control rats per time point). Following three months of alachlor exposure, the mutant frequency (ratio of confirmed mutant plaques to total plaques screened) in the olfactory mucosa of treated rats was approximately 4 times higher than that of the concurrent control (1.3E-4 vs. 3.1E-5, p=0.002; [913, 000 plaques screened]). There was similarly a trend toward an elevated olfactory mucosal mutant fraction following two months of exposure, although statistical significance was not achieved. In contrast, nasal respiratory mucosa, which is not a target tissue for alachlor carcinogenesis and is located adjacent to the olfactory mucosa in the nasal cavity, did not display an elevated mutant frequency in alachlor-treated rats compared to concurrent (3 mo) controls. DNA sequence analysis will be performed to determine the nature of alachlor-induced olfactory mucosal mutations. These observations lend further support to the hypothesis that olfactory mucosal bioactivation to a mutagenic metabolite is pivotal to the carcinogenic mechanism in this tissue.

1112 IDENTIFICATION OF CARCINOGENS USING TRP53 HETEROZYGOUS NULL MICE AND LOSS OF HETEROZYGOSITY AT THE TRP53 LOCUS.

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Mice heterozygous for a Trp53 null and wild type allele are p53 haploinsufficient and dysfunctional for cell cycle checkpoint control and induction of apoptosis under genotoxic stress. Exposure of p53 deficient mice to mutagenic carcinogens induced neoplasia during the period in which unexposed co-isogenic haploinsufficient and homozygous wild type mice were free from neoplasia. Maximum tolerated doses (MTD) have been, in general, effective in inducing neoplasia with reduced latency after 26-week exposure to p53 haploinsufficient mice. Latency was shortened by requiring only an additional genetic alteration(s) at the functional Trp53 locus (mutation or loss of heterozygosity) and/or inactivation of another tumor suppressor gene. Based on a chemical database of published studies, an analysis was carried out to determine the predictability of this model to identify known or suspected human carcinogens (IARC Group 1 or 2) versus those least likely to be carcinogens (IARC Group 3). Under the conditions of the short-term cancer bioassays in this model in p53 deficient mice, the model showed an accuracy of 80% (47/59 Group 1/2 vs. 3 correctly predicted). Accuracy improved to 88% (23/26) if comparison was restricted to genotoxic Group 1 and 2 carcinogens. Coupling genotoxicity and induction of loss of heterozygosity (LOH) at the Trp53 locus improved accuracy to 100% (17/17). Overall, the conventional 2-year cancer bioassay in rats and mice showed an overall accuracy of 72% (26/36) and 100% (16/16) for genotoxic carcinogens (Group 1/2 vs. 3). Interspecies extrapolation between rodents and humans is difficult due to the possibility of species differences, but demonstration of an operational mechanism similar between rodents and humans, e.g. mutation or loss of p53 function through LOH may reduce uncertainity.

1113 A PROSPECTIVE CLINICAL EVALUATION OF TYPE I SENSITIZATION AND DERMAL COMPATIBILITY OF A BACILLUS SERINE PROTEASE IN A BODY LOTION.

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A protease enzyme in a prototype beauty bar has been shown to induce allergic antibody (sensitization) in clinic subjects1. Skin compatibility and potential for protease-induced sensitization from use of enzyme in leave-on body moisturizers is not understood. This study tested potential for a body lotion containing Bacillus spp. subtilisin protease, used intermittently over 18 months to induce allergic antibody, as measured by skin prick test (SPT) and serum measurement of enzyme-specific IgE. 864 healthy atopic women, 18-60 years of age from the US, Canada, Germany and France used product that contained 100ppm of protease 5 consecutive days per month, for 18 months. Regular lotion was used the remaining days of each month. Aerosol exposures during showering averaged 0.24ng/m3 of enzyme protein, measured 12 hrs after lotion application. Previous work showed that enzyme remained on the skin for 8 to 12 hours2. Skin evaluation and SPTs were conducted every 3 months. Capacitance and TEWL measures were made in a subset of subjects at 3 month intervals: skin biopsies occurred at baseline and at the first 3-month time point. The data showed increased hydration of the skin over time. Clinical evaluation and histopathology showed no skin irritation. One subject became sensitized after 6 months product use, but exposure to a cross-reacting protease in a carpet cleaner may have contributed to this response. This subject also became sensitized to a non-cross reacting protease from exposure to another carpet cleaning product. At 15 months two subjects became sensitized. These subjects did not experience any other known exposures that may have contributed to the reactions. None of the subjects had allergic symptoms. While this study showed favorable skin compatibility of the protease containing lotion, the occurrence of allergic antibody to the enzyme was unacceptable for product commercialization. 1J. All Clin. Immun. 1998 101:179-87 2 Human Exper Toxicology 1999. 18(8): 527.

1114 EVIDENCE OF ALLERGIC ANTIBODY TO A BACILLUS SERINE PROTEASE IN ATOPIC WOMEN: A RETROSPECTIVE EVALUATION.

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There has been increasing use of enzymes in consumer products. Effective safety evaluation and exposure control has minimized the risk of enzyme-induced Type I allergy in consumers. Prevalence of allergic antibody to Bacillus spp. enzymes in a clinic population of 2500 was assessed in the early 1970's after introduction of enzyme detergents1. No subject had allergic antibody to the enzymes. In the present study, subjects were tested as part of screening for clinical studies testing skin compatibility of consumer products. From 1999 to 2002, atopic women within the ages of 18 to 60 years were tested for the presence of allergic antibody to a Bacillus spp. subtilisin protease. Subsets were tested for allergic antibody to 2 other proteases and 2 Bacillus spp. amylases. Allergic antibody was detected by skin prick test (SPT) and serology for specific IgE or IgG antibody. A total of 2549 subjects were tested: 535 in France, 1009 in Germany, 279 in Canada, and 726 in the USA. Of the 2549 subjects tested, 4 subjects were confirmed SPT (+) (wheal at least 3mm greater than the negative control + flare). Two of the 4 had IgE and/or IgG antibody to the enzyme. A fifth subject was SPT (+) on initial testing but refused follow-up tests. There was no evidence of allergic symptoms from use of cleaning products. Four of the 5 did not use laundry products that contained this enzyme and there was no clear explanation as to why any of them developed antibody that recognized the protease. Earlier studies have demonstrated that use of laundry products containing similar enzymes is unlikely to cause sensitization in consumers. Two subjects were in Canada, 1 in the USA and 2 in Germany. These data indicate that there is a prevalence of sensitization to this Bacillus protease, in comparison to the previous study1. These data indicate a need for industry to continue to monitor the population to ensure expanded uses of enzymes in consumer products do not increase the risk of Type I sensitization. 1 Clin Allergy, 1973 3:143-160

1115 EVALUATION OF THE SENSITIZATION POTENTIAL OF TWO LUBRICANT ADDITIVES, PHENYL-ALPHA-NAPHTHYLAMINE AND ALKYLATED PHENYL-ALPHA-NAPHTHYLAMINE: A COMPARISON OF DATA FROM THE LOCAL LYMPH NODE ASSAY, THE BUEHLER GUINEA PIG ASSAY, AND HUMAN REPEAT INSULT PATCH TEST.

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Phenyl-alpha-naphthylamine (PAN) and alkylated phenyl-alpha-naphthylamine (APAN), two high temperature anti-oxidants commonly used in aviation turbine lubricants have been widely used for many years with relatively few associated cases of contact allergy reported. In these studies PAN and APAN were evaluated for sensitization potential and potency using the local lymph node assay (LLNA), and these results were compared with data previously generated using a modified Buehler guinea pig test and the human repeated insult patch test (HRIPT). Chemicals were tested using female CBA mice at concentrations raging from 1-100%. Both chemicals tested positive in the LLNA inducing dose responsive and statistically significant increases in lymph node cell proliferation reaching a stimulation index (SI) of ∝3. A series of non-linear regression models were applied to the data and the model which fit the data best based on likelihood ratio tests was subsequently utilized in a bootstrap analysis to obtain an uncertainty distribution around the calculated EC3 (the chemical concentration required to induce a SI of 3). Based on this analysis, the mean EC3 values and 90 % confidence bounds were 2.29% (0.01%, 6.4%) and 11.76% (4.4%, 24.6%) respectively for PAN and APAN. This data correlated positively with the guinea pig data where induction and challenge with equal concentrations of chemicals resulted in a greater percentage of animals responding and higher severity indices for PAN versus APAN. The LLNA data also correlated positively with the human data where HRIPT showed that use levels of both PAN and APAN failed to induce sensitization when applied in lubricants at concentrations of 1.5% and 2.5%, respectively, levels lower than their calculated EC3 values.

1116 FACTORS AFFECTING BINDING OF NATURAL RUBBER LATEX (NRL) PROTEINS TO GLOVE DUSTING POWDER.

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Adverse reactions to NRL proteins are caused by either topical, parenteral or respiratory exposures. NRL proteins bound to glove powder are the major source of the respiratory exposure and can cause serious reactions in frequent users of NRL