PS 2169 Age-Dependence of Toxicokinetics of Deltamethrin in Sprague-Dawley Rats

C. Chen[1], S. Muralidhara[1], D. Gullick[1], M. Amaraneni[1], T. Mortuza[1], T. G. Osimitz[2], D. Minnema[5], D. W. Gammon[3], S. Anand[4], B. S. Cummings[1], J. V. Bruckner[1] and C. White[1]. *[1]PBS, University of Georgia, Athens, GA, [2]Science Strategies, LLC, Charlottesville, VA, [3]FMC Co., Ewing, NJ, [4]Dupont Haskell Labs, Newark, DE and [5]Syngenta Crop Protection Inc., Greensboro, NC.*

Pyrethroid insecticides are used extensively in the U.S. and Europe. Low-level exposure occurs frequently in humans. Empirical toxicokinetic data for construction and validation of refined physiologically-based toxicokinetic (PBTK) models are quite limited, particularly for low doses closer to "real life" exposure levels. This study was undertaken to determine the plasma and tissue time-courses of deltamethrin (DLM) after giving an oral bolus dose of 0.05 to 5 mg/kg in corn oil (5 ml/kg) to male Sprague-Dawley rats. Serial plasma samples were obtained from 4-7 cannulated rats/dose to characterize DLM plasma kinetics, and to assess the effect of vehicle/volume on kinetics. Additional groups of uncannulated rats were dosed to obtain plasma, brain, muscle, liver, and fat at selected time points from both adult male rats and 21-day-old pups. Larger volumes of corn oil delayed and decreased the absorption of DLM from the GI tract. DLM was slowly absorbed, yielding peak plasma concentrations after 5-7hr. At DLM doses ranging from 0.05-5.0 mg/kg, the peak concentrations and AUCs from 0-24hr increased proportionately with dose, while the effective half-life was constant. A slow terminal elimination phase was noted at all dose levels, which is most likely due to prolonged DLM release from body fat. In adults, liver concentrations were 20-40% higher than plasma concentrations. Brain concentrations were significantly lower than plasma levels, which was unexpected since DLM is a highly lipophilic compound. Extensive plasma protein binding (~90%) may limit distribution of DLM to the central nervous system. Plasma and brain levels of DLM were generally higher in 21-day-old pups than in adults at dosages of 0.1-0.5 mg/kg, while liver levels were lower in pups. This indicates age-dependency of DLM kinetics, which may be important in risk assessments in this dosage range. Supported by the Council for Advancement of Pyrethroid Human Risk Assessment.

PS 2170 Inhibition of Alpha-Cypermethrin Metabolism by Chlorpyrifos-Oxon and Profenofos in Human Liver Microsomes

S. T. Singleton, J. B. Knaak and J. R. Olson. *Pharmacology and Toxicology, University at Buffalo, Buffalo, NY.*

Pyrethroids (PYR) are neurotoxic insecticides that exert their effects by prolonging the opening time of sodium channels and increase the duration of neuronal excitation. PYRs are utilized throughout the world to combat insect pests in both residential and agricultural settings. Alpha-cypermethrin (aCM) is a PYR that is used to ensure optimal crop production in the cotton fields of the Nile River delta in Egypt. Exposure studies in Egyptian cotton field workers found that the urinary metabolites 3-phenoxybenzoic acid (3-PBA) and cis-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropane carboxylic acid (cis-DCCA) are suitable biomarkers of exposure to aCM. However, the detoxification of aCM in humans remains unclear. The present study investigated the metabolism of aCM in human liver fractions (cytosol and microsomes), and examined the potential inhibitory effects of the organophosphate insecticides (OPs), chlorpyrifos (CPF) and profenofos (PFF), which are also applied seasonally to the Egyptian cotton fields. A reverse-phase HPLC method was developed, and the results demonstrate that aCM undergoes metabolism to the detoxified metabolites 3-PBA and cis-DCCA in both liver fractions. In pooled human liver microsomes (HLMs), no significant difference was found for the formation of the hydrolysis product cis-DCCA in the absence or presence of NADPH, indicating that esterase-mediated hydrolysis is the major route of aCM detoxification in the liver. A five-minute pre-incubation with the activated CPF metabolite, chlorpyrifos-oxon, or PFF, significantly inhibited the formation of cis-DCCA in HLMs with mean IC50 values of 213 and 284 nM, respectively. These results suggest that the interaction potential of PYRs and OPs should be considered in real world situations where both classes of insecticides may be utilized together. The kinetic parameters (Km and Vmax) for aCM metabolism will be useful in efforts to model aCM exposures in humans and the impact that OP exposures may have on exposure estimates. (US EPA STAR R833454 and NIEHS RO1 ES022163, ES016308).

PS 2171 Biomarker Analysis of American Toad (*Anaxyrus americanus*) and Grey Tree Frog (*Hyla versicolor*) Tadpoles following Exposure to Atrazine

M. Snyder[1], W. M. Henderson[2], D. A. Glinski[1] and S. T. Purucker[2]. *[1]Ecosystems Research Division, ORISE/EPA, Athens, GA and [2]Ecosystems Research Division, EPA, Athens, GA.*

Atrazine is one of the most commonly detected herbicides in surface waters throughout the United States. It has been found at concentrations from 0.23-250 μg/L and therefore presents a likely exposure scenario for non-target species such as amphibians. Studies have examined the effect of atrazine on the metamorphic parameters of amphibians; however, these data are often contradictory. The objective of this study was to use a biomaker approach to investigate the influence of atrazine exposure on american toad (Anaxyrus americanus) and grey tree frog (Hyla versicolor) tadpoles. Gosner stage 22-24 tadpoles were exposed to 0 μg/L (control), 10 μg/L, 50μg/L, 250 μg/L, 1250 μg/L of atrazine for 48 hours. Endogenous metabolites were extracted and analyzed using gas chromatography coupled with mass spectrometry analysis. Statistical analyses of the acquired spectra demonstrated changes in biomarkers between exposed and control tadpoles. Biochemical fluxes observed in the exposed group of both A. americanus and H. versicolor displayed perturbations in a number of classes of biological macromolecules including fatty acids, amino acids, sugar derivatives, and AXPs. Understanding the influence of these fluxes on the biochemical pathways of tadpoles and similarities between species responses following exposure to atrazine will aid in developing predictive biomarkers of pesticide exposure in these non-target species.

PS 2172 Longitudinal Assessment of Exposures to Chlorpyrifos and Profenofos in Adolescent Egyptian Agriculture Workers

J. R. Olson[1], G. A. Rasoul[2], A. A. Ismail[2], O. Hendy[2], L. Hamad[1], S. T. Singleton[1], M. R. Bonner[1], K. Khan[3] and D. Rohlman[3, 4]. *[1]University at Buffalo, Buffalo, NY, [2]Menoufia University, Shebin El-Kom, Egypt, [3]University of Iowa, Iowa City, IA and [4]OHSU, Portland, OR.*

Chlorpyrifos (CPF) and profenofos (PFF) are organophosphorus (OP) insecticides that are applied seasonally by the Egyptian Ministry of Agriculture to cotton fields. Urinary trichloro-2-pyridinol (TCPy), a specific CPF metabolite, and 4-bromo-2-chlorophenol (BCP), a specific PFF metabolite, are biomarkers of exposure, while inhibition of blood butyrylcholinesterase (BChE) and acetylcholinesterase (AChE) activities are effect biomarkers. Urinary TCPy and BCP and blood BChE and AChE activities were measured over a 10 month period in 2010 in adolescent pesticide applicators (n=57; 12–21 years of age) and age-matched non-applicators (n=38) prior to, during and after 28-31 days of CPF application followed by 9-14 days of PFF application. Applicators demonstrated significantly higher TCPy and BCP levels and greater BChE depression than non-applicators throughout the OP application period. Urinary TCPy remained elevated for 4-7 weeks after the cessation of agricultural spraying, while BCP levels readily returned to baseline. While large interindividual differences in exposure were observed throughout this longitudinal study (peak urinary BCP and peak TCPy levels ranging from 1.3 to 1,726 and 10.8 to 5,715 μg/g creatinine, respectively), these OP exposure biomarkers were highly correlated within applicators ($r = 0.8$, $p<0.0001$). The highly variable exposures support the need for exposure biomarker data when assessing neurobehavioral and other health outcomes associate with pesticide exposures. While lower levels of pesticide exposure were found to be associated with showering or bathing and changing clothes immediately after work, and wearing clean clothes to work, it is necessary to identify other work practices that may contribute to the high degree of variability in exposures, with the goal to reduce exposures. (supported by the Fogarty International Center and NIEHS R21 ES017223 and R01 ES022163).

PS 2173 Weight-of-Evidence Evaluation of 1, 3-Dichloropropene Tumorigenesis Supports Application of a Threshold-Based Risk Assessment

Z. Yan[1], S. C. Gehen[1] and R. Sura[2]. *[1]Dow AgroSciences, Indianapolis, IN and [2]The Dow Chemical Company, Midland, MI.*

The soil fumigant 1,3-Dichloropropene (1,3-D) has been extensively tested across mammalian toxicity endpoints. Historically, 1,3-D was classified as a Group B2 (probable human) carcinogen based on induction of multiple tumors in studies using an obsolete form of 1,3-D containing the mutagenic stabilizer epichlorohydrin. A non-threshold risk assessment was applied as genotoxicity could not be excluded. In this study, data generated on 1,3-D were examined utilizing a weight of evidence approach, with a focus on integration of rodent oncogenicity and genotoxicity data to determine if a threshold-based risk assessment could be applied. First, the oncogenicity potential of 1,3-D was evaluated by assessing eight separate

The Toxicologist

Supplement to *Toxicological Sciences*

54th Annual Meeting and ToxExpo™

March 22–26, 2015 • San Diego, California

OXFORD
UNIVERSITY PRESS

ISSN 1096-6080
Volume 144, Issue 1
March 2015

www.toxsci.oxfordjournals.org

The Official Journal of the Society of Toxicology

SOT | Society of Toxicology

Creating a Safer and Healthier World by Advancing the Science of Toxicology

www.toxicology.org

55th Society of Toxicology Annual Meeting and ToxExpo™

New Orleans, Louisiana

March 13–17, 2016

Ernest N. Morial Convention Center

Some New Orleans photos are courtesy of New Orleans Convention & Visitors Bureau. Some photos by Pat Garin.

Deadline for Proposals for SOT 2016 Annual Meeting Sessions: April 30, 2015

Why Submit a Proposal?

1. To present new developments in toxicology
2. To provide attendees with an opportunity to learn about state-of-the-art technology and how it applies to toxicological research
3. To provide attendees with an opportunity to learn about the emerging fields and how they apply to toxicology

Session Types

Continuing Education—Emphasis on quality presentations of generally accepted, established knowledge in toxicology
Note: CE courses will be held on Sunday.

Symposia—Cutting-edge science, new areas, concepts, or data

Workshops—State-of-the-art knowledge in toxicology

Roundtables—Controversial subjects

Continuing Medical Education—Emphasis on state-of-the-art knowledge to assist medical doctors, health professionals, and researchers in lifelong learning for providing high-quality health care
Note: Any session type may be considered for CME.

Historical Highlights—Review of a historical body of science that has impacted toxicology

Informational Sessions—Scientific planning or membership development

Education-Career Development Sessions—Sessions that provide the tools and resources to toxicologists that will enhance their professional and scientific development

Regional Interest—Central topics of relevance that describe public health and/or ecological problems of a particular region

Submit your proposal online at www.toxicology.org