

the present study, we used TNF $\alpha$  deficient mouse (TNF $\alpha$ KO mouse) to investigate the role of TNF $\alpha$  in skin sensitization and CHS. We also studied on CHS in interleukin-1 $\alpha$ / $\beta$  (IL-1) deficient mouse (IL-1KO mouse). The efficiency of skin sensitization to 2,4,6-trinitrochlorobenzene (TNCB) measured 6 days later as a function of challenge-induced increases in ear thickness in IL-1KO mouse slightly diminished as compared with that in wild mouse. The ear thickness in TNF $\alpha$ KO mouse was about 47% of that in wild. Surprisingly, TNF $\alpha$ KO mouse was devoid of LC, which was stained with a monoclonal antibody against IAD in epidermis. However, draining lymph node cells (LNC) in TNF $\alpha$ KO 3 days after the treatment with 0.5% TNCB had almost the same ability to proliferate as that of LNC in wild. These results indicate that LC may not be necessary to establish skin sensitization step.

### P2C33

#### Immunological alterations in blood of toluene diisocyanate-sensitized mice

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Immune functions are known to be sensitive to a variety of chemical exposures. Availability of immunologic biomarkers in blood to evaluate environmental risks was investigated in toluene diisocyanate (TDI)-sensitized mice. Selected immunologic indicators in blood were total and TDI-specific IgE levels in serum and cytokine mRNA levels and lymphocyte composition in blood cells. Female BALB/c mice were sensitized with TDI painted 3 times on dorsal skin. Three days after the last TDI exposure blood samples were collected and analyzed for specific IgE by ELISA and mRNA levels of IL-4 (Th2 cytokine) and IFN- $\gamma$  (Th1 cytokine) by RT-PCR analysis. Results showed that TDI exposure produced no changes in lymphocyte subpopulations like T, B, CD4 + and CD8 + cells in spite of reduction of WBC numbers in blood. However, it significantly increased both total and TDI-specific IgE levels as compared to controls. Correspondingly the exposure also definitely induced IL-4 mRNA levels but suppressed IFN-RNA levels in blood cells, despite considerable variation in individuals. In conclusion our findings indicate that Th2 dominant status caused by TDI was confirmed from alterations in IgE levels and cytokine balance in blood, and those blood immunologic biomarkers would be applicable to risk evaluation in human population.

### P2C34

#### Modulation of the IgE reponse to natural rubber latex proteins by glutaraldehyde

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Latex allergic health care workers are exposed to numerous chemicals in addition to natural rubber latex (NRL) proteins. Time course studies have demonstrated a dose responsive increase in total and NRL specific serum IgE levels in female BALB/c mice exposed to 25  $\mu$ g NRL and increasing concentrations of glutaraldehyde from 0.05ppm — 1% (doses surrounding the recommended PEL). These studies investigated the mechanistic basis underlying the immunomodulation of the IgE response to NRL proteins following concurrent glutaraldehyde exposure. Using in vitro flow through cells and skin from hairless guinea pigs, penetration studies demonstrated no significant increases in NRL protein penetration through skin from animals that had been exposed dermally to 0.75 ppm glutaraldehyde 5 days a week for up to 56 days. Immunohistochemical staining of epidermal sheets demonstrated up regulation of MHC class II expression following 3 days of exposure to glutaraldehyde. No significant increase in MHC class II expression was observed in lymph node cells from animals exposed to NRL alone. Ten days following co-exposure to glutaraldehyde and NRL proteins, an increase in MHC class II expression (> 45%) was observed in lymph node cells draining the site of exposure. Draining lymph node cells demonstrated no exposure related changes in CD23 expression, however, a significant increase in the percent of CD40 + cells was observed in mice exposed to NRL proteins alone or concurrently with glutaraldehyde. These studies suggest that the observed immunomodulation by glutaraldehyde does not result from an increase in the dermal penetration of NRL proteins, but glutaraldehyde may enhance antigen presentation and B cell activation.

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### P2C35

#### Evaluation of the potential for dermal exposure to 3-Amino-5-mercapto-1,2,4-triazole (AMT) to induce pulmonary hyperreactivity

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3-Amino-5-mercapto-1,2,4-triazole (AMT) is an intermediate in the production of the herbicide DE498. Little toxicological information is available for either compound. These studies were conducted, using BALB/c female mice, to evaluate the potential of AMT to cause allergic sensitization and induce pulmonary hyper-reactivity following dermal exposure. Using the Local Lymph Node assay, AMT was identified as a sensitizer at concentrations of 15% and greater. AMT was negative for contact sensitization in the Mouse Ear Swelling Test. Phenotypic analysis of draining lymph node cells following 4 days of dermal exposure demonstrated an increase in B220 + cells at all concentrations of AMT tested and a significant increase in IgE + /B220 + cells in the 25% dose group. In sub-chronic



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## Abstracts

### Lectures

#### Deichmann Lecture

##### Apoptosis and toxicology — What relevance?

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All cells are mortal — i.e. they can be killed if a vital metabolic process is blocked. All cells can engage in a variety of stress responses, such as the heat shock response, when vital processes are slowly, or only partially, inhibited. These stress responses involve detection of the damage, transduction of signals, and activation of a response, such as production of heat shock proteins, proteases, or chaperones. Many cells possess mechanisms whose purpose is to kill the cell. Such physiological cell death mechanisms are used to remove unwanted or damaged cells. Among metazoans, physiological cell death is implemented by a family of cysteine proteases, termed caspases, that exist in a latent state even in healthy cells. Cells killing themselves via activation of their caspases typically exhibit an appearance termed 'apoptosis'. Apoptosis is not only used to remove cells in physiological circumstances, such as during development, but is also a common response to cell stress. Thus many cells will detect damage to, or malfunctioning of, vital metabolic processes, and generate signals that lead to activation of the caspases, and apoptotic death of the cell. This has led to a great deal of confusion, because many drugs and toxins with known biochemical functions have been found to induce apoptosis, and rather than this being interpreted as a stress response, it has often wrongly been assumed that apoptosis is a direct effect of the drug or toxin.

### Plenary Lectures

#### L1

##### The pathogenesis of prion diseases

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Prion diseases occur because the full length prion protein (PrP) can exist in two conformations: (1) a normal conformation in which the N-terminal half of the molecule has little or no  $\beta$ -sheet, which is characteristic of PrP<sup>c</sup>; and (2) an abnormal, pathogenic conformation in which the N-terminal half acquires a  $\beta$ -sheet conformation, which is characteristic of PrP<sup>Sc</sup> in scrapie and bovine spongiform encephalopathy (BSE) of animals and Creutzfeldt-Jakob disease (CJD) in humans. The property of the prion protein which gives prion diseases the characteristics of a slow virus infection is the efficient conversion of PrP<sup>c</sup> into nascent PrP<sup>Sc</sup> when the former physically interacts with 'infecting' PrP<sup>Sc</sup>. Sporadic CJD accounts for 85% of human prion diseases and appears to be initiated by the spontaneous conversion of PrP<sup>c</sup> to PrP<sup>Sc</sup> (a one per million event). Familial CJD (15%) is caused by mutations of the PRNP gene. The PrP<sup>Sc</sup> in sporadic and familial CJD is infectious. Prion strains are defined by the disease phenotype they produce in a host animal. Conformational dependent immunoassays indicate that the PrP<sup>Sc</sup> comprising each prion strain has a different conformation, possibly as a result of different amounts of  $\beta$ -sheet and different PrP<sup>Sc</sup> polymerization patterns. All of the parameters that define each prion strain can be modified by manipulating the amino acid sequence of PrP, which supports the protein only hypothesis. Finally, neuronal dysfunction and death in prion diseases require both the conversion of PrP<sup>c</sup> to PrP<sup>Sc</sup> and the accumulation of nascent PrP<sup>Sc</sup> in or on neurons and their processes.

#### L2

##### Food and cancer

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Food is an important factor in determining cancer incidence in many countries and regions. Food components relevant to cancer development can be divided into macro- and microcomponents. The former tends to act indirectly. The latter usually has a clearly defined action, for example as genotoxic agents. Food can have both positive (carcinogenic) and nega-