and n = 3 adults) and natural killer (NK)-cell activity (NKTEST®, Orpegen-Pharma, Heidelberg, Germany) in 3 infants and 3 adults. Infant animals were one and 24 months old and adult animals were older than six years. Blood IPT revealed cell numbers within the adult reference ranges for all lymphatic subsets by one months of age with NK cells being consistently in the lower range. The CD4:CD8 ratio decreased from 2.2 at one month to 1.3-.1.6 at 12 months of age. Compatible with the IPT data, infant NK cell activity at 12-25 months was lower compared to adult (> 6 years of age) animals and the response to the functional stimulator IL-2 was reduced in the infants. In contrast, lymphocyte proliferation in 15-18 months old infants was comparable to that of adult animals with or without the presence of IL-2 based upon thymidine incorporation. TDAR responses (functional antigen presenting cells, T-cells, and B-cells and antibody-producing plasma cells) were evident by 3 months of age and a pronounced secondary antibody response to a booster immunization approximately 3 months thereafter. Overall, these data demonstrate general functionality of the cynomolgus monkey immune system in early postnatal life.

1137 THE EFFECTS OF *IN VIVO* EXPOSURE OF METHOXYCHLOR TO IMMATURE RATS ON SERUM PROGESTERONE AND ESTRADIOL LEVELS AND THE *EX VIVO* FORMATION OF PROGESTERONE BY THECA-INTERSTITIAL CELLS.

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Sponsor: V. Castranova.

Exposure to the pesticide methoxychlor (MC) in rodents is linked to impaired steroid production, ovarian atrophy and reduced fertility. Effects of in vivo MC treatment are thought to be mediated mainly by the active metabolite, HPTE. Previous in vitro studies on cultured ovarian cells have reported that HPTE inhibited P450 cholesterol side-chain cleavage activity resulting in decreased progesterone (P) and estradiol (E) production, suggesting direct ovarian effects. The current studies examine whether in vivo exposure to MC (0, 20-200 mg/kg) for 5-6 days alters serum P or E levels or ex vivo production of P by theca-interstitial cells from immature female rats primed with or without pregnant-mare serum gonadotropin (PMSG). In animals not treated with PMSG, serum P levels declined progressively with the dose of MC administered starting at the 100 mg/kg dose (43% of control) to 30 % of control at the 200 mg/kg dose. In the studies where animals were exposed to MC and to PMSG during the last 2 days of MC exposure, serum P was no different than the control level (4.97 ± 0.58 ng/ml in control animals); however, serum E levels declined to ~72 % of control. In ex vivo studies on ovarian cells obtained from animals exposed in vivo to MC but without PMSG, P production under basal conditions of cells exposed to MC was no different than control; however, when cells were exposed to hCG, cells exposed in vivo to MC produced 2.1-fold more P than control cells. In ex vivo studies on ovarian cells obtained from animals exposed in vivo to MC but also to PMSG, ovarian cells incubated under basal conditions and exposed to MC produced 1.5-fold more P than control cells. These studies demonstrate that the pattern of circulating P or E and ovarian cell production of steroids in response to in vivo exposure to MC is influenced by the maturational status of ovarian follicles and to possible differences in how female rats metabolize MC and /or its major steroid products.

1138 ANALYSIS OF CYTOGENETIC AND DEVELOPMENTAL EFFECTS ON PRE-IMPLANTATION MOUSE EMBRYOS AFTER MATERNAL EXPOSURE TO TRICHLORFON.

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Presently, we assessed cytogenetic and developmental toxicity in 3-day mouse embryos following maternal exposure to trichlorfon by drinking water at low levels (2, 10, or 50 mg/kg/day) for one month before pregnancy. Then the females were paired with males overnight. The pregnant mice were administered continuously until they were killed on the day of gestation 3. On day 3 of gestation, blastocysts were collected and evaluated for gross morphology, micronuclei (MN) frequency, cell number, fragmented nuclei and pycnotic nuclei. Trichlorfon exposure neither affected mean MN number and MN frequency in pre-implantation mouse embryos, nor maternal weight gain, implantation rates, or reproductive success (P>0.05). A significant decrease in the embryo cell number of pre-implantation embryos indicating developmental damage was observed in the 50mg/kg trichlorfon treatment group in comparison to control but not in 2 and 10 mg/kg groups. There were also a significant decrease in the blastocysts proportion, and a significant increase in morula proportion of pre-implantation embryos in the 50mg/kg group. Therefore, trichlorfon exposure under the present doses did not affect maternal weight gain and reproductive success, nor where cytogenetic toxicity evident in pre-implantation embryos. The lack of effects of trichlorfon on any in vivo reproductive and fetal endpoints suggests that, for trichlorfon, a hazard of reproductive toxicity below 50 mg/kg/day (which includes the highest trichlorfon residue levels detected from vegetables in China) is not expected. However, a simultaneous decrease in the cell number, blastocysts proportion and increase in morula proportion in 50 mg/kg group may reflect an embryonic developmental disadvantage resulting from maternal treatment with trichlorfon.

1139 CONSEQUENCES OF PRENATAL PFOA EXPOSURE ON MOUSE MAMMARY GLAND GROWTH AND DEVELOPMENT IN F1 AND F2 OFFSPRING.

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Perfluorooctanoic acid (PFOA) is a known developmental toxicant with ubiquitous presence in industrial applications and the ambient environment. We previously reported that prenatal PFOA exposure results in delayed development of the mouse mammary gland (MG) in F1 female offspring. To determine consequences of this delayed MG development on lactational function and subsequent development of F2 offspring, F1 females exposed transplacentally to 0, 1 or 5 mg PFOA/kg/day (control, 1P, 5P; gestation days 1-17), were bred to generate F2 offspring (no direct exposure to PFOA). F2 offspring were monitored for growth and development from postnatal day (PND) 1-22, and F1 dam MG function was assessed on PND10 by lactational challenge. MG tissue was isolated from both F1 and F2 females at necropsy on PND10 and 22, and scored for age-appropriate development on a 1-4 scale. As hypothesized, MG morphological scores were lower ($p<0.05$) in 1P and 5P F1 dams evaluated on PND10, and in 5P F1 dams on PND22. However, no effect of treatment on milk production (volume after 30-min nursing) or maternal behavior (time to initiate nursing) was detected on PND10. Body weight of F2 pups was similar between groups on PND1-10, however, starting on PND14 and persisting through PND22 body weight of 1P F2 offspring was significantly higher than controls. MG developmental scores in F2 pups were similar to control at PND10, but lower among P5 F2 offspring on PND22. The time of eye-opening was similar in all groups. These findings confirm previous PFOA-induced delays in lactating mammary gland differentiation, with a current LOEL for these effects at 1 mg/kg/d, and suggest that these delays have little, if any, deleterious effects on the F2 offspring early in life; further evaluation of F2 offspring will illuminate whether adverse health effects may result in adult life. (This abstract does not necessarily reflect EPA policy; SSW funded by EPA CR833237, NIH T32 ES007126.)

1140 NEONATAL EXPOSURE TO DES INDUCES DOSE-DEPENDENT DELAYED EFFECTS AT DOSES SHOWING ESTROGENIC ACTIVITY IN FEMALE DONRYU RATS.

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The neonatal exposure to endocrine disrupting chemicals (EDCs) with estrogenic activity is known to induce irreversible damage to hypothalamo-pituitary-gonadal axis called as androgenization in females, which immediately disrupts reproductive organ development before puberty. Recently, delayed effects of the neonatal exposure to estrogenic EDCs, which are inducible by lower treatment, have been focused as another type of neonatal effects, because these effects can't be detected in short-term bioassays. This type has been already reported as 'delayed anovulatory syndrome' (DAS), but its disruption pathways and endpoint markers remain fully undetermined. We investigated the relationship between occurrence of delayed effects and dose dependency in long-term reproductive organ responses to neonatal exposure to diethylstilbestrol (DES) in female rats. Female Donryu rats treated with single dose of DES at 0.15 to 1500 ug/kg body weight within 24 hours after birth were observed for 12 months. In addition, the rats were initiated with ENNG at 10 weeks of age to investigate uterine carcinogenesis. Typical androgenization was observed at 1500 ug/kg and 150ug/kg before puberty. Although no changes were detected before puberty, early onset of persistent estrus was detected in rats at 1.5 ug/kg body weight (at 21 weeks of age) and higher. Uterine adenocarcinoma development was promoted at 150 ug/kg. In uterotrophic assay, single dose treatments with DES at 1.5 ug/kg and higher exerted estrogenic activity. These results indicate that delayed effects were induced by neonatal exposure to DES at the doses showing estrogenic activity with dose-dependent manner. Estrous cyclicity is a useful

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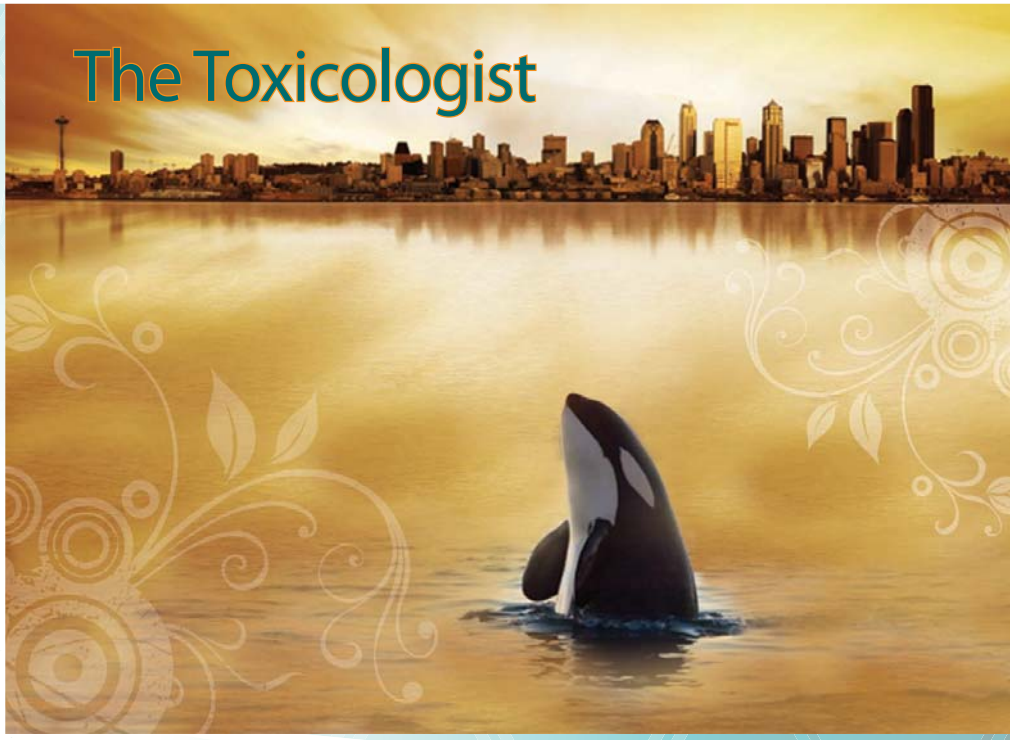

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