to dioxin-like compounds, which exert their effects by binding to the aryl-hydrocarbon receptor (AHR), exhibit a higher incidence of congenital heart disease, the leading cause of neonatal mortality and a major source of adult cardiac insufficiency. In humans and mice, NKX2-5 mutations lead to congenital heart defects and cardiomyopathies. We find that full-body ablation of the Ahr gene in mice or exposure to dioxin *in utero* cause a decreased of cardiac Ahr and Nkx2-5 expression with resulting abnormal transcriptome, as well as structure and function in the developing heart, and cardiomyopathy in the adult. Knock-in of the cre recombinase gene into an Nkx2-5 allele results in cardiomyopathy due to haploinsufficiency. To determine the role of AHR in the penetrance of this pathological NKX2-5 haploinsufficiency phenotype, we generated mice with a cardiac-specific deletion of the Ahr gene. Echosonography analyses revealed that the ejection fraction and other critical indices of cardiac function were significantly decreased with age in haploinsufficient Nkx2-5+/creAhr+/+ mice but not in Nkx2-5+/creAhrfx/fx, in which both copies of the Ahr had been deleted in cardiomyocytes. Our data show that deletion of the Ahr gene is sufficient to rescue normal cardiac function due to NKX2-5 haploinsufficiency and suggest that this pathological phenotype is a result of AHR-NKX2-5 interplay. These findings illustrate gene-gene-environment interactions as the targets of perinatal environmental exposures, underscoring significant implications to human health and disease. Supported by NIEHS R01006273.

PS 1704 Neonatal Gene Expression: Marks of Prenatal Exposure to PFOA, PFOS, PCB153, and DDE

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The prevalence of obesity and/or diabetes has reached alarming proportions globally. In the European FP7 project OBELIX (OBesogenic Endocrine disrupting chemicals: Linking prenatal eXposure to the development of obesity later in life) the hypothesis was examined that prenatal exposure to endocrine disrupting chemicals (EDCs) plays a role in the development of obesity later in life. One of the objectives of the project was to relate early life exposure to EDCs with neonatal effect biomarkers and health outcome data which are related to risk of obesity later in life. We examined associations between prenatal EDC exposure and changes in the cord blood transcriptome. The panel of EDCs included dichlorodiphenyldichloroethylene (DDE), perfluorooctanoic acid (PFOA), perfluorooctane sulfonate (PFOS), and polychlorinated biphenyl-153 (PCB153). Upstream transcription factor analysis (Ingenuity®) revealed that the progesterone receptor may be incriminated by PFOA exposure. Inhibition of ESR2 (estrogen receptor 2) was associated with exposure to PCB153. The most significant transcription factor associated to DDE was NR3C1 which is also known as the glucocorticoid receptor (GR). In addition to metabolic diseases, this receptor is also involved in asthma. It has been reported that the prevalence of asthma increases with increasing DDE levels. Therefore we hypothesize that adverse regulation of the glucocorticoid receptor during development is a candidate pathway that links prenatal exposure to adult onset of disease. The studies of the Flemish Center of Expertise on Environment and Health were commissioned, financed and steered by the Ministry of the Flemish Community. The research received funding from the European Community's Seventh Framework Programme (FP7/2007–2013) under grant agreement OBELIX 227391.

PS 1705 Transgenerational Effects of Developmental Exposure to Low-Dose Zeranol on Sexual Development, Reproduction, and Mammary Carcinogenesis

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Zeranol (Zer) is a potent semi-synthetic derivative of zearalenone, a myco-estrogen that contaminates grain. Livestock are deliberately dosed with Zer as a growth promoter in the US, it was developed as a substitute for the carcinogen diethylstilbestrol (DES). Zer is banned in Europe and Asia, it is detected in finished food products and extremely stable at cooking temperatures with a long half-life in humans. Occupational exposures to Zer are associated with precocious puberty. Our studies in prepubescent girls indicate that human exposure is primarily via the consumption of beef and corn, and urinary levels of unconjugated Zer are associated with altered onset of puberty, height and weight (Bandera et al., 2011). Our studies in F-344 rats indicated that developmental dietary exposure to Zer (between PND9 to weaning); at doses below the human ADI (1.25μg/kg/day) resulted in precocious puberty (defined as a 3 day decrease in age at vaginal opening) in F1 progeny, increased uterine weight and abnormally prolonged estrous cycle. F1 male progeny showed feminization assessed by both decreased anogenital distance and sperm count. F1 females treated with a single carcinogenic dose of N-nitroso-N-methylurea (NMU) showed decreased latency, increased incidence of mammary tumors and greater tumor mass. Similar effects on puberty and carcinogenesis were also observed in the F2 progeny, but only if both the dam and sire were exposed to Zer *in utero*, suggesting recessive epigenetic inheritance. Studies on the F3 generation demonstrated a significant decrease in fecundity, male offspring and delayed vaginal opening in F3 female progeny. Together these studies suggest that *in utero* exposure to the Zer produces transgenerational effects on sexual maturation and susceptibility to chemical-induced carcinogenesis. Support: The New Jersey Commission on Cancer Research, Rutgers-EOHSI and NIEHS-Center for Environmental Exposures and Disease Rutgers the State University of NJ

PS 1706 A Novel Mitochondrial Complex between Δ3, 5, Δ2, 4-Dienoyl-CoA Isomerase and Uncoupling Protein 3: Mechanisms and Implications

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Mitochondrial dysfunction and lipotoxicity are intricately linked to the pathophysiology of obesity-related metabolic disorders. One attractive approach in treating these clinical complications is to enhance cellular expenditure and prevent the accumulation of toxic lipid metabolites by targeting a key regulator in mitochondrial metabolism, uncoupling protein 3 (UCP3). The role of UCP3 in modulating fatty acid (FA) metabolism is often associated with non-shivering thermogenesis-the mitochondrial bioenergetic process by which fuel is metabolized and released in the form of heat in response to certain stimuli (cold environments). However, the underlying mechanisms of UCP3 function are unclear. We have identified a novel, mitochondrial fatty acid (FA)-metabolizing complex that is formed between UCP3 and the unsaturated FA metabolizing enzyme,Δ3,5, Δ2,4 dienoyl-CoA isomerase (DCI), which is involved in the complete oxidation of unsaturated FAs with double bonds in odd-numbered positions (e.g. oleate). Using a variety of biochemical approaches, we have shown that DCI interacts with UCP3 in the mitochondrial matrix, to increase unsaturated FA metabolism and uncoupled respiration in skeletal muscle (SKM). In terms of the physiological significance of this complex in FA-induced toxicity, we demonstrate that DCI and UCP3 protein expression is induced in mice fed high-fat diets, and that blockade of mitochondrial FA import diminishes complex formation. To further characterize the functional importance of DCI in UCP3-dependent non-shivering thermogenesis, we generated a DCI-knockout mouse and found that these mice were unable to defend their body temperature when challenged with fasting and cold-exposure, despite an increase in UCP3 expression. Collectively, these observations indicate the importance of the DCI:UCP3 complex in the protection against lipotoxicity.

PS 1707 Environmental Exposure to Benzyl Butyl Phthalate Promotes Adipogenesis in the Preadipocyte 3T3-L1

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Obesity is a growing health problem around the world. Convincing evidences suggest that environmental chemicals contribute to the development of obesity, called "Obesogens". Benzyl butyl phthalate (BBP) is used widely in the manufacture of plastics, and has been linked to the development and reproductive toxicity. In this study, we investigated whether BBP exposure promotes adipogenesis in the preadipocyte 3T3-L1 model, and examined the underlying mechanisms. Preadipocyte 3T3-L1 was treated with BBP at doses of 0.1~200.0 μM along with positive controls. Cell viability was measured by Neutral Red uptake assay. The lipid accumulation in 3T3-L1 cells was stained with oil-red, and quantified by AdipoRed fluorescence. Total RNA was extracted during various stages of differentiation, and gene expressions of the adipogenesis associated genes and epigenetic regulated genes were examined by Realtime qPCR. Protein expressions of Acetyl-CoA Carbooxykase (ACC), Adiponectin, C/EBP, Fatty acid synthase (FASN), PARPγ, and Perilipin were also conducted. BBP showed no significant effect on the cell viability at concentrations of 0.1-100.0 μM after 24 and 48h exposures. BBP significantly induced lipid accumulation dose-dependently. Gene expression of adipogenic transcription factors, PPARγ, C/EBP, AdipoQ, Adipokines, Fatty acid-binding protein 4 (FABP4) and enzymes that regulate adipogensis, Lipoprotein lipase (LPL), FASN were dose-dependently increased in cells treated with BBP. The protein expression of ACC, adiponectin, C/EBP, LPL, PARPγ, and Perilipin also showed significant increases as compared with the controls. Furthermore, the multiple genes that modifying chromatin remodeling were also evaluated. Methyl-CpG-binding domain protein was significantly increased in the BBP treated cell during the induction period of differentiation. In summary, BBP is demonstrated

to promote adipogenesis dose-dependently through the activation of adipogenesis pathway and the modification of epigenetic regulation (Supported by R21 OH010473).

PS 1708 BDE99 (2, 2', 4, 4', 5-Pentabromodiphenyl Ether) Treatment Promotes Adipogenesis in 3T3-L1 Cells

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Flame retardants, such as polybrominated diphenyl ethers (PBDEs), are chemical compounds added to materials such as, textiles, plastics, wire insulation, and automobile to delay the onset of fire. They are widely used for industrial purposes and household materials. NHANES data indicates that nearly all Americans have trace amounts of PBDEs in serum, with even higher levels associated with occupational exposure (foam recyclers and carpet installers). In particular, PBDEs have been detected in human adipose tissue. Therefore, it was hypothesized that PBDE congener, BDE-99 might modulate 3T3-L1 fibroblast cell differentiation to adipocytes. 3t3-L1 cells were grown in maintenance media (DMEM containing 10% fetal calf serum, 1% penicillin-streptomycin). Post-confluent cells were induced with supplemented treatment media (DMEM 10 % FBS, 1% penicillin-streptomycin and 1% glutamine) of 500 M IBMX, 0.25 μM dexamethasone, and 10 μg/ml insulin for 48 hrs. Pre-adipocyte morphology (fibroblasts with spiral morphology) was observed, and the cells were allowed to differentiate to adipocytes in the presence of 0.025% DMSO (control) or 5 μM BDE-99 for 4 and 6 days in treatment media. The treatment media was changed every 2 days. Oil Red O was used to detect lipid development within the pre-adipocytes during differentiation and the dye was measured via spectrophotometric assay for quantitative analysis. RNA was isolated in order to analyze gene expression of regulatory transcription factors related to adipocyte differentiation. BDE-99 treatment during differentiation of 3t3-L1 fibroblasts induced lipid accumulation by 36% compared to DMSO control. The transcription factor PPARγ is induced by 1.5-fold at Day 4 of differentiation with treatment of BDE-9. These preliminary findings suggest that BSE-99 has the potential to promote adipocyte differentiation.

PS 1709 Oculomotor Deficits in Aryl Hydrocarbon Receptor Null Mouse

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The Aryl hydrocarbon Receptor or AhR, a ligand-activated transcription factor, is known to mediate the toxic and carcinogenic effects of various environmental pollutants such as 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin (TCDD). Recent studies in *Caenorhabditis elegans* and *Drosophila melanogaster* show that the orthologs of the AhR are expressed exclusively in certain types of neurons and are implicated in the development and the homeostasis of the central nervous system. While physiological roles of the AhR were demonstrated in the mammalian heart, liver and gametogenesis, its ontogenic expression and putative neural functions remain elusive. Here, we report that the constitutive absence of the AhR in adult mice (AhR-/-) leads to abnormal eye movements in the form of a spontaneous pendular horizontal nystagmus. To determine if the nystagmus is of vestibular, visual, or cerebellar origin, gaze stabilizing reflexes, namely vestibulo-ocular and optokinetic reflexes (VOR and OKR), were investigated. The OKR is less effective in the AhR-/- mice suggesting a deficit in the visuo-motor circuitry, while the VOR is mildly affected. Furthermore, the AhR is expressedin the retinal ganglion cells during the development, however electroretinograms revealed no impairment of retinal cell function. The structure of the cerebellum of the AhR-/- mice is normal which is compatible with the preserved VOR adaptation, a plastic process dependent on cerebellar integrity. Finally, intoxication with TCDD of control adults did not lead to any abnormality of the oculomotor control. These results demonstrate that the absence of the AhR leads to acquired central nervous system deficits in the adults. Given the many common features between both AhR mouse and human infantile nystagmus syndromes, the AhR-/- mice might give insights into the developmental mechanisms which lead to congenital eye disorders.

PS 1710 Background Data of Wistar Hannover Rats for Developmental Toxicity Study: Comparison of Two Substrain of Rats

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Background data of the two sub-strains of Wistar Hannover rats (RccHanTM: WIST and Crl: WI (Han)) for developmental study were compared. Virgin female rats were mated overnight with male rats of the same strain and inspected for the presence of a vaginal plug or sperm the following morning. The day when a vaginal plug or sperm was detected was considered day 0 of gestation. Pregnant rats were observed for their general condition, body weight change, and food consumption during the gestation period. On day 20 of gestation, the rats were euthanatized and uterine horns were exposed. Live fetuses were examined for their external, skeletal and visceral anomalies. There was little difference in the body weight changes or food consumption of dams during the gestation period, number of implantations, number of live fetuses, fetal mortality, body weight of live fetuses, or placental weight between the two sub-strains of rats. The incidence of external, skeletal and visceral anomalies was low in both sub-strains. The total incidence of skeletal variation was similar between these sub-strains, however the incidence of lumber rib (especially shorter rib) was higher in the Crl: WI (Han) rats.

PS 1711 A Comparison of Rat and Rabbit Developmental Toxicity Study Outcomes of More Than 400 Pharmaceutical Compounds

A. H. Piersma[1, 2], P. T. Theunissen[1], S. Beken[3], G. D. Cappon[4], C. L. Chen[5], W. A. Harrouk[6], A. Hoberman[7], J. van der Laan[8] and J. Stewart[9]. *[1]RIVM, Bilthoven, Netherlands, [2]IRAS, Utrecht, Netherlands, [3]FAMHP, Brussels, Belgium, [4]Pfizer, Groton, CT, [5]ILSI-HESI, Washington, DC, [6]US FDA, Silver Spring, MD, [7]Charles River Laboratories, Horsham, PA, [8]MEB, Utrecht, Netherlands and [9]AstraZeneca, Macclesfield, United Kingdom.*

Nonclinical developmental toxicity testing of pharmaceuticals is regularly performed in two species, most often in rat and rabbit. Given the wealth of existing data, the question can be asked retrospectively to what extent the second species study (be it in rat or rabbit) has contributed significantly to the overall conclusion about developmental toxicity of the compound tested. In collaboration with the Dutch Medicines Evaluation Board (MEB) and with the HESI Developmental And Reproductive Toxicity (HESI-DART) technical committee we have collected and entered developmental toxicity test data in rat and rabbit of over 400 pharmaceutical compounds in a modified ToxRefDB database format. The compounds included registered as well as failed pharmaceutical products, and data originated from governmental agencies (through MEB) and industry (through HESI-DART). Between rat and rabbit studies, we have compared effective systemic doses (AUC,Cmax), the nature of developmental effects (death, malformations, growth retardation, variations), the role of maternal toxicity, and the influence of pharmacological targets and mode of action. Potency ratios between species were within one order of magnitude for >80% of compounds. Overall, rabbit studies were more likely to show fetal death, whereas malformations were observed more often in rat studies. The nature of developmental effects varied widely between the two species. Eliminating variations from the adverse effect analysis did not affect overall picture of relative sensitivity. Maternal toxicity was more often observed at the LOAEL in rabbit than in rat. Outliers in terms of relative species sensitivity demonstrated no clear pattern for specific pharmacological targets and mode of action. This study will feed into international discussions about innovations in nonclinical safety testing.

PS 1712 Nonclinical Embryo-Fetal Development Assessment of GLYX-13, an NMDAR Novel Modulator, in Rats and Rabbits

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GLYX-13 is a novel modulator of the NMDAR receptor that has been granted Fast Track designation by the FDA, for development as an adjunctive therapy for major depressive disorder (MDD). GLYX-13 has completed Phase 2 clinical proof-of-concept studies for MDD in patients with inadequate response to antidepressants. Dose-range finding and full embryo-fetal developmental studies were conducted in Sprague Dawley (SD) rats and New Zealand White (NZW) rabbits. In the dose-range finding studies, no maternal or fetal findings were noted in rats up to 300 mg/kg/day while in rabbits, maternal mortality at 500 mg/kg/day and clinical signs

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Preface

This issue is devoted to the abstracts of the presentations for the Continuing Education courses and scientific sessions of the 54th Annual Meeting of the Society of Toxicology, held at the San Diego Convention Center, March 22–26, 2015.

An alphabetical Author Index, cross referencing the corresponding abstract number(s), begins on page 529.

The issue also contains a Keyword Index (by subject or chemical) of all the presentations, beginning on page 553.

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

Scientific Session Types:

- EC Education-Career Development Sessions
- FS Featured Sessions
- IS Informational Sessions
- PL Platform Sessions
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- RI Regional Interest Session
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