(1→3)-β-D-glucan in the indoor environment

Yun-Wen Liu, Pei-Chih Wu, Chih-Hui Chang, Bi-Fang Gi, Huey-Jen Su*

Graduate Institute of Environment and Occupational Health, Medical College, National Chen Kung University, Taiwan, ROC

ABSTRACT

(1→3)-β-D-glucans are glucose polymers with variable molecular weight and degree of branching. They are present in the cell walls of most fungi and yeast, some bacteria and many plants, and considered as a potent airway proinflammatory agent inducing the release of cytokines, such as IL-8, IL-6 and TNF-α. Studies in the area of environmental health have directed attention to the adverse effects of (1→3)-β-D-glucan as it is considered a marker of fungal exposure in the indoor environments of schools, office buildings, homes, day-care centres and others. Yet, only limited studies have been able to demonstrate a dose–response relationship between (1→3)-β-D-glucan exposure and corresponding health outcomes. In addition, no conclusion has been established regarding the most suitable methodology for assessing indoor (1→3)-β-D-glucan exposures. This review article is organized to summarize the updated understanding on the health effects and exposure assessment of environmental (1→3)-β-D-glucan exposures to propose the research priorities in future study.

INDEX TERMS

Mould; (1→3)-β-D-glucan; Airway inflammation; Exposure assessment

INTRODUCTON

Many environment-related health symptoms, including dry cough; irritation in nose, throat; headache and tiredness, have been demonstrated in studies from different countries (Kilpelainen *et al.* 2001; Savilahti *et al.* 2001), and exposure to indoor microorganisms and their metabolic products is often considered to be one important factor involved in the reporting of these symptoms. A recent epidemiological study has further suggested that (1→3)-β-D-glucan may play a role in airway inflammation (Rylander and Megevand, 2000), and may induce respiratory symptoms in indoor environment (Rylander *et al.,* 1998; Wan and Li, 1999). The studies cited have adopted various methods to assess the concentration distributions of environmental (1→3)-β-D-glucan. Consequently, little consensus has been reached as to the environmental guidelines in this regard. Meanwhile, many animal studies were performed to demonstrate the inflammatory effect on the airway by (1→3)-β-D-glucan (Rylander and Holt, 1998; Ormstad *et al.,* 2000). This article will review the current knowledge on the topics of structure, health effects and exposure assessment regarding (1→3)-β-D-glucan in indoor environment to highlight the need of future research.

*Corresponding author.

STRUCTURE

(1→3)-β-D-glucans are glucose polymers with variable molecular weight and degree of branching (Rylander, 1997; Gehring *et al.,* 2001). They may have triple helix, single helix or random coil structures, and the triple helix appears to be the predominant form (Rylander and Lin, 2000) (1→3)-β-D-glucan is present in the cell walls of most fungi and yeast, some bacteria and many plants, and can be dissolved in an alkaline solution or in hot water (Douwes *et al.,* 2000; Gehring *et al.,* 2001). It is of importance to note that (1→3)-β-D-glucan retains its toxicity even after the death of the organism (Rylander and Lin, 2000).

HEALTH EFFECT

Biological Effects

(1→3)-β-D-glucan is known as an immunomodulator that stimulates the innate immune system, anti-infection and anti-tumour effects in rodent models (Ljungman *et al.,* 1998). Considered a potent airway proinflammatory agent, (1→3)-β-D-glucan induces the release of cytokines, and exerts their activity through phagocytosis by macrophages when attached to specific receptors on the macrophage's surface (Rylander and Lin, 2000). In addition, (1→3)-β-D-glucan is also closely associated with the presence of many other cells, including neutrophils, eosinophils and lymphocytes (Thorn *et al.,* 1998). Thorn *et al.* reported that the blood lymphocyte counts had dose-related increase in waste collectors with elevated exposure to airborne (1→3)-β-D-glucan (Thorn *et al.,* 1998). A dose-dependent increase in the expression of inducible nitric oxide synthase mRNA was also found with exposure to (1→3)-β-D-glucan. Similar effects were observed with the release of nitric oxide into the culture medium in both rats alveolar macrophages and RAW 264.7 cells (Ljungman *et al.,* 1998). Expression of other inflammatory mediators, such IL-1β, IL-6, TNFα and IL-8, were also found to increase with stimulation of (1→3)-β-D-glucan (Sigsgaard *et al.,* 2000).

In addition to the airway inflammatory effect caused by (1→3)-β-D-glucan, there is also evidence of complex interactive effects between (1→3)-β-D-glucan and other constituents, such as endotoxin, ovalbumin and cigarette smoke. Fogelmark *et al.*, among many others, have carried out a series of experimental studies to discuss the biological effects by endotoxin and (1→3)-β-D-glucan, and they demonstrated a prolonged depression of inflammatory cells of (1→3)-β-D-glucan, contradictory to the observation with endotoxin (Rylander and Holt, 1998; Fogelmark *et al.,* 2001). One study has found increasing number of neutrophils in the airways after a 5-week exposure to endotoxins, but no effect was observed with (1→3)-β-D-glucan exposure (Fogelmark *et al.,* 1994). In contrast, (1→3)-β-D-glucan induced more eosinophils and lymphocytes, which were not found after endotoxin exposure (Fogelmark *et al.,* 2001). (1→3)-β-D-glucan seemed to result in an effect on inflammation different from that of an endotoxin.

Related studies have also been conducted with ovalbumin (OVA). Mice, when pre-exposed to (1→3)-β-D-glucan, had significantly higher amounts of IgE and IgG1 with inhalation to OVA antigen than mice sensitized with OVA alone (Wan *et al.,* 1999; Ormstad *et al.,* 2000). In addition, the amounts of eosinophils increase after OVA exposure would be reduced with co-exposure to (1→3)-β-D-glucan (Rylander and Holt, 1998). When mice were exposed to (1→3)-β-D-glucan and cigarette smoke together, significantly increased numbers of macrophages, lymphocytes, neutrophils and eosinophils were observed (Sjostrand and Rylander, 1997). These experimental studies have partially illustrated the interactive effects resulting from concurrent exposure to multiple types of environmental microbes.

Field Studies

Epidemiological studies have reported relationships between (1→3)-β-D-glucan and symptoms in the indoor environments of schools, office buildings, homes, day-care centres and others. Research in Sweden showed a dose-depended relationship between (1→3)-β-D-glucan exposure and nasal irritation, throat irritation, headache and tiredness by dividing exposure into high, medium and low levels (Rylander 1997). Another study investigated the subjective symptoms before and after building renovation. They found the airborne (1→3)-β-D-glucan levels decreased from 11.4 to 1.4 ng/m^3 and the number of persons reporting airway responsiveness also decreased (Rylander, 1997). Higher (1→3)-β-D-glucan exposures may contribute to greater prevalence of symptoms such as dry cough, cough with phlegm and hoarseness in schools (Rylander *et al.*, 1998). Similar results were found in rowhouse, day-care centres and homes (Thorn and Rylander 1998; Wan and Li 1999). Douwes *et al.* demonstrated a significant association between dust (1→3)-β-D-glucan exposure and peak flow variability in asthmatic children (Douwes *et al.,* 2000). The indoor concentrations of (1→3)-β-D-glucan ranged from 0 to 27.4 ng/m^3 and from 182 to 6540 μg/g dust (Douwes *et al.,* 1996; Rylander *et al.,* 1998; Thorn and Rylander, 1998; Gehring *et al.,* 2001).

Most field studies have shown only a difference of symptom prevalence between subjects with high and low (1→3)-β-D-glucan exposure. The dose–response relationship between (1→3)-β-D-glucan and related symptoms is, therefore, inconclusive. Besides, even fewer studies were set to examine the relationship between (1→3)-β-D-glucan exposure and definitive health effects. Future endeavours remain essential to establish the causal effects of (1→3)-β-D-glucan on either the suspected symptoms or illnesses, and to better characterize the corresponding dose–response relationships.

EXPOSURE ASSESSMENT

Sampling and Analysis Methods

Sampling and analytical methodologies for assessing environmental (1→3)-β-D-glucan have varied to a great extent. Airborne and dust samples, each with different advantages, have been

the most frequent measurements to characterize the environmental exposure of (1→3)-β-D-glucan. Because most proven hazards related to (1→3)-β-D-glucan exposure are respiratory effects, airborne concentrations appeared to be a more suitable measurement to represent the direct exposure through inhalation. However, the current practice often results in several significant drawbacks. For instance, most air samples are unstable, and the concentrations measured are lower than the detection limit. In contrast, most dust samples are stable through the process and storage, and the amount of (1→3)-β-D-glucan is usually adequate for presenting significant measurements after laboratory analysis. Meanwhile, they serve as reasonable surrogates for long-term exposure of environmental (1→3)-β-D-glucan. Thus, finding a preferred exposure assessment method to best estimate (1→3)-β-D-glucan exposure indoors remains a top priority of future research.

Analytical methods for (1→3)-β-D-glucan include the Limulus Amebocyte Lysate test (LAL test) (Tamura *et al.,* 1994), specific inhibition enzyme immunoassay (EIA) (Douwes *et al.,* 1996), and enzyme-linked immunosorbent assay (ELISA) (Milton *et al.,* 2001). The LAL test was usually used to measure the airborne samples of (1→3)-β-D-glucan, and EIA analysis to measure the dust samples (Rylander, 1999). ELISA assay has not yet been used in practical analysis of environmental (1→3)-β-D-glucan. Among these three methods, the LAL test has the lowest detection limit and highest sensitivity, while EIA and ELISA assay have higher specificity and lower analytical cost (Dillon *et al.,* 1999). For analysing individual groups of microbes, the ELISA assay has the highest specificity for fungi-related (1→3)-β-D-glucan. At present, only review papers have compared the LAL test and EIA methods in measuring (1→3)-β-D-glucan. No studies have comprehensively and concurrently compared the above three methods, and the issue is critical and imperative.

The Distribution of (1→3)-β-D-glucan

The (1→3)-β-D-glucan concentrations in indoor environments are found to vary with mould growth conditions inside, as well as with the types of samples collected (Rylander, 1997; Rylander *et al.,* 1998; Douwes *et al.,* 2000; Gehring *et al.,* 2001). In general, dust samples have higher levels of (1→3)-β-D-glucan than airborne samples. The concentration ranged from 182 to 6540 μg/g dust, and from 0 to 27.4 ng/m^3 (Rylander *et al.,* 1998; Douwes *et al.,* 2000; Gehring *et al.,* 2001). Research in Sweden investigated the concentration of (1→3)-β-D-glucan in different condition of mould growth in schools. The averaged concentration was 15.3 ng/m^3 in schools with serious contamination, and 2.9 ng/m^3 in control schools (Rylander *et al.,* 1998). (1→3)-β-D-glucan concentrations in dust samples were also associated with building types and cleaning habits. Higher levels of (1→3)-β-D-glucan were found in concrete slab houses than in two family houses and lower levels in homes of high cleaning frequency (Gehring *et al.* 2001).

SUMMARY

A vast amount of knowledge has already been built in understanding the structure, health effects, sampling methodology and environmental exposures of (1→3)-β-D-glucan. However, no final conclusion has been adequately established in any of the topics, except better comprehension of the overall biological structure. More background data should be colleted, hopefully with relatively standardized methodology, from other parts of the world to generate a more complete picture for their environmental reservoirs. The underlying mechanism for each variation associated with either the concentration distribution or health effects of (1→3)-β-D-glucan should be given greater attention and should be a top research priority in future studies. Confronting the issues above is merely a fundamental effort required to construct an effective strategy for reduction or elimination of such a recognized environmental hazard.

REFERENCES

Dillon, H.K., Miller, J.D., Sorenson, W.G. *et al.* (1999). Review of methods applicable to the assessment of mold exposure to children. *Environmental Health Perspectives* **107** (3), 473–480.

Douwes, J., Doekes, G., Montijn, R. *et al.* (1996). Measurement of beta (1→3)-glucans in occupational and home environments with an inhibition enzyme immunoassay. *Applied & Environmental Microbiology* **62** (9), 3176–3182.

Douwes, J., Zuidhof, A., Doekes, G. *et al.* (2000). (1→3)-beta-D-glucan and endotoxin in house dust and peak flow variability in children. *American Journal of Respiratory & Critical Care Medicine* **162**(4 Pt 1), 1348–1354.

Fogelmark, B., Thorn, J. and Rylander, R. (2001). Inhalation of (1→3)-beta-D-glucan causes airway eosinophilia. *Mediators of Inflammation* **10** (1), 13–19.

Gehring, U., Douwes, J., Doekes, G. *et al.* (2001). Beta(1→3)-glucan in house dust of German homes: housing characteristics, occupant behavior, and relations with endotoxins, allergens, and molds. *Environmental Health Perspectives* **109** (2), 139–144.

Kilpelainen, M., Terho, E.O., Helenius, H. *et al.* (2001). Home dampness, current allergic diseases, and respiratory infections among young adults. *Thorax* **56** (6), 462–467.

Ljungman, A.D., Leanderson, P. and Tasgesson, C. (1998). (1→3)-beta-D-glucan stimulates nitric oxide generation and cytokine mRNA expression in macrophages. *Environmental Toxicology and Pharmacology* **5**, 273–281.

Milton, D.K., Alwis, K.U., Fisette, L. *et al.* (2001). Enzyme-linked immunosorbent assay specific for (1→6) branched, (1→3)-beta-D-glucan detection in environmental samples. *Applied & Environmental Microbiology* **67** (12), 5420–5424.

Ormstad, H., Groeng, E.C., Lovik, M. *et al.* (2000). The fungal cell wall component beta-1,3-glucan has an adjuvant effect on the allergic response to ovalbumin in mice. *Journal of Toxicology & Environmental Health Part A* **61** (1), 55–67.

Rylander, R. (1997). Airborne (1→3)-beta-D-glucan and airway disease in a day-care center before and after renovation. *Archives of Environmental Health* **52** (4), 281–285.

Rylander, R. (1997). Investigations of the relationship between disease and airborne (1→3)-beta-D-glucan in buildings. *Mediators of Inflammation* **6**, 275–277.

Rylander, R. (1999). Indoor air-related effects and airborne (1→3)-beta-D-glucan. *Environmental Health Perspectives* **107** (3), 501–503.

Rylander, R. and Holt, P. G. (1998). (1→3)-beta-D-glucan and endotoxin modulate immune response to inhaled allergen. *Mediators of Inflammation* **7** (2), 105–110.

Rylander, R. and Lin, R. H. (2000). (1→3)-beta-D-glucan—relationship to indoor air-related symptoms, allergy and asthma. *Toxicology* **152** (1–3), 47–52.

Rylander, R. and Megevand, Y. (2000). Environmental risk factors for respiratory infections. *Archives of Environmental Health* **55** (5), 300–303.

Rylander, R., Norrhall, M., Engdahl, U. *et al.* (1998). Airways inflammation, atopy, and (1→3)-beta-D-glucan exposures in two schools. *American Journal of Respiratory & Critical Care Medicine* **158** (5 Pt 1), 1685–1687.

Savilahti, R., Uitti, J., Roto, P. *et al.* (2001). Increased prevalence of atopy among children exposed to mold in a school building. *Allergy* **56** (2), 175–179.

Sigsgaard, T., Bonefeld-Jorgensen, E.C., Kjaergaard, S.K. *et al.* (2000). Cytokine release from the nasal mucosa and whole blood after experimental exposures to organic dusts. *European Respiratory Journal* **16** (1), 140–145.

Sjostrand, M. and Rylander, R. (1997). Pulmonary cell infiltration after chronic exposure to (1→3)-beta-D-glucan and cigarette smoke. *Inflammation Research* **46** (3), 93–97.

Tamura, H., Arimoto, Y., Tanaka, S. *et al.* (1994). Automated kinetic assay for endotoxin and (1→3)-beta-D-glucan in human blood. *Clinica Chimica Acta* **226** (1), 109–112.

Thorn, J., Beijer, L. and Rylander, R. (1998). Airways inflammation and glucan exposure among household waste collectors. *American Journal of Industrial Medicine* **33** (5), 463–470.

Thorn, J. and Rylander, R. (1998). Airways inflammation and glucan in a rowhouse area. *American Journal of Respiratory & Critical Care Medicine* **157** (6 Pt 1), 1798–1803.

Wan, G.H. and Li, C.S. (1999). Dampness and airway inflammation and systemic symptoms in office building workers. *Archives of Environmental Health* **54** (1), 58–63.

Wan, G.H. and Li, C.S. (1999). Indoor endotoxin and glucan in association with airway inflammation and systemic symptoms. *Archives of Environmental Health* **54** (3), 172–179.

Wan, G. H., Li, C. S., Guo, S. P. *et al.* (1999). An airbone mold-derived product, beta-1,3-D-glucan, potentiates airway allergic responses. *European Journal of Immunology* **29** (8), 2491–2497.