1583 ASSESSMENT OF THE AGES AT WHICH VENTRAL PROSTATE DEVELOPMENT IN MICE IS MOST VULNERABLE TO 2,3,7,8-TETRACHLORODIBENZO-*p*-DIOXIN (TCDD) EXPOSURE.

U. Simanainen, T. M. Lin and R. E. Peterson. *University of Wisconsin-Madison, School of Pharmacy, Madison, WI.*

Among the most sensitive effects of *in utero* and lactational TCDD exposure is a permanent reduction of ventral prostate (VP) growth and development. The goals of this study were to determine the role of prenatal *versus* postnatal TCDD exposure in inhibiting VP growth and function, and to determine the most sensitive period of TCDD exposure. Pregnant C57Bl/6 mice were given 5 μg TCDD/kg or vehicle on Gestation Day (GD) 13 and litters were fostered at birth to dams of the same or opposite treatment. Four treatment groups were assessed: males not exposed to TCDD by either route (Control), and males exposed to TCDD *in utero* (IU), *via* lactation (L), or *in utero* and *via* lactation after GD 13 (IUL 13). A fifth group of male pups was exposed to the same dose of TCDD from GD 16 through weaning (IUL 16). Pups were weaned on Postnatal Day 21 and necropsied on Postnatal Day 35. Lactational TCDD exposure decreased VP weight to 59% of Control, while effects of IU exposure on VP weight were far more severe (8% of Control) and were similar to effects of IUL 13 exposure (14% of Control). However, a much less dramatic decrease was seen in IUL 16 males (29% of Control). Effects of TCDD on VP function were evaluated by mRNA abundance of an androgen-dependent, VP-specific secretory protein, MP25, using LightCycler real-time RT-PCR. The decrease in cyclophilin-normalized MP25 mRNA expression followed a pattern similar to that seen with VP weight. IU and IUL 13 TCDD exposure decreased expression to 3%, IUL 16 to 11%, and L to 42% of Control. These results demonstrate that TCDD acts both prenatally and postnatally to inhibit VP growth and function, although prenatal TCDD exposure is far more effective than postnatal exposure. Furthermore, exposure to TCDD between GD 13 and GD 16 appears to be the most sensitive period for impairing VP development. (Supported by NIH Grant ES01332 and Fulbright Grant 2000-2001)

1584 DEVELOPMENTAL TOXICITY OF MITOMYCIN C IN *DROSOPHILA MELANOGASTER.*

D. W. Lynch. *NIOSH, BHAB, Cincinnati, OH.*

To further characterize the Drosophila-based prescreen to detect developmental toxicants, Mitomycin C (Ametycine, Mutamycin [MMC]; CAS No. 50-07-7), was studied. MMC, a documented animal teratogen, is an antibiotic used clinically as an antineoplastic agent. During metabolism multiple metabolites capable of alkylation and/or redox cycling may be formed. Initially, 7 MMC concentrations ranging from 5 - 500 μg/vial were evaluated. No flies were found to emerge at concentrations greater than 20 μg/vial. In the second experiment, 3 concentrations from the first experiment were replicated, and 4 new, lower concentrations were added, to better characterize any developmental toxicity and to determine if a threshold could be observed. Each experiment included a concurrent control. Drosophila were exposed throughout development (egg through third instar larva) in culture vials to medium containing MMC. A mated, untreated, Oregon-R wild-type female (Mid-American Drosophila Stock Center, BGSU, Ohio) was added to each vial and allowed to oviposit for 20 hours, then removed. Emerging offspring were collected over 10 days, and examined microscopically (25x) for bent humeral bristles and wing blade notches; morphological defects shown to occur with an increased incidence in flies exposed to developmental toxicants. In each experiment, the incidence of the two defects at each concentration was compared to the controls using chi-square. In cases where replicate data were available at a given concentration, incidence data were also pooled and compared to the pooled controls. In the first experiment the incidence of bent humeral bristles was significantly increased at 10 μg/vial, 11/128 ($p < 0.05$); in the second experiment bristle defects were increased at 5 μg/vial, 10/277 ($p < 0.01$) and at 10 μg/vial, 18/260, 15 μg/vial 26/234, and 20 μg/vial 14/188 (all $p < 0.001$). No wing blade notches were observed. These results with MMC parallel the teratogenicity reported in mammals and provide additional support for increased utilization of this assay as a prescreen for the detection of developmental toxicants.

1585 DEVELOPMENTAL TOXICITY OF METHOPRENE AND ITS DEGRADATION PRODUCTS IN *XENOPUS LAEVIS.*

S. J. Degitz, E. J. Durhan, P. A. Kosian, G. T. Ankley and J. E. Tietge. *NHEERL, USEPA, Mid-Continent Ecology Division, Duluth, MN.* Sponsor: S. Bradbury.

Methoprene is an insect growth regulator which is used for the control of mosquitos. It acts by mimicking natural juvenile hormone, which inhibits pupae from developing to adults. Methoprene and methoprene acid are transcriptionally-active in a mammalian retinoic X receptor reporter cell line, suggesting that they may be active in vertebrates as well. This has lead to speculation that methoprene use may have a negative impact on amphibians. Specifically, it has been suggested that methoprene used in the Midwest may be a contributing factor to the recent increase in malformed amphibians found in that region. However, there is little data on the developmental toxicity of methoprene and its degradation products in amphibia. Our objective was to examine the developmental toxicity of methoprene and its degradation products (methoprene acid, methoprene epoxide, methoxycitronellal, and methoxycitronellic acid). Xenopus laevis embryos (stage 8) were exposed to the parent compound and the 4 degradation products for 96 hrs. The exposure solutions were changed every 24 hours and chemical concentrations were measured at 0, 8 and 24 hrs. In these experiments methoprene exposure did not result in developmental toxicity at or below water solubility (1.4 ppm). Methoprene acid, a relatively minor degradation product, produced developmental toxicity only when concentrations exceeded 1.25 ppm. Methoprene epoxide and methoxycitronellal produced developmental toxicity at concentrations >1 ppm. Methoxycitronellic acid was the least toxic of the chemicals tested, with no signs of developmental toxicity at 10 ppm. These data indicate that methoprene and its degradation products are not potent development toxicants to Xenopus laevis. This, in combination with the fact that field applications of sustained-release formulations of methoprene result in methoprene concentrations which do not typically exceed .01 ppm, suggest that concerns of methoprene-mediated developmental toxicity to amphibians are unwarranted.

1586 POSITIVE DUV PHOTORESIST-INDUCED TERATOGENICITY IN CHICK EMBRYO.

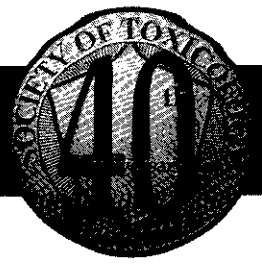
V. M. Steele[1], R. J. Keller[1], R. C. Gupta[2] and D. R. Canning[1]. [1]*Murray State University, Murray, KY and* [2]*Murray State University, Hopkinsville, KY.*

The objective of this investigation was to study the teratogenic potential of positive deep ultraviolet (DUV) photoresist (polyhydroxystyrene derivative) on chick embryos during very early stages of development and correlate these with axial development in human embryos. The adapted methodology of chick embryo culture was derived from the New vitelline membrane system. The effects of DUV photoresist were studied at three concentrations (1.5, 3, and 6 ppm) on neural tube closure, heart defects, cephalic formation, and axial defect. At 6 ppm, embryolethality occurred in 3 of 4 embryos tested. The surviving embryo showed a failure of neural tube closure in the trunk region (spina bifida-like malformation) At 3 ppm, 7 embryos showed various malformations in axial development, including abnormal head development (failure of optic vesical development, arrested development of the prosencephalon, mesencephalon and hind brain), and incomplete neural tube closure, or in some cases failure of head formation with extensive axial defects in somitogenesis. At 1.5 ppm, 7 of 10 embryos exhibited deformities in mesodermal segmentation along the body axis. Affected embryos appeared to have deformities related to perturbations of cellular developmental mechanisms responsible for generation of the embryonic axis. The present findings suggest that DUV in this test method targets neural tissue and mesoderm differentiation associated with correct patterning of the embryonic axis.

1587 A NOVEL PERFUSION SYSTEM FOR TOXICANT EXPOSURES TO DEVELOPING FISH EMBRYOS USING ^{31}P NMR SPECTROSCOPY.

C. A. Pincetich[1], M. R. Viant[1], R. S. Tjeerdema[1] and D. E. Hinton[2]. [1]*University of California, Environmental Toxicology, Davis, CA and* [2]*Duke University, Nicholas School of the Environment, Durham, NC.*

Nuclear Magnetic Resonance (NMR) spectroscopy is a powerful tool to observe biochemical changes in live, intact organisms. A novel perfusion system was designed and built around the constricts of a 10 mm NMR sample tube to allow delivery of oxygenated water to developing medaka fish (*Oryzias latipes*) embryos (~800 embryos, 1.1 mm diameter). ^{31}P NMR was used to detect levels of high-energy phosphagens, such as ATP and phosphocreatine (PCr), inorganic phosphate (P_i), and intracellular pH_i in the developing embryos. Fertilized eggs were sorted into groups according to their embryonic developmental stage, allowing the entire development of the medaka embryo, from fertilization through hatch (7-8 d), to be determined at 24 h intervals. Preliminary results from the stage specific ^{31}P NMR analysis show a significant drop in phosphomonoesters and phosphodiesters concurrent with a rise in PCr and ATP as the embryos develop from 96 h to 144 h. The characterization of high-energy phosphagens during embryonic development was followed by stage specific exposures to model respiratory toxicants, an uncoupler of oxidative phosphorylation and an electron transport inhibitor in the mitochondria. Embryos from toxicant exposures were preserved and prepared for histological examination by light and electron microscopy to detect tissue level and



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Preface

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An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 451.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 479.

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