1737 *ASPERGILLUS VERSICOLOR* ISOLATED FROM INDOOR AIR OF A MOISTURE-DAMAGED BUILDING PROVOKED ACUTE INFLAMMATION IN MOUSE LUNGS.

J. Jussila[1], H. Komulainen[1], K. Huttunen[1], M. Roponen[1], A. Hyvärinen[1], V. M. Kosma[2], J. Pelkonen[3,4] and M. R. Hirvonen[1]. [1]*Division of Environmental Health, National Public Health Institute, Kuopio, Finland,* [2]*Department of Pathology and Forensic Medicine, University of Kuopio and Kuopio University Hospital, Kuopio, Finland,* [3]*Department of Clinical Microbiology, University of Kuopio, Kuopio, Finland and* [4]*Department of Pediatrics, Kuopio University Hospital, Kuopio, Finland.*
Sponsor: M. Viluksela.

Moisture related microbial growth in buildings is associated with respiratory symptoms and inflammatory reactions. *Aspergillus versicolor* is a mycotoxin producing fungus detected in the air and materials of water-damaged buildings. We investigated the dose-response and time course of the effects induced by the spores of *A. versicolor*, isolated originally from indoor air of a moisture-damaged building, after a single intratracheal dose instilled into NIH/S mouse lungs. In dose-response study ($1x10^5$, $1x10^6$, $5x10^6$, $1x10^7$ and $5x10^7$ spores) lungs were lavaged at 24 hours, and in time course study ($5x10^6$ spores) at time points 6 h, 24 h, 3 d, 7 d, 14 d, 21 d and 28 d. The concentrations of the cytokines (tumor necrosis factor alpha (TNFα) and interleukin (IL)-6) in bronchoalveolar lavage fluid (BALF) were measured by ELISA method, total cell number was counted by the Trypan blue exclusion method, and cell differentials were determined from cytospin plates. The spores caused dose- and time dependent increase in both TNFα and IL-6 concentrations. Both cytokines peaked at 6 h, and the responses were over by 3 days. The number of neutrophils peaked at 24 h, and practically leveled off by 3 days. Macrophages peaked at 3 and lymphocytes at 7 days. Lymphocyte response was transient, but macrophages remained at a slightly higher level until the end of the study. Our results suggest that *A. versicolor*, isolated from a moldy building, is able to cause an acute inflammation in mouse lungs. (Supported by the SYTTY Programme, Academy of Finland.)

1738 CYCLOOXYGENASE-2 INHIBITION DOES NOT AFFECT MONONUCLEAR PHAGOCYTE FUNCTION.

W. J. Komocsar[1], A. Crosbie[1], J. Stapleton[1], K. McGehee[1], K. Kowalkowski[1], V. L. Peachee[2], K. L. White, Jr.[2], K. N. Khan[1] and S. M. Furst[1]. [1]*G.D. Searle & Co., Skokie, IL and* [2]*ImmunoTox, Inc., Richmond, VA.*

Two isoforms of cyclooxygenase (COX), COX-1 and COX-2, catalyze the production of prostaglandins (PGs) involved in various physiologic and pathophysiologic processes. COX-2 is the only isoform induced at the site of inflammation and is responsible for the generation of pro-inflammatory PGs. It is not known whether inhibition of COX-2 at the site of inflammation will affect primary inflammatory cell functions. Therefore, a series of *in vitro* and *in vivo* studies were conducted to evaluate the functional capacity of mononuclear phagocytes following treatment with a selective COX-2 inhibitor (SC-58236) and a non-selective COX inhibitor (naproxen sodium). The *in vitro* studies evaluated the effects of these drugs (1, 10, or 100μM) on the capacity of rat peritoneal macrophages to phagocytose opsonized *S. aureus* coated bioparticles. Cytochalasin B, a microfilament disruptor, was used as a positive control. The *in vivo* study evaluated the functional activity of tissue-specific macrophages by monitoring the clearance of ^{51}Cr-labeled sheep erythrocytes (sRBC). Female B6C3F1 mice were treated orally for 3 days with vehicle or 3, 10, and 30 mg/kg SC-58236 or naproxen sodium. Maleic vinyl ether was used as positive control. Peripheral blood clearance of labeled sRBC was monitored for 60 minutes, then the animals were sacrificed, exsanguinated, and liver, kidney, spleen, lungs, thymus, skin, intestine and kidneys were removed and analyzed for radioactivity. The *in vitro* data showed no effect at any concentration with SC-58236 and a statistically significant inhibition of phagocytosis at all naproxen sodium concentrations tested. The *in vivo* study showed no effect of SC-58236 or naproxen sodium on phagocytic indices (organ weights, %uptake or total counts/mg tissue). Collectively, these data indicate that COX-2 is not involved in the phagocytic function of macrophages and that its inhibition at the site of inflammation does not affect the primary phagocytic activity of inflammatory cells.

1739 PERIPHERAL BENZODIAZEPINE RECEPTOR (PBR) EXPRESSION AS A MARKER OF LIPOPOLYSACCHARIDE (LPS)-INDUCED INFLAMMATION.

M. J. Hardwick, M. K. Chen, K. Baidoo and T. R. Guilarte. *Environmental Health Sciences, Johns Hopkins University, Baltimore, MD.*

Inflammatory diseases afflict millions of people each year. The ability to visualize the immune response with compounds targeted to immune cells will enhance our understanding and diagnosis of inflammatory disease. PBR is present in neutrophils and monocytes, as well as in microglia, the macrophages of the brain. Specific PBR ligands have been used to visualize brain tumors and inflammation using non-invasive imaging techniques such as positron emission tomography. To further develop the use of PBR as a non-invasive marker of inflammation, we used LPS as a model of inflammation in mice. Mice were injected with 0, 10, or 30mg/kg LPS. Two days later, mice were injected with the PBR specific radioligand 123I-(R)-PK11195. Static planar images revealed increased radioactivity in the chests of both 10 and 30mg/kg LPS animals (48±13% and 161±24%, respectively) above control levels. Immediately after the scan, animals were sacrificed and various organs harvested. In the heart, gamma counting revealed significant increases in radioactivity for both 10 and 30mg/kg LPS above controls (86±30% and 232±31%, respectively; $p<0.05$). In the lungs and spleen, only the 30mg/kg LPS mice were significantly increased above control levels (191±51% and 272±70%, respectively-$p<0.05$). To determine the specificity of the PBR response, 30mg/kg LPS mice were treated with excess non-radioactive (R)-PK11195 30 minutes prior to tracer injection. Static planar images revealed that activity in the chest of blocked animals was lower than in 30mg/kg animals (decreased 31±5%, $p=0.013$). Gamma counting revealed that specific tracer activity in the blocked animals was decreased in the lungs (39±7%; $p=0.023$) and spleen (54±6%; $p=0.012$). These data show that LPS induces specific increases in PBR ligand binding in the lungs and spleen. Further, this study indicates that PBR expression is a promising non-invasive marker for imaging inflammatory responses. [supported by grant # ES07062 to TRG]

1740 CRISTOBALITE AND αQUARTZ SILICA ACTIVATES NF-κB-DEPENDENT GENE TRANSCRIPTION IN MOUSE MACROPHAGES.

S. Mowbray[1], C. Giardina[2], J. J. Helble[3] and A. K. Hubbard[1]. [1]*Pharmaceutical Sciences, University of Connecticut, Storrs, CT,* [2]*Molecular & Cell Biology, University of Connecticut, Storrs, CT and* [3]*Chemical Engineering, University of Connecticut, Storrs, CT.*

Exposure *in vitro* of mouse macrophages to inorganic particles increases expression of several inflammatory cytokines whose promoter regions contain binding sites for specific transcription factors. Past studies by others have demonstrated the ability of crystalline silica particles to induce transactivation of the transcription factor, NF-κB (Rojanasakul et al; Mol Cell Biochem 200:119, 1999). However, few studies have evaluated particle characteristics responsible for this effect. To investigate if two forms of crystalline silica, αquartz and cristobalite, or amorphous silica (all ~1um) could activate NF-κB dependent gene transcription in mouse macrophages, RAW264.7 cells were transiently transfected (DEAE/chloroquine) with an NF-κB luciferase construct. The following day, cells were exposed to increasing concentrations of particle (6, 12 or 25 ug/cm^2) for 8 or 24 hrs. Both αquartz and cristobalite increased gene transcription by approximately 2 fold with a maximal activation at 25 ug/cm^2 for 8 hrs. Activation was specific for crystalline silica since exposure of cells to amorphous silica did not activate NF-κB dependent gene transcription. These data suggest that particle characteristics may influence transcription factor activity altering cytokine expression and eventual cell activation. (Funded by ES NIH09433).

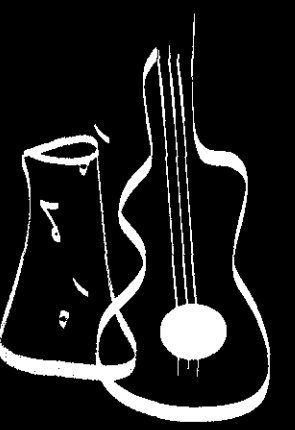
1741 INHIBITION OF TNFα PROMOTER/ENHANCER ACTIVITY BY PHENOLIC ANTIOXIDANTS.

K. L. Kinneer[1], J. Ye[2] and Q. Ma[1]. [1]*HELD/TMBB, CDC/NIOSH, Morgantown, WV and* [2]*Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA.*

Exposure to occupational chemicals often elicits inflammatory responses, resulting in tissue damage and disease. The cytokine Tumor necrosis factor alpha (TNFα) is an important mediator in the early stages of inflammation and plays an essential role in many inflammatory diseases. Certain phenolic antioxidants exhibit anti-inflammatory activity and thereby protect against chemical toxicity. The mechanism of anti-inflammation by the antioxidants is largely unclear. In a previously study, we demonstrated that phenolic antioxidants block signal-induced TNFα protein and mRNA production in macrophage cells. In this study, we further investigate the molecular mechanism of this inhibition by analyzing the effect of the antioxidants on the promoter/enhancer activity of TNFα. We used a stable reporter cell line that expresses luciferase under the control of TNFα promoter/enhancer for measuring TNFα gene transcription. The data reveal that bacterial endotoxin LPS induces luciferase production and tert-butylhydroquinone (tBHQ), a prototype of phenolic antioxidants, blocks this induction in the cell. The inhibition is both time- and dose-dependent. Inhibition of LPS-induced transcription of TNFα by diphenols (hydroquinone, HQ; catechol, and resorcinol) correlates with their capacity to undergo redox cycling. Furthermore, tBHQ and HQ blocked LPS-induced H_2O_2 generation within the cell, while resorcinol did not. Treatment with N-acetyl-cysteine, a general ROS inhibitor, blocks LPS-induced luciferase expression similarly. Taken together, these findings demonstrate phenolic antioxidants inhibit TNFα gene transcription and implicate redox cycling in the inhibition.

Society of Toxicology

41st Annual Meeting & ToxExpo™

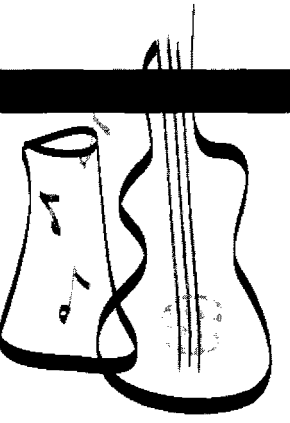


An Official Journal of the
Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES

Society of Toxicology

41st Annual Meeting & ToxExpo™



An Official Journal of the Society of Toxicology
Supplement

TOXICOLOGICAL SCIENCES
Formerly Fundamental and Applied Toxicology

Abstracts of the 41st Annual Meeting

The Toxicologist

Oxford University Press

Volume 66, Number 1-S, March 2002

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, roundtable, and poster sessions of the 41st Annual Meeting of the Society of Toxicology, held at the Opryland Hotel and Convention Center, Nashville, Tennessee, March 17–21, 2002.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 385.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 411.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

Additional Late-Breaking Abstracts are issued in a supplement to this publication and are available at the 41st Annual Meeting and through the Society of Toxicology Headquarters office.

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1767 Business Center Drive, Suite 302
Reston, VA 20190-5332

http://www.toxicology.org