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NON-MALIGNANT RESPIRATORY DISEASES AND OCCUPATIONAL EXPOSURE TO WOOD DUST. PART I. FRESH WOOD AND MIXED WOOD INDUSTRY

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Abstract: This paper reviews associations in literature between exposure to wood dust from fresh wood and non-malignant respiratory diseases. Criteria for inclusion are epidemiological studies in English language journals with an internal or external control group describing relationships between wood dust exposure and respiratory diseases or symptoms. The papers took into account smoking, and when dealing with lung function took age into consideration. A total of 25 papers concerning exposure to fresh wood and mixed wood formed the basis of this review. The results support an association between fresh wood dust exposure and asthma, asthma symptoms, coughing, bronchitis, and acute and chronic impairment of lung function. In addition, an association between fresh wood dust exposure and rhino-conjunctivitis was seen across studies. Apart from plicatic acid in western red cedar wood, no causal agent was consistently disclosed. Type 1 allergy is not suspected of being a major cause of wood dust induced asthma. Concurrent exposure to microorganisms and terpenes probably add to the inherent risk of wood dust exposure in the fresh wood industry.

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INTRODUCTION

Approximately 3.6 million workers in the European Union are exposed to wood dust [45].

Wood is processed in many industries including sawmills with processing of fresh wood, plywood mills producing plywood from fresh wood, other types of mills producing wood composites, and furniture factories or smaller workshops using dry wood only. Studies from recent years indicate different exposure response relationships for dry wood compared to fresh wood [19, 25, 51].

Wood dust is a known inducer of cancer in the nasal cavity and recent reviews have focused on this [14, 40]. Wood dust has also been associated with a variety of respiratory diseases including asthma, chronic bronchitis, nasal symptoms and eye symptoms, as well as chronic impairment in lung function. Although the occurrence of non-malignant respiratory diseases related to wood dust has been reviewed earlier [18, 29, 65], a number of studies have also been performed in recent years. The earlier reviews, however, did not specifically consider the difference between dry and wet wood. Hence, updated reviews concerning non-malignant respiratory diseases divided into dry wood and wet wood is warranted. This review focuses on fresh wood and mixed wood exposure to wood dust. A second review focuses on dry wood exposure [41].

In the reviews, we have not included papers concerning occupational exposure to wood dust and cryptogen fibrosing

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alveolitis, as only a few case control studies have been performed concerning this rare disease and its association to wood dust [7, 30, 39, 54, 58].

Allergic and toxic alveolitis is seen among fresh wood dust exposed workers, especially among sawmill workers, where up to 20% had experienced symptoms consistent with toxic alveolitis [8, 55]. Allergic alveolitis is rare, also among sawmill workers [55], but cases has been reported [32, 60]. Microorganisms are suspected to be by far the most important agent, especially Rhizopus microspores [24]; therefore, all papers on these two diseases are not systematically included in this review, but the importance of allergic and toxic alveolitis with respect to respiratory impairment among fresh wood dust exposed workers are discussed.

METHODS

The literature search for the reviews covered Medline for papers published in English for the period 1969 to June 2009, with the following search conditions: "Wood" [MeSH Terms] AND "Occupational Diseases" [MeSH Terms] NOT "Case Reports" [Publication Type]. This revealed 422 publications. The search was accompanied by a scan of list of references in the identified studies and supplemented with updates until August 2009. Criteria for inclusion were epidemiological studies describing associations between upper or lower respiratory diseases, or symptoms and exposure to fresh or mixed wood dust. Studies not having an internal control group (high or low exposure) or an external control group were excluded. Papers which did not take smoking into consideration, or which did not adjust for age when dealing with lung function were discounted.

In total, 25 original papers were included. To allow for comparison between papers, odds ratios (OR) for symptoms from data provided in the papers, whenever OR's were not stated, were calculated with Chi square test using exact confidence intervals.

Chronic bronchitis was defined as daily coughing and phlegm for at least 3 month during at least 2 consecutive years [13].

RESULTS

Table 1 shows the main results from the reviewed papers. This review focuses on: asthma, asthma symptoms, coughing, chronic bronchitis, rhino-conjunctivitis, and impairment in lung function.

Asthma and Asthma symptom. Seventeen papers including one register-based follow-up study and 15 cross-sectional studies (where one study population was reinvestigated after 2 years) have reported on asthma, asthma symptoms or bronchial hyper responsiveness (BHR).

In a register-based population study, Heikkilä *et al.* [33] determined incidence rates of clinically verified asthma for different industries handling both fresh and dry wood. Relative Risk (95% Confidence interval) RR (95% CI) for asthma for all wood exposed males and females compared to administrative control workers were 1.5 (1.2–1.8) and 1.5 (1.2–1.7), respectively. For workers handling primarily fresh wood RR varied between 1.5 (1.2–18) (males forestry and logging) and 1.9 (1.5–2.5) (males sawmilling).

Four studies reported prevalence's between 5–14% for **physician diagnosed asthma** [16], **ever asthma** [35], **current asthma** [36] or asthma [34], with OR's comparing exposed with unexposed workers ranging from 2.5–5.5, being statistically significant in two studies [34, 35]. In addition, 3 studies [16, 19, 25] defined asthma from a combination of symptoms and reported prevalence's between 10–73%, with OR 1.5–2.7, significant in 2 studies [16, 19].

Six studies reported significantly increased prevalence's of **wheezing** (15–42%) **chest tightness** (36–43%), **shortness of breath (SOB) with wheezing** (15%), and **chest tightness with wheezing** (20%) with OR's ranging from 1.1–2.7 when comparing exposed to non-exposed [15, 19, 25, 34, 36] or groups with different exposures [15, 20]. In contrast, 2 studies from Thailand and Indonesia did not find any relation between wet wood exposure and asthma symptoms [11, 46].

Prevalence's of **work-related asthma (WRA) symptoms** (wheezing, SOB with wheezing) (6–20%) were reported in 4 papers with OR's ranging from 0.7–7.0 when comparing exposed to non-exposed [4, 19, 52] or to groups with lower exposure [31], with significantly increased OR's in [19, 31].

In 5 studies prevalence's of **WRA** ranged from 1.1–8.3% with OR's from 1.5–2.7 when comparing exposed to non-exposed [4, 15, 16, 52], or years of exposure [63], although only one study found significant differences [63]. Another study reported a 1.1% prevalence of red cedar asthma (RCA) based on "a typical history of RCA" in the exposed group, but no information on the control group was available [15]. A 1 year incidence of RCA of 4–5% was estimated based on information on workers having left the work place.

The effect of red cedar (RC) exposure on BHR was explored in 2 studies. In [16] an increased prevalence of BHR among non-atopic RC workers (76%) *vs* non-atopic controls (4%) and an association between BHR and duration of employment was revealed. In a later follow up [64], persistent BHR was found to be related to exposure levels above 1 mg/m^3. Furthermore, BHR was associated to specific IgE for plicatic acid.

Chronic bronchitis and cough. Seven cross-sectional papers reported chronic bronchitis with prevalence's ranging from 10–69% and OR's ranging from 1.0–9.6 when woodworkers were compared with controls [4, 31, 34, 36, 46, 52], lower exposure level [46] or lower seniority [57]. Findings were significant in 4 papers [4, 31, 46, 52]. In one study, chronic bronchitis was associated with duration of employment [36].

Coughing was reported in 9 cross-sectional studies with prevalence ranging from 11–46% and OR's 0.9–26, 4 with significant results [16, 19, 34, 62], in studies comparing exposed to non-exposed [15, 16, 19, 34, 35, 36, 46, 62] or lower exposed groups [11, 46, 63]. **Work related coughing** was reported in 4 papers with prevalence's between 14–59% comparing exposed to non-exposed controls [4, 19, 52], or lower exposed [31]. OR's were ranging from 0.8–18.7, two with significant results [19, 52].

Post-shift decline in lung function. A total of 6 cross-sectional studies have investigated acute changes in lung function among workers exposed to fresh wood. Gandevia *et al.* reported a day to day reversible post-shift decline in FEV_1 among a group of RC workers [27], while Herbert *et al.* in two studies at oriented strandboard mills showed a significant post-shift decline in FEV_1 and FVC among wood workers [34, 35]. Likewise, Mandryk *et al.* reported a post-shift decline in FEV_1, FVC, FEV_1/FVC among sawmill workers for both green mill workers and dry mill workers, but they could not confirm a DRR to wood dust exposure [51, 52]. Only one study, Ashley *et al.,* reported no changes in lung function during a work week among woodworkers compared to non-exposed controls [5].

COPD. Seventeen studies including 2 industry-based follow-up studies, one register based follow-up study and 14 cross-sectional studies have reported on lung function parameters and exposure to fresh or mixed wood dust.

In an 11 year follow up study, Noertjojo *et al.* [53] reported a greater decline in FEV_1 and FVC among RC sawmill workers compared to controls, and reported a DRR between mean average exposure during follow up and annual decline in lung function. Friesen *et al.* in a register-based follow-up study reported a DRR between cumulative wood dust exposure and COPD hospitalisation rate. In contrast, Glindmeyer *et al.* in a 5-year follow-up study found no association between wood dust of any size fraction and lung function indices.

Twelve cross-sectional studies found associations between baseline lung function parameters and exposure to wood dust. Douwes *et al.* [20] found high current exposure to wood dust to be associated to reduction in FEV_1, PEF and FVC for green mill and dry mill workers, the latter only significant for workers in green mills. Mandryk *et al.* revealed a DRR between decreased FEV_1 and current inhalable dust concentration and for green mill workers a DRR between respirable dust and decrease in FVC, but also a positive correlation between baseline lung function indices and years of exposure to wood dust [51, 52]. Likewise, Teschke *et al.,* using different exposure models, reported a DRR between inhalable dust and decreased FEV_1 [61]. Borm *et al.* [11] found no association between cumulative exposure and lung function indices. They found, however, an association between years of employment and lung function indices for male workers.

Ashley *et al.* [5] found a borderline significant association between duration of exposure and reduced FEV_1 and FVC among RC workers, while Vedal *et al.* [63] found a DRR between current wood dust exposure and FEV_1, FVC and FEV_1/FVC, but no association with years of employment.

Liou *et al.* [46] found a DRR between current exposure level and PEF, mean FEV_1, and mean FVC.

A number of studies found decreased PEF, FEV_1 or FEV_1/FVC among exposed workers compared to non-exposed controls [16, 34, 35, 36, 37, 46, 51, 52, 62, 63].

Only two cross-sectional studies found no association between wood dust exposure and baseline FVC or FEV_1 [31, 57].

Rhino-conjunctivitis. Two studies reported significantly increased prevalence's of rhinitis (17–31%) with OR's 1.6–2.6, when comparing woodworkers to non-exposed controls [15, 19] or groups with lower exposure [19]. One study did not find exposure to wood dust associated with rhinitis [25]. Three papers reported **WR nasal symptoms** (9–49%) [4, 31, 52], and 2 [4, 52] found significantly increased prevalence's of runny nose and sneezing with OR between 3.5–7.0 in green and dry mill workers compared to controls. Significantly increased occurrence of **conjunctivitis** was reported in one study with OR 9.9 (1.7–400) between exposed and non-exposed workers [19]. One study did not find current inhalable wood dust exposure associated to conjunctivitis [25]. Three papers comparing woodworkers and controls reported increased prevalence of **WR conjunctivitis** [4, 19, 52], significant in [19], while the others reported significantly increased prevalence of **WR eye irritation**, especially among green mill workers [4, 52]. In addition, one study reported a non-significant increase in WR eye irritation among sawmills workers [31].

One paper reported a significant negative association between exposure duration and an irritation syndrome including nasal or conjunctival irritation [57].

NAL (nasal lavage) performed in one study revealed a higher cell count among females in the highest exposure category (>5 mg/m^3) [11].

DISCUSSION

When estimating respiratory health effects of occupational exposure to wood dust it is crucial to have valid exposure estimates. In the presented papers, wood dust exposure was assessed in different ways. Some studies estimated exposure solely on employment status [16, 19, 62], but most studies included dust measurements at least on a limited number of workers. Group exposure estimates were based on additional information about work area, job title, etc. Some studies based exposure assessment on a substantial amount of measurements [11, 20, 26, 28, 52, 53, 61].

Exposure misclassification in many of the studies is likely. When comparisons are made between groups of more

Table 1. Characteristics of studies included. Unless otherwise stated, symptom risk is given as OR.

Author, country, year	Type of study/ Number	Industry; wood species	Exposure measure mg/m^3; unless otherwise stated personal dust in GM (GSD)
Glindmeyer, US, 2008 [28]	FU 5 yr. E: 385	Sawmill, planning, plywood, milling Various wood types	Dust N=647 3 size fractions (<4<10<100) µm 150 analysed for % WS and % RPM GM resp: 0.10–0.19 %WS mean: 2–28 GM inhal: 0.77–1.07 %WS mean: 8–39 JEM: Mean individual exp. during FU, mg/m^3, for 3 size fractions, WS, RPM
Heikkilå, FI, 2008 [33]	R-FU Registers: Wood processing industries. Incident AS reimbursement register E: 56,721 Other blue-collar W: 101,413 C: 12,839	Wood processing industries various, 10 industries wet and dry pine, spruce, birch	JEM 5 exp levels based on industrial meas. total dust Woodworkers (E_w): E_{low}: 0.02–<0.05 E_{med}: 0.5–<1.5 E_{high}: ≥1.5 E_b: Other bluecollar workers, wood exp. unknown C (administrative) Also divided into types of work
Rusca, SW, 2008 [57]	CS E: 111	Sawmills; spruce, fir	Area inhal. dust N=? AM: 1.7 (range 0.2–8.5) Also bacteria, fungi
Friesen, CA, 2007 [26]	R-FU E: 11,273	Sawmills; softwood	Inhal. dust N=1399; JEM non-spec. particulate and wood dust Cum. exp. particulate: mean (max): 9.8 (220) mg yr/m^3 Cum. wood dust: mean (max.): 6.8 (89) mg yr/m^3
Douwes, NZ, 2006 [20]	CS E: 167 3 exp. levels	Sawmills; pine	Inhal. dust N=183 GM: 0.5 (2.7) JEM: 3 exp. catagories E_{low}: 0.4 (2.8) $E_{high\text{-}dry}$: 0.6 (2.2) $E_{high\text{-}green}$: 0.8 (2.3)
Ugheoke, NI, 2006 [62]	CS E: 150 C: 150	Sawmills; mansonia, iroko, walnut	E *vs* C
Teschke, CA, 2004 [61]	CS E: 105 C: 483	Sawmills; pine, spruce	Inhal. dust N=103 GM: 0.54 (2.9)

Lower airway symptoms OR (95% CI) * OR calculated	Upper airway symptoms OR (95% CI) * OR calculated	Objective measurements	Confounders included
		No ass. between WS and lung function indices for any size fraction Neg. ass. between resp. RPM and annual change in FEV_1, FEV_1/FVC, or $FEF_{25–75}$ in milling, Neg. ass. between resp. RPM and annual change in FEV_1 and FVC in sawmill-planning-plywood	Age, sex, height, weight change, ethnicity, smoking, baseline lung function
RR: AS men E *vs* C: E_w: 1.5 (1.2–1.8) E_{low}: 1.4 (1.1–1.7) E_{med}: 1.7 (1.4–2.2) E_{high}: 1.2 (0.9–1.6) E_b: 1.4 (1.1–1.8) $E_{sawmill}$: 1.9 (1.5–2.5) **RR: AS women E *vs* C:** E_w: 1.5 (1.2–1.7) E_{low}: 1.4 (1.2–1.8) E_{med}: 1.6 (1.3–2.0) E_{high}: 1.2 (0.8–1.6) E_b: 1.4 (1.1–1.6)			Sex, age No adj. for smoking, but has been considered
No ass. dust or yr. exp. CB, AS.	S neg. ass. yr. exp. and nasal/eye irritation No ass. to dust	No ass. between current dust level or yr. of exp. and FEV_1% pred.	Sex (all males), smoking, atopy, bacteria, fungi
COPD hospitalisation rate: No ass. cum. non-spec. dust DRR cum. wood dust RR 1.93 $E_{cum\text{-}high}$ *vs* $E_{cum\text{-}low}$			Sex (all males) age, ethnicity No adj. for smoking, but has been considered
$E_{high\text{-}dry}$ *vs* E_{low}: AS: 2.1 (1.0-4.4) **$E_{high\text{-}green}$ *vs* E_{low}:** AS: 1.4 (0.6–3–3)		**$E_{high\text{-}dry}$ *vs* E_{low}:** ↓FEV_1, ↓PEF, Borderline ↓FVC $E_{high\text{-}green}$ ***vs*** E_{low}: ↓FEV_1, ↓FVC, ↓PEF No ass between exp. and FEV_1/FVC or exp. FEV_1/FVC<70%	Sex, age, ethnicity, smoking, height, symptom status
Non-Smokers E *vs* C: WH: 5 *vs* 0%, p=0.01 SOB+WH: 1 *vs* 0%, NS CO*: 25.5 (9.7–77) **Smokers E *vs* C:** WH: 4 *vs* 0%, NS SOB+WH: 2 *vs* 0%, NS CO*: 6.4 (0.8–289)		**E *vs* C:** lover PEF for both smokers and non-smokers	Sex (all males), smoking, age, height
		Using diff. models of exp.: DRR Exp. & ↓FEV_1	Smoking, sex, age, ethnicity

Author, country, year	Type of study/ Number	Industry; wood species	Exposure measure mg/m^3; unless otherwise stated personal dust in GM (GSD)
Fransman, NZ, 2003 [25]	CS E: 112 C: 415	Plywood mill; pine	Inhal. dust N=57 GM 0.7 (1.9) Job titles: low/high Yr. of exp. Also endotoxins, abietic acid, terpenes formaldehyde
Borm, IN, 2002 [11]	CS E_{Low}: 572 E_{Med}: 271 E_{High}: 87	Plywood plant; meranti	Dust meas. N=243 JEM: E_{Low}: <2 E_{Med}: 2–5 E_{High}: >5 Yr. of exposure, cum. exp.
Douwes, NZ, 2001 [19]	CS E: 704 3 exp levels C_w: 65 C_p: 592	Sawmills; pine	JEM (work area, job title) 4 exp. categories: C_w (non-exp.) E_{low} (non/low) $E_{high\text{-}green}$ $E_{high\text{-}dry}$
Mandryk, AU, 2000 [52] Part of study [51]	CS E_{dry}: 34 E_{gren}: 53 C: 34	Sawmills (green mills, dry mills); eucalypt	Inhal. dust N=93 GM_{green}: 1.5 (3.7) GM_{dry}: 1.7 (2.5) Also resp. dust, endotoxins, glucans, bacteria
Mandryk, AU, 1999 [51]	As [4]	Sawmills, chip mill; eucalypt	

Lower airway symptoms OR (95% CI) * OR calculated	Upper airway symptoms OR (95% CI) * OR calculated	Objective measurements	Confounders included
Yr. exp. *vs* C: <2yr.; 2–6.5 yr.; > 6.5 yr. AS: 0.5 (0.2–1.7); 1.0 (0.3–2.7); 3.1 (1.3–7.2) WH: 0.4 (0.1–1.6); 1.4 (0.6–3.6); 1.8 (0.7–4.3) SOB+WH: 1.1 (0.4–3.0) 1.0 (0.4–2.7); 2.6 (1.1–5.8)	RH: 35.7% E CJ: 25% E NS increase of nasal and eye symp. in rel. to exp. level		Sex, age, ethnicity No smoking information for C
Males: WH 1.6%; CO: 23.5% **Females:** WH: 1.8%, CO: 22.3%, No ass. exposure level, cum. exp. or yr. exp.		Neg. ass. between year of employment & FEV_1, FVC, FEV_1/FVC for men. No ass. between exp. & lung function indices; NAL: tendency to lower cell counts among the highest exp. women.	Smoking, sex, age
E_{all} *vs* C_p: AS: 1.6 (1.1–.2.3) WH: 1.4 (1.1–1.9) **E_{low} *vs* C_w:** AS 1.9 (0.7–4.9) CO: 2.7 (1.2–6.5) WR-WH/SOB/CT: 4.7 (1.3–16) **$E_{high\text{-}green}$ *vs* C_w:** AS 2.7 (0.9–7.6) CO: 5.2 (2.1–13) WR-WH/SOB/CT: 4.0 (1.1–15) **$E_{high\text{-}dry}$ *vs* Cw:** AS 2.1 (0.8–5.7) CO 3.3 (1.4–7.9) WR-WH/SOB/CT: 7.0 (2.0–25)	**E_{all} *vs* C_p:** RH: 2.1* (1.0–4.9) CJ: 9.9* (1.7–400) WR-RH: 5.3 (1.4–45) WR-CJ: 47 *vs* 0% ($p<0.05$) **E_{low} *vs* C_w:** RH: 1.7 (0.7–4.0) CJ: 8.0 (1.0–63) WR-RH: 2.6 (NS) WR-CJ: 4.8 *vs* 0% (NS) **$E_{high\text{-}green}$ *vs* C_w:** RH: 2.6 (1.0–6.5) CJ: 15 (1.8–118) WR-RH: 3.9 (0.8–18) WR-CJ: 9 *vs* 0% ($p<0.01$) **$E_{high\text{-}dry}$ *vs* C_w:** RH: 2.5 (1.0–6.0) CJ: 11 (1.4–85) WR-RH: 6.0 (1.3–27) WR-CJ: 7 *vs* 0% ($p<0.05$)		Smoking, sex, age, ethnicity, mill No smoking information for C_p:
WR **Green mills *vs* C** AS: 1.3* (0.2–15) WH: 2.4* (0.7–11) CO: 3.4* (1.2–10) CB: 4.5* (1.3–20) **Dry mills *vs* C:** AS: 2.1 (0.3–24.9) WH: 0.7* (0.1–4.7) CO: 0.8* (0.3–3.1) CB: 1.0* (0.1–5.9)	**WR** **Green mills *vs* C:** BN: 2.3* (0.9–6.5) RN: 3.6* (1.2–12) IN: 2.7* (0.8–11) SN: 7.0* (2.2–26) CJ: 1.3* (0.1–79) EYD: 4.5* (1.5–15) **Dry mills *vs* C:** BN: 1.7* (0.6–4.6) RN: 3.7* (1.2–11.2) IN: 1.5* (0.4–6.7) SN: 5.2* (1.4–21) CJ: 1.0* (0.0–81) EYD: 1.9* (0.5–7.5)	FEV_1, FVC decreased in both green and dry mill FEV_1/FVC decreased in dry mill E_{green}: neg. corr between resp. dust and FVC% predicted, and between inhal. dust and VC% predicted Post shift decline FEV_1, FVC, FEV_1/FVC; Pos. corr. between inhal. dust and post shift decline in VC, $FEV_{25–75\%}$	Smoking, sex (all males), age, height
		E *vs* C: FVC↓, FEV_1↓ Post shift decline FEV_1, FVC, FEV_1/FVC, PEF No DRR	

Author, country, year	Type of study/ Number	Industry; wood species	Exposure measure mg/m^3; unless otherwise stated personal dust in GM (GSD)
Alwis, AU, 1999 [4]	CS E: 108 C: 34	Sawmills, chip mill; eucalypt	Inhal. dust N=93 GM sawmill: 1.6 (3.2) GM chip mill: 2.9 (1.7) Yr. of exp, resp. dust, endotoxins, glucans, bacteria
Liou, TA, 1996 [46]	CS E_{High}: 34 E_{Low}: 38 C: 262	Wood mill; powder	Total dust E_{High} AM (N=6): 12.0 E_{Low} (N=1): 2.9
Noertijojo, CA, 1996 [53]	FU 11 yr. E: 243 C: 140	Sawmill; red cedar	Dust meas. N=1,132 (during 12 years) JEM, cum. exp. Mean daily: <0.2, 0.2 to 0.4, >0.4
Hessel, CA, 1995 [36]	CS E: 94 C: 165	Sawmill; pine, spruce	Area resp. N=5 AM (range): 1.35 (0.1–2.2)
Herbert, CA, 1995 [35]	CS E: 127 C: 165	OSB-production; aspen, balsam	Area dust resp. N = 4 AM 0.05–0.5 Also formaldehyde, MDI
Herbert, CA, 1994 [34]	CS E: 99 C: 165	OSB-production; aspen	Area dust total sawline N=1 (0.27) Also formaldehyde
Halpin, UK, 1994 [31]	CS E: 103 2 exp. levels C: 52 (incl. paint sprayer & welders)	Sawmill; spruce, pine	Total dust N=62 GM low range: 0.2–1.1 GM high range: 1.3–6.3 GM control: 2.3 Fungal spores
Vedal, CA, 1988 [64] FU of [16]	FU E: 227 2 exp. levels	Sawmill; red cedar	Dust meas. N=? (personal, area) job, location
Vedal, CA, 1986 [63], Same study as [16]	CS E: 652 2 exp. levels	Sawmill; red cedar	Dust meas. N=78 (personal, area) JEM, 334 assign. AM: 0.46 (range 0–6) Yr. of exp.

Lower airway symptoms OR (95% CI) * OR calculated	Upper airway symptoms OR (95% CI) * OR calculated	Objective measurements	Confounders included
WR E *vs* C: AS: 1.5* (0.3–14.5) WH: 1.4* (0.4–6.2) CT: 1.3* (0.4–4.2) CO: 4.6* (1.8–13) CB: 3.2* (1.0–13)	**WR:** BN: 2.1* (0.8–5.3) RN: 3.5* (1.3–11) IN: 2.0* (0.7–7.3) SN: 4.6* (1.6–16) CJ: 1.3* (0.1–64) EYD: 5.4* (2.0–17)		Smoking, sex (all males), age, height
E_{High} *vs* E_{Low}: CO: 3.9* (0.6–41) CB: 9.6* (1.1–443) **non-smoking:** **E_{High} *vs* E_{Low}:** CO: 23 *vs* 0%, p<0.05 CB: 23 *vs* 0%, p<0.05		**E *vs* C:** Decreased FEV_1, PEF. For smokers: ↓FEV_1/FVC **E:** DRR exp. decrease in, FEV_1, FVC, PEF	Smoking, sex, age, height
		FEV_1, FVC: Larger decline in E. DRR between exp. and annual decline in FVC	Smoking, sex (all males), height, ethnicity, atopy
AS: 2.5 (0.8–8.3) WH+CT: 2.6 (1.2–5.6) CO: 1.5 (0.7–3.2) CB: 1.5 (0.8–2.9) **>3 yr employment *vs* C** AS: 3.7 (1.0–14) CB: 2.2 (1.0–4.5)		FEV_1, FEV_1/FVC reduced in E	Smoking, sex (all males), age, height, atopy
AS: 2.9 (1.0–8.0) WH+ CT: 3.4 (1.7–6.8) CO: 1.2 (0.6–2.5)		FEV_1/FVC decreased in E. Post shift decline in FVC, FEV_1 in E.	Smoking, sex (all males), age, height, atopy
AS: 5.5 (1.9–16.2) WH+CT: 5.7 (2.8–11.8) CO: 2.4 (1.2–4.7) CB: 1.4 (0.7–2.6)		**E *vs* C:** ↓FEV_1/FVC; FEV_1/FVC<75%: smokers: 3.0 (1,1–8,1) non-smokers: 1.4 (0.7–2.6) **E:** Post shift decline in FVC, FEV_1	Smoking, sex (all males), age, height, atopy
WR: **E_{all} *vs* C:** WH: 0.5* (0.2–1.4) CO: 1.0* (0.3–3.5) CB: 3.5* (1.1–14) **E_{high} *vs* E_{low}:** WH: 7.0* (1.3–69) CO: 2.0* (0.5–8.4) CB: 1.2 * (0.4–3.5)	**WR:** **E_{all} *vs* C:** NAD: 1.9* (0.5–8.3) EYD: 1.9* (0.6–6.8) **E_{high} *vs* E_{low}:** NAD: 2.7* (0.7–11) EYD: 2.8* (0.8–10)	No differences in FEV_1 and FVC between E and C	Smoking, sex (all males), age, height, atopy
Tendency more resp. symp. when persistent BHR		Pos. corr. between exp. and BHR Pos. corr. between BHR and plicatic acid IgE	Smoking, sex (all males), age, height, ethnicity
WR Asthma ass. to exp. >10 yr: OR: 2.1 (1.2–3.9)	**WR** NAD: not related to exp **Exp >2 mg/m^3** EYD: increased	Corr. between FEV_1, FVC and exposure No ass. to yr. of exposure	Smoking, sex (all males), age, height, ethnicity 2 exp. levels

Author, country, year	Type of study/ Number	Industry; wood species	Exposure measure mg/m^3; unless otherwise stated personal dust in GM (GSD)
Chan-Yeung, CA, 1984 [16]	CS E: 652 C: 440	Sawmill; red cedar	
Ashley, CA, 1978 [5] Same study as [15]	CS E: 405 C: 187	Sawmill, shingle mill; E: red cedar C: spruce, fir, hemloch	Area dust meas. N=92. AM E: 2.6 AM C: 1.7 Year of exposure
Chan-Yeung, CA, 1978 [15]	CS E: 405 C_1: 187 C_2: 65 (C_2 earlier work with Red Cedar)	As. [5]	
Gandevia, AU, 1970 [27]	CS E_{high}: 30 E_{low}: 17	Saw Mill; red cedar	Area dust meas. N=? 250–270 particles/m^3

Countries: AU: Australia. CA: Canada. FI: Finland; NZ: New Zealand. SW: Sweden; TA: Taiwan; UK: United Kingdom; US: United States of America

Type of study/Number: C: controls; CS: Cross sectional study; E: exposed; FU: follow-up study; R-FU: Register follow-up study

Exposure measure and statistics: AM: arimetric mean; Ass: associated; CI: confidence interval; Conc: concentration; Corr: correlation; Cum: cumulative; Diff: difference: DRR: dose response relationship; Exp: exposure; GM: geometric mean; GSD: geometric standard deviation; JEM: job exposure matrix; Inhal: inhalable; MDI: methylene diisocyanate; NS: non-significant; OR: odds ratio; OSB: oriented strand board; P: population; Pred: predicted; RR: relative risk; Resp: respirable; RPM: residual particulate matter; SD: standard deviation; S: significant; W: worker; WS: wood solids

Symbols symptoms and objective measurements: AS: asthma, BN: blocked Nose; CB: chronic bronchitis; CJ: conjunctivitis; CO: cough; CT: chest tightness; EYD: eye irritation; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; IN: itchy nose; NAD: nasal discomfort; NAL: nasal lavage; RH: rhinitis; RN: runny nose; SOB: shortness breath; SN: sneezing; WR: work related; WH: wheeze.

or less exposed wood workers this misclassification might attenuate the dose-response relation. For example, Douwes *et al.* [19] ascribed misclassification of exposure as the reason for finding associations between exposed and non-exposed workers for WR asthma symptoms, without being able to show any association to exposure level.

There are large differences in exposure level in the papers reviewed. When dust measurements were performed, low exposure levels of total or inhalable dust ranged from < 0.05–2.9 mg/m^3 (AM or GM) and high exposure levels from 0.6–12 mg/m^3. Compared to the dry wood industry reviewed in [41], there is a tendency towards lower exposure levels in the fresh wood industry, which is also clear from the European wood dust exposure survey from 2006 [45].

All but 5 follow-up studies were cross-sectional studies. A cross-sectional design hampers the possibilities to study associations between exposure and chronic diseases with latency time, for example asthma, chronic bronchitis and chronic impairment of lung function. In addition, a "healthy worker effect", i.e. a tendency of workers experiencing respiratory complaints to leave a dusty job or to transfer to less dusty jobs, can cause skewing of risk estimates due to selection bias.

Ideally, cases and controls should be identical, apart from contrasts in exposure, and in most studies other industrial workers were selected as controls, while in some studies groups that probably differed markedly from the workers in the wood industry had been chosen (including office workers, general population) making interpretation difficult [16, 19, 25, 31, 46, 53].

Smoking is strongly causally related to the development of respiratory symptoms and decline in lung function, including COPD and chronic bronchitis, and therefore we have excluded studies without information on smoking. The

Lower airway symptoms OR (95% CI) * OR calculated	Upper airway symptoms OR (95% CI) * OR calculated	Objective measurements	Confounders included
AS: 2.7 (S) CO: 2.2 (S) WR-AS: 2.7 (S)		**E *vs* C:** FEV_1, FVC, FEV_1/FVC reduced in E. **E:** non-atopic more BHR compared to atopics. BHR pos. corr. to exp. time	Smoking, sex (all males), age, height, ethnicity
E *vs* C: exp. duration related to prevalence of PH, WH & SOB		**E *vs* C:** ↑duration exp. related ↓ FEV_1, ↓FVC No ↓lung function during week **E&C:** no relation atopy & lung function	Smoking, sex (all males), age, height, atopy
E *vs* C_1: WH: 1.8 (p=0.07) CO: 2.0 (p<0.01) SOB: 2.3 (p<0.01) **C_2 *vs* C_1:** (SOB: 2.3 (p=0.02) **E:** WR asthma. 1.1%. Incidens 4–5%. C_2 more resp. symp. compared to C_1	**E *vs* C_1 (RR):** RH: 1.6 (S)	E *vs* C No diff. in lung function	Smoking, sex (all males), age,
3 cases of clinical WR AS	4 cases WR rhinitis	E_{high} post shift decline in FEV_1 E_{low} NS post shift decline No diff. during work week	Smoking

expected lung function depends on age, sex and height, and these factors have generally been included in the studies. Atopy is a known risk factor for asthma and rhinoconjunctivitis, but only some studies have taken atopic status into consideration [5, 31, 34, 35, 57, 64].

Although only a few studies revealed significant associations between wood dust exposure and occurrence of asthma and WRA, it is evident when looking across studies, that a consistent pattern of elevated prevalence's and OR's of asthma and asthmatic symptoms is revealed. The positive findings were confirmed in the only follow-up study [33]. No clear pattern between exposure level or duration and prevalence of asthma is seen across studies, i.e. very heterogeneous methodologies across a wide range of countries make it difficult directly to compare the different studies.

From the studies reported in this review it seems evident that exposure to fresh wood dust may cause CB. All but one study reported OR's above 1.0 and several studies reported significant OR's above 2.0 when comparing woodworkers to controls. CB could be related to exposures mostly or only present when handling wet wood, for example, moulds and endotoxin, and therefore one might argue it is not an effect of wood dust exposure per se. On the other hand, studies in the dry wood industry with little or no exposure to these have reported high OR's [41].

Coughing is an unspecific symptom, which may reflect acute irritation of the airways and toxic alveolitis, as well as diseases like asthma, bronchitis, COPD or allergic alveolitis. Coughing and work-related coughing in relation to wood dust exposure seems to be a consistent finding across studies. Eduard *et al.* found DRR between prevalence of coughing and the exposure level of mould spores among wood trimmers [24], which suggests the microbial exposure to be of importance. However, increased prevalence of coughing has also been found in the dry wood industry, where studies revealing DRR between wood dust exposure per se and coughing support an inherent wood dust effect [41].

An acute obstructive effect of fresh wood dust exposure during workdays or during work weeks seems likely, as most studies measuring lung function showed a post-shift decline in lung function, although DRR did not support the finding for fresh wood, as opposed to a number of studies in the dry wood industry [41].

When studying lung function, a cross-sectional design as used in most of the reviewed papers is at best suboptimal. Even so, a number of studies revealed reduced baseline lung function (FEV_1, FVC, or FEV_1/FVC) among wood workers, and some studies revealed an association to current exposure or to years of exposure. The two follow-up studies [28, 53] investigating trends in lung function showed conflicting results. Both studies were performed among low exposed workers, but wood types differed as Noertjojo *et al.* studied a cohort exposed to RC, a known

asthmagen while RC exposed workers were excluded by Glindmeyer *et al.* Individual exposure assignments in both studies were based on JEMs and exposure duration. Noertjojo *et al.* based JEM on measurements of total dust, whereas Glindmeyer *et al.* divided measurements into wood solids (WS), residual particulate matter (RPM) and 3 size fractions. While Glindmeyer *et al.* found no association between any size fraction of WS and change in lung function, they reported significant effects of inhalable and thoracic dust on excess annual decline in lung function in the pooled population, including workers exposed to dry wood, but ascribed the findings to the RPM component of the respirable fraction. In the dry wood industry, one follow-up study of equally low exposed workers showed a DRR between wood dust exposure (baseline and cumulative) and decline in FEV_1 and FVC among female workers, supporting a chronic effect of wood dust, suggested as being caused by a greater susceptibility for females [41, 42].

There seem to be a consistent trend across studies on rhinitis, nasal symptoms, conjunctivitis, and eye irritation supporting an effect on exposure to fresh wood dust on nasal mucosa and conjunctiva. This is in accordance with finding from studies of exposure to dry wood [41].

The mechanisms for wood dust inducing respiratory impairment are far from being fully understood. For RC, a low molecular compound, plicatic acid has been revealed to be a causal factor, and both immunological and non-immunological mechanisms are involved [10]. Apart from RC no causal agent has consistently been disclosed. Specific sensitization has been reported, but type 1 allergy is not suspected to be a major cause of wood dust induced asthma [1, 17, 59, 66].

Apart from IgE mediated sensitization several other mechanisms are possible. Animal studies have shown that wood components, for example the major constituent in pine resin abietic acid, causes direct toxicity via lytic damage to alveolar, tracheal and bronchial epithelial cells [6]. Wood dust extracts from both hard and soft wood are able to induce the release of pro-inflammatory mediators from macrophages [47, 49], express and induce the release of inflammatory mediators in human epithelial cell line [12], and modulate the expression of cytokines and chemokines [48].

Workers handling fresh wood are concurrently exposed to inflammatory components like moulds, bacteria and natural volatile components of fresh wood. Mould exposure may, apart from asthma, lead to allergic or toxic alveolitis, which has been described in sawmill workers and wood trimmers [9, 23, 32, 55]. Symptoms consistent with alveolitis, for example, coughing, wheezing, dyspnoea, are also associated to asthma and bronchitis. Hence, the different diseases, as well as the exposure of relevance (wood dust, microorganisms), can hardly be disentangled in an epidemiological setting. Biohazards, mostly endotoxins and mould exposure, have mainly been studied at sawmills processing fresh wood [22, 51], but have also been found at lower concentrations in the dry wood industry associated to chronic bronchitis [4], and cross-shift decrease in lung function [51]. Thus, respiratory effects caused by work in the fresh wood industry is probably a combination of exposure to wood dust *per se* and other exposures, such as endotoxins, glucans and mould spores.

Monoterpenes are volatile substances naturally occurring in pine and other coniferous trees and may be liberated mainly during handling of fresh wood. Terpenes have been documented as causing irritation of the mucous membranes, and are suspected of causing impairment of lung function and BHR at levels of 100–450 mg/m^3 [2, 44]. Only one of the reviewed studies explored terpene exposure. Fransman *et al.* [25] found low levels in sawmills ranging from GM 0.5–4.4 mg/m^3 and did not find respiratory symptoms associated to these low levels. On the contrary, studies solely focusing on terpene exposure [3, 50, 56] have shown considerably higher levels of terpenes with GM's ranging from 35–250 mg/m^3. In one Swedish study of sawyers exposed to levels above 150 mg/m^3, more BHR was revealed compared to lower exposed sawmill workers [50]. It was suggested that oxidative products of monoterpenes or abietic acid could cause airway inflammation through immune reactions. This was supported in an experimental study, which showed increased alveolar cell concentration, mainly macrophages in BAL after exposure to 450 mg/m^3 of terpenes [43].

It has been documented that processing of plywood may cause exposure to formaldehyde [50] and asthma symptoms among woodworkers exposed to formaldehyde alone or in combination with wood dust [38]. A number of the reviewed papers in fact included evaluations of the formaldehyde concentration [25, 34, 35] and found formaldehyde levels ranging from 0.04–0.33 mg/m^3. A health-based recommended 8-hour time-weighted occupational exposure limit (OEL) of 0.15 mg/m^3 has been recommended in the Nederland's [21]. In the reviewed papers, it is generally not possible to distinguish the effects of wood dust and formaldehyde, although in one recent study [25] at ply mills, an association between asthma symptoms and formaldehyde was revealed, with the highest level of GM 0.16 mg/m^3. Thus, it cannot be rejected that formaldehyde alone or in combination with wood dust may have influenced results, especially from the part of the industry processing plywood.

In conclusion, this review supports, despite the limitations in study design and exposure assessments, that wood dust exposure is a risk factor for development of asthma, chronic bronchitis, rhino-conjunctivitis and chronic impairment in lung function. The mechanisms are mostly unknown. Concurrent exposures, such as moulds, endotoxin and terpenes, contribute to the health effects in the wet wood industry.

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