1091 EVOLUTION OF THE SCIENCE OF DEVELOPMENTAL IMMUNOTOXICITY.

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The value of incorporating immunological data for the toxicological assessment of drugs, chemicals, biologicals and medical devices for human risk assessment has been increasingly accepted. Since the 1970s, experimental animal studies, and to a lesser extent human studies, have been published describing immunological effects in neonates exposed to toxic agents during the prenatal or early postnatal period . Of particular concern was that immunotoxicity often appeared more severe and/or persistent when the exposure occurred perinatally when compared to exposure in adult animals. These concerns were addressed in a 1993 report from the National Research Council (NRC) entitled Pesticides in the Diets of Infants and Children in which the immune, as well as the reproductive and nervous systems, were identified as potential targets for pesticide exposure. Efforts are presently being undertaken to identify appropriate methods and approaches to identify and study developmental immunotoxicants. In addition to immunosuppression, there is increasing evidence that transplacental priming of the immune system occurs in response to certain environmental agents which possess allergic or inflammatory properties. This subsequently results in T-helper 1 (Th1) or, more often, T-helper 2 (Th2) skewing of the immune system. Consistent with this general postulate is experimental and clinical evidence that individuals exposed early in life to these environmental agents are predispose to increased prevalence and/or severity of immune diseases

1092 SUSCEPTIBILITY OF THE DEVELOPING IMMUNE SYSTEM TO IMMUNOSUPPRESSIVE AGENTS: DIFFERENTIAL RISK ACROSS LIFE STAGES.

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Recent findings from *in utero* vs. adult exposures to toxicants will be used to demonstrate the specific challenges associated with developmental immunotoxicity evaluation. Differential risk to immunotoxicants can result from life-stage-specific differences in metabolism, differential susceptibility of the developing immune system target, potential latency effects, and heterogeneous susceptibility of populations (i.e. toxicogenomics). Likewise, the challenge in selecting an appropriate age of assessment capable of revealing these comparative risks will be discussed. Data from early exposures to low-levels of the heavy metal, Pb, will be presented to support the concept of critical developmental windows of differential immunotoxic risk. Additionally, the Pb-induced immunotoxicity results are consistent with an emerging paradigm of gestationally-induced immunotoxicity. Disrupted T helper balance with the hallmark of suppressed T helper 1 (Th1) function appears to represent a common immunotoxic outcome of early chemical insults. Because Th1 function develops later in gestation than the default T helper 2 (Th2) function, the potential for impairing Th1 function with *in utero* exposure to toxicants appears to be significant. It should be noted that this type of immune alteration (elevated Th2 function with suppressed Th1 activity) would contribute to an increased risk of childhood asthma and allergic disease.

1093 TEMPORAL SPECIFIC EXPRESSION OF TOXICANT-METABOLIZING ENZYMES: IMPLICATIONS FOR LIFE-STAGE-DEPENDENT TOXICITY.

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Substantial changes in toxicokinetics and toxicodynamics occur during human development that contribute to differential susceptibility. Although certainly not the only component, the temporal-specific expression of toxicant metabolizing enzymes contribute significantly to these changes. A better knowledge of these processes and their underlying mechanisms will be required if we wish to understand and predict the dynamic dose-response relationships that occur during ontogeny and develop strategies that would prevent developmental toxicity. The objective of this symposium is to present recent advances in our understanding of how developmental, genetic, and environmental factors interact to define the risk from toxicant exposure. The symposium will cover research results on longitudinal pediatric phenotyping and present a dramatic example of the importance of phenotyping in identifying potential risk. Studies also will be presented on the characterization of both phase I and phase II developmental expression patterns in the human and animal models, explore molecular mechanisms underlying the regulation of such expression patterns, and begin to explore how genetic factors might contribute to both interindividual differences in expression as a function of age.

1094 PEDIATRIC PHARMACOGENETICS: DEVELOPMENTAL "PHENOTYPES" AND THEIR POTENTIAL CONSEQUENCES.

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Individual cytochrome P450 (CYP) isoforms have characteristic developmental profiles, and phenotypic measures of those activities change throughout maturation. Thus, in children, gene-environment interactions that contribute to the pharmacogenetic determinants of drug disposition and response are influenced by an additional variable, development. The goals of our research program are to define the ontogeny of drug biotransformation pathways *in vivo*, and to identify the pharmacogenetic basis of variation in the developmental patterns observed, a process we refer to as "developmental pharmacogenetics." To achieve these goals, we employ a longitudinal phenotyping strategy using probe compounds that are considered safe by health care professionals and perceived as safe by parents, such as dextromethorphan (DM) and acetaminophen (APAP). Phenotyping studies are coordinated with well baby visits to primary care providers. At two weeks postnatal age, CYP2D6 activity (as estimated by the ratio of DM to its *O*-demethylated metabolite, dextrorphan) is consistent with *CYP2D6* genotype (n=96). However, the data also suggest that DM *N*-demethylation activity, attributed to CYP3A, becomes quantitatively more important to overall DM biotransformation as infants mature and become toddlers. For example, the fraction of total DM and metabolites recovered as 3-hydroxymorphinan increases from 0.156 ± 0.154 at two weeks to 0.531 ± 0.157 at 12 months of age while the fraction recovered as dextrorphan decreases from 0.799 ± 0.164 to 0.450 ± 0.148 over the same period. Developmental changes in CYP activity clearly have the potential to affect dosage requirements at different ages but may have toxicologic significance as well. Following APAP dosing to two week old infants, thioether metabolites represent 10.4 ± 0.4% of recovered drug and metabolites, similar to adults. Further investigation is required to determine if developmental differences in bioactivation and detoxification processes result in periods of susceptibility that are unique to children at a specific developmental stage.

1095 MOLECULAR MECHANISMS REGULATING *FMO* TEMPORAL-SPECIFIC EXPRESSION.

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The flavin-containing monooxygenase genes (*FMO1-5*) encode enzymes important for the metabolism of numerous environmental toxicants. Studies to date have demonstrated temporal-, tissue-, & species-specific *FMO* expression patterns that impact susceptibility. However, a complete picture of these patterns and underlying regulatory mechanisms remain unknown. To characterize human hepatic *FMO1 & 3* developmental expression, microsomal protein levels were quantified in 240 liver samples representing ages from 8 wks gestation to 18 postnatal yrs. FMO1 expression was highest at 8-15 wks gestation (7.8 ± 5.3 pmol/mg protein) then slowly declined with complete suppression within 3 postnatal d through a mechanism tightly coupled to birth, but not gestational age. Low FMO3 levels also were detected at 8-15 wks gestation, but at no other prenatal period. Most individuals failed to express FMO3 during the first 21 postnatal days. FMO3 was detected by 10 mo & was expressed at 20% of adult values between 10 mo & 11 yr. Thus, birth is necessary, but not sufficient for the onset of FMO3 expression. A gender-independent increase in FMO3 expression was observed between 11 and 18 yrs (maximum of 26.9 ± 8.6 pmol/mg protein), although adult expression levels were not attained by the latter age. Data from transient expression studies suggest that fetal hepatic FMO1 expression is largely regulated by HNF1α, although as yet unidentified upstream-binding factors also are involved. Preliminary data implicate DBP as playing a role in regulating postnatal hepatic *FMO3* expression. Results from SNP discovery suggests a high degree of *FMO1* conservation, but did identify a functional, regulatory polymorphism in a basal promoter YY1 element that may account for up to a 2-fold variation in expression. Other novel genetic variants may partially explain interindividual variability in *FMO1 & 3*expression (Supported by PHS CA53106).

1096 HUMAN CYP2E1 DEVELOPMENTAL EXPRESSION: A ROLE IN FETAL & PEDIATRIC SUSCEPTIBILITY TO TOXICANTS?

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CYP2E1 is important in the bioactivation of small molecular weight toxicants such as toluene, benzene & trichloroethylene. Developmental changes in human CYP2E1 expression likely impact susceptibility of the fetus and young child to these compounds. Two previous studies of human CYP2E1 ontogeny yielded conflicting results. To define human hepatic CYP2E1 developmental expression pattern, microsomes were prepared from human liver samples [N=72 fetal (8-37 wks);