Genetically altered mice for evaluation of mode-of-action (MOA).

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(Presented by B. Abbott).

This presentation provides an example of the use of genetically modified mice to determine the mode-of-action of related compounds. Perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) are members of a family of fluorinated chemicals that have a variety of commercial/industrial applications. PFOA and PFOS are environmental contaminants found in wildlife and humans. Both compounds are developmentally toxic in rodents. The effects of in utero exposure include decreased fetal survival and growth, increased neonatal death, developmental delay, and deficits in postnatal and post weaning growth. PFOA and PFOS are peroxisome proliferators that activate peroxisome proliferator-activated receptor-alpha (PPARα), a member of the nuclear receptor superfamily of transcription factors. There are three PPAR isoforms, PPARα, PPARβ/δ and PPARγ, that are expressed in the adult and developing embryo with tissue-specific expression patterns. PPARs have significant physiological roles, regulating many cellular and metabolic processes. PPARs control energy homeostasis and are important regulators of adipogenesis, lipid metabolism, inflammatory responses and hematopoiesis. PPARs also have critical roles in reproduction and development. PPARα, PPARβ/δ and PPARγ exhibit specific patterns of expression in the embryo, extra-embryonic membranes, uterus, and placenta and have roles in implantation of the embryo, development of the embryo, maintaining pregnancy and initiation of labor at term. This presentation will evaluate the use of PPARα knockout (KO) mice to reveal the role of PPARα in the production of developmental toxicity by PFOA and PFOS. Wild type (WT) and PPARα KO mice were exposed to PFOA at 0 – 20 mg/kg/day from GD1-17 or PFOS at 0-10.5 mg/kg/day from GD15-17. These studies demonstrated that PFOA-induced postnatal lethality, growth effects, and delayed eye opening were dependent on expression of PPARα, but that the effects on early pregnancy loss were independent of PPARα. To confirm that the postnatal lethality depends on expression of PPARα, and to eliminate the possibility that potential variability in WT and KO genetic background was a factor, experiments were also conducted in which heterozygous embryos/pups were exposed to PFOA, (KO dams mated with WT males, and WT dams mated with KO males, to produce heterozygous offspring). The results from these experiments supported the conclusion that PPARα signaling is required for induction of postnatal lethality, developmental delay, and growth deficits by PFOA and that one functional copy of the gene is sufficient. Studies of the effects of PFOS in KO mice showed that PFOS-induced neonatal lethality and delayed eye opening are not dependent on activation of PPARα. It was concluded that PFOA, but not PFOS, has a PPARα-dependent mode-of-action for developmental toxicity in the mouse. This abstract does not necessarily reflect US EPA policy.