LE Gray Jr Abstract for Workshop
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Presentation Title:
Using fetal endocrine and genomic signatures to predict the relative potency of phthalate esters and their effects on postnatal development of the male rat reproductive tract

The first part of this presentation will address concerns expressed by some scientist that the screening and testing protocols for endocrine disrupting chemicals (EDCs) are 1) unable to adequately detect the low dose effects of EDCs, 2) they are unable to define the shape of the dose response curve in low dose range, 3) they do not include the most sensitive endpoints for specific modes of EDC action and 4) they do not thoroughly examine enough animals to detect adverse effects that occur at low doses. Addressing all these concerns would involve a considerable expansion of the time and resources required to execute a multigenerational test.

Rather than increasing the size and complexity of current multigenerational tests, an alternative approach is to study the molecular initiating events (MIE) and key events (KEs) in the adverse outcome pathway (AOP) of an EDC to try to predict if the chemical will alter development, the doses that alter development and the shape of the dose response curve in the low dose region. The main part of this presentation will describe a short-term in vivo protocol, termed the Fetal Phthalate Screen (FPS), designed to identify chemicals and mixtures that induce the Phthalate Syndrome (PS) in male rat offspring, by examining fetal testosterone production and testis gene expression, KEs in the PS AOP. Using this protocol, we were able to correctly classify all the known positives and negatives for PS induction (n= about 30 chemicals) based upon reductions in testosterone production and reductions in the expression of 20-25 testis genes. In addition, we found that the magnitude of the fetal testis alterations is predictive of the potency of the chemical to produce PS malformations in F1 males. Phthalates that are not active in this protocol fail to produce the phthalate syndrome in the male offspring, eliminating the need to conduct a postnatal study for these effects. The final segment of the presentation will discuss the utility and limitations of this approach and the use of AOPs in general for hazard identification.

Background for the Workshop (don't review- see next page)

Workshop Title: Windfall or Pitfall: Is There a Need for Modification of Developmental and Reproductive Toxicology Studies When Endocrine Disruption is the Mode of Action?

Workshop Abstract:

Endocrine disruption has become an important topic of public concern. Despite an increasing amount of attention, little consensus exists about if/how environmentally relevant doses of endocrine disrupting chemicals affect homeostasis or even how these activities should be measured or regulated. It has been suggested that in cases where the compounds assessed have an endocrine disrupting (ED) mode of action, there are gaps in the way that standard developmental and reproductive toxicity studies are performed. This may result in an insufficient prediction of human safety. To address these concerns, an increasing number of research studies are conducted using protocols modified to include mixtures, additional (low) dose groups, further generations, alternative non-validated endpoints and 'omics' technologies. These enhancements of regulatory studies may provide many new avenues for scientific discovery, but come at a price of increasing complexity. At the same time we see a move away from animal studies to *in vitro* models. Are such changes helpful or do they increase the uncertainty?