) was found in these cohorts, compared with general population norms, but significant five- to eightfold increases in mortality from nasal cancer were observed, with all of the nasal cancers among the UK furniture workers being adenocarcinomas.

In North America, cohort studies of woodworkers with potential to evaluate nasal cancer include an up to 38-year follow-up of 12,000 members of the United Furniture Workers of America Union;[7,8] a 12-year follow-up of 10,000 participants in the American Cancer Society cohort who reported woodworking jobs;[9] an up to 32-year follow-up of 2300 plywood mill workers in the states of Oregon and Washington:[10] an up to 45-year follow-up of 2300 North American automobile wooden model and pattern workers[11]; and an up to 29-year follow-up of 2309 plywood mill workers[12] incorporated in a pooled reanalysis of cohort studies.[13] Rates of nasal cancer were not reported to be significantly elevated, however, in any of the American studies (Table 1). The significantly elevated mortality of nasal cancer reported in the pooled reanalysis was primarily a result of the excess cases among the British furniture workers.[5]

Several other cohort studies assessed cancer risks of individuals with woodworking jobs, but were too small in size to evaluate nasal cancer, a cancer that is relatively uncommon in the general population.[1] In Europe (Sweden, Denmark, Switzerland), studies linking census data on occupation with cancer-registry files reported increased rates of nasal cancer among woodworkers, particularly furniture makers.[1] The largest was a nationwide survey of all incident nasal cancers during 1961 to 1979 in Sweden.[14] Among the 648 cases, 77 were adenocarcinomas, of which 25% occurred among men who had been employed in the furniture manufacturing industry in 1960, whereas less than 2% of the working population was employed in this industry. This national survey in Sweden also showed that there was no excess risk of squamous cell cancers among furniture makers.

Given the rarity of nasal cancer, the numbers of nasal cancers in the cohort studies are typically small (even in the large European cohorts, there were only four deaths in Denmark, and nine in the United Kingdom), so that dose-response or other characteristics of the association with woodworking jobs could not be adequately explored via the cohort approach. Because of their limited statistical power and the absence of wood-dust–exposure information, the cohort studies of woodworkers are of limited usefulness in risk assessment. A geographic discrepancy is suggested, however, with sharply elevated rates of nasal cancer among Europeans in the furniture industry but inconclusive results in the United States.

Case-Control Studies

As in the cohort studies, the case-control studies reporting the highest risks of nasal cancer were mostly conducted in western Europe, including Germany, the Netherlands, Italy, and France.[1] The relative risks (RRs) for nasal cancer (all cell types combined) often exceeded 5. All of the European studies that reported risks separately for adenocarcinomas found much greater risks for adenocarcinomas than for squamous cell carcinomas, with RR of adenocarcinoma among wood-dust–exposed workers often greater than 10 and sometimes exceeding 50. Indeed, when the data from case-control studies are combined, the excess risk associated with woodworking occupations is limited to adenocarcinoma (summary RR, 13.5; 95% confidence interval [CI], 9 to 20) with no increased risk of squamous cell nasal cancer (summary RR, 0.8; 95% CI, 0.6 to 1.1).[15]

TABLE 2
Case-Control Studies Assessing Risks of Nasal Cancer Among North American Workers Exposed to Wood Dust*

First Author, Year	Industry	Number of Exposed Cases†	RR	95% CI Studies Obtaining Occupation from Death Certificates or Medical Records
Ball, 1967[18]	Wood workers	28	1.2‡	0.6 to 2.2‡
Brinton, 1977[16]	Furniture	8	4.4	1.3 to 15
	Other	5	1.5	0.4 to 4.3
Roush, 1980[17]	Wood-related	8 (2)	4.0	1.5 to 11
Elwood, 1981[20]	Wood-related	28 (3)	2.5	1.0 to 4.5‡
Finkelstein, 1989[51]	Wood-related	9	1.9	0.7 to 5.4
Viren, 1989[19]	Wood-related	30	1.5	0.9 to 2.5‡
	Lumber	22	2.0	1.0 to 3.4‡
	Furniture	7	1.0	0.4 to 2.8‡
Studies Obtaining Occupational Histories and Risk-Factor Data from Questionnaires				
Brinton, 1984[22]	Furniture	8 (4)	0.8	0.3 to 2.0
	Lumber	26 (4)	1.4	0.7 to 2.6
	Carpentry	13 (3)	1.5	0.6 to 3.4
	Other wood	3 (0)	0.6	0.1 to 2.3
Vaughan, 1991[24]	Wood-related	7 (0)	2.4	0.8 to 6.7
Mack, 1995[15§]	Wood-related	1 (0)	0.2	0.0 to 1.5‡
Zheng, 1993[21]	Wood-related	8	1.7	0.6 to 4.3

* RR, relative risk; CI, confidence interval.
† Number of adenocarcinomas in parentheses (when reported)
‡ Estimated value (original data not reported by authors)
§ As reported by Demers et al, 1995[15]

In the few case-control studies conducted in North America (Table 2), the association between nasal cancer and woodworking occupations has been less strong than in Europe. The North American studies can be classified into two categories: those in which information on occupation came primarily from death certificates or medical records (typically with no information on smoking, diet, or other potential risk factors for nasal cancer), and those involving questionnaires eliciting occupational histories as well as lifestyle, medical, and other data on the cancer cases and controls.

The highest RR were reported in two death-certificate–based studies. Brinton et al[16] reported a relative risk of nasal cancer of 4.4 (95% CI, 1.3 to 15) for furniture workers, and 1.5 (95% CI, 0.4 to 4.3) for a combined group of other woodworkers, whereas Roush et al[17] reported a relative risk of 4.0 (95% CI, 1.5 to 11) among those with a variety of woodworking jobs. The number of exposed subjects in both of these studies was small. However, in the largest studies evaluating occupation as recorded on death certificates,[18,19] no significant increases in risk of nasal cancer were found among woodworkers overall. Viren and Imbus,[19] evaluating nasal cancer deaths in Washington, Oregon, Mississippi, and North Carolina, reported a significant excess risk among the subgroup of loggers and lumber workers, but no increase for furniture workers. In a Canadian study in which information on occupation was abstracted from medical records,[20] for which standardization of reporting is suspect, patients diagnosed with nasal adenocarcinoma and squamous cell carcinoma each had over twice the proportions of wood-exposed occupations than did the control subjects. All of these studies had only the death certificate or medical-record statements on occupation/industry to classify the subject with respect to woodworking employment, and thus had no opportunity to assess duration, level, or history of exposure to wood dust, although in a subgroup of cases, Viren and Imbus[19] found a "good degree of correspondence" between occupation on the death certificate and longest job reported via questionnaire. Nor did these case-control studies (except for the Canadian study[20]) have any information on cigarette smoking or other risk factors for nasal cancer.

Only four North American case-control studies have involved questionnaires whereby information on occupation, smoking, and other potential nasal cancer risk factors has been obtained. In a study of all persons in the United States who died of nasal cancer in 1985, information from a mailed questionnaire revealed a nonsignificant relative risk of 1.7 (95% CI, 0.6 to 4.3) among white men whose usual occupation was carpentry or other woodworking jobs, after taking into account the effects of cigarette smoking.[21] Information on nasal-cancer cell type was not available (death certificates often do not specify the cell type of this or other cancers).

In the largest North American study based on interviews with study subjects or their next of kin,[22] risk of nasal cancer (all cell types combined) was not significantly linked to employment in woodworking industries, either in the furniture industry, lumber industry, or carpentry. It is noteworthy that the risk of nasal cancer associated with the furniture industry in this study in North Carolina and Virginia was 0.8 (95% CI, 0.3 to 2.0), in contrast to the RR of 4.4 estimated in the death-certificate study in the same area by the same authors.[16] When men diagnosed with adenocarcinomas were examined separately, however, Brinton et al[22] found a significantly elevated risk associated with employment in the furniture industry (RR, 5.7; 95% CI, 1.7 to 19), with insignificant excesses linked to the lumber industry

(RR, 1.6) and carpentry (RR, 2.9). The overall RR of nasal adenocarcinoma associated with employment in any job with potential for wood exposure was 3.7, with ten of the 13 cases of adenocarcinoma classified as exposed under this system, which included construction workers as exposed. No wood-dust–exposure estimates were available for any job. The 5.7-fold increased relative risk in this study of nasal adenocarcinoma among furniture workers must be interpreted cautiously because there was a corresponding fourfold deficit of squamous cell cancers among furniture workers. These sharply opposing figures suggest that each RR is exaggerated (one too high, the other too low). In combination, they cancel each other out.

In the two other North American interview studies, which had data essentially only on squamous cell nasal cancers, one in Washington[23,24] showed a twofold excess and the other in Los Angeles (described in Reference 15) a fivefold deficit among those with wood-related occupations. In each study, however, the number of exposed cases was small. In the study in Washington, the excess risk was primarily among those who had worked for 10 or more years in wood-related jobs.[23,24]

When viewed together, the North American case-control studies are consistent with no or at most a modest increase in risk of nasal cancer among workers exposed to wood dust, but the excess is much smaller than among wood workers heavily exposed to wood dust in Europe.

Dose-Response Assessment

Because of the rarity of nasal cancer and the small number of cases with wood-related employment in most studies, few individual studies had sufficient size to examine trends in risks by exposure levels. Indeed, dose-response assessments were not performed in any of the North American studies. A pooled reanalysis of 12 case-control studies (including three in North America), with a combined number of 680 male and 250 female nasal cancer cases and 2349 male and 787 female control subjects, provided the most detailed and stable risk estimates by level of exposure.[15] Using a job-exposure matrix, each unique occupation/industry combination was classified as low, moderate, or high wood-dust exposure, corresponding approximately to <1 mg/m^3, 1 to 5 mg/m^3, or >5 mg/m^3 on assumed 8-hour time-weighted-average exposures that might have been expected to have occurred in the 1970s. The exposure assignments were informed guesses, because no industrial hygiene sampling data were available for individual workplaces. Furthermore, it seems likely that for many jobs, exposure levels in the past—particularly before 1945—were higher than in the 1970s.

Under this exposure classification scheme, relative risks of nasal cancer overall among men varied from 1.0 among the unexposed to 0.8 (95% CI, 0.4 to 1.5) in the low-exposure group to 1.2 (95% CI, 0.9 to 1.6) in the mid exposure group and 5.8 (95% CI, 4.2 to 8.0) in the high-exposure group. Hence the excess risk was limited to high-exposure jobs. For adenocarcinomas, the corresponding RRs were 1.0, 0.6 (95% CI, 0.1 to 4.7), 3.1 (95% CI, 1.6 to 6.1), and 45.5 (95% CI, 28.3 to 72.9) in the non, low-, mid-, and high-exposure categories, respectively. There was no trend of rising risk of squamous cell carcinoma with increasing wood-dust exposure. Among women, no clear dose-response trend was seen with exposure levels, but the number of women who held wood-dust–related jobs was small.

The risk of nasal cancer also increased with duration of exposure. Among men, the RR for nasal cancer overall rose monotonically from 1.5 (95% CI, 1.0 to 2.2) for those with less than 5 years of exposure to 3.9 (95% CI, 2.8 to 5.6) for those with 30 or more years. The excess was accounted for by adenocarcinomas, with RRs of 7.3 (95% CI, 3.7 to 14.6) at <5 years to 31.7 (95% CI, 18.6 to 54.3) at 30 or more years of exposure. Among women, risks of nasal cancer overall also increased with duration of exposure, from 1.5 (95% CI, 0.6 to 3.6) for those with less than 5 years to 2.8 (95% CI, 0.7 to 12.1) for those with 5 or more years of exposure.

It should be noted that the findings in this pooled case-control study analysis were dominated by one French study[25,26] that found exceptionally high risks (up to several hundredfold) of nasal adenocarcinoma among heavily exposed workers, although large excess risk of up to about 30- to 50-fold were also seen in a study from the Netherlands[27] and several Italian studies.[28–30] In contrast, the US studies included in this pooled analysis generally showed no or small excess risks. It is therefore questionable whether the dose-response relationship observed in this pooled analysis could be generalized to work situations in the United States. It is also notable that in the exposure classification system used in the reanalysis of the pooled case-control data, Demers et al[15] classified only four of the adenocarcinomas in the Virginia/North Carolina study as exposed to wood dust, whereas Brinton et al[22] listed ten as potentially exposed. The difference highlights the lack of information in the epidemiologic studies on actual wood-dust–exposure levels experienced by workers.

Only limited information on dose-response trends is available from the cohort investigations. In the UK survey of woodworkers in High Wycombe,[5] the cohort was divided into three levels based on jobs classified by likelihood of exposure to wood dust. The entire excess risk of nasal cancer occurred among those in the highest exposure level (those with "very dusty" jobs, ie, cabinet and chair makers, sanders, and wood machinists), although no quantitative exposure measurements were available. In this cohort study, the excess

risk of nasal cancer was concentrated among those who had worked for 40 or more years in the furniture industry.

Issues of latency were addressed in the reanalysis of the 12 case-control studies.[15] The RR of sinonasal adenocarcinoma associated with wood-dust exposure increased with increasing years since first employment, from 1.0 (95% CI, 0.2 to 4.6) for less than 20 years since first employment, to 4.1 (95% CI, 1.6 to 10.7) and 17.4 (95% CI, 11.4 to 26.6) with 20 to 29 years and 30 or more years, respectively. In addition, lagging exposure by 5, 10, or 20 years tended to increase the strength of the associations observed. It also has been reported that discontinuation of wood-related occupations for 15 or more years did not reduce the risks.[27] Risk by latency period has not been examined in US studies, except in Washington, where risk of squamous cell cancer was higher when analysis was restricted to employment at least 15 years before diagnosis, but the numbers of cases were too small for adequate analysis.[23,24]

The long latency observed raises the possibility that wood-dust exposures may affect the early stages of nasal carcinogenesis. It should be noted, however, that effects attributed to long latency may be intertwined with effects because of higher levels of exposure in the past. Both the British[31] and the Dutch[27] studies reported a higher risk of adenocarcinomas for those first exposed to occupational wood dust before 1945, whereas no excess risk was found among workers first exposed in later years. In France, risk was higher for those first exposed before 1945, but an increased risk was also found for those first employed in woodworking jobs after World War II.[26] Although a long latency might hinder the detection of nasal cancers related to occupational exposures after 1950, a more plausible alternative explanation for the decrease (or absence) of excess nasal cancers in the 1960s to 1980s among Europeans first exposed to wood dusts after World War II is that the levels of wood dust in the more recent work environment were much lower, perhaps below a level needed to induce nasal cancer. In none of the North American studies was the date of first employment in wood-related occupations reported, but it appears that even before 1950, wood-dust–exposure levels in American industry were not high enough to produce the large excess risks of nasal adenocarcinoma seen among European furniture makers before World War II.

Precursor Lesions

The process of carcinogenesis is for some cancers thought to involve a series of transitions whereby normal mucosa undergoes a change from a normal state to hyperplasia, metaplasia, and dysplasia before the onset of malignancy. Such a model has been proposed for stomach cancer, in which normal mucosa is transformed to chronic atrophic gastritis, which in turn leads to intestinal metaplasia, dysplasia, and finally adenocarcinoma.[32] Endoscopic surveys in high-risk areas of China and Columbia have documented that these precancerous lesions are common, and that risk of stomach cancer progressively rises as the lesions become more advanced.[33] A somewhat similar model has been proposed for esophageal cancer, with dysplasia preceding the onset of squamous cell carcinomas,[34] although supporting data are not as strong.

It has been suggested[35] that nasal cancers also may evolve through a series of precancerous changes involving hyperplasia, metaplasia, and dysplasia. There appears, however, to be no direct evidence for this transition. Perhaps the strongest indirect evidence appears in one investigation in Sweden,[35] where the presence—adjacent to tumor tissue—of cuboidal metaplasia was found in 19, and of dysplasia was found in 16, of 22 wood-dust–exposed patients with nasal adenocarcinoma. The authors postulated that cuboidal metaplasia may be a precursor to nasal adenocarcinoma, and that squamous metaplasia may be a precursor to squamous cell carcinoma. Other descriptive studies of the pathology of nasal adenocarcinoma in woodworkers indicate that the tumors often present with distinctive patterns, notably a predominance of cylinder cell (papillary) adenocarcinomas showing similarity to intestinal-type cancers.[36] In a review of German and other findings, however, Kleinsasser and Schroeder[36] noted the lack of data to determine whether the nasal tumors arise from areas of intestinal metaplasia in nasal tissue or whether there are any obligate precursor lesions for nasal adenocarcinoma.

Several investigations in northern Europe have assessed the relation between wood-dust exposure and nonmalignant nasal pathology (without addressing the question of whether the nonmalignant lesions are on the pathway to nasal cancer). In Norway, Sweden, and Germany, nasal biopsies were taken from furniture workers exposed to wood dusts and from unexposed control subjects. Often the biopsies were given scores, with higher scores assigned to more advanced lesions (eg, 0 for normal to 5 for dysplasia). In Norway, the mean score was higher for 113 furniture workers than for 54 control subjects, with squamous metaplasia affecting 40% of the furniture workers vs 17% of control subjects and dysplasia affecting 12% of the exposed vs 2% of the control subjects.[37] The excess score among the exposed nearly disappeared, however, after adjustment for cigarette smoking. In a second smaller survey of furniture workers handling soft woods, the same authors showed that the mean histology score again was higher in the exposed workers, with the excess primarily among smokers.[38] In neither survey was cuboidal metaplasia detected.

On the other hand, in Sweden, cuboidal metaplasia—but not squamous metaplasia—was more common among 45 wood-dust–exposed

furniture workers than among 17 unexposed control subjects.[39] A further Swedish study, however, reported no association between wood dust per se and histologic scores.[40] Biopsies were taken from 70 chemical workers exposed to formaldehyde, 100 furniture workers exposed to wood dust plus the same average level of formaldehyde, and 36 office clerks with no history of exposure to either wood dust or formaldehyde. Histology scores were highest for those workers exposed to formaldehyde alone. Furthermore, among the group with joint formaldehyde and wood-dust exposure, there was no rising trend in histology score with increasing level of wood-dust exposure. These findings not only suggest that certain workplace chemical exposures may influence nasal pathology, but also underscore the necessity of adjusting for other exposures (such as exposures to formaldehyde and cigarette smoking) before attribution of any effect on nasal pathology to wood-dust exposure.

In the largest study of this kind, Wolf et al[41] obtained nasal biopsy specimens from 144 wood-dust–exposed and 33 unexposed workers in Germany, as well as information on levels of exposure to wood dust, formaldehyde, chromium, solvents, and tobacco. Overall, the wood-dust–exposed group had a nonsignificant increase of abnormal vs normal pathology (we calculated an RR of 1.6, with a 95% CI of 0.6 to 4.2). The mild excess was primarily the result of an increased prevalence of hyperplasia, but the association appeared confounded by concomitant exposure to solvents, reported to be a significant risk factor for hyperplasia. Furthermore, no significant increases in the prevalence of either squamous or cuboid metaplasia were found among the wood-dust–exposed (in fact squamous metaplasia was less common among the exposed).

Taken as a whole, the European nasal histology studies do not present a clear or consistent pattern as to whether wood-dust exposure increases risk of precursor lesions. No nasal biopsy surveys have been reported among American workers exposed to wood dusts. Furthermore, evidence is lacking to demonstrate that the process of nasal carcinogenesis involves a series of transitions through metaplastic and dysplastic states for either adenocarcinoma or squamous cell cancer.

Mucostasis

Several European cross-sectional surveys reported on nasal symptoms and function, including mucociliary clearance and mucostasis. One of the earliest used radioactive labeling to measure nasal clearance in a group of nine British woodworkers and 12 younger unexposed volunteers, finding slower clearance among the exposed.[42] In a larger survey of 68 furniture workers and 66 control subjects in Denmark, Anderson et al[43,44] reported a higher prevalence of mucostasis, defined as nasal clearance time >30 minutes, using a saccharine staining test procedure for the exposed. Mucostasis was reported in nine of the 66 control subjects and in 1 of 9, 4 of 16, 4 of 13, 5 of 11, and 12 of 19 workers among groups of workers estimated to have been recently exposed to wood-dust concentrations, mostly from teak, of 1 to 3, 3 to 5, 5 to 7, 7 to 10, and 10+ mg/m^3, respectively.[44] The average concentration in the 10+ mg/m^3 group was 25 mg/m^3, and maximum dust exposures reached nearly 80 mg/m^3. The dose response is consistent with an effect of dust of the wood species involved, although only those workers with estimated wood-dust–exposure levels exceeding 7 mg/m^3 had a significantly higher prevalence of mucostasis than the unexposed control subjects. Furthermore, information was not given to determine whether other exposures affecting mucostasis, such as age, smoking prevalence, and other occupational exposures, varied concomitantly with wood-dust level. The mucostasis in these workers appears predominantly to be an acute rather than chronic effect, because in a subset of nine workers with mucostasis remeasured 48 hours after cessation of wood-dust exposure, six were found to have normal mucus transit times.

Anderson[45] reported in a chapter the effect of various pollutants on nasal mucus flow among healthy subjects during a 6-hour experiment under controlled conditions. The substances studied included sulfur dioxide, formaldehyde, toluene, inert plastic dust, and wood dust. Reduced clearance rate was associated with sulfur dioxide and formaldehyde, but not with toluene, plastic dust, or wood dust. For the wood-dust experiment, 16 subjects were exposed to dust from either pine, beech, oak, mahogany, or chipboard (but not teak as in Andersen's earlier occupational studies[43,44]) in a concentration of 10 mg/m^3. This level of exposure did not result in reduced clearance. The findings raise the possibility that occupational substances besides wood dust may increase mucostasis and signal the importance of controlling for exposure to other industrial pollutants in surveys of workers.

Mucociliary clearance was also measured in some of the surveys mentioned in the previous section on precursor lesions. In one Swedish study, 54% of furniture workers were reported to have mucostasis, defined as clearance times exceeding 20 minutes, whereas clearance times ranged from 9 to 18 minutes in control subjects whose characteristics were not reported.[39,46] The average area air wood-dust concentration was reported to be 2 mg/m^3, but no analysis of mucostasis as a function of wood-dust level was presented. In a later Swedish study, Holmstrom and Wilhelmsson[47] reported a higher prevalence of mucostasis in wood-dust plus formaldehyde-exposed furniture workers (15%) vs unexposed workers (3%), but the contribution of wood dust per se is doubtful because chemical workers exposed to approximately the same levels of form-

aldehyde in the absence of wood dust had an even higher mucostasis rate (20%). Tobacco use was said to be similar in the two exposed groups. In another study, Holmstrom et al[48] found mucostasis rates to be higher among furniture workers involved in ultraviolet and acid curing than in office workers, but concomitant exposure to wood dust had no adverse effect on clearance times. In a recent study in Sweden comparing mucociliary clearance among 39 woodwork teachers with wood-dust exposures less than 2 mg/m^3 with that of a control group of 32 other teachers, Ahman et al[49] found clearance times to be similar between the two groups on Monday. Clearance time was increased among woodwork teachers as the workweek progressed, resulting in a significant difference in mean clearance time between the woodwork teachers (16.4 minutes and the control subjects (11.3 minutes) when measurements were taken on Thursday, but information on concomitant exposure to solvents and other substances used in the woodwork classrooms was not recorded. These results again suggest that the increase in mucociliary clearance time among woodworkers is reversible after a period of nonexposure—in this case, over the weekend.

In a recent German study of 182 men in the wood industry, Wolf et al[41] found no higher mean mucociliary clearance times, as measured either by subjective saccharine (sweetness) or objective fluorescent tests, among groups exposed to hard or soft wood dusts. Furthermore, there was no evidence of longer clearance times in those with the heaviest wood-dust exposures. In contrast, workers with either chromium or formaldehyde exposures tended to have longer clearance times than control subjects.

The findings from these cross-sectional studies of mucociliary transport times thus are mixed. The wood workers studied sometimes (but not consistently) had longer clearance times, but when wood dust was assessed in relation to other job exposures (such as formaldehyde), it was typically exposures other than wood dust that accounted for the mucostasis. Furthermore, the role of mucostasis itself as a risk factor for nasal cancer has not been established. It seems plausible that mucostasis may prolong contact with potential nasal carcinogens, but there is no epidemiologic evidence that mucostasis increases risk of nasal cancer. In addition, any wood-dust–related mucostasis appears to be short-lived, with normal clearance returning within 2 days of cessation of exposure.

Several of the cross-sectional studies compared self-reported nasal symptoms between the wood-dust–exposed and unexposed groups.[1] One of the symptom surveys was conducted in the United States. Based upon questionnaire responses regarding respiratory disease symptoms from workers in a North Carolina hardwood furniture plant, Goldsmith and Shy[50] reported no significant differences between 55 exposed and 16 unexposed workers for most chronic symptoms, although the acute symptoms of frequent sneezing and eye irritation were reported more often among the exposed. Some of the European surveys also tended to report higher prevalences of some symptoms in the exposed groups. The difficulty in accurately quantifying the frequency of symptoms (such as sneezing or runny nose) and the subjective nature of self-reported responses, however, hinder interpretation of the differences and preclude attributing any of the symptoms to wood-dust exposure per se.

Implications for Industrial Hygiene Standards

The exceptionally high rates of nasal adenocarcinoma, a cancer that is ordinarily very rare, among groups of furniture workers in several parts of Europe leave little doubt that the tumors were occupationally induced. Although definitive evidence on the causative agent is lacking and perhaps more than one agent is involved, a common denominator has been wood-dust exposure. Because of the excess of nasal adenocarcinoma in woodworkers and the belief that hardwood dust was most likely responsible, the International Agency for Research on Cancer recently classified wood dust as a known human carcinogen.[1]

Information to assess in detail the relationship between wood-dust exposure and risk of nasal adenocarcinoma is limited. As described in this report, when the data from case-control studies are combined, the dose-response trend observed indicates that nearly all the excess risk of nasal cancer occurs among those in jobs in which wood-dust exposures were the heaviest (generally exceeding >5 mg/m^3). Furthermore, because most of the excess of nasal cancer is associated with work begun before World War II, the wood-dust concentration levels responsible for the exceptional clustering of adenocarcinoma in Europe in all likelihood were considerably above 5 mg/m^3. No concomitant clustering has been observed in North American workers. Hence, from direct observations on risk of nasal cancer, a wood-dust threshold limit value standard of 5 mg/m^3 (8-hour time-weighted average) seems adequate to eliminate essentially the large excess of nasal adenocarcinoma in Europe and prevent the occurrence of a similar problem in the United States.

Information on the effects of wood dust on mucostasis and nasal metaplasia and dysplasia could be relevant to standard setting if it is assumed that these are precursors on the pathway to nasal adenocarcinoma. This assumption is not yet empirically verified, however. Thus knowledge of the effects of wood dust on mucostasis or the potential precancerous lesions is secondary, for purposes of setting standards to prevent nasal adenocarcinoma, to the

direct data on risks of the cancer itself. Furthermore, as reviewed in the previous sections of this article, the link between wood-dust exposure per se and precursor histology is not clear. Nor is it known whether preventing acute, reversible episodes of mucostasis will have any impact on long-term risk of nasal cancer. In any event, the evidence shows no consistent association between wood-dust exposure and nasal metaplasia or dysplasia, and studies of mucostasis have often been confounded by exposure to other agents.

Concluding Remarks on North American Studies

The epidemiologic studies reviewed in this report document a disparity in findings between investigations conducted in North America and Europe. The exceptional clustering of nasal adenocarcinoma among furniture makers has been primarily a European phenomenon. Surveys of cohorts of American furniture makers and other wood-dust–exposed groups do not reveal large excesses of nasal cancer, and results from case-control studies are consistent with either no association or at most a modest increase in risk of nasal cancer among workers exposed to wood dusts. Hence, if the only data available were from North American studies, it seems unlikely that wood dust would be considered a proven human carcinogen, especially because there is little experimental (bioassay) evidence of a carcinogenic effect of wood dust.

Reasons for the different epidemiologic findings between North America and Europe are not known. Possible explanations include differing species or types of woods, wood processing methods, and/or the presence of co-carcinogenic or independent carcinogenic exposures in European workplaces. Alternatively, assuming a universal effect of wood-dust exposure, the geographic differences may primarily be a matter of dose. Exposures in Europe, particularly in the 1920s through 1940s when ventilation methods were less well developed, may have substantially exceeded those of American workers. Even in the 1970s, Andersen et al[44] found that 28% of Danish furniture workers experienced personal levels of dust exposure over 10 mg/m^3. In addition, the limited available dose-response data showing significant increases of nasal cancer concentrated among those with estimated wood-dust exposures higher than 5 mg/m^3, suggest that lower levels of exposure may be among the likely explanations for the lower risk of nasal cancer in North American woodworkers. Further research may help clarify these issues and further delineate the determinants of wood-dust–related nasal adenocarcinoma and the differing levels of risk between continents.

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TIPPING

Weather dramatically shapes our mood and influences our behavior in surprising ways. Take tipping. At an Atlantic City hotel where the room design masks outside conditions from guests, Temple University psychologist Bruce Rind, PhD, discovered that a room-service waiter could boost his tips simply by mentioning favorable weather. When the server told guests that it was raining, tips averaged 19% of the bill. But describing sunny skies sent his gratuity rate soaring to 24%... . In a second experiment, it was found that adding a smiley face to the bottom of the bill boosted tips by 5% for a waitress—but did not help male waiters any.

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