used for sensitization and challenge, allow the detection of differential cytokine responses regardless of chemical concentration. Lack of an IFN*gamma* response to DNCB may be due to the Th2-prone nature of the BALB/c mouse; therefore studies are currently underway to evaluate cytokine mRNA levels in Th1-prone C57BL/6 mice. (This abstract does not reflect EPA policy. This work was supported in part by The Dow Chemical Co. & DuPont Co.)

1183 CYTOKINE PROFILING FOR CHEMICAL SENSITIZERS USING THE RIBONUCLEASE PROTECTION ASSAY: DETERMINATION OF CYTOKINES GENERATED BY ISOCYANATES.

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Certain diisocyanates and acid anhydrides, which have been associated with occupational asthma, appear on the Hazardous Air Pollutant list (Clean Air Act 1990). Recent reports suggest that respiratory sensitizers may be identified based on their ability to induce a cytokine profile characteristic of a Th2 T cell response. Previous studies from this laboratory have shown that RNA message levels for the Th2 T cell cytokines IL4, IL10 and IL13 are elevated in response to the respiratory sensitizer trimellitic anhydride (TMA) and these increases may be detected by ribonuclease protection assay (RPA). In the current study, 4 additional chemicals (toluene diisocyanate (TDI), diphenylmethane-4, 4'-diisocyanate (MDI), dicyclohexylmethane-4, 4'-diisocyanate (HMDI) and isophorone diisocyanate (IPDI)) have been evaluated for their ability to induce Th2 cytokine mRNA expression. TDI and MDI are known respiratory sensitizers; however, there is conflicting data in the literature concerning the respiratory sensitizing potential of HMDI and IPDI. In the studies outlined here, female BALB/c mice were topically exposed to each of the isocyanates, and total mRNA was isolated from draining lymph nodes (LN) 14 days post challenge. RPA analysis showed that all 4 isocyanates tested induced cytokines characteristic of a Th2 T cell response (IL4, IL10 and IL13). These data support previous studies indicating that HMDI and IPDI are in fact respiratory sensitizers. (This abstract does not reflect EPA policy. This work was supported in part by The Dow Chemical Co. & DuPont Co.)

1184 AIRWAY RESPONSES AFTER SPECIFIC CHALLENGE OF RATS SENSITIZED *VIA* SKIN EXPOSURE TO TRIMELLITIC ANHYDRIDE (TMA).

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TMA is a low-molecular-weight chemical that can induce production of specific IgE and occupational asthma in sensitized individuals. The respiratory tract is considered to be a major exposure route leading to immunological and airway sensitization, but the relationship between dermal exposure and subsequent airway responses to TMA is not known. Our previous work, using Brown Norway (BN) rats, demonstrated that topical skin exposure to dry TMA powder induces dose-dependent production of specific IgE. The present study investigated the airway responses to inhaled TMA of BN rats that have been sensitized dermally with TMA. Twenty mg of dry TMA powder was applied to the rat's back (clipped with scissors) on days 0, 7, 14 and 21, and occluded overnight with surgical tape. Rats were challenged by a 10 min, 40 mg/m3 TMA aerosol inhalation on day 35. Enhanced pause (Penh), an index of airway narrowing, was recorded overnight in a whole body plethysmography system. Compared to non-sensitized rats, the sensitized BN rats displayed both distinct early (EAR) and late airway responses (LAR), as noted by an increase in Penh after TMA inhalation. The EAR occurred immediately following the challenge and lasted approximately 0.5 to 1 hour. This was followed by 2 hours of normal breathing. The LAR began from 3 to 4 hours after challenge and the increase in Penh lasted up to 19 hours following exposure. This work and our previous studies demonstrate that dermal exposure to TMA powder can lead to both immunological sensitization and obstructive airway responses upon aerosol challenge. This BN rat model, with both EAR and LAR, may be valuable for further study of pathophysiological mechanisms of organic acid anhydride-induced asthma.

1185 CHEMICAL AND VEHICLE RESPONSES TO TRIMELLITIC ANHYDRIDE (TMA) AFTER INTRATRACHEAL (IT) CHALLENGE OF SENSITIZED MICE.

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Exposure to some low molecular weight (LMWT)chemicals has been known to produce respiratory hypersensitivity (RH), especially in occupational settings. Methods to predict the RH potential of new chemicals are needed by the regulatory community. While mouse models for RH to proteins are available, mouse models for LMWT chemicals have not been developed. Our goal was to assess the effect of IT-exposure of TMA (free or conjugated) in selected vehicles. We evaluated lung responses to the known respiratory sensitizer TMA by dermally sensitizing and IT challenging mice. The contact sensitizer, 2, 4-dinitrofluorobenzene (DNFB) was the negative control. Abdomens were exposed to 25% TMA for 2 consecutive days for 2 weeks. In week 3, TMA was applied to the ears. Two weeks later mice were IT-exposed to: TMA in Hanks' Balanced Salt Solution (TMA-HBSS), TMA in olive oil (TMA-O), mouse serum albumin-TMA conjugate in HBSS (MSA-TMA). Serum and bronchoalveolar lavage fluid (BALF) were collected before (D 0) and 1, 2, 3, and 7 D post IT (PIT). TMA-sensitized mice challenged with TMA-HBSS had an increase in BALF total IgE at D1and D2. Serum total IgE increased in TMA-HBSS and MSA-TMA IT groups as compared to controls. While DNFB-HBSS challenge did not increase in serum total IgE, an increase in the MSA-DNFB challenged group suggests that once conjugated to a protein, even "non-respiratory" sensitizers may stimulate IgE. Serum IgE increased in agent-oil and oil alone at D 7 PIT in non-sensitized groups only, indicating that oil IT alone can evoke an independent serum total IgE increase. Our results suggest that none of these methods for delivering TMA to the lung were entirely satisfactory. It is clear that attention is needed in the area of chemical structure, stability, solubility, chemical- vehicle compatibility and compatibility with the biological system in order to develop appropriate models for the evaluation of LMWT chemicals for RH potential. (This abstract does not reflect EPA policy.)

1186 CD11C/CD1A POSITIVE DENDRITIC CELLS FOR THE IDENTIFICATION OF CONTACT SENSITISERS.

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The use of human blood derived dendritic cell (DC) cultures has been examined as an *in vitro* alternative for the identification of contact sensitisers, although often with variable outcome and not always with evidence of specificity. Thus we aimed to derive a purified 'Langerhans cell (LC) like' DC population, a cell type more relevant for the identification of skin allergens. Pure populations of DC were isolated from human peripheral blood using BCDA-1 magnetic bead separation. The cells were cultured for 5 days in a combination of granulocyte-macrophage colony stimulating factor, interleukin-4 and transforming growth factor-b to generate LC-like cells. The cells generated were approx. 95% CD11c/CD1a positive, expressed HLA-DR but not CD86 or CD83 as determined by flow cytometry, demonstrated endocytic ability (FITC-dextran uptake), were weak stimulators of the mixed lymphocyte reaction and thus could be regarded to possess an 'immature' phenotype. Cells obtained by this method (from either human peripheral blood or leucopacs) were exposed to subtoxic doses of the potent contact sensitiser DNCB (2, 4-dinitrochlorobenzene). This resulted in elevated expression of HLA-DR (2-7 fold increase in mean fluorescence intensity [MFI]) and CD86 (15-20 fold increase in MFI) compared with control cells or those treated with subtoxic doses of the irritant sodium lauryl sulphate. Culture of blood derived CD11c+ dendritic cells thus may provide a population of Langerhans like cells for potential future *in vitro* approaches to the identification of skin sensitisers. Further investigation will determine whether this approach will provide a robust predictive model that stands up to future challenges of specificity and sensitivity.

1187 EVALUATION OF ANTIGEN SPECIFIC IgE RESPONSES IN C3H/HeJ MICE EXPOSED WEEKLY BY ORAL GAVAGE FOR SIX WEEKS WITH COW'S MILK PROTEIN AND CHOLERA TOXIN.

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The objective of this study was to evaluate the antigen specific IgE Dose-Response in mice intragastrically exposed to cow's milk protein (CMP) and cholera toxin (CT) over a six-week period and to compare the responses to a cow's milk hypersensitivity model published by Li et al. (J Allergy Clin Immunol 103:206-214, 1999). Three-week-old female C3H/HeJ mice were sensitized by oral gavage to CMP plus CT and boosted 5 additional times at weekly intervals. Sera were collected at weekly intervals and the level of casein specific IgE measured by ELISA. Test groups (n=7 to 8) included naïve controls, 0.1 mg/g CMP + CT, 1 mg/g CMP + CT, 2 mg/g CMP + CT, 1 mg/g CMP without CT, and a CT only control. CT was administered at 0.3 µg/g. Casein specific IgE concentrations were determined by comparing individual or pooled serum samples to a mouse IgE anti-DNP standard curve. All analyses were performed in duplicate. As reported by Li et al., the maximal response occurred in the 1.0 mg/g CMP + CT group. However, differences in several measurements also occurred. We observed statistically significant differences in casein specific IgE levels between the 1.0 mg/g CMP + CT group and

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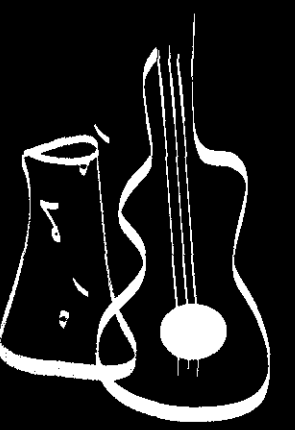

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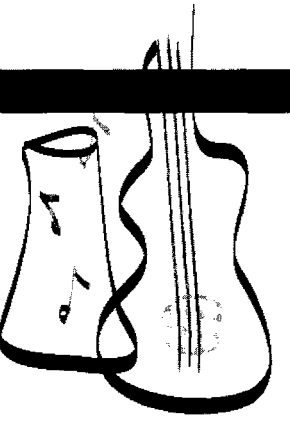

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Preface

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 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.

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