

in BALF IL-4 or IFN- $\gamma$  levels. We conclude respiratory SCE-1 exposure causes increases in both pulmonary immune cell numbers and cytokines associated with allergic responses. Further study is needed to determine the active components. (Supported by NCSU/EPA Cooperative Training Agreement CT826512010.) (This abstract does not reflect EPA policy.)

**835** SPECIFIC-UNRESPONSIVENESS TO DICLOFENAC-SERUM ALBUMIN CONJUGATES FOLLOWING ORAL PRIMING WITH UNCONJUGATED-DICLOFENAC.

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The nonsteroid anti-inflammatory drug diclofenac (DF) is associated with anaphylaxis as well as several other distinct allergic reactions including rash, idiosyncratic hepatotoxicity and anemia. The relevant immunogen leading to anaphylaxis may be DF-serum protein adducts. In this study, the popliteal lymph node assay (PLNA) was used to examine DF-specific peripheral immune reactions in BALB/c mice that had been orally primed (day -21) with a single dose of DF (treatment: TR) or vehicle (control: CON). On day 0, the PLNA was conducted using DF, D-penicillamine (D-PEN), streptozotocin (STZ), high- or low-density DF-bovine serum albumin (DF<sup>10</sup>-BSA, DF<sup>3</sup>-BSA), and high- or low-density DF-ovalbumin (DF<sup>2</sup>-OVA, DF<sup>1</sup>-OVA) conjugates. After the footpad injection animals were coded and the footpad diameter (mm) was determined daily along with the PLN diameter (mm), PLN weight (mg) and PLN cellularity on day 5 (direct PLNA) or day 7 (conjugate PLNA). When injected with STZ or D-PEN, there was no difference between TR and CON animal footpad mm, PLN mm, PLN mg or PLN cellularity. In contrast, when injected with DF, coded TR animals had a significant increase in footpad mm, PLN mm, PLN mg and PLN cellularity compared to CON. In additional experiments, TR and CON animals were challenged on day 0 with either DF-BSA or DF-OVA. There was no difference between TR and CON animal PLN mm, PLN mg or PLN cellularity following injection of DF<sup>2</sup>-OVA or DF<sup>1</sup>-OVA. However, when injected with either DF<sup>10</sup>-BSA or DF<sup>3</sup>-BSA, TR animals had a significant decrease in PLN mm, PLN mg and PLN cellularity. Collectively these data suggest a single oral dose of DF primed BALB/c mice for DF-specific PLN reactions and concomitantly induced a state of peripheral unresponsiveness specific for DF-BSA. These data suggest that although mice appear sensitized to DF, they may also be specifically protected from anaphylaxis. This may be similar to patients sensitized by DF, as evidenced by rash, hepatotoxicity or anemia, who never-the-less show no signs of DF-induced anaphylaxis.

**836** INVESTIGATION OF A BROWN NORWAY RAT MODEL OF FOOD ALLERGY.

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Assessment of the allergenicity of modified foods is a key part of their toxicological safety evaluation and is a formal requirement of regulations governing the introduction of such foods. Although much can be done using *in vitro* methods and sequence analysis to assess the potential allergenicity of a protein, for totally novel proteins it does not provide sufficient data. An ideal model would predict both the allergenic potency of a novel protein in man (hazard) and provide a measure of the amount of the protein that is likely to be safe for allergic individuals (risk). A number of animal models of food allergy have been proposed. As the rat is used widely in toxicological evaluation we decided to investigate a daily gavage model which did not require the use of adjuvants. Brown Norway rats fed a semi-purified diet (MODAIN) were gavaged daily for 8 weeks with 0.01, 0.1, 1, 10, 50 and 100mg/day ovalbumin (OA; 98%) in 1ml water; controls received water only. Total and specific IgG and IgE responses to ovalbumin were measured at various time points by enzyme assay (ELISA). Passive cutaneous anaphylaxis (PCA) was used to measure the specific IgE content of selected sera. Total IgG and IgE levels were unaffected by OA treatment. OA doses <sup>3</sup> 1 mg/day induced strong specific IgG responses in a dose dependent manner. The specific IgE response, measured by ELISA, did not show a consistent relationship with dose at any time point. Moreover, sera positive by ELISA, all proved negative by PCA. Since PCA is considered a more reliable measure of IgE-mediated reactivity, this lack of correlation casts doubt on the apparently positive ELISA results for antigen specific IgE. The results call into question the reproducibility of the model in its current form and the validity of the ELISA method for the detection of specific IgE antibodies. This indicates that further investigation of the variables influencing the outcome will be required before it can be considered for application to hazard identification.

**837** CHARACTERIZATION OF CATHELICIDIN-INDUCED LUNG TOXICITY IN A *KLEBSIELLA* INFECTION MODEL.

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Cathelicidins are innate anti-microbial peptides that aid host defense against bacterial infections. Synthetic analogs offer the promise of potent broad-spectrum anti-microbial efficacy. To characterize the toxicity and efficacy of synthetic cathelicidin-derived peptides, we developed a combined lung infection and *ex vivo* whole blood assay model. Methods: Male C57BL/6 mice were i.t. instilled with saline or *Klebsiella pneumoniae* (2-5 x 10<sup>8</sup> CFU) at time 0. At 5 hr, *Klebsiella*-infected mice were instilled with saline, tobramycin (1 mg/kg or 10 mg/kg), cathelicidin (Cath 2205) (0.4 mg/kg), or a combination of tobramycin (1 mg/kg) and Cath 2205 (0.4 mg/kg). At 24 hr, lungs were lavaged with saline and solutions were assayed for leukocyte counts, cytokine concentrations and viable bacteria. Blood samples from treated and control mice were analyzed in a whole blood assay (WBA) with stimulation *in vitro* using saline or LPS (1000 EU/ml). IL-6 release into the blood was measured after 5 hr. Results: There was a positive correlation between recovery of *Klebsiella* from the lung, PMN recruitment and production of IL-6 in BAL samples (p<0.01). Animals treated with Cath 2205 or Cath 2205 + tobramycin had increased hemoglobin (p<0.001) and protein (p<0.001) than *Klebsiella*-infected, or tobramycin alone-treated animals. In blood, mice instilled with *Klebsiella* had lower lymphocyte counts (48% vs. 84% in controls) and higher PMN and monocyte counts (p<0.05) than controls. In the WBA, mice infected with *Klebsiella* demonstrated 1000- to 10000-fold higher levels of IL-6 than non-infected mice. The highest levels of IL-6 were measured in mice given Cath 2205 alone or in combination with tobramycin. WBA results agreed well with the other indicators of toxicity measured in BAL. These studies showed that Cath 2205 was relatively non-toxic in mice pre-treated with saline, but was highly toxic in *Klebsiella*-treated animals. Further, the WBA effectively characterized the pulmonary toxicity of the cathelicidin.

**838** INTERLEUKIN 1-DEPENDENT REGULATION OF INTERLEUKIN 6 PRODUCTION BY WOUNDING IN HUMAN EPITHELIAL KERATINOCYTE.

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Wound healing in the skin is accompanied by inflammation. Increasing evidence indicates that the proinflammatory cytokine interleukin 6 (IL-6), plays an important role in wound healing. However, the mechanisms of IL-6 production and its involvement in wound healing remain unclear. The present study was designed to examine the molecular mechanism of IL-6 production, and its involvement in wound healing in normal human epidermal keratinocyte (NHEK) using an *in vitro* wounding model. Herein, we demonstrate that IL-6 mRNA expression and immunoreactive IL-6 release were increased following wounding. The transcription factors NF- $\kappa$ B and NF-IL6 (C/EBP $\beta$ ), which are known to be involved in IL-6 induction, were also activated following wounding. Addition of IL-1 $\alpha$  increased IL-6 production and induced NF- $\kappa$ B and C/EBP $\beta$  activation in NHEK. Exogenous IL-1 receptor antagonist inhibited IL-6 mRNA expression and transcription factor activation following wounding. Immunoreactive IL-1 $\alpha$  was detected in the culture medium following wounding, but mRNA was not increased. Additionally, mRNA expression of keratins 1 and 10, which are differentiation markers of keratinocytes, was decreased in wounded NHEK or keratinocytes treated with exogenous IL-6. Thus, these data indicate that the primary stimulus for IL-6 production in wounded epidermis is autocrine/paracrine stimulus with IL-1 $\alpha$ , and the mechanism by which IL-6 aids in wound healing is associated with the inhibition of differentiation in epidermal keratinocytes.

**839** WHOLE BODY IMAGING OF INDUCIBLE NITRIC OXIDE SYNTHETASE EXPRESSION PATTERNS IN TRANSGENIC MICE TREATED WITH LIPOPOLYSACCHARIDE AND INTERFERON-GAMMA.

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The ability to detect and quantify light coming through a living animal has led to major advances in studying gene expression patterns *in vivo*. We evaluated inducible nitric oxide synthetase (iNOS) transcription profiles using FVB mice trans-



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# Preface

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**The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.**

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