block in dopamine-beta-hydroxylase activity. This study was designed to explore a potential effect of longer MS exposures on estrous cyclicity, the LH surge & ovulation. Normally cycling 90d S-D rats were administered MS (0,50,100 or 200 mg/kg/d, oral gavage) for 3 weeks and cyclicity monitored daily over this period. In animals cycling normally during the 3rd week, a small amount of proestrous blood was sampled for LH at 1430, 1600, 1730, 1900 and 2030 hrs. On the day of estrus between 21 & 26 days of dosing, cycling animals were euthanized for oocyte retrieval. The hypothalamus, along with caudate (CAU) tissue, was dissected out and analyzed by HPLC for catecholamine concentrations. Results showed that shortly after the beginning of exposure there occurred a dose-related period of extended diestrus (possibly reflecting a pseudopregnancy) that typically lasted 8-16 days. Cycling was then reinstated, and no effects were seen on the magnitude/timing of the LH surge or ovulated oocyte numbers. Anterior and posterior hypothalamic NE and dopamine (DA) were not significantly different from controls, although DA turnover (as reflected by the DOPAC/DA ratio) in both anterior hypothalamic and CAU regions was decreased at all MS dosages. The data indicate that a 3 week oral exposure to MS induced an initial period of extended diestrus before the resumption of apparently normal reproductive activity, with previously reported catecholamine alterations (apart from a persistent alteration in the DOPAC/DA ratio) being normalized by the end of exposure. (This abstract does not represent USEPA policy)

390 THE REPORTED ACTIVE METABOLITE OF THE PESTICIDE METHOXYCHLOR (MC), 2,2-BIS(P-HYDROXYPHENYL)-1,1,1-TRICHLOROETHANE (HPTE), INHIBITS ANDROGEN PRODUCTION BY RAT OVARIAN THECA INTERSTITIAL (TI) CELLS

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HPTE is reported to be the active metabolite of the pesticide, MC, which is commonly used on agricultural crops and livestock. Following in vivo administration of MC, it is rapidly converted to HPTE by the liver. Both MC and HPTE have been shown to have weak estrogenic and antiandrogenic activities through estrogen and androgen receptors, respectively. Previous in vivo studies in female animals demonstrated decreased progesterone production and no change in estrogens in the blood following exposure to MC. The current in vitro studies examined the effects of HPTE on androgen and progesterone production by cultured ovarian TI cells from immature rats. To isolate TI cells, 24-25 day-old female Sprague-Dawley rats were injected (s.c.) with 20 I.U. of pregnant mare serum gonadotropin. Approximately 48 h following treatment, TI cells were isolated following collagenase digestion of isolated ovarian tissue. TI cells, were cultured in DMEM / F12 medium at 37 0C in a humidified atmosphere of 95 % air and 5 % CO2. Cells were exposed to HPTE for 24 h on the day of plating. The current studies showed that HPTE (0, 10, 25, 50, 100 nM) inhibited testosterone and androstenedione formation in a dose dependent manner with a significant decline to ~45 % of control at 100 nM HPTE. Progesterone production was also inhibited with progressive declines to ~12 % of control at 100 nM HPTE. Among the steroidogenic enzymes involved in estrogen biosynthesis, HPTE, specifically, inhibited P450 cholesterol side-chain cleavage (P450-SCC) activity in a dose dependent manner. These studies demonstrate that the formation of the main substrates for estrogen production by granulosa cells of the ovarian follicle is inhibited by HPTE.
The findings and conclusions in this abstract have not been formally disseminated by NIOSH and should not be construed to represent any agency determination or policy.

391 METHOXYCHLOR AND ITS METABOLITES INHIBIT GROWTH AND INDUCE ATRESIA OF ANTRAL FOLLICLES IN BABOON OVARIES

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Methoxychlor (MXC), an organochlorine pesticide, is used against insects that attack fruits, vegetables, and home gardens. MXC and its metabolites, mono-OH MXC and bis-OH MXC (HPTE), are known to cause atresia (follicle death via apoptosis) in rodents. Although studies have examined the effects of MXC in rodents, few studies have evaluated the effects of MXC in primates. Therefore, the present study tested the hypothesis that MXC and its metabolites (mono-OH MXC and HPTE) inhibit growth and induce atresia of baboon antral follicles. Antral follicles were isolated from ovaries of normal cycling adult baboons and cultured in supplemented media with vehicle (dimethylsulfoxide; DMSO), MXC (1-100µg/ml), mono-OH MXC (0.1-10µg/ml), or HPTE (0.1-10µg/ml) for 96 hr. Growth was monitored at 24 hrs intervals in response to MXC and its metabolites. After culture, follicles were processed for histological evaluation of atresia during which each follicle was rated for atresia on a scale from 1-4 (1-healthy follicle, 2≤10%, 3≤10 to 30%, and 4≥30% pyknotic bodies/follicle). Differences between treatment groups were analyzed by analysis of variance. The results indicate that MXC, mono-OH MXC, and HPTE significantly inhibit antral follicular growth by 96 hrs at all the doses compared to DMSO (n=23; p≤0.005). MXC and its metabolites also increase atresia by 96hrs compared to DMSO. The mean atresia rating for DMSO-treated follicles was 1.41±0.15, while the mean ratings for MXC, mono-OH MXC, and HPTE-treated follicles were 3.92±0.08, 3.56±0.16, and 4.00±0.00 respectively (n=12; p≤0.001). Moreover, adverse effects of MXC and its metabolites on growth and atresia in baboon antral follicles were observed at lower doses than those causing similar effects in rodents. In conclusion, these data suggest that MXC and its metabolites inhibit growth and induce atresia of antral follicles in baboons, and that primate follicles may be more sensitive to MXC than rodent follicles. Supported by U54 HD36207.

392 METHOXYCHLOR INDUCES ATRESIA OF ANTRAL FOLLICLES IN ER ALPHA OVEREXPRESSING MICE

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Methoxychlor (MXC) is a pesticide that is known to bind to estrogen receptor alpha (ERα) and to induce atresia of antral ovarian follicles. Although studies have shown that MXC is toxic to the ovary, we hypothesize that perturbation to the estrogen signaling system (i.e., increases or decreases in estrogen sensitivity) might alter ovarian responsiveness to MXC. Thus, we examined whether ERα overexpression alters the ability of MXC to increase follicle atresia. To do so, we employed a transgenic mouse model in which ERα can be inducibly overexpressed in animal tissues (ERα overexpressors). We dosed female ERα overexpressors and controls with sesame oil (vehicle control) or MXC (32mg/kg/day and 64mg/kg/day) for 20 days. After dosing, ovaries were collected for histological evaluation of atresia and blood was collected for measurements of hormones. In controls, the percentage of atretic follicles for each treatment group was as follows: sesame oil=9.9±1.3; MXC (32mg/kg/day)=14.6±4.7, n=4, p=0.5 vs. sesame oil; and MXC (64mg/kg/day)=22.3±2.7, n=3, p≤0.05 vs. sesame oil. In ERα overexpressors, the percentage of atretic follicles was as follows: sesame oil=9.1±1.7; MXC (32mg/kg/day)=19.2±1.8, n=7, p=0.1 vs. sesame oil; and MXC (64mg/kg/day)=34.2±5.5, n=7, p≤0.001 vs. sesame oil. Estradiol and follicle-stimulating hormone levels did not differ between sesame oil- and MXC-treated mice. These data indicate that MXC and E2 increase atresia compared to vehicle in both controls and ERα overexpressors. Although the differences between controls and ERα overexpressors did not reach statistical significance (probably due to the small group size), there was a clear trend towards greater sensitivity to E2 and MXC in ERα overexpressors. Thus, this study indicates that ERα overexpressors may be a sensitive tool for screening xenobiotics that act through ERα. Supported by NIH R21 ES1306 (J.A.F.).

393 ANTI-MULLERIAN HORMONE CORRELATES WITH OVARIAN FOLLICLE POPULATIONS IN MICE

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The presence or absence healthy oocytes (eggs) in a woman's ovaries determines her reproductive status. Women are born with a finite population of dormant oocytes that cannot proliferate. Quantifying the oocytes remaining to a female has proven to be difficult, because we have not identified anything that is produced or influenced by dormant follicles. With at least 8% of US and Canadian women seeking infertility counseling or treatment, having a non-invasive marker of true ovarian reserve, the number of gametes remaining to an individual, would be an important diagnostic tool for clinicians. Anti-mullerian hormone (AMH) has been implicated in maintaining follicle dormancy. Thus, although this hormone is made only in growing follicles, its secretion may be controlled by the numbers of dormant follicles present in ovaries. In the clinic, AMH correlates with fertility as well or better than current methods. In order to test AMH as a predictor of ovarian reserve, we have used a chemical, 4-vinylcyclohexene diepoxide (VCD), to manipulate ovarian follicle populations. Prior studies showed VCD specifically depletes dormant and earliest growing ovarian follicles in rodents, without any other toxicity. Mice were given daily doses of VCD (240mg/kg/day) on days 1-5, and ovarian follicle populations and hormone levels were compared with vehicle-treated mice. Exposures

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Preface

This issue of *The Toxicologist* is devoted to the abstracts of the presentations for the symposium, platform, poster discussion, workshop, and poster sessions of the 45th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, San Diego, March 5–9, 2006.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 500.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 534.

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

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