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# Non-eosinophilic occupational asthma due to exposure of Merbau and Bangkirai Wood



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## ABSTRACT

**Objectives:** To evaluate the association between exposure to wood dust and occupational asthma and investigate the immunopathogenesis behind the disease by examining IgE, CD4, and eosinophil levels.

**Methods:** Subjects were diagnosed with occupational asthma based on the findings derived from the questionnaire titled "Work-Related Asthma Questionnaire" and Peak Expiratory Flow Rate (PEFR) variability for two weeks. Exposure to wood dust exposure was measured using a personal dust sampler for two days on the subjects during working hours.

**Results:** Out of the 104 samples chosen for the study, 17% of the subjects were diagnosed with occupational asthma. Analysis showed that there were correlations between exposure to wood dust exposure and occupational asthma ( $r = 0.384$ ,  $p = 0.000$ ). ROC methods

revealed that exposure to wood dust was 70.5 mg/m<sup>3</sup>/year, which is associated with a greater risk of occupational asthma, especially in light of the higher values measured for sensitivity at 87.5% and specificity at 75%. Study findings showed that exposure to wood dust was significantly correlated with higher serum CD4 level ( $r = 0.455$ ,  $p = 0.000$ ). However, eosinophil level did not correlate with CD4 level or exposure to wood dust.

**Conclusion:** Exposure to Merbau and Bangkirai wood is indeed a risk factor for occupational asthma. The process of how exposure to wood induces occupational asthma can be defined as a non-eosinophilic mechanism and denotes a significant correlation between occupational asthma and the elevated presence of CD4 serum.

**Keywords:** Non-eosinophilic, Asthma, Merbau, Bangkirai

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## INTRODUCTION

Occupational asthma is one of the most common forms of occupational lung diseases in industrial countries. The adverse effects of the disease include mortality, morbidity, and disability. Approximately 15% of asthma cases in the United States are caused by exposure to airborne dust particles in workplace environments<sup>1</sup>. Occupational asthma is a disease characterized by variable airflow limitation and airway hyperresponsiveness due to causes and conditions attributable to a particular occupational environment and not to stimuli encountered outside the workplace<sup>2</sup>.

Wood dust is one of the main asthma genes present in the workplace. Exposure to dust from certain kinds of woods, such as Western red cedar, oak, iroko, abachi, and mahogany, can cause asthma. The pathogenesis mechanism of how asthma is induced by exposure to wood dust exposure is unclear. Wood dust is a low-molecular-weight (LMW) agent. The study showed elevated eosinophil levels in sputum induction and bronchoalveolar lavage in subjects who were exposed to wood dust. Lemiere et al. reported that occupational asthma induced by LMW exposure would elevate eosinophil count in sputum and serum during working hours compared

to periods outside of working hours, for example, during vacations<sup>3</sup>. However, Di Franco et al. reported higher levels of neutrophil in the sputum of asthma patients due to exposure LMW agents compared to HMW agent or non-occupational asthma. There are two variants of occupational asthma due to exposure to LMW agents, which are (a) eosinophilic and (b) non-eosinophilic<sup>4</sup>.

In South East Asia, wood-cutting and processing are a major industry. Indonesia's natural forest reserves are the largest in Asia, and the second largest in the world and is estimated to extend over 100 million hectares. Merbau, bangkirai, teak, and other trees in Indonesia are tropical hardwood tree species. In this study, we investigate how exposure to hardwood dust induces occupational asthma and analyze the immunopathogenesis behind the development of occupational asthma.

## METHODS

This is a cross-sectional analytic study. The study was conducted in wood manufacture industrial units in Indonesia. Subjects eligible for this study are in the age range of 17–60 years and have worked in the wood industry for more than 1-year. The exclusion criteria include subjects with

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**Table 1** Characteristics of the samples (n = 104)

No	Variable	Frequency (%)
1.	Sex	
	Male	53 (51)
	Female	51 (49)
2.	Department	
	Administration	34 (32.7)
	Sandpaper	21 (20.2)
	Sewing	17 (16.3)
	Assembling	32 (30.8)
3.	Smoker	28 (26.9)
	Nonsmoker	76 (73.1)
4.	Precaution (Mask)	
	Never	7 (6.7)
	Seldom	16 (15.4)
	Often	12 (11.5)
	Always	69 (66.3)

**Table 2** Measured levels of exposure to wood, IgE, CD4, and eosinophil

No	Variable	Mean
1.	Wood dust exposure (mg/m <sup>3</sup> /year)	74.95 ± 39.5
2.	Total IgE level (IU/ml)	644.4 ± 930.7
3.	Serum CD4 level (cell/μl)	803.93 ± 35.05
4.	Serum eosinophil level (cell/μl)	0.343 ± 0.037
5.	IL-8 serum level (pg/ml)	33.10 ± 1.73 pg/ml
6.	Years of service	5.91 ± 4.04

tuberculosis, diabetes mellitus, HIV infection, and malignancy and subjects who have been using any corticosteroid or immunosuppressant drugs for 1-month.

Subjects eligible for this study were examined for occupational asthma symptoms using the American Thoracic Society's Work-Related Asthma Questionnaire (2011) and later subjects underwent a spirometry examination. Subjects with occupational asthma and airflow limitation then underwent a variant of the peak expiratory flow rate examination twice every day, once in the morning and once in the afternoon, for 2-weeks.

Exposure to wood dust was measured using a personal dust sampler (SKC model 224-PXCR-8) in five sites for 2 days during working time; the dust sampler was placed closed to workers' nose. Blood samples were obtained to measure the levels of IgE, CD4, eosinophil, and IL 8.

Chi-square analysis was used to evaluate the association between occupational asthma and

exposure to wood dust. Pearson and Spearman's analysis was used to determine the correlations between exposure to wood dust and CD4 level, eosinophil, and IL 8 levels.

## RESULTS

Out of the 104 study subjects, 17 were working in the sewing department, 21 in sandpaper department, 32 in assembling department, and 21 in the administration department. The subjects' characteristics are presented in Table 1. The mean of exposure to wood dust was 74.95 (±39.5) mg/m<sup>3</sup>/year. The levels of CD4 and eosinophil serum were 803.93 ± 35.05 and 0.343 ± 0.037, respectively. The level of IL-8 was 33.10 ± 1.73 pg/ml.

Seventeen (16%) subjects were diagnosed with occupational asthma based on the results of a variability test conducted for the study. Exposure to wood dust in occupational asthma was 111.5 (±41.0) mg/m<sup>3</sup>/year with total IgE level at 297.3 (±410.8), whereas for those subjects without occupational asthma exposure to wood dust was 67.8 (±35.2) mg/m<sup>3</sup>/year, with total IgE level at 712.2 (±988.8; see Table 2). Tables 3 and 4 show a comparison between subjects with occupational asthma and subjects without occupational asthma.

Analysis showed that there were correlations between exposure to wood dust and occupational asthma ( $r = 0.384$ ,  $p = 0.000$ ). ROC methods revealed that exposure to wood dust at 70.5 mg/m<sup>3</sup>/year was associated with a greater risk of occupational asthma, with sensitivity and specificity of 87.5% and 75%, respectively. We evaluated the atopy status by measuring the serum IgE level, and we found there was a negative correlation between atopy status and occupational asthma ( $r = -0.277$ ,  $p = 0.002$ ).

Exposure to wood dust was significantly correlated with serum CD4 level ( $r = 0.455$ ,  $p = 0.000$ ). The correlation coefficient for the relationship between exposure to wood dust and eosinophil level was measured and found to be not significant at  $r = -0.38$  and  $p = 0.755$ . Therefore, it was concluded that there was no significant correlation between both the variables, that is, exposure to wood dust and eosinophil levels. We also analyzed the correlation between the levels of CD4 and eosinophil and found that there was no significant correlation between them ( $r = 0.01$ ,  $p = 0.996$ ). Years of service or working was significantly correlated with serum CD4 level ( $r = 0.278$ ,  $p = 0.020$ ). Exposure to wood dust was also significantly correlated with IL-8 level ( $r = 0.443$ ,  $p < 0.011$ ).

**Table 3** A comparison between the characteristic of subjects with occupational asthma and subjects without occupational asthma

No	Characteristic	Occupational asthma	Non-asthma
		(total n = 17), mean n (%)	(total n = 87), mean n (%)
1.	Sex		
	Male	7 (41.2)	46 (52.9)
	Female	10 (58.8)	41 (47.1)
2.	Department		
	Administration	2 (11.8)	32 (36.8)
	Sandpaper	7 (41.1)	14 (16.1)
	Sewing	2 (11.8)	15 (17.2)
	Assembling	6 (35.3)	26 (29.9)
3.	Smoker	2 (11.8)	26 (29.9)
	Nonsmoker	15 (88.2)	61 (70.1)
4.	Precaution (Mask)		
	Never	2 (11.7)	5 (5.7)
	Seldom	2 (11.7)	14 (16.1)
	Often	2 (11.7)	10 (11.5)
	Always	11 (64.9)	58 (66.7)

**Table 4** A comparison between the levels of exposure and IgE in subjects with occupational asthma and subjects without occupational asthma

No	Characteristic	Occupational asthma	Non-Asthma
		(total n = 17), mean	(total n = 87), mean
1	Age	39.5 ± 3.41	40.1 ± 7.4
2	Wood dust exposure (mg/m <sup>3</sup> /year)	111.5 ± 41.0	67.8 ± 35.2
3	Total IgE level	297.3 ± 410.8	712.2 ± 988.8

## DISCUSSION

Occupational asthma is one of the most common forms of occupational lung diseases characterized by variable airflow limitation and airway hyperresponsiveness due to causes and conditions in particular occupational environments and not from exposure outside the workplace. Work-related asthma is diagnosed by determining the relationship between exposure and the symptoms and measurement of airflow limitation. One test, in particular, that is, the PEFR monitor was found to be particularly useful in the investigation of work-related asthma. This study used the PEFR monitoring to assess the level of presence of work-related asthma<sup>1,2,5</sup>.

Borneo teak/merbau wood (*Instia bijuga*) and Yellow balau/bangkirai wood (*Shorea sp*) are

classified as hardwood species. Merbau is mainly used in heavy construction works, such as beams, poles, and bearings, in houses and bridges. Tannin (polyphenol), carbohydrate, pigment, starch, resin, and oil are all substances commonly found in Merbau wood<sup>6</sup>. *Shorea* is a genus of about 196 species found mainly in rainforest trees in the family of Dipterocarpaceae, which is commonly used for making doors, windows, and floors. Olygostibenoid, polyphenol, quinones, and resin were extracted from this wood. Quinones, polyphenol, and resin are known to cause skin rash and work-related asthma<sup>7</sup>.

Study analyses showed that there was a correlation between exposure to wood dust and work-related asthma ( $r = 0.384$ ,  $p = 0.000$ ). Dust from Merbau and bangkirai woods is a part of the low-molecular-weight agent (LMW) that causes asthma. There was a negative correlation between atopy status and occupational asthma ( $r = -0.277$ ,  $p = 0.002$ ). We had also found lower levels of IgE in subjects with occupational asthma.

Atopy refers to the genetic tendency to develop allergic diseases such as asthma, which is identified by positive skin prick test, elevated total serum IgE, or the presence of serum-specific IgE antibody<sup>2</sup>. Agents that cause occupational asthma are categorized as follows: high-molecular-weight agents and low-molecular-weight agents. High-molecular-weight agents are proteins of animal or vegetable origin that act through an IgE-mediated mechanism. Low-molecular-weight agents include organic and inorganic compounds that are not associated with an IgE mechanism. Atopy is a predisposing factor in occupational asthma caused by high-molecular-weight agents, but it is a weak predictor of sensitization and development of OA. Gautrin et al. reported that skin reactivity to pets (relative risk = 4.11, 95% CI: 1.6–10.8) was a significant predictor of laboratory workers who develop occupational asthma. After exposure to laboratory animals, whereas atopy was not associated with OA (relative risk = 2.09, 95% CI: 0.8–5.6)<sup>8</sup>. Gautrin et al. also conducted a study of about 800 apprentices working in different fields, such as animal health technology, pastry making, and dental hygiene, and they found that 32% of sensitization cases and 27% of OA cases were found in nonatopic subjects<sup>9</sup>. A study conducted using a large cohort of bakers in Belgium showed that there was no relationship between atopy and sensitization to bakers' allergens and these two conditions were independent of each other<sup>10</sup>.

Exposure to wood dust was significantly correlated with serum CD4 level ( $r = 0.455$ ,

$p = 0.000$ ). The correlation coefficient between wood dust exposure and eosinophil level was  $r = -0.38$ ,  $p = 0.755$ . Therefore, there was no significant correlation between both variables. We also analyzed the correlation between CD4 and eosinophil levels but did not find any significant correlation between them ( $r = 0.01$ ,  $p = 0.996$ ). Years of service or working was significantly correlated with serum CD4 levels ( $r = 0.278$ ,  $p = 0.020$ ). Our results are in general similar to those of previous studies that showed that a correlation exists between exposure to pine wood dust in normal subjects and CD4 levels, which was proven by a higher level of CD4-Th2 cytokines production, IL-4, IL-5, and IL-13.

Wood dust particles entering the airway are flushed out by the mucociliary system. If dust particles reach alveoli, then macrophages engulf the dust particle, but the dust particles still manage to get to the tissues and then migrate via chemotactic signals to the T cell-enriched lymph nodes. During migration, macrophages undergo a process of maturation in which they lose most of their ability to engulf other particles and develop an ability to communicate with T-cells. CD4+ lymphocytes, also called “helper” or “regulatory” T-cells, are immune response mediators and play an important role in establishing and maximizing the capabilities of the adaptive immune response. These cells have no cytotoxic or phagocytic activity and cannot kill affected cells or clear particles but in essence “manage” the immune response by directing other cells to perform these tasks. Helper T-cells express T-cell receptors (TCR) that recognize antigen bound to Class II MHC molecules. The activation of a naive helper T-cell causes it to release cytokines, which influences the activity of many types of cells, including the APC (Antigen-Presenting Cell) that activates it. Classically, two types of effector CD4+ T helper cell responses can be induced by a professional APC, designated as Th1 and Th2. Th1 produces IFN $\gamma$ , and Th2 excretes IL-4, IL-5, and TGF $\beta$ <sup>11</sup>.

Although it is clear that work-related asthma induced by HMW agents is mediated through an IgE-dependent mechanism, there is no clear explanation regarding asthma caused by LMW agents such as wood dust. For known agents like acid anhydrides, platinum salts, and dyes, work-related asthma is accompanied by secretion of IgE, while for most other agents the presence of specific IgE has been documented in a small number of affected workers<sup>12-14</sup>. Other studies showed that the non-eosinophilic mechanism that causes airway hyperresponsiveness could be due to lipopolysaccharide (LPS) produced by bacteria in the wood. This

process activates the immune system to produce various cytokines, such as IL-8, IL-1 $\beta$ , and TNF- $\alpha$ , accompanied by the deployment of neutrophils. The effect of LMW exposure in airway also can stimulate P substance release and cause a contraction in smooth muscles and impairment of vascular permeability<sup>15-17</sup>.

Some studies have described the elevated neutrophil chemotactic activity as associated with recruitment and activation of neutrophils during asthmatic reactions induced by diisocyanates<sup>18-20</sup>. Di Franco et al. found more neutrophils and fewer eosinophils in the sputum of subjects with occupational asthma caused by LMW agents than in that of subjects with HMW agent-induced occupational asthma or non-occupational asthma<sup>4</sup>. Lemiere et al. documented an increase in both eosinophils and neutrophils in sputum after asthmatic reactions induced by LMW and HMW agents, and these cellular changes occurred independently from the temporal pattern of asthmatic reactions<sup>3</sup>. Sputum neutrophilia, however, was observed more frequently after challenge exposure to diisocyanates, even at very low concentrations<sup>21</sup>. Anees et al. suggested that occupational asthma caused by LMW agents could be differentiated into eosinophilic and non-eosinophilic variants, with the latter predominating, although both groups had sputum neutrophilia<sup>22</sup>.

In many studies, non-eosinophilic asthma was associated with increased neutrophil and IL-8 levels, which suggests that non-allergic neutrophil-driven airway inflammation was the underlying mechanism for non-eosinophilic asthma. The inflammatory profile appears to be very similar to that described for non-eosinophilic occupational asthma and is consistent with the activation of innate immune mechanisms mediating the inflammatory process in non-eosinophilic asthma<sup>23-28</sup>.

Although the exact pathophysiology is not clear, it is well established that non-allergic occupational asthma is mediated by an acute inflammatory response involving some cytokines, including IL-1, IL-6, IL-8, and tumor necrosis factor (TNF)- $\alpha$ . The subsequent massive infiltration and activation of neutrophils in the lower and upper airways, which is very similar to the inflammatory response observed in non-eosinophilic asthma in the general population. The primary agent inducing these inflammatory responses in workers exposed to organic dust is believed to be bacterial endotoxin. Macrophages carry specific endotoxin-binding receptors (CD14, TLR4) that play a crucial role in the activation of these cells and the subsequent inflammatory reactions<sup>29,30</sup>.

This study revealed that there was no regulation of eosinophil-induced by the activation of mast cells and CD4 cells in pathogenesis mechanism of work-related asthma due to exposure to dust from Merbau and bangkirai hardwoods. We suggest that the role of neutrophilic inflammation is important. Elevated IL-8 levels found in this study are the cause of the production of the neutrophil. The role of neutrophilic inflammation is uncertain and needs further investigation.

To our knowledge, there was no previous study about exposure to dust from merbau and bangkirai wood that can induce occupational asthma. Their woods are common in Southeast Asia. This study may contribute to the health regulation of woodworkers. A limitation of our study is that we used CD4, IgE, and eosinophil serum levels rather than using the sputum or bronchoalveolar lavage samples. Therefore, any direct effect that exposure to wood dust may have on the airway cannot be explained and needs further investigation.

## CONCLUSION

Exposure to dust from merbau and bangkirai woods is indeed a risk factor for occupational asthma. Development of occupational asthma due to exposure to wood dust is a non-eosinophilic mechanism and is associated with elevated CD4 serum levels. This study should encourage workers and wood companies to prevent exposure to wood dust by implementing and enforcing the use of personal protective equipment or any other regulatory improvements in the workplace.

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