Safety & Toxicology Research

Yeast Beta 1,3 / 1,6 Glucan	
Citation	**Abstract**
Nicolosi R, Bell SJ, Bistrian BR, Greenberg I, Forse RA, Blackburn GL. **Plasma lipid changes after supplementation with beta-glucan fiber from yeast**. Am J Clin Nutr. 1999 Aug;70(2):208-12. PMID: 10426696 [PubMed - indexed for MEDLINE]	**BACKGROUND**: Dietary fiber has been shown to improve blood lipids. OBJECTIVE: The purpose of this study was to evaluate the effect on serum lipids of a yeast-derived beta-glucan fiber in 15 free-living, obese, hypercholesterolemic men. **DESIGN**: After a 3-wk period in which subjects ate their usual diet, 15 g fiber/d was added to the diet for 8 wk and then stopped for 4 wk. Plasma lipids were measured weekly during baseline and at week 7 and 8 of fiber consumption, and again at week 12. **RESULTS**: Compared with baseline, fiber consumption significantly reduced plasma total cholesterol (by 8% at week 7 and 6% at week 8; $P < 0.05$ using Bonferroni correction); week 12 values did not differ from baseline. No significant differences were noted between baseline LDL cholesterol and values at weeks 7, 8, or 12 when comparing individual groups by using Bonferroni correction, even though the overall one-way analysis of variance with repeated measures was highly significant ($P < 0.001$). LDL-cholesterol concentrations did decline by 8% at week 8 compared with baseline. There was a significant effect of diet on plasma HDL-cholesterol concentrations ($P < 0.005$ by one-way ANOVA with repeated measures). However, a group difference was observed only between baseline and week 12 (16% increase; $P < 0.05$ by Bonferroni correction). Triacylglycerol concentrations did not change. **CONCLUSIONS**: The yeast-derived beta-glucan fiber significantly lowered total cholesterol concentrations and was well tolerated; HDL-cholesterol concentrations rose, but only 4 wk after the fiber was stopped.
Ikeda Y, Sunakawa T, Okamoto K, Hirayama A. **Toxicological studies on sophorolipid derivatives. (II). Subacute toxicity study of polyoxypropylene (12) [2'-0-beta-D-glucopyranosyl-beta-D-glucopyranosyl) oxy-] fatty acid ester-** J Toxicol Sci. 1986 Aug;11(3):213-24. Japanese. PMID: 3795299 [PubMed - indexed for MEDLINE]	Five groups of 12 male and 12 female rats each were fed diets containing 0, 0.06, 0.25, 1.00 and 4.00% PSL for a period of one month. Food consumption of PSL-fed groups did not differ from that of control. Urinalysis and autopsy findings were within normal in every group of rats treated. With 4.00% in the diet, body weight gain was significantly retarded and water consumption was increased, and soft stool occurred. In the hematological examination, decrease of red blood cells and increase of white blood cells were observed at the levels of 1.00 and 4.00% PSL. Changes of white blood cell differentials were also seen at the same levels. Serum Na+ concentration was slightly decreased at the 0.25, 1.00, 4.00% levels and serum glucose was also decreased at the 1.00, 4.00% levels, but the values were within the normal limits. Significant increase of relative liver weight, without histopathological changes, was observed at the 4.00% level. Histopathological examination revealed slight erosion, necrosis or intestinitis in small intestine, at the levels of 0.25, 1.00, 4.00% PSL. It was considered that these findings were attributed to the irritation potential of PSL or its metabolite. These results indicated that the non-effect level was 0.06% (53 mg/kg/day) and the level causing no toxicological effect was 0.25% (208 mg/kg/day), but no deleterious effects was observed in the levels greater than 0.25%.

Safety & Toxicology Research

Williams DL, Sherwood ER, Browder IW, McNamee RB, Jones EL, Di Luzio NR. **Pre-clinical safety evaluation of soluble glucan.** Int J Immunopharmacol. 1988;10(4):405-14. PMID: 3262594 [PubMed - indexed for MEDLINE]	Soluble glucan, a beta-1,3-linked glucopyranose biological response modifier, is effective in the therapy of experimental neoplasia, infectious diseases and immune suppression. Currently, soluble glucan is undergoing phase I clinical trials. The present study describes the pre-clinical safety evaluation of soluble glucan in mice, rats, guinea pigs and rabbits. ICR/HSD mice and Harlan Sprague-Dawley rats received a single i.v. injection of soluble glucan in doses ranging from 40 to 1000 mg/kg. Soluble glucan administration did not induce mortality, appearance or behavioral changes in mice or rats. In subsequent studies, mice and guinea pigs were injected i.p. with glucan (250 mg/kg) for 7 consecutive days. ICR/HSD mice gained weight at the same rate as the saline-treated controls. In contrast, guinea pigs receiving i.p. injections of soluble glucan showed a significant (P less than 0.05) 10-13% decrease in weight gain over the 7 day period. No other toxicologic, behavioral or appearance changes were noted. To examine chronic toxicity, soluble glucan was administered twice weekly for a period of 30 or 60 days to ICR/HSD mice in the dose of 40, 200 or 1000 mg/kg. No deaths were observed in any group. Chronic glucan administration did not alter body weight, liver, lung or kidney weight. However, a significant splenomegaly was observed in both the 30 and 60 day study. Histopathologic examination showed no tissue alterations at 40 or 200 mg/kg. However, at 1000 mg/kg a mononuclear infiltrate was observed in the liver. Pyrogenicity testing, employing New Zealand white rabbits, revealed that parenteral glucan administration (5 mg/kg) did not significantly alter body temperature. These data indicate that the systemic administration of soluble glucan, over a wide dose range, does not induce mortality or significant toxicity, an important consideration in preparing soluble glucan for parenteral administration to human populations.
Ishii H, Usami S, Fujimoto T, Moriyuki H, Hashimoto S, Ichimura M. **Subacute toxicity study of lentinan in rats. 5-week intravenous treatment (author's transl)** J Toxicol Sci. 1980 Dec;5 Suppl:11-31. Japanese. PMID: 7265322 [PubMed - indexed for MEDLINE]	Male and female JCL : SD rats were treated intravenously with lentinan in 5% mannitol solution at dose levels of 0, 0.03, 3.0 and 30.0 mg/kg/day for 5 weeks. Rats receiving 0.3, 3.0 and 30.0 mg/kg/day showed reddening in ear, tail and scrotum and edema in legs and scrotum after day 3 of treatment. Males receiving 30.0 mg/kg/day gained less body weight than control. Occult blood was found in the urine of rats receiving 30.0 mg/kg/day. With regard to haematology, rats from the treatment groups had low mean values relating to red blood cell count, packed cell volume and haemoglobin, while high white blood cell count were recorded for these rats. Biochemical examinations revealed decreases in albumin level and A/G ratio and increases in beta-globulin and gamma-globulin levels for rats from the treatment groups. Slightly high values of BUN were showed for rats receiving 30.0 mg/kg/day. Organ weight analysis showed dose-dependent increase in the spleen, liver and adrenal. Histopathological changes attributable to treatment included (1) changes in reticuloendothelial system such as proliferation of reticular cells and micronodule of epithelioid cells in the spleen, liver and lymph nodes; (2) arteritis in many organs especially notable in epididymis, intestines and mesentery; (3) haemorrhagic changes in lung, intestines and urinary bladder and secondary changes such as increased chronic nephropathy, hypospermatogenesis, spermatic granuloma in epididymis and granulomatous inflammation in ear, tail and scrotum. The maxim safe dose was estimated to be smaller than 0.03 mg/kg/day for males and 0.03 mg/kg/day for females in the present study.

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Yeast	
Citation	**Abstract**
Ikeda Y, Sunakawa T, Okamoto K, Hirayama A. **Toxicological studies on sophorolipid derivatives. (II). Subacute toxicity study of polyoxypropylene (12) [2'-0-beta-D-glucopyranosyl-beta-D-glucopyranosyl) oxy-] fatty acid ester-** J Toxicol Sci. 1986 Aug;11(3):213-24. Japanese. PMID: 3795299 [PubMed - indexed for MEDLINE]	Five groups of 12 male and 12 female rats each were fed diets containing 0, 0.06, 0.25, 1.00 and 4.00% PSL for a period of one month. Food consumption of PSL-fed groups did not differ from that of control. Urinalysis and autopsy findings were within normal in every group of rats treated. With 4.00% in the diet, body weight gain was significantly retarded and water consumption was increased, and soft stool occurred. In the hematological examination, decrease of red blood cells and increase of white blood cells were observed at the levels of 1.00 and 4.00% PSL. Changes of white blood cell differentials were also seen at the same levels. Serum Na+ concentration was slightly decreased at the 0.25, 1.00, 4.00% levels and serum glucose was also decreased at the 1.00, 4.00% levels, but the values were within the normal limits. Significant increase of relative liver weight, without histopathological changes, was observed at the 4.00% level. Histopathological examination revealed slight erosion, necrosis or intestinitis in small intestine, at the levels of 0.25, 1.00, 4.00% PSL. It was considered that these findings were attributed to the irritation potential of PSL or its metabolite. These results indicated that the non-effect level was 0.06% (53 mg/kg/day) and the level causing no toxicological effect was 0.25% (208 mg/kg/day), but no deleterious effects was observed in the levels greater than 0.25%.
Williams DL, Sherwood ER, Browder IW, McNamee RB, Jones EL, Di Luzio NR. **Pre-clinical safety evaluation of soluble glucan.** Int J Immunopharmacol. 1988;10(4):405-14. PMID: 3262594 [PubMed - indexed for MEDLINE]	Soluble glucan, a beta-1,3-linked glucopyranose biological response modifier, is effective in the therapy of experimental neoplasia, infectious diseases and immune suppression. Currently, soluble glucan is undergoing phase I clinical trials. The present study describes the pre-clinical safety evaluation of soluble glucan in mice, rats, guinea pigs and rabbits. ICR/HSD mice and Harlan Sprague-Dawley rats received a single i.v. injection of soluble glucan in doses ranging from 40 to 1000 mg/kg. Soluble glucan administration did not induce mortality, appearance or behavioral changes in mice or rats. In subsequent studies, mice and guinea pigs were injected i.p. with glucan (250 mg/kg) for 7 consecutive days. ICR/HSD mice gained weight at the same rate as the saline-treated controls. In contrast, guinea pigs receiving i.p. injections of soluble glucan showed a significant (P less than 0.05) 10-13% decrease in weight gain over the 7 day period. No other toxicologic, behavioral or appearance changes were noted. To examine chronic toxicity, soluble glucan was administered twice weekly for a period of 30 or 60 days to ICR/HSD mice in the dose of 40, 200 or 1000 mg/kg. No deaths were observed in any group. Chronic glucan administration did not alter body weight, liver, lung or kidney weight. However, a significant splenomegaly was observed in both the 30 and 60 day study. Histopathologic examination showed no tissue alterations at 40 or 200 mg/kg. However, at 1000 mg/kg a mononuclear infiltrate was observed in the liver. Pyrogenicity testing, employing New Zealand white rabbits, revealed that parenteral glucan administration (5 mg/kg) did not significantly alter body temperature. These data indicate that the systemic administration of soluble glucan, over a wide dose range, does not induce mortality or significant toxicity, an important consideration in preparing soluble glucan for parenteral administration to human populations.
Ishii H, Usami S, Fujimoto T, Moriyuki H, Hashimoto S, Ichimura M. **Subacute toxicity study of lentinan in rats. 5-week intravenous treatment (author's transl)** J Toxicol Sci. 1980 Dec;5 Suppl:11-31. Japanese. PMID: 7265322 [PubMed - indexed for MEDLINE]	Male and female JCL : SD rats were treated intravenously with lentinan in 5% mannitol solution at dose levels of 0, 0.03, 3.0 and 30.0 mg/kg/day for 5 weeks. Rats receiving 0.3, 3.0 and 30.0 mg/kg/day showed reddening in ear, tail and scrotum and edema in legs and scrotum after day 3 of treatment. Males receiving 30.0 mg/kg/day gained less body weight than control. Occult blood was found in the urine of rats receiving 30.0 mg/kg/day. With regard to haematology, rats from the treatment groups had low mean values relating to red blood cell count, packed cell volume and haemoglobin, while high white blood cell count were recorded for these rats. Biochemical examinations revealed decreases in albumin level and A/G ratio and increases in beta-globulin and gamma-globulin levels for rats from the treatment groups. Slightly high values of BUN were showed for rats receiving 30.0 mg/kg/day. Organ weight analysis showed dose-dependent increase in the spleen, liver and adrenal. Histopathological changes attributable to treatment included (1) changes in reticuloendothelial system such as proliferation of reticular cells and micronodule of epithelioid cells in the spleen, liver and lymph nodes; (2) arteritis in many organs especially notable in epididymis, intestines and mesentery; (3) haemorrhagic changes in lung, intestines and urinary bladder and secondary changes such as increased chronic nephropathy, hypospermatogenesis, spermatic granuloma in epididymis and granulomatous inflammation in ear, tail and scrotum. The maxim safe dose was estimated to be smaller than 0.03 mg/kg/day for males and 0.03 mg/kg/day for females in the present study.

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Fungus	
Citation	**Abstract**
Takahashi H, Ohno N, Adachi Y, Yadomae T. **Association of immunological disorders in lethal side effect of NSAIDs on beta-glucan-administered mice.** FEMS Immunol Med Microbiol. 2001 Jul;31(1):1-14. PMID: 11476975 [PubMed - indexed for MEDLINE]	(1-->3)-beta-D-Glucan (beta-glucan) is a biological response modifier that regulates host immune response. We have found that the combination of a beta-glucan and a non-steroidal anti-inflammatory drug (NSAID), indomethacin (IND), induced lethal toxicity in mice [Yoshioka et al. (1998) FEMS Immunol. Med. Microbiol., 21, 171-179]. This study was undertaken to analyze the mechanism of the lethal side effect. Combination of a beta-glucan and IND increased the number of leukocytes, especially macrophages and neutrophils, in various organs and these cells were activated. The activated state of these cells was supported by the enhanced production of interferon-gamma in the presence of IND in vitro culture of the peritoneal exudate cells. Intestinal bacterial flora was translocated into the peritoneal cavity in these mice to cause peritonitis. Comparing the toxicity of various NSAIDs, nabumetone, a partially cyclooxygenase-2-selective NSAID with weaker toxicity to the gastrointestinal tract, did not exhibit a lethal side effect. These facts strongly suggested that gastrointestinal damage by NSAIDs was more severe in beta-glucan-administered mice, resulting in peritonitis by enteric bacteria and leading to death.
Yoshioka S, Ohno N, Miura T, Adachi Y, Yadomae T. **Immunotoxicity of soluble beta-glucans induced by indomethacin treatment.** FEMS Immunol Med Microbiol. 1998 Jul;21(3):171-9. PMID: 9718206 [PubMed - indexed for MEDLINE]	(1 --> 3)-Beta-D-Glucan (beta-glucan) is a biological response modifier that regulates host immune response. However, the side effects of this drug have not been extensively examined. In this study, we found that the combination of a beta-glucan and a nonsteroidal anti-inflammatory drug, indomethacin, induced lethal toxicity in mice. Lethal toxicity of orally administered indomethacin (multiple administration to ICR mice; once a day for 2 weeks) was 0/8 (2.5 mg kg(-1)) and 5/8 (5 mg kg(-1)) (death/total) over 2 weeks. The toxicity was enhanced to 3/8 and 8/8 in mice treated with a clinical beta-glucan preparation, sonifilan (250 microg/mouse, single i.p. administration on day 0). A similar effect was observed for other beta-glucans, including SSG, grifolan, zymosan A and zymocel. Enhanced lethal toxicity resulted from a single p.o. administration of indomethacin on day 5 to day 9 after multiple beta-glucans administration. Interferon-gamma, interleukin-6 and colony stimulating factor concentrations in sera of indomethacin/beta-glucan-treated mice were significantly elevated. These results strongly suggest that indomethacin/beta-glucan treatment induces lethality in mice by maladjusting the cytokine network.
Iwamoto N, Yoshioka T, Nitta K, Ito K. **Glomerular endothelial injury associated with free radical production induced by a fungal cell wall component, (1-->3) beta-D glucan.** Life Sci. 1998;62(3):247-55. PMID: 9488103 [PubMed - indexed for MEDLINE]	Clinical evidence suggests that microangiopathy may be induced by fungal infection. The present study evaluated the toxic effect of (1-->3) beta-D glucan, a major component of fungal cell wall, on cultured transformed glomerular endothelial cells (TF-GEN). When TF-GEN were exposed to increasing concentrations of (1-->3) beta-D glucan (beta-DG; 115 to 430 pg/ml) for 1 to 3 hours, concentration- and time-dependent increases in hydroxyl radical production were demonstrated by electron paramagnetic resonance spectrometry using 5, 5-dimethyl-1-pyrrolyne-N-oxide as a spin trap agent. The amount of radicals induced by 230 or 430 pg/ml beta-DG was comparable to that induced by E. coli LPS (1 or 10 microg/ml). The beta-DG-induced free radical production was associated with a subsequent increase in LDH release from TF-GEN. When TF-GEN pretreated with U78517F (0.1 or 1.0 microM), a lipophilic antioxidant, were stimulated with LPS (1 or 10 microg/ml) or beta-DG (230 pg/ml) for 3 hours, free radical production by TF-GEN was significantly reduced in cells pretreated with the higher concentration of U78517F. Thus, fungal (1-->3) beta-D glucan induces glomerular endothelial injury by stimulating cellular free radical production. Such a mechanism may underlie microangiopathy in systemic fungal infections

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Fungus	
Citation	**Abstract**
Kata H, Inoue M, Mukai S, Kawahito Y, Yoshida T, Asai K, Kimura S, Hashiramoto A, Yamamura Y, Sano H, Sugino S, Kondo M. **Morphological study of cytotoxicity produced by PSK-induced polymorphonuclear leukocytes (PMNs) and Nocardia rubra cell wall skeleton.** Biotherapy. 1996;9(4):229-39. PMID: 9012542 [PubMed - indexed for MEDLINE]	The morphologic changes in PMNs induced by an i.p. injection of PSK, a polysaccharide from the mycelia of Coriolus versicolor, and tumor cells undergoing cell death, were evaluated by immunohistochemical staining and electron microscopy. Male C3H/He mice, 8-10 -weeks old, received an i.p. injection of 125 mg/kg of PSK. Their PMNs were obtained 6 h after the PSK injection by peritoneal lavage. N-CWS (Nocardia rubra cell wall skeleton) was added at the start of the chromium release assay using the MM46 mammary carcinoma cell line, which is syngeneic to C3H/He mice, as target cells. During the cytotoxic assay, the cells were fixed at various time points. The MM46 cells expressed ICAM-1 while the PMNs expressed both ICAM-1 and LFA-1 as determined by immunohistochemical staining and immunoelectron microscopy using anti-ICAM-1 and anti-LFA-1 antibodies. PMNs with ruffle-like microvilli adhered to the MM46 tumor cells 30 min after the addition of N-CWS. Immunoelectron microscopic findings suggested that the adhesion molecules were LFA-1 on the PMNs and ICAM-1 on the MM46 tumor cells, but cell fusion between the PMNs and tumor cells was not observed. The MM46 tumor cells gradually lost their microvilli, which showed cell damage, and died 6-7 h after the addition of the N-CWS. This time course of tumor cell death is compatible with the results of the cytotoxic assay. Pretreatment of PMNs by anti-LFA-1 antibody suppressed 1% lysis of MM46 tumor cells from 90% to 10% ($p < 0.01$). These data suggest that adhesion molecule on the surface of PMNs such as LFA-1 might play an important role on signal transduction of these PMNs cytotoxic function in this experimental system.
Sakurai T, Ohno N, Yadomae T. **Changes in immune mediators in mouse lung produced by administration of soluble (1-->3)-beta-D-glucan.** Biol Pharm Bull. 1994 May;17(5):617-22. PMID: 7920419 [PubMed - indexed for MEDLINE]	In this study, we showed that systemic administration of SSG, a highly branched soluble (1-->3)-beta-D-glucan obtained from Sclerotinia sclerotiorum, induced immunological changes in the alveolar space of mice in vivo, assessed by analysing some immune mediators in bronchoalveolar lavage (BAL) fluid. A single i.v. administration of SSG (250 micrograms/mouse) induced a rapid but transient leakage of the serum components, IgG and fibronectin, into the alveolar space. This was apparent 12 h post-administration and reached a peak on day 2. Similar kinetic changes were found for lysosomal enzyme activities and interferon gamma (IFN gamma) concentrations in BAL which are markers of activated alveolar macrophages (AMs) or pulmonary T cells. BAL prepared from SSG-treated mice stimulated lysosomal enzyme release from AMs in vitro. However, SSG did not provoke the chronic accumulation of serum proteins in alveoli and did not induce the release of detectable amounts of nitric oxide and the inflammatory cytokines, IL-1, IL-6 and TNF alpha, into BAL. However, their mRNAs were detected in lung tissue using the reverse-transcriptase polymerase chain reaction (RT-PCR) technique. Similar results were observed for multiple i.v. administration (250 micrograms, once a day for 10 consecutive days), and there were a little differences between single and multiple administration. In summary, systemic administration of SSG induces immune responses, including activation of AMs and lymphocytes, but does not provoke chronic inflammation in the alveolar space when administered either as single or multiple doses. This finding is very important for the clinical application of SSG in immunocompromised hosts as a biological response modifier (BRM) without toxic-side effects on lung tissue.
Chesterman H, Heywood R, Allen TR, Street AE, Edmondson NA, Prentice DE. **The intravenous toxicity of lentinan to the beagle dog.** Toxicol Lett. 1981 Sep;9(1):87-90. PMID: 7302979 [PubMed - indexed for MEDLINE]	The i.v administration of lentinan to the Beagle dog induced changes in the cytoplasm of macrophagic cells in the liver, spleen, kidney, lungs, lymph nodes, small intestine. Electron-lucent or filamentous inclusions were demonstrated in the liver, kidney and spleen. A dose level of 0.5 mg/kg/day was without adverse effect.

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Fungus	
Citation	**Abstract**
Sortwell RJ, Dawe S, Allen DG, Street AE, Heywood R, Edmondson NA, Gopinath C. **Chronic intravenous administration of lentinan to the rhesus monkey.** Toxicol Lett. 1981 Sep;9(1):81-5. PMID: 7302978 [PubMed - indexed for MEDLINE]	The prolonged effects of overdosage with lentinan in the rhesus monkey are associated with foam cell reactions in lung, liver, kidney, spleen, lymph nodes and bone marrow and with varying degrees of vasculitis and associated reactions. A dose level of 0.5 mg/kg/day was without adverse effect.
Shimazu H, Takeda K, Onodera C, Makita I, Hashi T, Yamazoe T, Kokuba Y, Tanigawa H, Ohkuma S, Shinpo K, Takeuchi M. **Intravenous chronic toxicity of lentinan in rats: 6-month treatment and 3-month recovery (author's transl)** J Toxicol Sci. 1980 Dec;5 Suppl:33-57. Japanese. PMID: 7265323 [PubMed - indexed for MEDLINE]	Chronic toxicity of lentinan was studied in male and female JCL : SD rats. Lentinan was given intravenously into tail vein. Dosage levels employed were 0 (5% mannitol), 0.01, 0.1, 1 (with or without dextran), and 10 mg/kg/day for 6 months in a volume of 1 ml/100 g body weight. After 6 months, the treatment was discontinued and a recovery study was performed for 3 months. Rats receiving 10 mg/kg had redness and necrosis of the tail, the treatment was stopped at week 5, and the rats were sacrificed. Rats receiving 1 mg/kg showed redness of the ear, tail, and scrotum, which was remarkable in the 2nd and 3rd months. Body weight gains were not adversely affected. Laboratory examinations revealed an increase in leukocyte count, decreases in differential eosinophil count and platelet count, and an increase in serum beta-globulin level in drug-treated rats. At autopsy after 6 months, rats from the drug-treated groups had pulmonary hemorrhage and enlargements of the spleen and mesenteric lymph nodes. Histologic changes attributable to treatment included (1) activation of reticulo-endothelial system such as small epithelioid cell nodule in the liver, spleen, and mesenteric lymph nodes, and mobilization of Kupffer cells; (2) arteritis in various organs, especially notable in the spleen, testis, and epididymis ; (3) hemorrhage in the lung; and (4) hypospermatogenesis. All these changes described above had a propensity to recover. The maximum no effect level was estimated to be less than 0.01 mg/kg in the present study in male and female rats.
Mandryk J, Alwis KU, Hocking AD. **Work-related symptoms and dose-response relationships for personal exposures and pulmonary function among woodworkers.** Am J Ind Med. 1999 May;35(5):481-90. PMID: 10212701 [PubMed - indexed for MEDLINE]	BACKGROUND: Four sawmills, a wood chipping mill, and five joineries in New South Wales, Australia, were studied for the effects of personal exposure to wood dust, endotoxins. (1-->3)-beta-D-glucans, Gram-negative bacteria, and fungi on lung function among woodworkers. METHODS: Personal inhalable and respirable dust sampling was carried out. The lung function tests of workers were conducted before and after a workshift. RESULTS: The mean percentage cross-shift decrease in lung function was markedly high for woodworkers compared with the controls. Dose-response relationships among personal exposures and percentage cross-shift decrease in lung function and percentage predicted lung function were more pronounced among joinery workers compared with sawmill and chip mill workers. Woodworkers had markedly high prevalence of regular cough, phlegm, and chronic bronchitis compared with controls. Significant associations were found between percentage cross-shift decrease in FVC and regular phlegm and blocked nose among sawmill and chip mill workers. Both joinery workers and sawmill and chip mill workers showed significant relationships between percentage predicted lung function (FVC, FEV1, FEV1/FVC, FEF25-75%) and respiratory symptoms. CONCLUSIONS: Wood dust and biohazards associated with wood dust are potential health hazards and should be controlled.

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Fungus	
Citation	**Abstract**
Sjostrand M, Rylander R. **Pulmonary cell infiltration after chronic exposure to (1-->3)-beta-D-glucan and cigarette smoke.** Inflamm Res. 1997 Mar;46(3):93-7. PMID: 9098721 [PubMed - indexed for MEDLINE]	OBJECTIVE AND DESIGN: To evaluate the effect of a microbial cell wall component--(1-->3)-beta-D-glucan--on the inflammatory effect induced by cigarette smoke in a subchronic exposure situation. MATERIAL: Groups of guinea-pigs were exposed 5 days/week to cigarette smoke, an aerosol of (1-->3)-beta-D-glucan, or to both. METHODS: The numbers of different inflammatory cells were studied in histological sections, enzyme digested lung tissue and in lung lavage. Cell enzyme production was measured. RESULTS: Exposure to (1-->3)-beta-D-glucan or cigarette smoke caused only minor alterations in inflammatory cells. Given together they caused an increase in cellularity in the tissue with significantly increased numbers of macrophages, lymphocytes, neutrophils and eosinophils. There was also an increase in subepithelial eosinophils. Lung lavage cell enzyme production was slightly lower in the combined exposure group. CONCLUSION: The results demonstrate that (1-->3)-beta-D-glucan synergistically increases the inflammation induced by cigarette smoke. The mechanism may be a downregulation of the macrophage control of inflammatory cell migration into the lung tissue.
Fogelmark B, Sjostrand M, Rylander R. **Pulmonary inflammation induced by repeated inhalations of beta(1,3)-D-glucan and endotoxin.** Int J Exp Pathol. 1994 Apr;75(2):85-90. PMID: 8199009 [PubMed - indexed for MEDLINE]	In an animal model of hypersensitivity pneumonitis (HP) guinea-pigs were exposed for 5 weeks to an aerosol of bacterial endotoxin, beta(1,3)-D-glucan (curdlan) or a combination. Exposure to endotoxin or curdlan showed only small changes in inflammatory cells in airways or the lung wall, histologically or in terms of enzyme secretion from alveolar macrophages. When the two agents were given together, a histology resembling HP was seen with alveolar infiltrates and early granulomas. Inflammatory cells in airways were increased and enzyme production of macrophages was changed, suggesting an effect of curdlan on the inflammatory regulating capacity of airway macrophages. The results suggest that interference with macrophage function and inflammation are important components in the development of HP.
Fogelmark B, Goto H, Yuasa K, Marchat B, Rylander R. **Acute pulmonary toxicity of inhaled beta-1,3-glucan and endotoxin.** Agents Actions. 1992 Jan;35(1-2):50-6. PMID: 1509978 [PubMed - indexed for MEDLINE]	The number of inflammatory cells was studied in lung walls and airways after inhalation of endotoxin or beta-1,3-glucan. In the water unsoluble form, beta-1,3-glucan caused a delayed response in terms of a decrease in macrophages and lymphocytes in the lung wall, 1 to 7 days after exposure but no invasion of neutrophils into the airways. When solubilized in 0.02 N NaOH, the cell response was the same as that observed after exposure to endotoxin.
Donham KJ, Zejda JE. **Lung dysfunction in animal confinement workers--chairman's report to the Scientific Committee of the Third International Symposium: issues in health, safety and agriculture, held in Saskatoon, Saskatchewan, Canada, May 10-15, 1992**. Pol J Occup Med Environ Health. 1992;5(3):277-9. PMID: 1362681 [PubMed - indexed for MEDLINE]	The session traced the course of health hazards in livestock confinement from anticipation of an emerging health hazard in 1974 to its full recognition as a significant health hazard in 1992. The session documented the major health hazards including hydrogen sulfide toxicity, bronchitis, non-allergic asthma, organic dust toxic syndrome, and mucus membrane irritation. In regard to exposures, bioaerosols seem to be the most significant hazard, with endotoxin evident as at least one of the major specific atiologic agents. Other agents were suspected, as newly recognized agents, specifically 1,3 beta-glucan. Previous epidemiological studies have revealed mild decrements in pulmonary function, however symptoms have always been excessively prevalent relative to controls. Recent results of a longitudinal observation showed a 12% drop out of workers with profound decrement in pulmonary function. In summary, the health hazard of livestock confinement workers is now well substantiated in North America and Europe and further work regarding prevention is highly indicated.

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Fungus	
Citation	**Abstract**
Rylander R, Lin RH. **(1-->3)-beta-D-glucan - relationship to indoor air-related symptoms, allergy and asthma.** Toxicology. 2000 Nov 2;152(1-3):47-52. Review. PMID: 11090939 [PubMed - indexed for MEDLINE]	(1-->3)-beta-D-glucan is a polyglucose structure in the cell wall of moulds, some bacteria and plants. Due to its unique (1-->3)-beta linkage it binds to specific receptors on phagocytosing cells and induces changes in their metabolism. Under realistic environmental concentrations, available data suggest that these changes express themselves as alterations of the defense mechanisms to other agents. Inhalation of (1-->3)-beta-D-glucan in humans causes symptoms from the upper respiratory tract and induction of cytokines in blood monocytes. (1-->3)-beta-D-glucan can be used as a marker of mould biomass in field studies. Relationships between the amount of (1-->3)-beta-D-glucan and the extent of symptoms as well as lung function changes and inflammatory markers have been described. In view of the mechanisms involved in the normal development of the immune system, children seem to be a particular group at risk due to (1-->3)-beta-D-glucan exposure.
Gordon M, Bihari B, Goosby E, Gorter R, Greco M, Guralnik M, Mimura T, Rudinicki V, Wong R, Kaneko Y. **A placebo-controlled trial of the immune modulator, lentinan, in HIV-positive patients: a phase I/II trial.** J Med. 1998;29(5-6):305-30. PMID: 10503166 [PubMed - indexed for MEDLINE]	Lentinan is a beta 1-->3 glucan isolated from Lentinus edodes (Shiitake mushroom) which has immune modulating properties. We have conducted two phase I/II placebo-controlled trials on a total of 98 patients. In one study at the San Francisco General Hospital (SFGH), ten patients each were administered 2, 5, or 10 mg of lentinan or placebo i.v. once a week for eight weeks. In the second study at the Community Research Initiative in New York (CRI), two groups of 20 patients each were administered 1 or 5 mg of lentinan i.v. twice a week for 12 weeks, and ten patients were administered placebo (vehicle containing mannitolplus dextran 40) i.v. twice a week. Entry criteria were an HIV positive test, CD4 levels of 200-500 cells, age 18-60 years, and without current opportunistic infections. This study confirms, in Caucasian subjects also, the good tolerability of lentinan observed in Japanese cancer patients. Side effects were mainly mild, especially when infusion was carried out over a 30-minute period. In the SFGH study, where administration was over a ten minute period, there were nine side effects severe enough to be reported to the FDA (one case each of anaphylactoid reaction, back pain, leg pain, depression, rigor, fever, chills, granulocytopenia and elevated liver enzymes) and there were four patients who discontinued therapy because of side effects. In the CRI study, where infusion was over a 30-minute period, there were no side effects reportable to the FDA and there were four dropouts due to side effects or personal preference. Most side effects resolved promptly after the discontinuation of medication, and all of them were relieved within 24 hours. Patients in the study have shown a trend toward increases in CD4 cells and in some patients neutrophil activity. Because of the small numbers, these values do not have statistical significance. Inasmuch as no side effects such as anemia, leukopenia, pancreatitis or neuropathy were seen, and in view of the positive effects of lentinan on certain surrogate markers (recognizing that these were small studies), we recommended a long-term clinical trial of lentinan in combination with didanosine (ddI) or zidovudine in HIV positive patients. Most patients in these trials did not have measurable p24 levels. In the CRI trials of ten patients with elevated p24 levels, eight on lentinan and two on placebo had decreased p24 levels. Of these decreases, those with lentinan and one with placebo were marked. These results were provocative and needed confirmation. Subsequent to this study, a trial of lentinan in combination with didanosine (ddI) showed a mean increase of 142 CD4 cells/mm3 over a twelve month period, in contrast to a decrease in CD4 cells in patients on ddI alone (Gordon et al. 1995).

Beta 1,3-Glucan Toxicology Studies

Glucan Source: Bacteria	
Citation	**Abstract**
Spicer EJ, Goldenthal EI, Ikeda T. **A toxicological assessment of curdlan.** Food Chem Toxicol. 1999 Apr;37(4):455-79. PMID: 10418959 [PubMed - indexed for MEDLINE]	Curdlan was approved for use by the FDA in December 1996 as a formulation aid, processing aid, stabilizer and thickener or texturizer for use in food. It has been evaluated for safety by a series of animal studies and in vitro tests including acute, subchronic and chronic toxicity studies and reproduction and carcinogenicity studies. In addition, nutritional studies in rodents and tolerance and metabolic studies in man have been carried out. The only effects seen in these studies were reductions in weight gain at the higher dietary concentrations due to the replacement of part of the diet by curdlan, which is calorifically inert. No evidence of any toxicity or carcinogenicity nor of any effects on reproduction was seen, although there was an effect on body weights of the pups with the 15% diet, which was shown in additional studies to be due to the reduced food availability in the animals at this dose level. There was no evidence of effects on the nutritional status of the animals nor on the absorption of minerals. This reviews the available toxicological data on curdlan.