267 THE EFFECTS OF PERINATAL/JUVENILE PESTICIDE EXPOSURE ON ADULT CNS, IMMUNE, AND REPRODUCTIVE FUNCTION IN RATS

R E Chapin, M W Harris, M D Shelby, R J Smialowicz[1], V C Moser[2], S Padilla[2], R C MacPhail[2], Stan Berone[2], A C Lockhart[3], and M A Mauney[3]
NIEHS Reproductive Toxicology Group, [1]EPA Immuntoxicology Branch, [2] EPA Neurotoxicology Division, and [3]Analytical Sciences, Inc. RTP, NC

In 1988, Congress asked the NAS to evaluate the risk posed to children by pesticides in the food supply. The subsequent NAS report (''Pesticides in the Diets of Infants and Children'') identified numerous gaps in our knowledge of the effects of early pesticide exposure on adult immune, reproductive, and central nervous system function. A rodent study was designed to address these issues. Female SD rats are dosed from gd 14 to pnd 7, whereupon the pups are directly dosed and allowed to remain with the dam. Another group of treated dams provides samples on pnd 7 for measures of test compound and major metabolites in maternal blood and milk, and in pup blood. Some males are killed pnd 21 and 35 for Sertoli cell count and neurochemical measures. For the neurotoxicity studies, dosing ends on pnd 21 and the pups (10/sex/dose) are evaluated over a 2-month period in a neurobehavioral battery (FOB and motor activity). Cognitive function is evaluated as adults using a repeated-acquisition and performance operant paradigm. For immunotoxicity studies, rats (12/sex/dose) are dosed through pnd 42; at 8–10 wks of age they are evaluated for antibody response to SRBC, splenic subset analysis, NK activity, and mitogen- and alloantigen-stimulated proliferation responses. For reproductive studies, rats are evaluated at birth for anogenital distance, during dosing for reproductive development, and then for reproductive function as adults. Seven compounds are slated for this evaluation; the first study (methoxychlor) is complete, the second (carbaryl) is on-going.

268 DEVELOPMENT OF A FECAL TESTOSTERONE BIOMARKER IN RODENTS AS A NON-INVASIVE METHOD FOR DETERMINING MALE REPRODUCTIVE HEALTH

J E Billitti, B L Lasley, and B W Wilson. *University of California at Davis, Davis, CA*

An adverse effect on reproductive health is often one of the organism's first reactions to an environmental stressor. Thus the production and survival of young are frequently used to estimate the effect of exposures on free-ranging populations. More specific evaluations of the reproductive health of free-ranging individuals require capture, stressful restraint and often the removal of individuals from the study population. The present study focuses on the development and validation of a non-radiometric method to determine fecal testosterone levels as a biomarker for adverse effects in free-ranging, individual male rodents. For this development Peromyscus sp. was used as a model. A competitive enzyme immunoassay was adapted to measure fecal testosterone by the following steps: Fecal samples from the rodents were collected, dried, crushed and weighed. Samples were extracted using an organic solvent for 1 hour. Water was added, partitioning the testosterone into the organic phase. The organic solvent was removed via a quick freeze technique and evaporated. The extract was reconstituted in assay buffer and the efficiency determined using samples spiked with tritiated testosterone. Of the solvents tested ethyl ether gave the highest extraction efficiency with a recovery of 85.7% ± 0.9 STD. (n = 5) of the radiolabelled testosterone. Experiments are underway to validate the technique using a laboratory colony of Peromyscus before beginning tests with agricultural chemicals.

269 HEPATIC AND EXTRA-HEPATIC BIOCHEMICAL EFFECTS OF BENOMYL IN MALE SPRAGUE DAWLEY RATS

D M Banks, C C Kidd, C Moore and M R I Soliman. *College of Pharmacy, Florida A&M University, Tallahassee, FL.* Sponsor: M G Kolta

The toxic effects of methyl 1-(butylcarbamoyl)-2-benzimidazole-carbamate (benomyl) were evaluated in male Sprague-Dawley rats (170–230 g). Benomyl (200 mg/kg in olive oil) was administered via gastric gavage. Control animals received same volume of olive oil. Animals were treated for 18 days and fasted daily for 8–12 hours before treatment. A significant decline in body weight (16% decrease) was observed in animals treated with benomyl as compared to controls. There was also a significant decline in liver total protein in benomyl-treated rats. These changes were not accompanied with any significant alteration in hepatic or extra-hepatic reduced glutatione levels. However, lipid peroxidation in benomyl-treated rats was significantly higher (138.7% increase) than controls ($p<0.001$). Serum gamma glutamyl transferase (GGT) activity was elevated in benomyl-treated rats but was not significantly different from control. Benomyl treatment resulted in a significant elevation (71.5% increase) in GGT activity in the ileum. In addition, superoxide dismutase (SDO) levels were not significantly decreased. These findings clearly indicate that benomyl increases lipid peroxidation. This increased lipid peroxidation and the possible generation of free radicals may explain in part the hepatotoxicity and cytotoxicity induced by benomyl. (Supported by NIH grants GM08111 and RR03020)

270 EFFECTS OF SOLVENTS ON RECOVERY OF SELECTED PESTICIDES FROM AN *IN VITRO* PORCINE SKIN MODEL

[1]J L Campbell, [2]M A Eiteman, [1]P L Williams, [3]M Boeniger, and [1]M A Smith. *[1]Environmental Health Science Program, University of Georgia, Athens, GA; [2]Dept. of Biological and Agricultural Engineering, University of Georgia, Athens, GA; and [3]Industrial Hygiene Sec., USPHS/NIOSH, Cincinnati, OH*

Skin exposure to pesticides are a health concern for agricultural workers. Historically, worker's hand exposure has been evaluated by washing or wiping the hands with a solvent-moistened towelette and determining recoveries. Recent evidence indicates that solvents can facilitate percutaneous absorption by: 1) acting as carriers of pesticides, 2) decreasing the skin barrier properties, and 3) by irritating the skin. The purpose of this study was to evaluate the efficiency of 1-propanol, polyethylene glycol, soap and water, or D-TAM® in removing selected pesticides from skin. Alachlor (Al) and glyphosate (Gl) were selected as test pesticides based on their chemical properties. ^{14}C-labeled pesticide was spiked into formulations (Roundup® for Gl and Lasso® for Al) and applied to isolated porcine skin (2.5μg/cm^2). After a 90 min exposure, the skin was wiped with a solvent-moistened gauze. The gauze was analyzed for radioactivity. Based on recovery of radiolabled pesticide, soap and water was the most efficient at removing Gl in the porcine model system. Recovery from the wipe was 48 ± 6%. Recoveries for other wipe solvents were <40%. For Al, 1-propanol, PEG, and soap and water gave recoveries between 42 and 45% in this model system. Two other pesticides, trifluralin and methyl parathion, have been selected for further investigations based on solubility and other chemical properties.

271 DIFFERENCES IN THE PHARMACOKINETICS AND TOXICITY OF ALACHLOR AND ITS ETHANE SULFONATE METABOLITE

W F Heydens, A G E Wilson, L J Kraus, W E Hopkins, and K J Hotz. *Monsanto Company, St Louis, MO*

The ethane sulfonate (ESA) metabolite of alachlor is formed by soil microbes *via* glutathione conjugation and subsequent oxidative metabolism. A series of studies was conducted to determine possible health effects and to compare ESA's toxicity to that of parent alachlor. These investigations included: acute oral and subchronic toxicity, teratology, genotoxicity, ecotoxicology and pharmacokinetic studies. Mechanistic investigations were also conducted to determine the oncogenic potential of ESA relative to alachlor. The oral LD50 in rats was found to be >6000 mg/kg, while the trout LC50 and *daphnia* EC50 values were >104 mg/l. The NOEL for subchronic toxicity was 20 mg/kg/day, although equivocal changes at the next higher dose (182 mg/kg/day) were minimal and not considered biologically relevant. The NOEL for developmental toxicity was ≥1000 mg/kg/day. These results indicate that the acute, subchronic and developmental toxicity of ESA is 7-20 times less than that of alachlor. ESA was not genotoxic in Ames and micronucleus assays. Unlike alachlor, ESA underwent little metabolism, was rapidly excreted, and did not accumulate in tissues. These findings are consistent with ESA's overall low degree of toxicity. ESA did not induce the same pre-neoplastic changes caused by alachlor; thus, there is no basis to expect that ESA would produce tumors as found in alachlor chronic bioassays. In summary, results from various studies show that the toxicity of ESA is substantially lower than that of parent alachlor and support the conclusion that ESA is not of toxicological concern.

272 MIXED INHIBITION OF MOUSE HEPATIC MICROSOMAL 2-HYDROXYLATION OF 17β-ESTRADIOL BY FENITROTHION

C W Berger and L G Sultatos[1]. *Department of Pharmacology and Toxicology, UMDNJ, Newark, NJ*

Oxidative desulfuration of phosphorothioate insecticides like fenitrothion (FS) (*O,O*-dimethyl *O*-4-nitro-*m*-tolyl phosphorothioate) by cytochromes P450 (P450s) is thought to release atomic sulfur that can covalently bind to,

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster / discussion, workshops, roundtables, and poster sessions of the 35th Annual Meeting of the Society of Toxicology, held at the Anaheim Convention Center, Anaheim, California, March 10-14, 1996.

An alphabetical Author Index, cross-referencing the corresponding abstract number(s), begins on page 351.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 375.

The abstracts are reproduced as accepted by the Program Committee of the Society of Toxicology and appear in numerical sequence.

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1767 Business Center Drive, Suite 302
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Society of Toxicology
1767 Business Center Drive
Suite 302
Reston, VA 22090-5332

Phone: (703) 438-3115
Fax: (703) 438-3113
E-mail: sothq@toxicology.org