ation of Th2 cytokines (IL-4, IL-10, and IL-13) in restimulated LN cells. TDI induced marked increases in levels of cytokines (IL-4, IL-10, IL-13, and IFN-γ) produced by restimulated LN cells. In contrast, DNCB treatment yielded, at most, small, nonsignificant increases in all parameters. Our protocol thus detected respiratory allergic responses to low-molecular-weight chemicals and may be useful for detecting environmental chemical–related respiratory allergy.

PS 1509 4-OXOPENTANAL IDENTIFIED AS A POTENTIAL INDOOR AIR IRRITANT AND ALLERGEN.

J. L. Franko, A. E. Munson, J. Ham, L. Jackson, R. Wells, L. Butterworth and S. E. Anderson. *CDC/NIOSH, Morgantown, WV.*

Over the last two decades, there has been an increasing awareness regarding the potential impact of indoor air pollution on human health. People working in an indoor environment often experience symptoms such as eye, nose and throat irritation, headache, and fatigue. Investigations into these complaints have ascribed the effects to volatile organic compounds (VOC) emitted from building materials, cleaning formulations or other consumer products, and indoor chemistry. The dicarbonyl 4-Oxopentanal (4-OPA) is generated through the ozonolysis of squalene and several high volume production compounds that are commonly found indoors. Measureable levels of 4-OPA have been detected in simulated indoor air environments. 4-OPA was tested in a combined local lymph node assay (LLNA) and identified to be an irritant and extreme sensitizer with an EC3 value of 0.08%. Significant increases were observed in the B220+ and IgE+B220+ cell populations in the draining lymph nodes after exposure to 4-OPA concentrations of 6.25% and higher. Total serum IgE levels were also significantly elevated after exposure to 25% 4-OPA. These results suggest that 4-OPA may function as an IgE-mediated sensitizer. The identification of this compound as an irritant and sensitizer may help to explain some of the adverse health effects associated with indoor air exposure.

PS 1510 *ORTHO*-PHTHALALDEHYDE INHALATION INDUCES IMMUNE ACTIVATION IN THE NASAL MUCOSA AND DRAINING LYMPH NODES IN MICE.

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ortho-Phthalaldehyde (OPA) is increasingly being substituted for glutaraldehyde as a high-level disinfectant for sensitive medical devices, however, toxicological data on OPA safety is lacking. Concerns regarding the safety of glutaraldehyde include acute nasal toxicity and sensory irritation as well as sensitization leading to occupational rhinitis and asthma. Since OPA is a dialdehyde like glutaraldehyde and functions as a disinfectant due to its high reactivity for biological macromolecules, it is reasonable to hypothesize that OPA may pose similar respiratory hazards. Several case reports have been published supporting this hypothesis showing development of respiratory hypersensitivity reactions in healthcare workers and patients exposed to OPA. The purpose of this study was to determine the respiratory toxicity of OPA using a murine model. A nose-only vapor inhalation system was used to expose mice to OPA vapor for 4 hours/day for 3 consecutive days followed by sacrifice on day 5. The lungs, nasal mucosa and head-draining lymph nodes were collected and processed for cytokine gene expression analysis. Expressions of TNFα and IL-1β, cytokines important for activation and migration of dendritic cells, were increased in the draining lymph nodes as well as the nasal mucosa. Increased IL-4 and IL-10 expression was observed in the draining lymph nodes as well as increased IL-4 expression in the nasal mucosa. In contrast, the expression of IFNγ was not changed in either tissue following OPA inhalation. Lung cytokine expression was also examined; however, no changes were evident. These data demonstrate that OPA inhalation induces an immune response locally in the nasal mucosa. Importantly, OPA inhalation induced activation of lymphocytes in the mandibular lymph nodes that drain the nasal mucosa, thus supporting the potential for sensitization to this chemical. The Th2-dominant expression pattern in the draining lymph nodes suggests that OPA may have the potential to cause respiratory sensitization.

PS 1511 IDENTIFICATION OF INDOOR AIR CONTAMINATES USING AN *IN VITRO* EXPOSURE SYSTEM.

L. Jackson, R. Wells, A. E. Munson and S. E. Anderson. *CDC/NIOSH, Morgantown, WV.*

On average, U.S. citizens spend 80% or more of their daily lives indoors whether at home, work, or in other commercial buildings. Over the last two decades, there has been increasing awareness regarding the potential impact of indoor air pollution on health. These studies use an in vitro monitoring system called the VitroCell which utilizes the air/cell interface allowing for direct contact between cells and components of a test atmosphere to assess chemicals found in the indoor air environment. The structurally similar dicarbonyls diacetyl, 4-oxopentanal, gluteraldehyde and methylglyoxal were selected for use in this system. Exposure to these compounds, which are found in the indoor environment, has been suggested to contribute to adverse health effects. The VitroCell module was used to evaluate immune-related gene and protein expression generated after a non-immune (pulmonary epithelial A549) and immune (alveolar macrophage) cell line were exposed to these aerosolized chemicals. A low density real time PCR gene array, screening 84 immune-related genes, was used to investigate the exposure effects of these compounds. Alterations in the inflammatory cytokines IL-8 and TNF-alpha were identified after exposure to these compounds. The identified cytokines can potentially be used as biomarkers to screen contaminated indoor air environments. These studies may provide an in vitro method for the identification and characterization of chemical hazards including indoor air pollutants in work environments such as office buildings, allowing for the reduction of worker illness and more specifically reducing respiratory consequences of exposures to allergens and irritants.

PS 1512 TH17 INVOLVEMENT IN PENICILLAMINE-INDUCED AUTOIMMUNITY.

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Rationale: At present idiosyncratic drug reactions (IDRs) are impossible to predict, largely because the mechanisms involved are poorly understood. The most recently identified subtype of helper T cells, Th17 cells, are characterized by the production of proinflammatory cytokine, IL-17, and have been shown to be involved in the pathogenesis of many types of autoimmune syndromes. This study investigated the involvement of Th17 cells in penicillamine-induced autoimmunity in Brown Norway (BN) rats. Experimental Procedures: BN rats were given penicillamine (1.0 mg/ml in drinking water). Serum IL-6 and TGF-beta concentrations were determined by ELISA. At the end of the experiment, spleen CD4+ T cells were purified via an immunomagnetic column from 3 treated and 3 control animals and cytokine mRNA levels were determined. Results: 4/7 treated rats developed autoimmunity. A significant increase of serum IL-6 was detected only in sick animals and did not occur until shortly before animals developed signs of autoimmunity. Serum TGF-beta was found to go up by the 2nd week in nonsick animal compared to a decease in the two sick animals. In addition, a two-fold increase of IL-17 mRNA was observed only in sick rats. Moreover, in preliminary experiments we detected a marked increase in IL-17 and IL-6 in several patients with idiosyncratic drug-induced liver injury. Conclusions: IL-6 is known to favor the development of Th17 cells and the elevation of IL-6 only in animals that develop autoimmunity is consistent with the involvement of Th17 cells in this animal model. The increase in IL-17 mRNA further supports this hypothesis. The finding of an increase in IL-17 in patients with idiosyncratic drug-induced liver failure suggests that Th17 cells may also be involved in drug-induced liver injury. This work was supported by a grant from the Canadian Institutes of Health Research.

PS 1513 GENISTEIN INCREASES BLOOD GLUCOSE LEVELS IN STREPTOZOTOCIN-TREATED FEMALE B6C3F1 MICE.

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Previously, we have reported that oral exposure to phytoestrogen genistein (GEN), a major isoflavone in most soy products, protected female NOD (non-obese diabetic) mice from developing type 1 diabetes when fed a soy- and alfalfa-free diet. When given in multiple low doses (MLD), administration of streptozotocin (STZ, a selective β-cell cytotoxin) can cause type 1 diabetes with an autoimmune pathology in mice that do not develop diabetes spontaneously. The objective of present study was to determine if exposure to GEN by gavage had any effects on blood glucose levels in the MLD-STZ-induced diabetic female B6C3F1 mice. Adult mice were administered GEN (2, 6, and 20 mg/kg; 0.1 ml/10 g body weight) for two weeks before STZ injection (5 X 50 mg/kg, i.p.) was performed to induce diabetes. GEN administration was continued to the end of study. Vehicle mice (25 mM Na2CO3) had moderate levels of blood glucose (250 - 350 mg/dL) in the 13 weeks of dosing period, and treatment with GEN produced increases in blood glucose levels. In the 2 mg/kg GEN group, significant increases were observed at weeks 7, 8, 9, 10, 11 and 12 following STZ injection. In the 6 mg/kg GEN group, significant increases were observed at weeks 7, 9, and 12 following STZ injection. In the 20 mg/kg GEN group, significant increases were observed at weeks 3, 5, 7, 10, 11 and 12 following STZ injection. When the percentages of mice with blood glucose levels over 650 mg/dL (the detection limit of our Accu-Chek Diabetes monitoring kit) were plotted against time, there were significant decreases at week 7 for the 2 mg/kg GEN group and at week 12 for the 6 mg/kg GEN group, and a significant increase at week 13 for the 2 mg/kg GEN group; however, the overall differences were minimal. Taken together, GEN exposure had no protective effect in MLD-STZ-induced diabetes in female B6C3F1 mice. These results suggest that the mechanism

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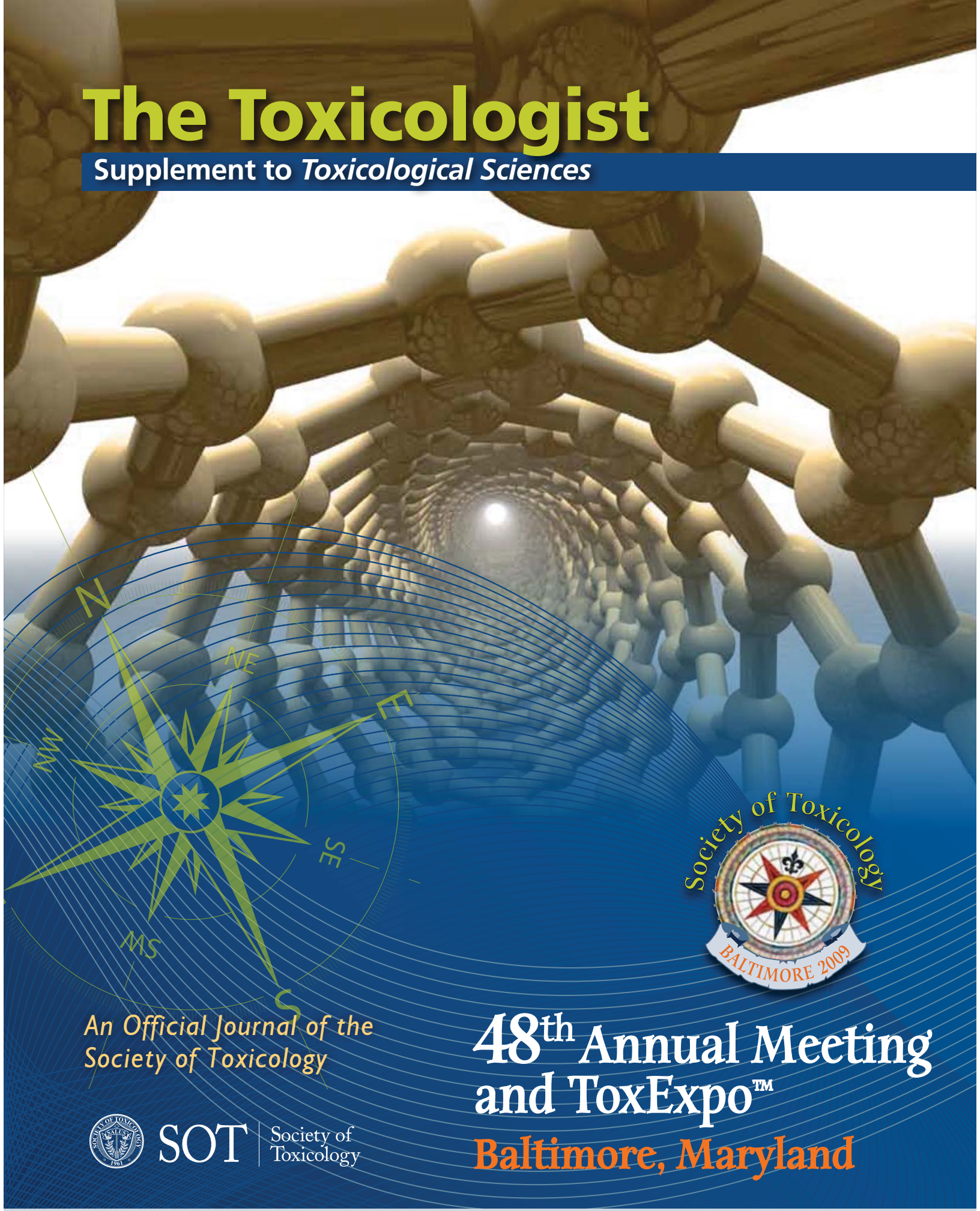

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