

1214 FORMATION OF DHP-DERIVED DNA ADDUCTS FROM METABOLIC ACTIVATION OF CLIVORINE, A REPRESENTATIVE OTONECINE-TYPE PYRROLIZIDINE ALKALOID, AND *LIGULARIA HODGSONNII* HOOK PLANT EXTRACT.

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Plants that contain pyrrolizidine alkaloids (PAs) are widely distributed in the world. PA-containing plant extracts and pure PAs have been shown to be genotoxic and tumorigenic in experimental animals. Our recent mechanistic studies indicated that riddelliine, a tumorigenic retronecine-type PA, induced liver tumors *via* a genotoxic mechanism mediated by the formation of eight 6, 7-dihydro-7-hydroxy-1-hydroxymethyl-5H-pyrrolizine (DHP)-derived DNA adducts. To date it is not known whether this mechanism is general to PAs of other types, such as otonecine-type PAs. The *Ligularia hodgsonnii* Hook, an herbal plant used as antitussive Chinese medicine, was found to contain several otonecine-type PAs and clivorine is the predominant PA present in this plant species. Clivorine has been shown to induce tumors in rats. In this study, we report that metabolism of the PA-containing extract of this plant by F344 rat liver microsomes results in the formation of DHP. When incubation of this plant extract in the presence of calf thymus DNA, eight DHP-derived DNA adducts were formed. Similar results were obtained from metabolism of the isolated pure clivorine under similar experimental conditions. These results indicate eight DHP-derived DNA adducts were also formed from metabolic activation of otonecine-type PAs in the presence of DNA. This metabolic activation pathway involves (i) formation of the corresponding dehydropyrrolizidine (pyrrolic) derivatives through oxidative N-demethylation of the necine base followed by ring closure and dehydration; and (ii) binding of the pyrrolic metabolites to DNA leading to the DNA adduct formation and tumor initiation. The results also suggest that these eight DHP-derived DNA adducts are potential biomarkers of PA exposure and tumorigenicity.

1215 ASSESSMENT OF DNA STRAND BREAKS IN LEUKOCYTES OF WORKERS OCCUPATIONALLY EXPOSED TO 1-BROMOPROPANE.

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As part of two NIOSH Health Hazard Evaluations, the comet assay was performed on peripheral leukocytes from workers to determine if occupational exposure to 1-bromopropane (1-BP) induced DNA strand breaks. Start-of- and end-of-workweek blood and urine samples were collected from 41 and 22 workers at 2 facilities where 1-BP was used as a solvent for spray adhesives in furniture manufacturing. Exposure to 1-BP was assessed from personal breathing zone samples collected for 1-3 days up to 8 hrs per day for calculation of 8 hr time weighted average (TWA) 1-BP concentrations. Bromide was measured in blood and urine as an internal biomarker of exposure. Overall, 1-BP TWA concentrations ranged from 0.2 - 271 ppm at site 1 and from 4 - 42.7 ppm at site 2. The highest exposures were in workers classified as sprayers. 1-BP TWA concentrations were statistically significantly correlated with blood and urine bromide concentrations. For estimation of DNA damage, comets were produced by alkaline microgel-electrophoresis and analyzed using VisComet image analysis software. One hundred leukocytes from each blood sample (stored at -80 °C until analysis) were evaluated for comet extent, tail extent, tail moment, and tail integrated intensity among other endpoints as a indexes of DNA single strand breaks/alkali labile sites. Start-of- and end-of-workweek comet endpoints were compared with environmental and internal exposure indices using linear regression analysis. Comet results were also stratified based on job classification. Preliminary analyses indicate that occupational exposures to 1-BP at these two facilities were not associated with the level of DNA strand breaks in leukocytes of exposed workers.

1216 THE OCCURRENCE OF SEVERE ALLERGIC REACTIONS TO FOOD IN NORWAY, BASED ON DOCTORS REPORTS TO THE NORWEGIAN REGISTER OF SEVERE ALLERGIC REACTIONS TO FOOD.

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Background: It is important to know the incidents of severe allergic reactions to food. We have limited information about the problem in Norway, and the current register has been undertaken to obtain information about risk groups, offending foods, the circumstances under which the reactions take place, treatment and diag-

nostic follow-up. Methods: The reporting system became active July 1. 2000. Information material, reporting and informed consent forms were mailed to all identified first line care providers. Serum samples were analysed for specific IgE antibodies to common food allergens. Results: The first 18 months 100 cases were reported. There were 47% males and 53% females. There were marked peaks for young adults and small children. About 2/3 of cases were reported to have known allergies, and 55% had known food allergies. Asthma was reported in 26%. The location of food intake was restaurant (8%), party/visit (7%), institution (3%) home (1%) and unknown (81%). In about half of the cases some assumption could be made about the causative food, and most common were nuts, peanuts and shellfish. Of 12 food allergens used as a standard battery, seropositivity (UniCap*) was most common against peanut, hazelnut; shellfish; and celery (falling order). First symptoms were edema/swelling, urticaria, pruritus and gastrointestinal symptoms. About 50% had their reaction within 30 min after food intake. A strong correlation between seropositivity and early symptom onset was observed. The combination adrenalin/steroids/antihistamine was given in 30% of cases, 9% got adrenalin only, 34% were given various combinations without adrenalin. Bronchodilators was the main treatment in 3% of cases. No deaths were reported.

1217 REDUCTION OF FUMONISIN MYCOTOXINS IN BT. CORN.

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Biotechnology has made it possible to develop corn hybrids that are protected against a major corn pest, the European corn borer (*Ostrinia nubilalis*). The coding sequence for Cry1Ab protein derived from *Bacillus thuringiensis* (Bt.) has been introduced into corn plants (event MON 810). Cry proteins are the active insecticidal ingredients of Bt. microbial insecticides that have been safely used on agricultural crops around the world for 40 years. The Cry1Ab protein is produced throughout corn plant tissues providing season-long protection against corn borers. Decreased insect damage to corn kernels reduces ports of entry for fungi that produce fumonisin mycotoxins. Fumonisin are toxic to farm animals, cause cancer in rodents and may contribute to high cancer rates in farmers in Africa and China that consume large amounts of fumonisin contaminated corn. Field trials with event MON 810 hybrids conducted in the US, France, Argentina and Turkey found generally reduced fumonisin levels in event MON 810 hybrids. In US field trials, fumonisin levels in Bt hybrids were on average 57% of levels in non transgenic controls. Many sites had a 3 fold or greater reduction in fumonisin levels. In Argentina, fumonisin levels in a Bt hybrid were on average, 39% of controls. In France, fumonisin levels were decreased several fold in Bt. hybrids. In Turkey, fumonisin levels were decreased 7 fold in a Bt. hybrid. Implications of reduction in fumonisin on human animal health will be discussed. In countries where fumonisin mycotoxin contamination is high and corn is a major dietary staple, fumonisin exposures can considerably exceed the TDI of 2 ug/kg body weight/day established by Codex. Biotechnology can help improve the food security of corn grain for human and animal consumption.

1218 SAFETY EVALUATION OF AN α -AMYLASE ENZYME PREPARATION DERIVED FROM THE ARCHAEL GENUS *THERMOCOCCALES* EXPRESSED IN *PSEUDOMONAS FLUORESCENS* BIOVAR I.

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The engineered α -amylase, BD5088, derived from the domain *Archaea* and the genera *Thermococcus* and *Pyrococcus*, was selected based on its characteristics of low-pH optimum and high thermotolerance, properties that are suited to corn wet milling applications. The host organisms of the three α -amylases from which BD5088 was derived were isolated from marine hydrothermal systems. The recipient strain of the host that is used to produce amylase BD5088, *Pseudomonas fluorescens* DC88, was avirulent after oral administration to mice. An extensive battery of studies designed to meet FDA requirements for Generally Recognized As Safe (GRAS) substances was performed on the enzyme preparation. Analytical characterization confirmed the identity and composition. Repeat-dose oral gavage studies of the BD5088 enzyme preparation in rats, for up to 13-weeks duration, showed no systemic toxicity. Inflammation of the nasal mucosa and the lung was seen in some