PS 1887 COMPARATIVE PHARMACOKINETICS OF CHLORPYRIFOS *VERSUS* ITS MAJOR METABOLITES FOLLOWING ORAL ADMINISTRATION IN THE RAT.

C. Timchalk[1], J. A. Campbell[1], A. L. Busby[1], J. N. Smith[1], S. Lee[1], T. S. Poet[1] and D. B. Barr[2]. *[1]Biological Monitoring and Modeling, Pacific Northwest National Laboratory, Richland, WA and [2]Centers for Disease Control and Prevention, National Center for Environmental Health, Atlanta, GA.*

Diethylphosphate (DEP), diethylthiophosphate (DETP) and 3,5,6-trichloro-2-pyridinol (TCPy) are products of both in vivo metabolism and environmental degradation of the insecticide chlorpyrifos (CPF) and are routine urinary biomarkers of exposure. However, biomonitoring of TCPy, DEP and DETP may be reflective of an individual's contact with both the parent pesticide and exposure to these metabolites in the environment. In the current study, simultaneous dosing of 13C- or 2H- isotopically labeled CPF (13C-labeled CPF, 5 13C on the TCPy ring; or 2H-labeled CPF, diethyl-D10 (deuterium labeled) on the side chain) were exploited to compare the pharmacokinetics of CPF with TCPy, and DETP. The study objective was to quantitatively evaluate the pharmacokinetics of the individual metabolites relative to their formation following a dose of CPF. Individual metabolites were co-administered (gavage) with the parent compound at equal molar doses (14 μmol/kg; ~5mg/kg CPF). Major differences in the pharmacokinetics between CPF and metabolite doses were observed within the first 3 h of exposure, due to the required metabolism of CPF to initially form TCPy and DETP. Nonetheless, once a substantial amount of CPF has been metabolized (≥ 3 h post-dosing) pharmacokinetics for both treatment groups and metabolites were very comparable. Urinary excretion rates for orally administered TCPy and DETP relative to 13C-CPF or 2H-CPF derived 13C-TCPy and 2H-DETP were consistent with blood pharmacokinetics, and the urinary clearance of metabolite dosed groups were comparable with the results for the 13C- and 2H-CPF groups. Since the pharmacokinetics of the individual metabolites were not modified by co-exposure to CPF; it suggests that environmental exposure to low dose mixtures of pesticides and metabolites will not impact their pharmacokinetics. (Supported by CDC/NIOSH grants R01 OH008173 and R01 OH003629)

PS 1888 UP-REGULATION OF AROMATASE BY O, P'-DDT IS MEDIATED THROUGH CYCLOOXYGENASE-2 EXPRESSION IN HUMAN BREAST CANCER CELLS.

E. Ha[1, 2], J. Park[1, 2], J. Im[1, 2] and H. Jeong[1]. *[1]Pharmacy, Chungnam National University, Daejeon, Republic of Korea and [2]Pharmacy, Chosun University, Gwangju, Republic of Korea.*

DDT (from its trivial name, dichlorodiphenyltrichloroethane) is one of the most well-known synthetic pesticides. It has potent insecticidal properties, where it kills by opening sodium ion channels in the neurons, causing them to fire spontaneously leading to spasms and eventual death. o,p'-DDT is a DDT isomer that can induce inflammation and cancer. However, the effect of o,p'-DDT on aromatase is unclear. Therefore, we investigated the effect of o,p'-DDT on aromatase expression in human breast cancer cells. We also studied whether cyclooxygenase (COX-2) was involved in o,p'-DDT-mediated aromatase expression. o,p'-DDT induced aromatase protein expression in human breast cancer MCF-7cells. In addition, o,p'-DDT enhanced aromatase gene expression and activity of enzyme and promoter in MCF-7 cells. o,p'-DDT also markedly increased the levels of COX-2 protein levels in MCF-7cells. o,p'-DDT induced COX-2 mRNA expression and promoter activity in MCF-7 cells. o,p'-DDT enhanced the production of prostaglandin E2 (PGE2) and the gene expression of PGE2 (EP2 and EP4) receptor. Moreover, o,p'-DDT induced cyclic AMP response element (CRE) activation, cAMP level and binding of CREB. o,p'-DDT increased the phosphorylation of PKA, Akt, ERK and JNK in their signaling pathways. Taken together, these results suggest that o,p'-DDT increased aromatase and o,p'-DDT-induced aromatase was correlated with COX-2 up-regulation mediated via PKA and PI3-kinase/Akt signaling pathways in breast cancer cells.

PS 1889 UP-REGULATION OF CYCLOOXYGENASE-2 EXPRESSION BY ENDOSULFAN IN MACROPHAGES.

J. Park[1, 2], E. Han[1, 2] and H. Jeong[1]. *[1]Pharmacy, Chungnam National University, Daejeon, Republic of Korea and [2]Pharmacy, Chosun University, Gwangju, Republic of Korea.*

Endosulfan is an organochlorine compound that is used as an insecticide and acaricide. This colourless solid has emerged as a highly controversial agrichemical due to its acute toxicity, potential for bioaccumulation, and role as an endocrine disruptor. However, its mechanism on inflammation of macrophages is unclear. This study examined the effects of endosulfan on cyclooxygenase (COX-2) expression and examined the molecular mechanism in macrophages. Exposing macrophages to endosulfan induced the production of prostaglandin E2 (PGE2). In addition, endosulfan enhanced COX-2 gene expression, protein level and luciferase activity. The transient transfection and electrophoretic mobility shift assays with the NF-κB binding sites showed that the NF-κB transcription factor mediated the endosulfan-induced increase in the expression levels of COX-2. These results show that endosulfan stimulates the production of PGE2 and COX-2 expression and up-regulate the gene expression levels through NF-κB transactivation. Overall, these results suggest that endosulfan has inflammatory potential.

PS 1890 INVESTIGATION OF ETHYLENEBISDITHIOCARBAMATE PESTICIDE TOXICITY IN HT-29 AND CACO-2 HUMAN COLON CELLS.

L. Hoffman and D. Hardej. *Pharmaceutical Sciences, St. John's University, Jamaica, NY.*

Ethylenebisdithioncarbamate (EBDC) pesticides maneb, mancozeb and zineb are widely used in the prevention of fungus on a variety of plants and crops. While these agents are reported to possess low human toxicity, recent scientific studies have suggested that human toxicity to these agents do occur. These agents are rapidly degraded and their main metabolite is ethylenethiourea (ETU), a known carcinogen, teratogen and goitrogen. As metal containing compounds, participation in Fenton-like reactions might also contribute to oxidative stress. In addition, binding of metal moieties to critical sulfhydryl groups in enzymes is a common mechanism of metal induced toxicity. The purpose of this study was to investigate the acute toxicity of these three EBDC pesticides in human Caco2 and Ht-29 colon cells. Each cell type was grown to subconfluency and treated with concentrations of each agent ranging from 400 to 0.39μM for a period of 24 hrs. Cell viability was assessed by MTT assay. HT-29 cells showed significant decreases in viability in concentrations of 400 and 200μM for both maneb and mancozeb treatments and Caco2 cells in concentrations ranging from 400-100μM. for both compounds. In sharp contrast, zineb treatment showed no significant decrease in cell viability in either cell type in treatment up to 3.2 mM. Both phase contrast and scanning electron microscopy were performed to confirm viability results with maneb and mancozeb treatment and to observe morphologic changes observed with exposure. Microscopic studies confirm significant loss of viability observed with MTT analysis. Cell damage such as blebbing, decreased cell attachment fibers and disruption of cell structure, was observed in these groups. We conclude that maneb and mancozeb treatment results in toxicity in cells tested and that zineb possesses lower toxicity in these cell types. These data suggest that the metal moiety of EBDC pesticides may play a key role in toxicity.

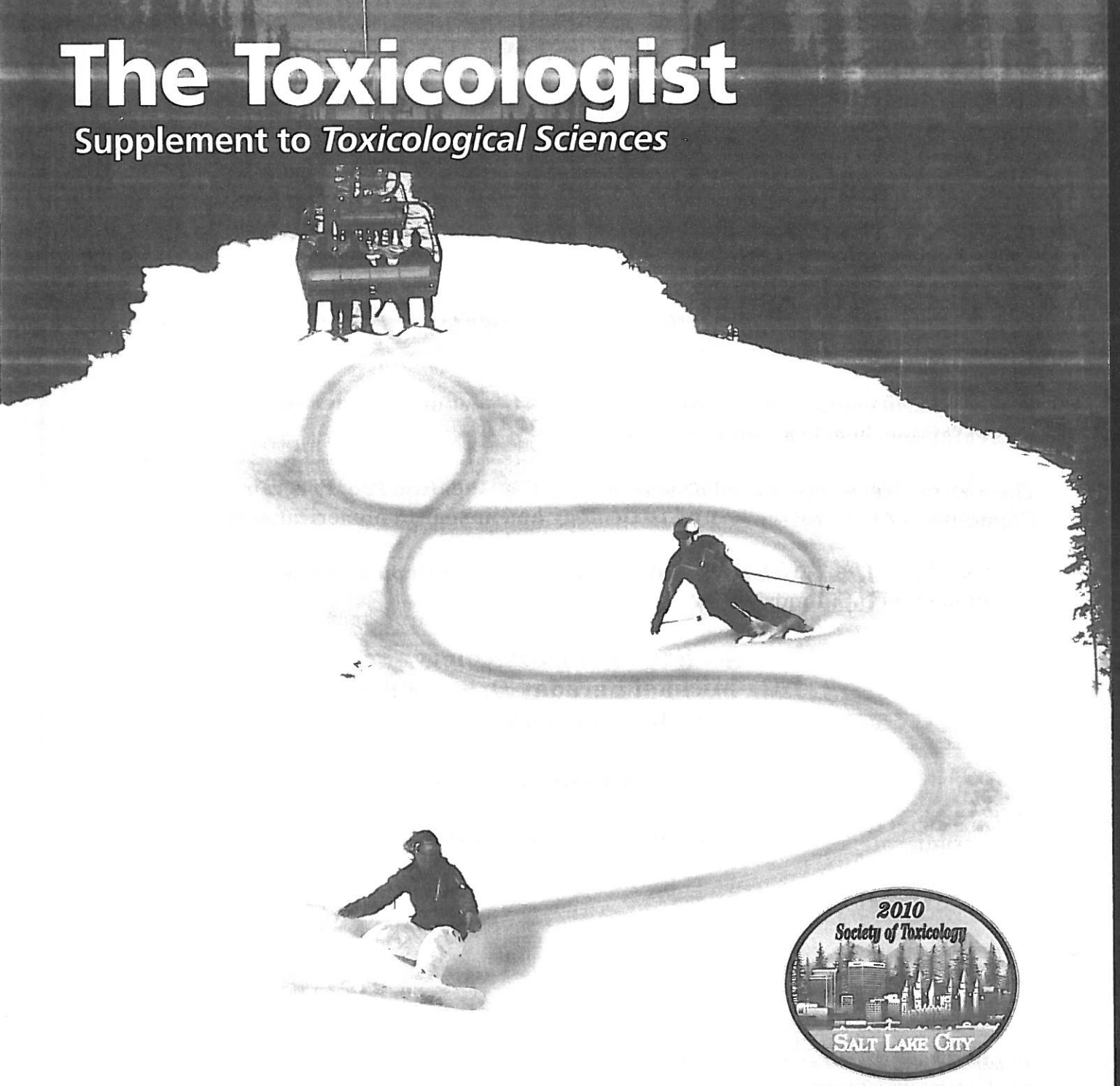
PS 1891 MULTI-RESIDUE DETERMINATION OF PESTICIDES IN THE MILK OF CATTLE AND GOAT IN FAISALABAD-PAKISTAN.

F. Muhammad[1], Z. U. Rahman[1], I. Javed[1], M. Akhtar[2], T. Khaliq[1] and M. I. Anwar[3]. *[1]Physiology and Pharmacology, University of Agriculture Faisalabad, Faisalabad, Pakistan, [2]Department of Parasitology, University of Agriculture Faisalabad, Faisalabad, Pakistan and [3]Department of Livestock and Dairy Development, Government of Punjab, Lahore, Pakistan.* Sponsor: J. Riviere.

The aim of study was to determine the contamination in the milk of cattle and goat reared in pesticide spraying areas of Faisalabad, Pakistan. Because no such published information is available in this region. The milk was collected from villages situated within the radius of 25-35 Km on four different localities (Jhang, Aminpur, Sitiana, and Sheikhupura roads) in the Northeast and Northwest of city during winter and spring seasons of 2007-08. Five pesticides (cyhalothrin, endosulfan, chlorpyrifos, cypermethrin and methyl parathion) were analyzed in the collected cattle milk (n=240) and goat milk (n=240) with solid phase microextraction and high performance liquid chromatography techniques. The residue analysis revealed that 46% and 50% samples were contaminated with pesticides in cattle and goat milk, respectively. The concentration of cyhalothrin and chlorpyrifos was higher in the milk collected from northeast (0.401 ± 0.01mg/kg and 0.047 ± 0.01 mg/kg respectively) as compared to the northwest of city (0.310 ± 0.03 mg/kg and 0.025 ± 0.007 mg/kg respectively). The milk samples collected during the winter season were found to be relatively more contaminated with pesticides as compared to spring. All the pesticides except endosulfan exceeded the maximum residual limits (MRL) established by the international health regulatory agencies, while methyl parathion was not detected in any milk sample. The species comparison revealed that only endosulfan residues were significantly ($P<0.05$) different in milk of cow and goat. About 19-25 % milk samples surpassed the MRL for cypermethrin, cyhalothrin and chlorpyrifos in both species. These findings suggest the need to create awareness in dairy farmers regarding the avoidance of pesticide residues in milk. (This work was supported by the Higher Education Commission, Islamabad, Pakistan.)

The Toxicologist

Supplement to *Toxicological Sciences*



An Official Journal of the Society of Toxicology

SOT | Society of Toxicology

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

49th Annual Meeting and ToxExpo™

Salt Lake City, Utah

www.toxsci.oxfordjournals.org

OXFORD UNIVERSITY PRESS

ISSN 1096-6080
Volume 114, Number 1, March 2010

Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 49th Annual Meeting of the Society of Toxicology, held at the Salt Palace Convention Center, March 7–11, 2010.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 473.

The issue also contains a Key Word Index (by subject or chemical) of all the presentations, beginning on page 496.

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

Copies of *The Toxicologist* are available at $45 each plus $5 postage and handling (U.S. funds) from:

Society of Toxicology
1821 Michael Faraday Drive, Suite 300
Reston, VA 20190

www.toxicology.org