1, to consider skin irritants those chemicals which induce only IL-1 relase and, to exclude as potential allergens or irritants those chemicals which fail to induce changes in IL-1 production.

1315 INDUCTION OF SKIN LESIONS BY HEXACHLOROBENZENE IN THE BN RAT IS T-CELL DEPENDENT.

C P P C Michielsen[1], N Bloksma[2], F A Klatter[3], J Rozing[3], J H G Hoekman[4], P J M Roholl[4], and J G Vos[1,4]. [1]*Faculty of Veterinary Medicine,* [2]*Research Institute of Toxicology, Utrecht,* [3]*Dept. of Histology and Cell Biology, Groningen, and* [4]*Natl. Inst. of Public Health and the Environment, Bilthoven, the Netherlands.*

Oral administration of hexachlorobenzene (HCB) causes dose-dependent immunomodulation and inflammatory skin and lung lesions in the rat. In the BN rat, skin lesions were very marked and, in contrast to lung lesions, correlated with parameters of immunomodulation. Therefore we concluded that HCB-induced skin and lung pathologies have different etiology (Michielsen et al., 1997, Toxicol. Appl. Pharmacol. 144, 12–26). To investigate whether T cells are involved in the HCB-induced skin and lung pathology we depleted BN rats of T cells by thymectomy followed by lethal irradiation and syngeneic bone marrow transplantation, resulting in strong T cell depletion as shown by FACS analysis and immunohistochemistry of the spleen. These T cell depleted (Tx) rats as well as normal BN rats were exposed to diets with 0 or 450 mg/kg HCB for four weeks. Time of onset as well as incidence of the skin lesions were higher in normal rats as compared to Tx rats. Histology of lesional skin showed no difference between HCB-treated Tx and normal rats. In addition, typical HCB induced lung pathology was the same in both groups. Immunohistochemistry of lesional and non-lesional skin of HCB-treated BN rats revealed that ED2-positive macrophages are increased in non-lesional and especially lesional skin. In lesional skin these cells have more dendritic morphology and are sometimes also CD8a-positive. CD8a single positive cells with macrophage-like morphology are found in lesional skin only. It is suggested that these are CD8a-positive macrophages. It is concluded that induction of skin pathology by oral HCB-exposure is T cell dependent whereas the lung pathology is T cell independent. These results support a possible autoimmune/allergic etiology of the HCB-induced skin lesions.

1316 SKIN SENSITIZATION POTENTIAL OF TOPICAL DRUGS USING THE LOCAL LYMPH NODE ASSAY (LLNA).

K L Hastings[1], I Kimber[2], J Hilton[2], R Dearman[2], G F Gerberick[3], C A Ryan[3], D Basketter[4], L Lea[4], R V House[5], G S Ladics[6], S E Loveless[6]. [1]*CDER/USFDA, Washington, DC;* [2]*Zeneca Central Laboratory, Macclesfield, UK;* [3]*The Proctor and Gamble Co., Cincinnati, OH;* [4]*Unilever Environmental Safety Laboratory, Bedford, UK;* [5]*IIT Research Institute, Chicago, IL;* [6]*The DuPont Co., Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE.*

The murine LLNA is a method for the identification of chemicals with the potential to cause skin sensitization. Following topical application of test materials, activity is assessed as a function of induced proliferation of cells in the draining lymph node. Chemicals that induce a three-fold or greater increase in proliferation or a statistically significant increase compared with concurrent vehicle controls are classified as skin sensitizers. The sensitization potential of six compounds used in topical drugs was evaluated: five known human contact allergens, benzoyl peroxide (BP), hydroquinone (HQ), penicillin G (PG), streptomycin sulfate (SS), ethylene diamine dihydrochloride (EDD), and the nonsensitizing skin irritant, methyl salicylate (MS). Each chemical was evaluated in all five laboratories using the same batches and test concentrations. BP, HQ, and PG elicited positive LLNA responses in all laboratories. SS evoked a positive LLNA response in only one laboratory and only at the highest concentration. EDD was uniformly negative when dissolved in a 3:1 mixture of acetone:water, or in 4:1 acetone:olive oil (AOO). Limited further testing of the free base of ethylene diamine dissolved in AOO yielded a positive LLNA response. Finally, MS was negative at all test concentrations in each laboratory. Collectively, these data confirm that the LLNA is sufficiently robust to yield equivalent results when performed independently in separate laboratories and indicate that the LLNA is of value in assessing the skin sensitization potential of chemicals used in topical drug products.

1317 MURINE LOCAL LYMPH NODE ASSAY (LLNA) USING MALE CBA/J MICE.

J M Hurley, T G Kern, D W Sved, J J W M Mertens, and C P Chengelis. *WIL Research Laboratories, Inc., Ashland, OH.*

The basic procedures for the murine local lymph nodes assay (LLNA) for the identification of contact sensitizers have been defined and its repeatability and adaptability to minor modifications has been demonstrated in an international collaborative study (Toxicol. 108, 141–152, 1996). One major benefit of the assay over traditional guinea pig sensitization studies is the ability to obtain results five days following initiation as compared to five to six weeks. Females have typically been used in the assay due to reduced fighting among cagemates when group housed. Mice are routinely housed individually at the testing facility allowing for the use of male mice in the LLNA. Commercially available, disposable nylon mesh cell strainers (70 μm pore size) were selected for disaggregating the auricular nodes as opposed to the 100 μm nylon or 200 mesh (approximately 70 μm) stainless steel screens used in the collaborative study. Groups of mice were topically exposed to known sensitizers, a nonsensitizer or vehicle alone. Vehicle treated animals gave a mean radiolabel incorporation of 50 dpm/animal. Stimulation indices (treated dpm/control dpm) of 3.8, 5.5, 23.4, 65.9, 8.8 and 1.3 were obtained for animals treated with 5%, 10%, 25% and 50% hexyl cinnamaldehyde, 0.1% dinitrochlorobenzene and 10% p-aminobenzoic acid, respectively. Indices of 3 or greater are generally considered to be indicative of a sensitization response. It was demonstrated that the use of male mice and 70 μm nylon mesh did not compromise the ability of the assay to identify moderate and strong sensitizers. The results were consistent with those from the international collaborative study.

1318 THE ROLE OF SENSITIZATION ROUTES IN THE DEVELOPMENT OF TYPE I HYPERSENSITIVITY TO NATURAL RUBBER LATEX IN B6C3F1 MICE.

M R Woolhiser[1,2], B J Meade[1,2], and A E Munson[1,2]. [1]*Health Effects Laboratory Division, National Institute for Occupational Safety and Health, Morgantown, WV and* [2]*Medical College of Virginia/VCU, Richmond, VA.*

Latex allergy has become recognized internationally as a serious health hazard. Different allergen-specific IgE profiles have been associated with latex allergic adults as compared to younger patients (e.g. health care workers vs. spina bifida patients). As health care workers are thought to be primarily exposed to latex allergens dermally and by inhalation, and spina bifida children are additionally exposed subcutaneously to latex via numerous surgical procedures, a leading hypothesis is that the route of latex sensitization results in varied allergen-specific IgE repertoires. We are developing murine models representative of these routes of exposure. Preliminary studies were designed to demonstrate the ability of B6C3F1 mice to mount IgE responses to latex proteins. Mice were dosed intranasally with ~10μg of latex protein every fifth day over 52 weeks (9 exposures total). ELISA determinations of total IgE concentrations demonstrated IgE levels which were almost 4-fold higher than those of control mice (3,500 ng/ml vs. 900 ng/ml). In addition, splenocytes and lymphocytes analyzed by flow cytometry demonstrated an increased expression in B220 (B-cells) and surface IgE. 73% of the B220(+) lymphocytes from latex treated mice stained positive for surface IgE while only 13.5% did so for vehicle exposed mice. Likewise, 43% of B220(+) splenocytes stained positive for IgE compared to 9% from vehicle mice. In a second study, mice were injected s.c. with 50, 100, or 150 μg of latex proteins on days 1, 8, 15, and 22. Total IgE concentrations reached 5,000 ng/ml by day 14 for all three latex groups. The 50 μg injections resulted in IgE concentrations on day 28 greater than 10,000 ng/ml while the IgE levels following the 100 μg and 150 μg injections were 7,500 and 5,800 ng/ml respectively. These experiments suggest that the B6C3F1 mouse will serve as an acceptable test system to mimic the latex exposure routes which lead to latex hypersensitivity.

1319 INVESTIGATION OF DRUG-INDUCED HYPERSENSITIVITY IN HUMANS: MEASUREMENT OF IL-4 and IFN-γ mRNA EXPRESSION AS ENDPOINTS FOR DIAGNOSIS OF SENSITIZATION TO β-LACTAM ANTIBIOTICS.

I Gaspard[1], M T Guinnepain[2], J Laurent[2], J Bertoglio[1], M Pallardy[1], and H Lebrec[1]. [1]*Immunotoxicology, INSERM U 461, Faculté de Pharmacie, Châtenay-Malabry, France;* [2]*Institut Pasteur, Paris, France.*

Drugs such as β-lactam antibiotics behave as haptenic compounds and elicit

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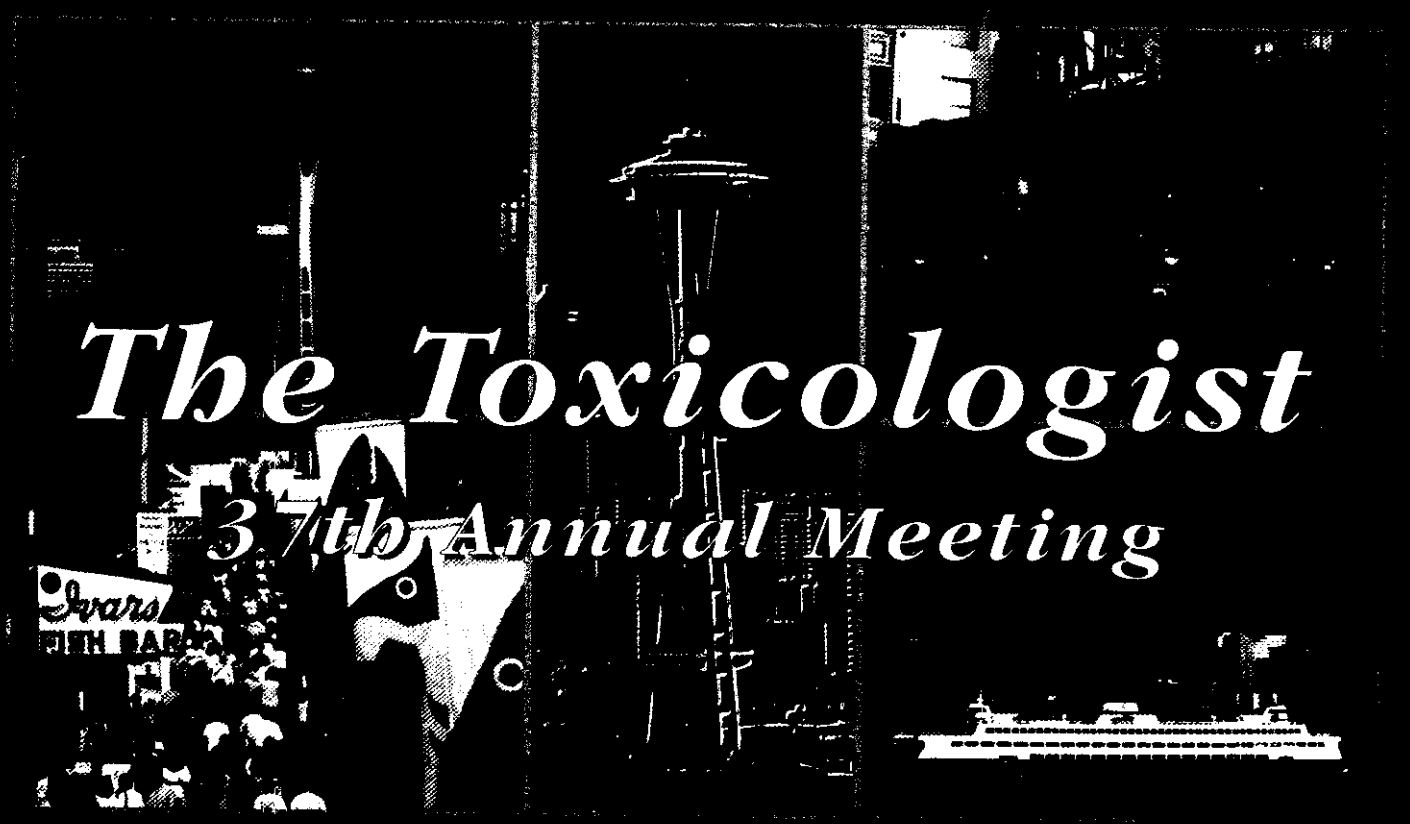

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Preface

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 37th Annual Meeting of the Society of Toxicology, held at the Washington State Convention Center, Seattle, Washington, March 1-5, 1998.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 407.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 433.

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