section on day 21 of gestation and examined for external and visceral abnormalities. Maternal plasma levels of these test compounds were measured on day 12 of gestation. In *in vitro* study, rat embryos were explanted on day 11 of gestation, incubated in 100% rat serum containing those test compounds for 46 hours according to the whole embryo culture method, and examined for growth, heart rate, mortality and morphosis. In *in vivo* study, fetal body weights decreased at 20 mg/kg of MON and 100 mg/kg of NIF, fetal mortality increased at 30 mg/kg of MON, 100 mg/kg of NIF and 40 mg/kg of VER, the incidence of ventricular septal defect (VSD) increased at 20 mg/kg of MON, 25 mg/kg of NIF and 40 mg/kg of VER, and the incidence of abnormalities of tail and limbs increased at 40 mg/kg of VER. Cmax values in dams showing an increase in the incidence of VSD were 1,049 ng/ml at 20 mg/kg of MON, 7,833 ng/ml at 25 mg/kg of NIF and 1,014 ng/ml at 40 mg/kg of VER. In *in vitro* study, the heart rate of embryos decreased at 300 ng/ml of MON, 100,000 ng/ml of NIF and 1,000 ng/ml of VER, fetal mortality increased at 1,000 ng/ml of MON, 100,000 ng/ml of NIF and 1,000 ng/ml of VER, and edema of forelimbs appeared at 1,000 ng/ml of VER. The *in vivo* study revealed that oral administration of MON, NIF and VER caused growth retardation, lethality and an increase in the incidence of VSD or external abnormalities in fetuses, and the teratological effect level was just the same to a fetal lethal level for VER and lower than that for MON and NIF. The *in vitro* study revealed that application of these test compounds caused a decrease in heart rate, lethality or external abnormalities in embryos, and exposed concentrations that caused these changes tended to relate to the Cmax in dams showing fetal toxicity in the *in vivo* study.

P4C36 THE EFFECTS OF PENTACHLORONITROBENZENE ON THE FIBRONECTIN DISTRIBUTION DURING LUNGS AND KIDNEY DEVELOPMENT IN CHICK EMBRYOS

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In this study the effect of pentachloronitrobenzene (PCNB) on fibronectin (FN) distribution on the early stages of White Leghorn chick embryos was investigated by using immunohistochemical-staining method. PCNB was dissolved in vegetable oil and two different PCNB solutions of 10 and 100 fold of the daily acceptable dose was applied to fertilized chick eggs. After incubation, sections from the desired stages of embryos were taken and stained.

On the sections of the control group, especially on stage 18, high FN density around extracellular matrix of the cells was observed in the regions where organs like lungs and kidney were expected to develop. A decrease in growth was observed on the further stages like stages 23 and 25 of PCNB treated embryos. Compared to the control group, it was found that a delay on the formation of the organs occurred due to the delay on the differentiation of the cells migrating to the regions where organs like lungs and kidney were to be formed.

As a result, it was found out that application of PCNB at doses of 10 and 100 fold of the daily acceptable dose on chick embryos affected the FN distribution and the embryo development and also caused a delay on the formation of certain organs.

P4C37 BIOACCUMULATION AND INDUCTION OF CYP450 LIVER ENZYMES BY SYNTHETIC MUSK FRAGRANCES IN DEVELOPING AND ADULT RATS

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Nitro musks and polycyclic musks are used as substitutes for natural musks derived from the musk deer (*Moschus moschiferus*). These highly lipophilic compounds have recently been found to bioaccumulate in human fat and milk. Toxicity data and, in particular, data on developmental toxicity of these compounds are scarce. We are investigating the developmental toxicity in Long Evans rats. Adult male and female rats were fed with chow containing a nitro musk, musk xylene (MX) (0.033, 0.1, 1.0 g MX/kg food pellets) for 10 weeks before mating. After mating, treatment continued during pregnancy and lactation. At postnatal day (PN) 14, MX levels in body fat were similar in male and female offspring and amounted to 1/2–3/4 of adult female and 3–4 times adult male values. In adult rats fed on a diet of 0.1 gMX/kg food pellet, MX concentrations were highest in adipose tissue. Adult females exhibited 3.7–6.8 times higher levels than males. An analogous sex difference was observed in kidney, liver, adrenal, gonads and brain of the parent generation, with highest female to male ratios in the gonads (Suter-Eichenberger et al., Chemosphere, in press).

A dose-dependent induction of CYP450 1A1 and 1A2 was observed in liver microsomes of adult rats by measuring EROD (7 ethoxyresorufin-o-dealkylase) and MROD (methoxyresorufin-o-dealkylase) activities and by Western blotting. A dose-dependent induction of these enzymes in the same order of magnitude as in adult animals was found in PN14 pups. However, the enzyme-induction pattern differed insofar as CYP450 1A1 activity was induced more than CYP 4501A2 in the offspring, whereas MX was a stronger inducer of CYP450 1A2 in adult rats. According to preliminary Western blot data, CYP 450 2B also is induced in adults and offspring.

Experiments on developmental effects of the polycyclic musk fragrant Galaxolide (HHCB) and diethylphthalate which is used as a carrier for HHCBin commercial preparations, are in progress.

P4C38 INTERACTIVE DYSMORPHOGENIC EFFECTS OF TOXAPHENE OR TOXAPHENE CONGENERS AND HYPERGLYCEMIA ON CULTURED WHOLE RAT EMBRYOS DURING ORGANOGENESIS

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Diabetes mellitus, one of the most common maternal illnesses resulting in congenital defects is on an upgrowth trend in many native communities. In addition, many of their traditional foods have been contaminated with persistent organic pollutants, such as the pesticide toxaphene. The potential interactive effects is becoming a health concern. We studied the interactive effects of toxaphene (TOX) and its two congeners, T_2 (*2-exo,3-endo,5-exo,6-endo*,8,8,10,10-octachlorobornane) and T_{12} (*2-exo,3-endo,5-exo,6-endo*,8,8,9,10,10-nonachlorobornane), and high glucose concentration using rat embryo culture. Whole rat embryos (0-2 somite) were explanted and cultured into a normal (8 mM) or hyperglycemic 12.5 mM (12.5 G) or 18.75 mM (18.75 G) culture medium containing TOX, T_2, or T_{12} at various concentrations (0, 100, 1000, 5000 ng/ml) for 48 h at 37-C. The treatment period corresponds to gestational days (GD) 10–12, the critical time of morphogenesis and organogenesis. All treatments, except mild hyperglycemic exposure (12.5 G), had significant adverse effects on the total morphological score, somite number, head and crown rump length, and the central nervous system scores. The embryos cultured with TOX under severe hyperglycemic conditions exhibited a concentration related interactive effect. Interactive effect with hyperglycemia (18.75 G) was shown in two, five, and eight parameters at 100, 1000, and 5000 ng/ml TOX exposure respectively. Similar concentration related additive effects were present between T_2 or T_{12} and hyperglycemia (18.75 G). T_{12} was less toxic compared with TOX and T_2. The major malformations were abnormalities in the development of the central nervous system. Hyperglycemia combined