1822 OVULATORY BLOCKADE IN THE RAT BY LOCAL OVARIAN EXPOSURE TO SODIUM DIMETHYLDITHIOCARBAMATE (DMDC).

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Dithiocarbamates, acting as catecholamine synthesis inhibitors, can block ovulation in female rats after systemic exposure by affecting the neural signals involved in triggering the ovulatory surge of luteinizing hormone. Since the ovaries also receive sympathetic noradrenergic neural input, there is some evidence that such input may have a role in follicular maturation and ovulation. The current experiments investigated whether the fungicide DMDC could block ovulation in adult, cycling Long-Evans rats when ovaries were locally exposed by intrabursal (IB) injection late on the day of vaginal proestrus. Unilateral IB DMDC (0, 3, 30, 100, 300 μmol/ovary) caused a dose-related ovulatory suppression on the injected side only, although no alterations were seen in ovarian norepinephrine (NE) levels. Unilateral IB injections (300 μmol/ovary) 24h earlier (diestrus II) blocked oocyte release on both sides, an effect overcome in the non-injected ovary by systemic hCG administration, which implied that the diestrous DMDC exposure acted to suppress the LH surge. The data show that unlike a systemic exposure to DMDC, which can block ovulation by markedly lowering hypothalamic NE, the ovulatory suppression by IB injection involves some other mechanism. Moreover, the blockade in response to diestrous IB exposure likely involves two separate mechanisms, one involving an alteration in ovarian hormonal feedback to the brain (or pituitary), inhibiting the LH surge, and the other linked to a direct, as yet undermined effect on local events within the ovary.

1823 COMPARISON OF THE ESTROGENIC ACTIVITY OF 4-TERTOCTYLPHENOL, NONYLPHENOL, BISPHENOL A AND METHOXYCHLOR IN LONG EVANS FEMALE RATS.

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We have previously reported data from in vitro competitive receptor binding assays which demonstrate that 4-tertoctylphenol (OP), nonylphenol (NP), bisphenol A (BPA) and a metabolite of methoxychlor (MXC), HPTE, inhibit ligand binding to the estrogen receptor (IC_{50} 0.8, 0.9, 1.4 and 0.06 μM, respectively). Here we compare the ability of these environmental chemicals to elicit estrogenic responses in sexually immature female rats following exposure by oral gavage or s.c. injection. Vaginal opening (VO) was accelerated by 4.6 and 6.8 days in rats dosed daily by oral gavage with OP (200 mg/kg) and MXC (50 mg/kg) from 21-35 days-of-age. BPA (400 mg/kg/gavage) did not accelerate VO. NP (50 mg/kg), OP (100 mg/kg) and BPA (400 mg/kg) induced uterine growth after oral or s.c. exposure from 21-23 days-of-age when measured 6 hr. following the last dose. The magnitude of change in uterine wt. was greater with s.c. injection than with oral gavage. The difference in uterine wt. was no longer apparent 24 hr. after the last oral dose of OP and BPA. Although increased uterine wt. was observed 6 and 24 hr. after the last oral dose of MXC (50 mg/kg), this chemical had no effect on uterine wt. following s.c. injection. Using the physiological responses as a measure of estrogenic activity following oral exposure (molar eq.) MXC > NP > OP > BPA. These data also demonstrate that study results may vary depending upon observation time and exposure route for each environmental chemical.

1824 EVALUATION OF THE REPRODUCTIVE AND DEVELOPMENTAL TOXICITY OF THE ESTROGEN RECEPTOR ANTAGONIST/AGONIST IDOXIFENE IN FEMALE RATS AND RABBITS.

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Idoxifene, a species and tissue specific estrogen receptor antagonist or agonist, was evaluated in female Sprague Dawley rats and New Zealand White rabbits after oral administration of 0.003, 0.03 and 3.0 mg/kg/day and 0.01, 0.1 and 1.0 mg/kg/day, respectively, for effects on fertility and/or embryo-fetal development. In all studies, adult toxicity was evident at doses ≥ 0.03 mg/kg/day in rats and ≥ 0.1 mg/kg/day in rabbits as evidenced by decreased body weight and/or food consumption. In the female fertility study, rats were treated for 2 weeks prior to mating until insemination. Disrupted estrous cycles, impaired fertility, increased pre-implantation loss and increased vaginal fluid at necropsy were evident at ≥ 0.03 mg/kg/day. In the early embryonic development study, pregnant female rats were treated from days 0-6 postcoitus (pc). Complete or partial pre-implantation loss was seen at 3.0 and 0.03 mg/kg/day, respectively. In the embryo-fetal development study, pregnant rats were treated from days 6 to 17 pc. Mortality occurred at 3.0 mg/kg/day. Developmental toxicity at 3.0 mg/kg/day was demonstrated by embryo-fetal death, increased incidence of generalized fetal edema and developmental delays. In the rabbit embryo-fetal development study, pregnant rabbits were treated from days 6 to 20 pc. Mortality, abortion/premature deliveries and embryolethality occurred at 1.0 mg/kg/day. Vaginal or uterine bleeding was seen at doses ≥ 0.1 mg/kg/day. There were no drug-related effects at 0.003 or 0.01 mg/kg/day in rats or rabbits, respectively. Although maternal toxicity was evident in all studies, the effects of Idoxifene on rat and rabbit reproduction were considered to be due to the pharmacologic activity of the compound.

1825 THE EFFECT OF PHENOLPHTHALEIN ON B6C3F1 MOUSE OVARIES.

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Phenolphthalein (PhTh) is widely available in over-the-counter laxatives, thus, it is difficult to estimate annual exposures resulting from self medication. It is estimated that 90% of chronic laxative abusers are women, especially those with eating disorders such as anorexia nervosa or bulimia nervosa. Therefore, it is important to consider potential risks of PhTh exposure to reproductive health in women. Because PhTh was reported to increase the incidence of ovarian hyperplasia and neoplasms, the purpose of this study was to determine whether short-term exposure of mice to PhTh reduces the number of ovarian follicles. Female B6C3F1 mice were exposed orally to PhTh (1895 mg/kg-d, p.o.) with daily dosing for 30d or 60d. Control groups were vehicle (sesame oil) and benzo[a]pyrene (BaP, 200mg/kg i.p., d1 and d7; to cause oocyte destruction). Body weights were recorded daily, and ovarian cyclicity was determined by vaginal cytology the final 30d in the 60d mice. Following dosing, animals were euthanized (CO_2 inhalation). Ovaries were collected and prepared for histological evaluation, and follicles were classified (primordial, primary, growing, antral) and counted. Oocytes contained in primordial follicles were reduced ($p<0.05$) in BaP-treated mice at 30d and 60d (49.1% and 50.6% control, respectively). PhTh caused no changes ($p>0.05$) in weight gain, estrous cyclicity, or numbers of oocyte-containing follicles of any class on d30 or d60. Additionally, PhTh caused no detectable pathological changes in ovarian cells. In conclusion, short-term oral exposure (60d) of mice to PhTh does not produce detectable ovarian changes. 1P30ES06694, CDM# N01 ES35367.

1826 LEAD EXPOSURE CAUSES ALTERED SPERMIOGENESIS IN RABBITS.

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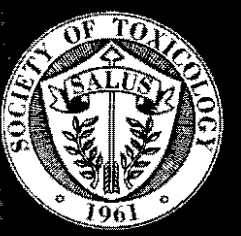
Testicular lesions that might explain lead-induced decreases in sperm counts in man and laboratory animals have not been described. Male Dutch-Belted rabbits (n = 95) were divided into 8 groups and administered lead acetate subcutaneously to achieve and hold target blood lead levels (0, 20, 40, 50, 70, 80, 90, 110 μg/dl; n = 22, 15, 15, 7, 7, 15, 7, 7, respectively) for 15 weeks. Animals were then sacrificed and necropsied. Mean testis weight was not altered. When seminiferous tubules of lead-exposed rabbits were examined by light microscopy, membrane-bound cytoplasmic bodies (CBs), containing ≥ 1 elongate spermatid(s), were seen on the luminal surfaces of the germinal epithelium. CBs were most frequently found in tubules that were at the stage of spermatid release. No treatment effect on either the quantity or quality of Sertoli cells or pre-spermatid germinal cells could be detected by light microscopy. The percent of animals with CBs in each treatment group were (from control to high dose) : 0%, 7%, 33%, 43%, 43%, 47%, 14%, and 100%, respectively. Lead exposure to male rabbits causes a lesion in spermiogenesis which is characterized by retention of spermatid cytoplasm.

1827 LACK OF TRANSGENERATIONAL REPRODUCTIVE EFFECTS FOLLOWING TREATMENT WITH DI-ISODECYL PHTHALATE.

A I Nikiforov, G W Trimmer, L H Keller, S B Harris.[1] *Exxon Biomedical Sciences, Inc., Toxicology Division, East Millstone, NJ; [1]Stephen B. Harris Group, San Diego, CA.*

Di-isodecyl Phthalate (DIDP) (CAS RN 68515-49-1) was administered in diet to four groups of parental (P) and their adult offspring (F1), male and



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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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