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In recent research using zebrafish, we demonstrated that pharmacologic response to 10 well-characterized cardiotoxicants is similar to response in humans. Drugs that elicited cardiomyopathy, arrhythmia, negative inotropic effects, or QT prolongation in humans also caused bradycardia, decreased contractility, and slow circulation in zebrafish. Zebrafish rapidly responded to potent inotropic effectors and exhibited bradycardia, irregular rhythmicity, weak contractility, and slow circulation. At sublethal concentrations (~100  $\mu$ M for mitoxantrone, terfenadine, clomipramine and thioridazine), hemorrhage, and edema were also observed. In zebrafish, acute atrioventricular block (A/V= 2/1 to 4/1) was observed after treatment with drugs that caused arrhythmia and QT prolongation in humans, but not after treatment with classes of drugs that cause cardiomyopathy, mild ion imbalance, or coronary vasospasm. The acute atrioventricular block can be used as an index to predict drug-induced arrhythmia and QT prolongation in humans. Severe impairment of cardiac function after treatment with terfenadine and clomipramine resulted in formation of edema and hemorrhage, arrested heart beat and even death. These results indicate that the zebrafish exhibits cardiac toxicity comparable to humans and is a predictive model for drug induced cardiotoxicity in humans.

### 1536 DIOXIN AND DIABETES: DOES THE CURRENT WEIGHT OF EVIDENCE DEMONSTRATE A RELATIONSHIP?

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Studies of United States veterans exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) during Operation Ranch Hand in Vietnam suggest an apparent association between increasing blood lipid TCDD and increased insulin sensitivity or fasting serum glucose. However, overall rates of diabetes mellitus were essentially identical in exposed and comparison populations in the Ranch Hand study. An evaluation of mean fasting serum glucose in the NIOSH dioxin cohort did not reveal associations with blood lipid TCDD, and other dioxin-exposed cohorts to date have not affirmed these Ranch Hand study findings. We review dose-response trends in cohorts with markedly elevated TCDD levels and in cohorts with lower TCDD levels, and explore the potential influence of confounding variables such as age, obesity, and family history of diabetes. We also examine the potential influence of concentration- and age-dependent toxicokinetics on possible TCDD-diabetes associations. Although a substantial concentration-dependent influence is unlikely for the Ranch Hand cohort, the age-dependent toxicokinetic model predicts that greater age and greater adipose volume lead to greater retention of TCDD body burden (i.e., longer half life). Since greater age and adipose volume (i.e., obesity) are strongly correlated with diabetes risk, the observed TCDD-diabetes association could be artifactual and/or due to inadvertent selection bias within the Ranch Hand study populations. The similar diabetes incidence trends in the Ranch Hand exposed and comparison groups and the absence of supporting evidence in more highly exposed populations makes the TCDD-diabetes association somewhat tenuous. Further studies are needed to clearly discern any meaningful TCDD dose-related trends from inherently correlated diabetes risk factors.

### 1537 ALTERATION IN CARCINOGENIC POTENCY OF PCB126 BY PCB153 FOLLOWING CHRONIC EXPOSURE IN FEMALE RATS

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The dioxin Toxic Equivalency Factor (TEF) approach is currently used worldwide for assessing and managing the risks posed by exposure to mixtures of polychlorinated dibenzodioxins (PCDDs), dibenzofurans (PCDFs) and biphenyls (PCBs). While the TEF approach is only applied to dioxin-like PCBs (non-ortho and mono ortho substituted PCBs), previous studies have shown the potential for interactions between different classes of PCBs for nonneoplastic responses. To test for interactions between dioxin-like and non dioxin like PCBs for carcinogenic responses, the National Toxicology Program conducted multiple 2-year rodent bioassays in female Harlan Sprague Dawley rats examining the carcinogenicity of PCB126, PCB153 and a binary mixture of PCB126 and PCB153. Chronic exposure to PCB126 or the mixture of PCB126+PCB153 led to treatment related increased incidences of cholangiocarcinoma and hepatocellular neoplasms in the liver, cystic keratinizing epithelioma of the lung and gingival squamous cell carcinoma of the oral mucosa. In contrast, chronic exposure to PCB153 led to only marginal increases in cholangioma of the liver. Statistically based, dose-response modeling was used to evaluate the dose-responses for induction of both neoplastic and non neo-

plastic effects seen in these studies, and to test for interactions between compounds within mixture. In comparison to PCB 126 alone, a higher potency of carcinogenicity of PCB126/PCB153 was observed for cholangiocarcinoma and hepatocellular adenoma. In contrast, a lower potency of the mixture of PCB126 +PCB153 was observed for cystic keratinizing epithelioma of the lung. These data indicate that interactions between different classes of PCBs can occur for neoplastic responses and may impact upon the interpretation of the predicted "dioxin-like" carcinogenic activity of mixtures of PCBs.

### 1538 RELATIVE CARCINOGENIC POTENCY OF PCB 126 AND PECDF IN DERMALLY EXPOSED FEMALE TG.AC MICE

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The Toxic Equivalency Factor (TEF) methodology was developed to assess the cancer risk posed by complex mixtures of dioxin-like compounds and is based on the relative potency of these compounds with respect to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), the most potent congener. Tg.AC mice develop epidermal neoplasms in response to oral or dermal treatment with TCDD following a considerably shorter duration of exposure than in traditional bioassays. To evaluate the use of the Tg.AC mouse as a biologically-based model for the prediction of relative potency for other dioxin-like chemicals, the induction of epidermal neoplasms was determined for the dioxin-like compounds 3,3,4,4,5-pentachlorobiphenyl (PCB 126) and 2,3,4,7,8-pentachlorodibenzofuran (PeCDF). Total TCDD equivalent (TEQ) doses were selected for PCB 126 and PeCDF based on the established TEF values of 0.1 and 0.5, respectively. Female Tg.AC mice were dermally exposed three times a week for 26 weeks to PCB 126, PeCDF, or a 1:1 (TEQ) mixture of PCB 126 and PeCDF at average daily doses of 0, 15, 52, 154, and 326 ng/kg/day. The incidences of cutaneous papillomas and squamous cell carcinomas were increased in a dose-dependent manner for PCB 126, PeCDF, and the mixture, without an effect on the time of tumor onset for any of the compounds. Based on dose-response modeling for papilloma formation in the Tg.AC mouse, the relative potency of PCB 126 was lower and PeCDF was higher than the WHO established TEF values. These data are in contrast to relative carcinogenic potencies in female Sprague-Dawley rats, which were consistent with 0.1 for PCB 126, and lower than 0.5 for PeCDF. These differences may reflect differences in potency due to the route of administration and/or species differences in sensitivity.

### 1539 DISRUPTION OF SALT-HANDLING IN THE DEVELOPING MOUSE KIDNEY AS A POSSIBLE CAUSE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN-INDUCED HYDRONEPHROSIS

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Hydronephrosis is a typical hallmark of teratogenicity of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the fetus and newborns, that has been recognized since 1970s. Since the etiology of TCDD-induced hydronephrosis is still largely unknown, the present study was undertaken to clarify the mechanism of this toxicity. Pregnant mice were given a single oral dose of 10  $\mu$ g TCDD/kg on postnatal day (PND) 1, and pups exposed to TCDD through milk were sacrificed on PNDs 7, 14, and 21. Histopathological study clearly showed that TCDD produced neither hyperplastic lesions of renal tubular epithelium nor the occlusion of the lumen. Abnormally elevated levels of electrolytes in urine and polyuria were detected in TCDD-exposed pups. Real-time PCR analyses showed that, in the kidney of the TCDD-exposed pups, several genes that are known to be involved in salt handling in the thick ascending limb of Henle's loop and distal convoluted tubules, such as K<sup>+</sup> (ROMK) channel and sodium potassium 2 chloride cotransporter (NKCC2) were down-regulated markedly on PND 7 whereas a drastic induction in gene expression of cyclooxygenase-2 (COX-2) mRNA was observed in developing kidney on PND 7 in response to TCDD exposure. Immunohistochemical examinations demonstrated COX-2 protein to be restricted in macula densa and the distal convoluted tubules with greater staining intensity in TCDD-treated pups. Taken together, the present results shed a light into the mechanism pathogenesis of hydronephrosis caused by TCDD and suggested the possibility that the impaired salt transport pathway via an induced COX-2 is responsible for TCDD-induced hydronephrosis.