fetal development studies, via an indwelling femoral catheter, have been developed in this laboratory. The continuous infusion of females during the period of major organogenesis presents challenges (i.e., mating of tethered animals, size of jacket, choice of control article/carrier and infusion rate). The protocol compared a naive group, a tethered (non-surgical) group and two infusion groups. Femoral vein cannulas were surgically implanted in anesthetized female rats. After recovery, they were paired with proven male breeders. Presumed pregnant females were assigned to a naive control group of 25 rats, a tethered control group of 10 rats, a 0.9% saline group of 25 rats and a 5% dextrose group of 25 rats. The infusion groups (0.9% saline and 5% dextrose) were maintained on a constant infusion rate of 0.3 ml/hour from surgery through a seven-day recovery period, during mating and continuing until day 6 of gestation. From gestation day 6 until the scheduled laparohysterectomy on gestation day 20 the infusion rate was approximately 1.5 ml/kg/hour. Maternal status was evaluated by monitoring body weight, food consumption and clinical signs. Laparohysterectomies were performed on day 20 post conception. Maternal body weight and body weight gain inhibition (of ~10%) occurred throughout the infusion period in both the 0.9% saline and 5% dextrose groups. However, non-pregnant animals also gain weight less rapidly following cannulation. Otherwise, animals displayed no clinical signs of ill health. Slight decreases in the mean number of *corpora lutea*, implantation sites and % per litter of viable fetuses were observed in the 0.9% saline group and 5% dextrose group. A slight, but not statistically significant, increase in prenatal mortality (% per litter) was also noted in the 5% dextrose group. Fetal examinations did not reveal differences in the incidence of external, visceral or skeletal malformations or developmental variations.

1324 CONTINUOUS INFUSION IN REPRODUCTIVE STUDIES: TO ADORN A TAIL.

S K Clubb and K P Hazelden. *Inveresk Research, Tranent, Scotland.*
Sponsor: A B Wilson.

There is much interest in using continuous intravenous infusion as a means of administering certain types of drug in toxicological testing. Potentially, reproductive studies present problems for this route of administration. For example, physical interference with actual mating and extraneous effects on the outcome of pregnancy (embryo- or foeto-toxicity) are major concerns. Inveresk Research has already been performing conventional toxicity studies in rats by continuous infusion, using a tailcuff system. The dosing cannula is implanted through the femoral vein and exits from the tail, protected by a metal cuff and flexible conduit, leading to an infusion pump located outside the cage. It was decided to apply this system to reproductive studies, initially in fertility and developmental toxicity studies in rats. Inveresk has conducted a validation study in which a typical group of at least 20 female rats were cannulated, continuously infused with saline at 8 ml/kg/hour for 2 weeks prior to mating, mated to untethered males, continuing on infusion until sacrifice at day 20 of pregnancy. Their pregnancies were then evaluated as for a developmental toxicity study. The results of this work demonstrate that there was no adverse effect of this administration technique on mating success or on the outcome of pregnancy. Further studies are to be completed using cannulated males and modelling other typical reproductive study designs. Rabbit developmental toxicity studies will also be addressed, but a jacket system will be used for this species.

1325 DEVELOPMENTAL TOXICITY OF L-PHENYLALANINE IN INTACT *DROSOPHILA*.

D W Lynch. *Experimental Toxicology Branch, DBBS, NIOSH, Cincinnati, OH.*

In order to further characterize the *Drosophila* bioassay for screening developmental toxicants, l-phenylalanine (LPA; CAS 63-91-2), a documented human and animal teratogen, was evaluated using our published protocol (*Teratogenesis, Carcinogenesis, and Mutagenesis* 11:147–173, 1991). *Drosophila* were exposed throughout development (egg through third instar larva) in culture vials to medium containing 0–140 mg/vial LPA. Each vial contained 1g of powered medium and 5ml of distilled deionized water or a solution of test chemical in water. A mated, untreated, Oregon-R wild-type female (Mid-American *Drosophila* Stock Center) was added to each culture vial and allowed to oviposit for 20 hours, then removed. Emerging offspring were collected over 10 days, and examined microscopically (25×) for bent humeral bristles and wing blade notches, morpohological defects shown to occur with an increased incidence in files exposed to developmental toxicants. Mortality ranged from 33% in the controls to 75% in the 140 mg/vial LPA group. The incidence of bent bristles was statistically increased ($p<0.05$) compared to concurrent controls (chi-square) at all LPA concentrations, and ranged from 1.0% (2/209) in the controls to 8.4% (10/119) in the 123 mg/vial group, the estimated LC_{50}. No wing blade notches were observed. These results provide additional support for increased utilization of this test as a prescreen for developmental toxicants.

1326 EVALUATING MECHANISMS OF ACTION OF DEVELOPMENT TOXICANTS USING FETAX AS A MODEL.

D J Fort, T Propst, and E L Stover. *The Stover Group, Stillwater, OK.*

The mechanisms of action of 2-acetylaminofluorene, coumarin, and 4-bromobenzene were evaluated with FETAX and an exogenous metabolic activation system (MAS). Cimetidine (CIM), ellipticine (ELL), and carbon monoxide (CO) were used to selectively modulate P-450 activity. Cyclohexene oxide (CHO) and diethyl maleate (DM) were used to selectively modulate epoxide hydrolase and glutathione conjugation, respectively. Addition of the ELL- and CO-inhibited MAS inhibited bioactivation of the test compounds. Addition of the CIM-inhibited MAS did not alter bioactivation of the test compounds. Addition of the DM- or the CHO-inhibited MAS dramatically increased the developmental toxicities of coumarin, 4-bromobenzene, and 2-acetylaminofluorene (DM-inhibited MAS only). These results suggested that ELL-inhibited P-450 (arylhydrocarbon hydroxylase) was responsible for the bioactivation of coumarin, 4-bromobenzene, and 2-acetylaminofluorene. Furthermore, increased toxicity of 4-bromobenzene and coumarin following co-incubation with the DM- or CHO-inhibited MAS suggested that a highly toxic epoxide intermediate may be produced from oxidative P-450 biotransformation and that glutathione may play a role in conjugation. Oxidative biotransformation of 2-acetylaminofluorene did not appear to produce an epoxide intermediate, however, glutathione may assist in detoxification of the bioactivated metabolite(s).

1327 DEVELOPMENT OF WHOLE-EMBRYO LIMB DEVELOPMENT ASSAY USING *XENOPUS LAEVIS*.

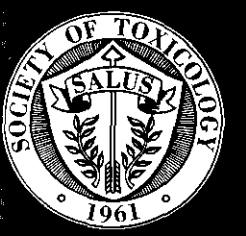
E L Stover and D J Fort. *The Stover Group, Stillwater, OK.*

Short-term, static-renewal studies were performed from day 5 (Stage 46) to day 26 (Stage 54) [21-d test] with thalidomide, copper, acetylhydrazide, 6-aminonicotinamide, and semicarbizide to evaluate effects on hind limb development in *Xenopus laevis*. Both copper and thalidomide caused abnormal development of the hind limbs at concentrations of ≥0.5 mg/L and ≥10.0 mg/L, respectively. Malformation of the hind limbs were primarily characterized as reduction deficiencies with copper and thalidomide. No development was noted distal to the femur in *X. laevis* larvae exposed to either thalidomide or copper at concentrations ≥1.0 and ≥0.5 mg/L, respectively. 6-aminonicotinamide also induced limb reduction deficiencies at concentrations ≥100 mg/L, however, in the form of adactyly. Acetylhydrazide and semicarbizide primarily induced flexure defects of the hind limb, resulting in completely developed twisted limbs at concentrations ≥25 and ≥110 mg/L, respectively. Based on these results, the short-term *Xenopus* limb assay developed to compliment the standard Frog Embryo Terntogenesis Assay—*Xenopus* (FETAX) test appears to be capable of screening for development toxicants, as well as studying mechanisms of action.

1328 DEVELOPMENTAL TOXICITY SCREENS OF MILITARY PROPELLANTS USING *Hydra attenuata*.

P D Confer[1,3] and R E Wolfe[2,3] [1]*GEO-Centers, Inc. and* [2]*ManTech Environmental Technology, Inc.,* [3]*Toxicology Division, Armstrong Laboratory, Wright-Patterson AFB, OH.*

In vitro developmental toxicity screens were performed to determine the developmental hazard indexes (A/D ratios) for liquid propellant XM46 (LP), ammonium dinitramide (ADN) and ammonium perchlorate (AP) using the hydra assay. *Hydra attenuata* is the most primitive invertebrate composed of complex tissues and organs and it is the highest form that has the capability for whole body regeneration. In the hydra assay, both adult *Hydra attenuata* and "artificial embryos," composed of disassociated *Hydra attenuata* cells, were exposed to each test compound to investigate potential developmental toxicity. The A/D ratios for LP, ADN and AP were determined to be 1.25, 2.14 and 1.71, respectively. By definition, a low A/D ratio (<3) predicts a test chemical being toxic to an embryo only at levels that will also cause toxic signs in the adult animal. Therefore, the A/D ratios for LP, ADN and AP demonstrate that these propellants should not be considered primary



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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 36th Annual Meeting of the Society of Toxicology, held at the Cincinnati Convention Center, Cincinnati, Ohio, March 9-13, 1997.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 371.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 395.

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SOCIETY OF TOXICOLOGY

1767 Business Center Drive
Suite 302
Reston, VA 20190-5332

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