4. Other Data Relevant to an Evaluation of Carcinogenicity and its Mechanisms

4.1 Deposition and clearance

4.1.1 Humans

No studies of the deposition of wood dust in human airways were available to the Working Group. Particle deposition in the airways has been the object of several studies (for reviews, see Brain & Valberg, 1979; Warheit, 1989). Large particles (> 10 μm) are almost entirely deposited in the nose; the deposition of smaller particles depends on size but also on flow rates and type of breathing (mouth or nose); there is also inter-individual variation (Technical Committee of the Inhalation Specialty Section, Society of Toxicology, 1987). Particles deposited in the nasal airways are removed by mucociliary transport (for reviews, see Proctor, 1982; Warheit, 1989).

4.1.2 Experimental systems

No data on the deposition or clearance of wood dusts in animals were available to the Working Group.

4.2 Toxic effects

4.2.1 Humans

(a) Effects on the nose

In a cross-sectional study in eight furniture factories in Denmark, 68 workers were exposed to total dust at concentrations > 5 mg/m³ in 63% of the measurements (Solgaard & Andersen, 1975; Andersen et al., 1977). The workers were exposed to a variety of hardwoods, including teak, and to pine and composites, including chipboard and Masonite. Analysis of particle size

showed that 33% of the particles were < 5 μm. These workers had significantly lower nasal mucociliary transport rates than a group not exposed to dust; there was also a concentration-dependent decrease in the rates of the exposed workers: mucostasis was found in 63% of workers exposed to an average of 25.5 mg/m^3 and in 11% of those exposed to 2.2 mg/m^3 (mean concentration). Of nine subjects with mucostasis re-examined after 48 h with no exposure to wood, three still had mucostasis, while the six others had clearance rates within normal limits. Middle-ear inflammation and common colds were more frequently reported by people exposed to concentrations > 5 mg/m^3 than among those exposed to lower levels.

The nasal mucociliary transport-rate was investigated in nine woodworkers, 48–66 years of age, with 6–27 years of employment in the furniture industry in England (Black *et al.*, 1974). They had slower rates than 12 people not exposed to wood dust. Only the worker with the shortest length of employment (six years) had a clearance rate within normal limits. Three workers had complete stasis. The results of cytological examination of nasal smears were reported only for the exposed workers: squamous cells were found in four workers, cuboidal cells in one and 'less mature basal cells' in another.

Boysen and Solberg (1982) studied 103 workers in five Norwegian furniture factories in a cross-sectional study. The subjects constituted about 60% of workers who had been employed for at least 16 years. Ten retired workers and 54 people without nasal disease or an occupation associated with nasal cancer, who were not employed in woodworking industries, were examined. Nasal biopsy samples taken from the middle turbinate showed metaplastic squamous epithelium in 40% of the furniture workers and 17% of controls; the corresponding figures for dysplasia were 12 and 2%, respectively. Mechanical processing of wood was associated with histological changes of the nasal mucosa. Dysplasia occurred in four of 15 furniture workers with exposure mainly to birch, spruce and pine and in nine of 84 exposed mainly to hardwoods.

Nasal biopsy samples taken from the middle turbinate of 44 workers who had been exposed for 10–43 years to softwood dust but not to hardwood dust showed more changes than biopsy samples taken from age-matched men without nasal disease or an occupation associated with nasal cancer (mean score, 2.0 versus 1.4; $p < 0.05$) (Boysen *et al.*, 1986). Four woodworkers and no control had dysplasia; these four men had been exposed for 20 years (one man) and more than 26 years (three men). Nasal symptoms were more frequent among the furniture workers (14% versus 4%; $p < 0.05$).

Biopsy samples were taken from the nasal mucosa of the middle turbinate, at least 5 mm behind the anterior curvature, of 45 randomly selected workers in five furniture factories and one parquet flooring factory and 17 hospital workers in Sweden (Wilhemsson & Lundh, 1984). The mean length of exposure was 15 years (range, 1–39 years). Metaplastic cuboidal epithelium was significantly more prevalent among the woodworkers (26/45 versus 4/17; $p < 0.05$), and columnar epithelium was significantly less frequent (34/45 versus 17/17; $p < 0.05$). The prevalence of metaplastic squamous epithelium was not significantly increased (9/45 versus 4/17), and that of goblet-cell hyperplasia was somewhat more frequent (10/45 versus 1/17).

Cuboidal metaplasia of the nasal mucosa was found in 19 of 22 cases of ethmoidal adenocarcinoma associated with exposure to wood dust in Sweden (Wilhemsson *et al.*,1985c). Histological examination of non-tumour nasal mucosa from 22 woodworkers with ethmoidal

adenocarcinoma, who had been exposed to wood dust for an average of 38 years (range, 18–55 years), showed cuboidal metaplasia in 19; 16 also had dysplasia. A transitional zone with dysplastic cuboidal epithelium in continuity with the tumour was observed in 10 cases. Squamous metaplasia was also seen in five cases, but there were no cases of squamous dysplasia.

A cross-sectional study in Germany involved 149 male workers with at least 15 years' exposure to wood dust in different industries and 33 workers with no exposure to dust or chemicals (controls); people who had worked as farmers, welders or metal workers or were exposed to cement dust were excluded. Current exposure to wood dust varied between < 1 mg/m^3 and > 5 mg/m^3. Mucociliary clearance was not significantly different in workers exposed to unprocessed woods (oak, beech and softwood) and controls. Woodworkers with concomitant exposure to formaldehyde or chromium had decreased clearances ($p = 0.04$ and 0.01, respectively), and workers exposed to particle-board had slower mucociliary clearance. The findings in nasal biopsy samples taken from the middle turbinate were reported for various single cell types (columnar-cell hyperplasia, squamous-cell metaplasia, cuboid metaplasia) and mixed cell types (Wolf et al., 1994). [The Working Group noted the inadequate reporting of the histological classification and the high prevalence of squamous epithelial metaplasia in the control group. The Group analysed the data according to hyperplasia and metaplasia in single cell types and found no significant differences between woodworkers and controls (Table 32). The odds ratios for woodworkers exposed to softwood or hardwood, but no additives, were 2.2 (95% CI, 0.81–6.2) for cuboid metaplasia, 0.40 (0.16–1.0) for squamous-cell metaplasia and 1.3 (0.47–3.5) for columnar-cell hyperplasia. Cuboid metaplasia was commoner in workers exposed to hardwood (3.5; 1.1–12), softwood (3.1; 0.77–12) or particle-board (2.5; 0.70–8.8) without additives than in controls but was significant only for workers exposed to hardwood.]

In a cross-sectional study of workers in furniture factories in Sweden who were exposed to formaldehyde alone and to formaldehyde plus wood dust, nasal discomfort was more frequent than in clerks (Holmström & Wilhemsson, 1988). The mean combined exposure to wood dust was 1.7 mg/m^3 and that to formaldehyde was 0.25 mg/m^3; however, the prevalence of symptoms was similar in workers exposed to formaldehyde alone (mean concentration, 0.26 mg/m^3). Impaired mucociliary clearance in the nose was seen in 15% of the group exposed to wood dust plus formaldehyde, in 3% of controls and in 20% of those exposed to formaldehyde alone exposure ($p < 0.05$). Workers exposed to formaldehyde alone or to formaldehyde plus wood dust had significantly ($p < 0.01$) decreased sensitivity in an olfactory test in comparison with controls. Marked histological changes were seen in the nasal mucosa of 25% of people exposed only to formaldehyde (score, 2.2; $p < 0.05$), but the difference between those exposed to both formaldehyde and wood dust (64% ($p < 0.01$); score, 2.1) and the controls (53% ($p < 0.01$; score, 1.6) was not significant. No correlation was found between histological score and either duration or concentration of exposure (Holmström et al., 1989b).

A total of 676 workers in 50 Swedish furniture factories were classified according to exposure to wood dust as 'heavily/moderately' or 'slightly/non-exposed' (Wilhemsson & Drettner, 1984) [the details of the classification were not reported]. Nasal hypersecretion (20%

Table 32. Frequency of histological findings in nasal biopsy samples from German woodworkers according to exposure

Type of wood	Additives[a]	No.[b]	Columnar-cell hyperplasia (1)	Squamous metaplasia (2)	Cuboid metaplasia (3)	Columnar hyperplasia, squamous (4)	Columnar hyperplasia, cuboid (5)	Squamous metaplasia, cuboid (6)	Any columnar hyperplasia (1+4+5)[c]	Any squamous metaplasia (2+4+6)[c]	Any cuboid metaplasia (3+5+6)[c]	Normal	Dysplasia
Hardwood	No	31	6	1	5	3	1	6	10	10	12	9	3
Softwood	No	17	2	1	4	2	1	1	8	4	6	6	0
Particle-board	No	26	5	5	4	4	3	1	13	10	8	4	0
Softwood	Yes	19	3	9	3	2	1	0	6	11	4	1	1
Hardwood	Yes	21	7	4	2	2	1	1	10	7	4	4	1
Mixed	Yes	30	9	5	3	7	0	3	16	15	6	3	2
Controls	-	33	2	12	3	3	3	1	6	14	5	9	1

From Wolf et al. (1994)
[a] Glues, solvents, etc.
[b] The Working Group noted that the total numbers of men and findings were different, indicating that some people were not biopsied.
[c] Calculated by the Working Group

versus 12%; $p < 0.05$), obstruction (40% versus 30%; $p < 0.05$) and more than two common colds per year (21% versus 9%; $p < 0.05$) were reported more often in subjects with heavy/-moderate exposure than in the other group.

A cross-sectional study was conducted of 101 woodworkers and 73 people not exposed to dust in Germany. The concentrations of dust were measured for each of the men [method of sampling was not reported]: 14 were exposed to < 5 mg/m^3, 15 to 5–9 mg/m^3, 36 to 10–19 mg/m^3 and 36 to ≥ 20 mg/m^3. An increased frequency of hyperplasia and reddening of the nasal mucosa was seen in the exposed workers (50–86% versus 7% in controls) (Ruppe, 1973). Radiographic signs of sinusitis were found in 25% of the woodworkers and 5% of controls. Cough, with or without phlegm (50% versus 11%), and conjunctivitis (15% versus 0%) were also reported more frequently among the exposed workers [significance values not reported].

In a cross-sectional study of the frequency of pulmonary and nasal symptoms in 168 wood-workers and 298 workers with no significant exposure to wood dust in furniture factories in South Australia (Pisaniello *et al.*, 1992), the mean concentration of hardwood dust was 3.8 mg/m^3, and the mean concentration of softwood dust produced by machining particle-board and medium-density fibre-board was 3.3 mg/m^3. There was a significant association (odds ratio, 2.2; 95% CI, 1.2–4.2) between exposure to hardwood dust and two or more nasal symptoms, after adjustment for smoking and age.

In a cross-sectional study, Goldsmith and Shy (1988) examined 55 people exposed to hardwood dust in the furniture industry in the United States. The mean length of employment in this industry was 16.6 years, and the current concentration of dust was ≤ 2 mg/m^3. Frequent sneezing and eye irritation were commoner in these workers than in workers with no exposure to wood dust or finishes (prevalence odds ratios, 4.1 and 4.0; $p < 0.05$) in an analysis with adjustment for age, sex and smoking habits. Significant differences were reported for nasal obstruction (61% versus 21%), nasal discharge (41% versus 13%) and sneezing (77% versus 32%).

Symptoms in the upper and lower airways were reported more frequently among 44 randomly selected woodworkers, exposed to concentrations of 1.0–24.5 mg/m^3 dust, than among 38 office workers examined in a cross-sectional study in New Zealand (Norrish *et al.*, 1992).

The effects of exposure to wood dust on the nose are summarized in Table 33.

(b) Effects on the lung

There are several case reports of asthma due to exposure to wood dust (for reviews, see Kadlec & Hanslian, 1983; Goldsmith & Shy, 1988). The asthmatic responses to western red cedar (Chan-Yeung, 1982, 1994) and eastern white cedar (Cartier *et al.*, 1986) are elicited by plicatic acid.

Cough (odds ratio, 2.2; $p < 0.001$), dyspnoea (2.5; $p < 0.001$) and asthma (2.7; $p < 0.001$) were reported more frequently among 652 western red cedar mill workers than among 440 office workers in a cross-sectional study in Canada (Chan-Yeung *et al.*, 1984). Impairment of pulmonary function, as measured by forced expiratory volume in 1 sec (FEV$_1$), forced vital capacity (FVC), forced mid-expiratory flow between 25 and 75% of FVC (FEF$_{25-75\%}$) and

Table 33. Effects (other than cancer) of exposure to wood dust on the nose

Study population		Geographical area	Industry	Wood type	Dust concentration in air (mg/m³)	Particle size, characteristic	Period of exposure (years)	Nasal effects		Reference
Exposed (age, years)	Controls (age, years)							Nasal region	Effect	
68 men (17–66)	66 men	Denmark, Aarhus county	Eight wood-working factories	Teak, oak, chipboard, palisander and other woods	> 5 in 63% of measure-ments	5–10 μm maximum	1–51; mean, 16		Mucostasis: 15% in controls, 38% in exposed, 63% in exposed with dust ≥ 10 mg/m³ (n = 17)	Solgaard & Andersen (1975); Andersen et al. (1977)
9 (48–66)	12 (31-69)	England, High Wycome area	One wood-working factory				6–27		Mucociliary clearance of polystyrene particles in controls, 6.8 (1.9–18.5) mm/min. Mucostasis in 7/9 exposed. In workers, nasal mucosa was normal columnar (3); normal + squamous cells (1); normal + cuboidal (1); normal + squamous metaplasia (3); normal + less mature 'basal' cells (1). Results for controls not given	Black et al. (1974)
103 active (32–69); 10 retired (68–81)	54 (35–79)	Norway, western	Five furniture factories	Birch, beech, oak, pine, mahogany, teak, chipboard (made of pine and spruce)			Active, 16–57; mean, 34; retired, 28–57; mean, 44	Anterior curvature of middle turbinate	Rhinoscopy: hyperplastic rhinitis: 5 controls, 37 workers (p < 0.05); mucosal polyps: 1 controls, 3 workers Histological score: controls, 1.5; all workers, 2.4 (p < 0.05); active workers, 2.4; retired workers, 2.9	Boysen & Solberg (1982)
44 (29–64)	37 men (35–66)	Norway	Six furniture factories	Exclusively softwood			10–43; mean, 24	Anterior curvature of middle turbinate	Histological score Controls Workers All 1.4 2.0 (p < 0.05) Age ≤ 44 1.2 1.6 Age 44–54 1.4 2.4 Age ≥ 55 1.6 1.9 Smokers 1.6 2.4 (p < 0.05) Non-smokers 1.3 1.6	Boysen et al. (1986)
45 (mean, 40)	17 (mean, 39)	Sweden, Småland county	Five furniture factories		0.3–5.1; mean, 2.0		1–39; mean, 15	Middle turbinate in widest nasal cavity	Columnar epithelium: 14/17 controls, 23/45* workers ciliated: 12/17 controls, 16/45 workers (p < 0.05); unciliated, 2/17 controls, 7/45 workers; Cuboidal epithelial metaplasia, 1/17 controls, 16/45 workers (p < 0.05) Squamous epithelial metaplasia, 2/17 controls; 6/45 workers	Wilhelmsson & Lundh (1984)

Table 33 (contd)

Study population		Geographical area	Industry	Wood type	Dust concentration in air (mg/m³)	Particle size, characteristic	Period of exposure (years)	Nasal effects		Reference
Exposed (age, years)	Controls (age, years)							Nasal region	Effect	
22 men with ethmoidal adeno-carcinoma (57–86)		Sweden	14 furniture makers, 3 french polishers, 2 boat builders, 2 wood machinists, 1 woodwork teacher				18–55; mean, 38		19 cases of cuboidal metaplasia, 16 with dysplasia 10 cases of transitional zone with dysplastic cuboidal epithelium in continuity with the tumour 5 cases of squamous metaplasia	Wilhelmsson et al. (1985c)
100 exposed to wood dust and HCHO (mean, 40.5) 70 exposed to HCHO (mean, 36.0)	36 (mean, 39.7)	Sweden	Furniture workers Chemical plant	Particle-board	Wood, 1.65±1.06; HCHO, 0.25±0.05 0.05–0.5	82% < 5 μm	1–30; mean, 9 1–36; mean, 10.4		Nasal discomfort: 6 controls, 53 wood + HCHO, 45 HCHO; eye discomfort: 2 controls, 21 wood + HCHO, 17 HCHO; deep airway discomfort: 5 control, 39 wood + HCHO, 31 HCHO; frequent headache: 2 control, 17 wood + HCHO, 17 HCHO	Holmström & Wilhelmsson (1988)
89 exposed to wood dust and HCHO 62 exposed to HCHO	32	Sweden	Furniture workers Chemical plant	Particle-board	Wood, 1.65±1.06; HCHO, 0.25±0.05 0.05–0.5	82% < 5 μm	1–30; mean, 9 1–36; mean, 10.4	Median or inferior aspect of middle turbinate	Nasal biopsy scores: control, 1.56; wood + HCHO, 2.07; HCHO, 2.16 (p < 0.05)	Holmström et al. (1989b)
484 with heavy or moderate exposure	192 with light or no exposure	Sweden, Småland county	50 furniture factories		Mean, 2.0; range, 0.30–5.06		1–60; mean, 27		Nasal hypersecretion: 12% light or no exposure 20% moderate/heavy exposure Nasal obstruction: 30% light or no exposure 40% moderate/heavy exposure	Wilhelmsson & Drettner (1984)

Table 33 (contd)

Study population		Geographical area	Industry	Wood type	Dust concentration in air (mg/m³)	Particle size, characteristic	Period of exposure (years)	Nasal effects		Reference
Exposed (age, years)	Controls (age, years)							Nasal region	Effect	
101 (18–65)	73 (18–65)	Germany			≤ 5–≥ 20				Sneezing: 0/73 controls 7/14 < 5 mg/m³ 11/15 5–9 mg/m³ 32/36 10–19 mg/m³ 30/36 ≥ 20 mg/m³ Mucosal changes: 5/73 controls 7/14 < 5 mg/m³ 8/15 5–9 mg/m³ 31/36 10–19 mg/m³ 25/36 ≥ 20 mg/m³	Ruppe (1973)
134 (mean, 33.6)	298 (mean, 40.1)	South Australia	15 furniture factories	Oak, teak, nyardoh, radiase pine, particle-board, fibre-board	Hardwood dust, 3.2; particle-board, fibre-board, 3.3				Two or more nasal symptoms (out of five): exposure to hardwood dust, odds ratio, 2.2 (1.2–4.2)	Pisaniello et al. (1992)
149 men (> 35)	33	Germany	Woodworkers	Oak, beech, softwood, particle-board	< 1–> 5		≥ 15	Middle turbinate	Mucociliary clearance longer in workers exposed to particle-board dust Columnar-cell hyperplasia: all wood workers versus controls, odds ratio, 4.4 ($p = 0.05$) Squamous-cell metaplasia: woodworkers versus controls, odds ratio, 0.37 ($p = 0.02$) Cuboid metaplasia: all woodworkers versus controls, odds ratio, 2.9 ($p = 0.3$)	Wolf et al. (1993)

Table 33 (contd)

Study population		Geographical area	Industry	Wood type	Dust concentration in air (mg/m^3)	Particle size, characteristic	Period of exposure (years)	Nasal effects		Reference
Exposed (age, years)	Controls (age, years)							Nasal region	Effect	
44 men (mean, 47.2) 11 women (mean, 41.3)	12 men (mean, 42.2) 4 women (mean, 44.5) and 7 men and 14 women in a finishing department	USA, North Carolina	One furniture factory	Hardwoods, fibre-board			Men, mean, 18.5; women, mean, 9		Frequent sneezing; odds ratio, 4.1 (1.1–15)	Goldsmith & Shy (1988)
44 men (mean, 33)	38 men (mean, 33)	New Zealand	11 furniture and joinery facilities	Rimu wood, kauri, tawa, medium-density fibre, Californian red wood	1–25.4				Nasal obstruction: 27/44 versus 8/38, $p < 0.01$ Nasal discharge: 12/44 versus 5/38, $p < 0.01$ Sneezing: 34/44 versus 12/38, $p < 0.01$	Norrish et al. (1992)

*$p < 0.05$

FEV_1/FVC, was significantly correlated ($p < 0.001$) with increasing length of employment in cedar mills. The odds ratios were adjusted for smoking, race and age.

Occupational asthma was diagnosed in 10 of 73 workers exposed to red cedar dust in a cross-sectional investigation in the United States, which also included 132 mill workers and 22 clerks and engineers not exposed to wood dust (Brooks *et al.*, 1981). The mean concentration of total dust was 4.7 mg/m^3. Pulmonary diseases (chronic bronchitis, occupational asthma, chronic nonspecific airways disease and non-occupational asthma) were commoner among the workers than among controls (34% versus 16%) [p value not reported]. The prevalence of chronic bronchitis in workers exposed to a mixture of woods, mainly Douglas fir, West Coast hemlock and red alder, was similar to that of the workers exposed to western red cedar.

In the study of Norrish *et al.* (1992), described on p. 177, differences were reported for persistent cough in winter (30% versus 5%; $p < 0.01$) and work-related cough (32% versus 0%; $p < 0.01$). Five woodworkers were identified as having occupational asthma. The authors stated that adjustment for smoking did not alter the results.

In a cohort study based on census data on occupational title in Sweden, the rate of mortality from asthma was greater in woodworking machine operators (SMR, 2.3; 95% CI, 1.1–3.4), after adjustment for smoking (Torén *et al.*, 1991).

Ávila (1972) reported on 23 Portuguese cork workers with bronchial asthma, all of whom gave positive responses in inhalation tests for immediate and late reactions to a skin prick with cork. A further 12 cork workers with diseases affecting mainly peripheral gas-exchange tissues all gave positive responses in skin tests for late (type III, arthris) reaction to cork; they showed diffuse, fine miliary mottling on chest radiographs, which disappeared within five weeks, except in a few cases where lesions attributable to fibrosis were reported. [The Working Group noted the lack of information on examination procedures].

The exposure of 334 workers to total dust was determined from job title and job location in a cross-sectional study in Canada (Vedal *et al.*, 1986). The workers were exposed mainly to wood dust from western red cedar. In 78 samples, the total dust concentration ranged from undetectable to 6.0 mg/m^3, with a mean of 0.46 mg/m^3; 33 workers were considered to be exposed to > 1.0 mg/m^3. Spirometric measurements (FVC and FEV_1) gave lower values ($p < 0.05$) for 13 men exposed to concentrations > 2.0 mg/m^3; chronic cough, dyspnoea, persistent wheeze and asthma were not related to duration of work or dust concentration.

Al Zuhair *et al.* (1981) studied workers in two furniture factories in the United Kingdom. In the first factory, 53 workers in a sawmill and an assembly department were exposed to dust concentrations of 2.9 and 0.5 mg/m^3, respectively. In the second factory, 60 workers on a machine floor and in a cabinet shop were exposed to mean total dust concentrations of 1.4 and 8.3 mg/m^3, respectively. These workers had significantly decreased FEV_1 and FVC over the workshift period (0.08–0.12 L; $p < 0.001$), while there was no consistent decrease in lung function over the workshift period among workers in the first factory.

Pulmonary function (FVC, FEV_1, FEV_1/FVC and maximal mid-expiratory flow [MMEF; identical to $FEF_{25-75\%}$]) was determined in 1151 subjects exposed to maple or pine wood dust in a cross-sectional survey in the United States (Whitehead *et al.*, 1981b). Suspended dust concen-

trations were measured in area samples, and a cumulative index of the dose was constructed for each person by multiplying the concentration in the job area by the working time. The workers were classified as having low (0–2 mg-years/m^3), medium (2–10 mg-years/m^3) or high (10 or more mg-years/m^3) exposure to wood dust. The authors classified the results of the spirometric tests as 'normal' or 'impaired' on the basis of external reference values and calculated the odds ratios between different categories of exposure. The ratio for FVC or FEV$_1$ was not significantly increased with increasing levels of exposure in the groups exposed to maple or pine wood, but FEV$_1$/FVC and MMEF were lower in people with high exposure. In a comparison of high and low exposure categories, the odds ratios for FEV$_1$/FVC and MMEF were 3.1 ($p = 0.01$) and 2.1 ($p = 0.02$) for workers exposed to maple dust and 4.0 ($p = 0.01$) and 2.5 ($p = 0.02$) for workers exposed to pine dust, after adjustment for smoking.

In a study of 145 nonsmoking furniture workers and 152 nonsmoking workers in a bottling firm with no exposure to dust in South Africa, cough (40.6% versus 23.7%; $p < 0.01$), phlegm (4.1% versus 10.5%; $p < 0.05$), dyspnoea (18.7% versus 5.7%; $p < 0.05$), wheezing (12.8% versus 4.8%; $p < 0.05$) and nasal symptoms (49.5% versus 18.7%; $p < 0.01$) were two to three times commoner in exposed than unexposed workers (Shamssain, 1992). Spirometric measurements were significantly lower for exposed men than for male controls (FVC: 3.64 versus 4.14 L, $p < 0.001$; FEV$_1$: 2.65 versus 3.20 L, $p < 0.001$; FEV$_1$/FVC: 73.2 versus 77.6%, $p < 0.01$; forced mid-expiratory flow between 25 and 75% of FVC [FMF$_{25-75\%}$]: 3.09 versus 3.68 L/s, $p < 0.01$; forced expiratory flow between the first 200 and 1200 ml of FVC [FEF$_{200-1200}$]: 4.94 versus 7.06 L/s, $p < 0.001$; peak expiratory flow [PEF], 6.14 versus 7.92 L/s, $p < 0.001$); there was no significant difference in these measurements between exposed and unexposed women. The frequency of an FEV$_1$/FVC below 70% was significantly higher among the woodworkers than the controls (30% versus 17%, $p < 0.01$), and the proportion was higher in men with 10–19 years of employment than in men with 1–9 years of employment (56% versus 27%, $p < 0.01$); 20% of the workers handled pine wood and 80% medium-density fibre-board. The mean total dust concentration in the factory was 3.8 mg/m^3.

In the study of Goldsmith and Shy (1988), described on p. 177, peak flow (but no other test of pulmonary function) was correlated with duration in jobs with exposure to wood dust.

The decrease in lung function over a work shift was greater in 50 carpenters and joiners than in 49 hospital workers (Holness et al., 1985). The decreases in FVC were 2.4 ($p = 0.001$) and 0.15% ($p = 0.77$), respectively. The mean total dust concentration was 1.8 mg/m^3.

(c) Other effects

Exposure to wood may cause irritant dermatitis, contact urticaria and allergic contact dermatitis (for reviews, see Woods & Calnan, 1976; Hausen, 1986). The contact allergens in a number of woods have been identified, e.g. R-3,4-dimethoxydalbergione was found in a tropical hardwood, Machaerium scleroxylum (Beck et al., 1984). Allergic conjunctivitis was reported in a worker exposed to spindle tree dust (Herold et al., 1991).

Of 162 patients with a positive response in a skin prick test to one of 14 woods, 107 had no allergic symptoms (Oehling, 1963).

Inhalation fever and extrinsic allergic alveolitis have been observed in studies of workers exposed to wood contaminated with moulds (Emanuel *et al.*, 1962; Belin, 1987; Dykewicz *et al.*, 1988).

4.2.2   *Experimental systems*

A mouse hepatoma cell line, Hepa-1, was used to study cytotoxicity (effect on cell growth) and induction of enzymes (cytochrome P450IA1 and aldehyde dehydrogenase). The cells were exposed for 24 h to acetone extracts (final concentration of acetone, 0.5%) of bleached cellulose materials, softwoods (pine and a mixture of pine and spruce) and hardwoods (alder and aspen), all of which are used as bedding materials in cages for small laboratory animals. The softwood and alder extracts (final concentrations corresponding to 1.25–5 mg bedding material/ml cell culture medium) were more cytotoxic to the hepatoma cells than the aspen extract, whereas the bleached cellulose materials were found to be nontoxic at doses up to and including 20 mg/ml. Both softwood and hardwood extracts induced the activity of cytochrome P450IA1 and aldehyde dehydrogenase at concentrations which caused little toxicity (Törrönen *et al.*, 1989).

In order to investigate the toxicity of plicatic and abietic acids, which are constituents of Western red cedar and pine woods, respectively, primary cultures of rat type II cells (isolated from Sprague-Dawley rats [sex unspecified]) and of human lung carcinoma cell line A549 were exposed to solutions of up to 1 mg/ml abietic acid and 5 mg/ml plicatic acid for 2–24 h. A time- and dose-dependent induction of cell lysis was seen with both cell types. Abietic acid was significantly more toxic (first observable effect after 2 h at 0.1 mg/ml) than plicatic acid (first effect after 4 h at 2.5 mg/ml). In studies with cultured tracheal explants from Sprague-Dawley rats [sex unspecified], both compounds produced dose-dependent desquamation of epithelial cells, abietic acid again having a higher toxic potential than plicatic acid (Ayars *et al.*, 1989).

In order to assess the tumorigenic effect of the combination of beech wood dust and formaldehyde (see also section 3.1), groups of 16 female Sprague-Dawley rats (11 weeks old) were exposed by inhalation in whole-body exposure chambers to freshly prepared wood dust (70% with a longest dimension of about 10 μm, 10–20% ≤ 5 μm) at 25 mg/m^3 for 6 h per day on five days per week for 104 weeks, with or without formaldehyde. There was also an untreated control group. Animals were exposed in an inversed 24-h cycle, which ensured that they were as active as possible during exposure. Apart from neoplastic and preneoplastic lesions (see section 3.1), histopathological evaluation showed a greater prevalence of pulmonary emphysema in rats exposed to wood dust than in the control animals ($p < 0.05$), but no differences in mortality rates and no significant difference in the histological appearance of pulmonary epithelium were observed (Holmström, *et al.*, 1989a).

In a study to assess the tumorigenic effects of a combination of beech wood dust and NDEA (see also section 3.1), groups of 19–23 male Syrian hamsters, weighing 90–120 g, received either wood dust or NDEA alone or the combination The animals were exposed by inhalation in whole-body exposure chambers to particles of fresh beech wood dust (30 mg/m^3) for 6 h per day on five days per week over a period of 40 weeks. In the group of hamsters exposed to wood dust alone, slight inflammatory reactions of the respiratory epithelium and

submucosal stroma were detected, which were not observed in the respective control animals (Wilhemsson *et al.*, 1985a,b).

Sixteen male guinea-pigs weighing about 300 g were given a single intratracheal instillation of 75 mg of sheesham or mango wood dust as an autoclaved suspension. Animals were killed 60 and 90 days after treatment. Treatment induced disintegration of giant cells, centrilobular emphysema and slight fibrosis in the lungs at both times (Bhattacharjee *et al.*, 1979).

The enzyme induction activity of shavings from Eastern red cedar and oil of cedarwood was studied indirectly in groups of 6–18 C3H-A, CBA/J and Swiss albino mice [sex unspecified] as barbiturate sleeping time, the time between loss and restoration of the righting reflex after intraperitoneal injection of hexobarbital at 125 mg/kg bw). In five separate experiments in which mice were reared and/or housed with cedar bedding material for at least three weeks, a reduction in sleeping time ($p < 0.01$) was seen, which was attributed to the induction of enzymes responsible for hexobarbital oxidation (Sabine, 1975).

4.3 Genetic and related effects

4.3.1 Humans

Chromosomal aberrations in peripheral lymphocytes were studied in 13 male nonsmokers employed in three plywood factories in Finland, who were reported to be exposed to fumes emitted from heated wood. The controls were 15 male nonsmokers matched for age but not employed in wood industries. The frequency of chromatid breaks was 2.1% in the exposed group and 1.0% in the controls ($p < 0.01$) (Kurttio *et al.*, 1993). [The Working Group noted that exposure to wood dust was not mentioned.]

4.3.2 Experimental systems

Extracts of certain woods prepared by a variety of methods (see Table 34 and section 1.3.2) gave weak positive or borderline effects for reverse mutation in *Salmonella typhimurium*. Unequivocal positive results have been obtained only with beech wood (Mohtashamipur *et al.*, 1986); however, other woods have not been examined to the same extent. [The Working Group noted that wood contains constituents that can reduce the activity of mutagens such as benzo[*a*]-pyrene, aflatoxin B_1 and methylmethane sulfonate.] Chemically and bacterially degraded beech wood lignin significantly induced reverse mutation in *S. typhimurium* (Mohtashamipur & Norpoth, 1990), but fumes produced during the drying of birch and spruce wood were not mutagenic to *S. typhimurium* (Kurttio *et al.*, 1990). [The Working Group noted the inappropriate correction for cell survival applied by the authors, which resulted in a different conclusion.]

Cyclohexane–ethanol extracts of beech, oak and particle-board increased the number of DNA single-strand breaks per fragile sites in rat hepatocytes *in vitro* (Schmezer *et al.*, 1994).

Alcoholic extracts of beech wood increased the frequency of micronuclei in the crypts of the small intestine of mice treated by gavage and in the nasal epithelium of rats after topical application (Nelson *et al.*, 1993).

Of several compounds isolated from wood, only quercetin and Δ^3-carene showed mutagenic activity (Table 35).

Table 34. Genetic and related effects of wood dusts

Test system	Result[a]		Extraction medium	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Ash				
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	(+)	Methanol	McGregor (1982)
Beech				
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	0	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	(+)	Methanol	Mohtashamipur *et al.* (1984)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Acetone/water	Kubel *et al.* (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	Methanol/ethyl acetate	Mohtashamipur *et al.* (1986)
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	Acetone/water; lignin degradation	Mohtashamipur & Norpoth (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	(+)	Methanol	McGregor (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Acetone/water	Kubel *et al.* (1988)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	(+)		Cyclohexane/ethanol	Schmezer *et al.* (1994)
MVM, Micronucleus induction, mouse duodenal crypts *in vivo*	+		Methanol/ethyl acetate	Mohtashamipur & Norpoth (1989)
MVR, Micronucleus induction, rat nasal epithelial cells *in vivo*	+		Methanol/ethyl acetate	Nelson *et al.* (1993)
Birch				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Drying fumes	Kurttio *et al.* (1990)
Chestnut				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Acetone/water	Weissmann *et al.* (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Acetone/water	Weissmann *et al.* (1989)
Elm				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Methanol	McGregor (1982)

Table 34 (contd)

Test system	Result[a]		Extraction medium	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Limba, obeche and walnut				
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	0	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)	0	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
Mahogany				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Methanol	McGregor (1982)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
Oak				
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	0	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Methanol	McGregor (1982)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Acetone/water	Weissmann et al. (1989)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)	0	Methanol; cyclohexane/water	Brockmeier & Norpoth (1981)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Acetone/water	Weissmann et al. (1989)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+		Cyclohexane/ethanol	Schmezer et al. (1994)
Spruce				
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Acetone/water	Kubel et al. (1988)
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Drying fumes	Kurttio et al. (1990)
SA2, *Salmonella typhimurium* TA102, reverse mutation	-	-	Drying fumes	Kurttio et al. (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Acetone/water	Kubel et al. (1988)

Table 34 (contd)

Test system	Result[a]		Extraction medium	Reference
	Without exogenous metabolic system	With exogenous metabolic system		
Spruce (contd)				
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Drying fumes	Kurttio *et al.* (1990)
DIA, DNA strand breaks, rat hepatocytes *in vitro*	-	-	Cyclohexane/ethanol	Schmezer *et al.* (1994)
Particle-board				
DIA, DNA strand breaks, rat hepatocytes *in vitro*	+		Cyclohexane/ethanol	Schmezer *et al.* (1994)

[a]+, considered to be positive; (+), considered to be weakly positive in an adequate study; -, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an adequate study); 0, not tested

Table 35. Genetic and related effects of wood-related compounds

Test system	Result[a] Without exogenous metabolic system	With exogenous metabolic system	Reference
Δ³-Carene			
SA0, *Salmonella typhimurium* TA100, reverse mutation	(+)	-	Kurttio *et al.* (1990)
SA2, *Salmonella typhimurium* TA102, reverse mutation	-	-	Kurttio *et al.* (1990)
SA9, *Salmonella typhimurium* TA98, reverse mutation	(+)	-	Kurttio *et al.* (1990)
Coniferyl alcohol			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
Deoxypodophyllotoxin			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
2,6-Dimethoxybenzoquinone			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
Eugenol			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-		IARC (1985a)
Quercetin			
SA0, *Salmonella typhimurium* TA100, reverse mutation	0	+	Bjeldanes & Chang (1977)
SA8, *Salmonella typhimurium* TA1538, reverse mutation	0	(+)	Bjeldanes & Chang (1977)
SA9, *Salmonella typhimurium* TA98, reverse mutation	0	+	Bjeldanes & Chang (1977)
Scopoletin			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)

Table 35 (contd)

Test system	Result[a]		Reference
	Without exogenous metabolic system	With exogenous metabolic system	
3,4,5-Trimethoxycinnamic acid			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
Vanillic acid			
SA0, *Salmonella typhimurium* TA100, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)
SA9, *Salmonella typhimurium* TA98, reverse mutation	-	-	Mohtashamipur & Norpoth (1984)

[a]+, considered to be positive; (+), considered to be weakly positive in an adequate study; -, considered to be negative; ?, considered to be inconclusive (variable responses in several experiments within an adequate study); 0, not tested