

## 1998 PROGRAM

- 9:00 a.m. Registration and Coffee - Room 137, Chemistry-Physics Building
- 9:30 a.m. Welcome by Dr. Fitzgerald Bramwell, Vice President for Research and Graduate Studies, University of Kentucky - Room 139, Chemistry-Physics Building
- 9:35 a.m. Introductory Remarks - Dr. Sylvia Daunert, University of Kentucky
- 9:40 a.m. Dr. Louis J. Guillette, Jr., University of Florida "EcoEstrogens and Embryos"

Since the onset of the industrial age, environmental contaminants have posed a threat to wildlife health. The focus of our concern on the health consequences of environmental pollution have, in the last three decades, been on lethal, carcinogenic and/or extreme teratogenic manifestations. Evidence from a number of sources suggests that another mechanism, endocrine-disruption must also be examined. There is excellent laboratory and field evidence that man-made chemicals - xenochemicals - released into the environment act as hormones or antihormones - endocrine disrupting contaminants (EDCs). The release of EDCs occurred in the past and continues today. We have used reptiles - primarily the alligator - as an ecosystem monitor for it exhibits limited mobility and feeds at the top of the food chain. Our recent studies show that reptiles living in contaminated environments exhibit (1) population declines due to lethal and reproductive effects of the contaminants on embryos, juveniles or adults, (2) developmental abnormalities of embryos, including subtle effects in the reproductive system of alligators, and (3) abnormalities of the endocrine system. A hypothesis will be presented suggesting that any compound that disrupts the normal steroid milieu of the developing embryo will have significant, life long, consequences on sex determination and the organization and function of the reproductive system.

10:25 a.m. Discussion

10:35 a.m. Dr. Stephen H. Safe, Texas A&M University "2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) as an Antiestrogen: Crosstalk Between Two Endocrine Pathways"

2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related halogenated aromatics (HAs) are industrial compounds or by-products, which have been identified as contaminants in air, water, fish, wildlife and humans. HAs induce a broad spectrum of biochemical and toxic responses and their effects on laboratory animals are species-, strain-, tissue-, age-, and sex-specific. The mechanism of action of HAs has been extensively investigated and results indicate that the aryl hydrocarbon receptor (AhR) protein is the initial intracellular target for TCDD. The bound AhR complex functions as a ligand-induced nuclear transcription factor and also modulates phosphorylation of critical regulatory proteins. TCDD and related compounds disrupt multiple endocrine pathways, and research in this laboratory has focused on charac-

terizing AhR-mediated antiestrogenicity in the rodent uterus and mammary and in human breast cancer cells. The mechanisms of AhR-mediated antiestrogenicity are complex; however, studies on the molecular biology of crosstalk between the AhR and estrogen-receptor (ER) signaling pathways have been initiated using several E2-regulated genes as models. The results indicate that the nuclear AhR complex targets specific genomic core inhibitory dioxin responsive elements (iDREs) in promoter regions of E2-responsive target genes to inhibit hormone-induced transactivation. Research has also focused on development of AhR-based antiestrogens which inhibit mammary tumor development and growth but do not exhibit prototypical AhR-induced toxic responses. The antitumorigenic activities of these new drugs will be discussed.

11:20 a.m. Discussion


11:30 a.m. Dr. Kenneth S. Korach, National Institute of Environmental Health Sciences "Molecular and Functional Phenotypes in Estrogen Receptor Knock-Out Mice"

The estrogen receptor (ER) is thought to play a crucial role in the regulation of many life processes, including development, reproduction, and normal physiology. We have produced a line of transgenic mice possessing a disrupted ER gene (ERKO). Comparable levels of ER- $\beta$  mRNA were detected in tissues of ERKO mice, suggesting that ER- $\beta$  expression is not dependent on ER. Estrogen insensitivity was confirmed using estradiol, hydroxy tamoxifen, and diethylstilbestrol treatment. Estradiol-treated wild type mice showed a 350-fold induction in lactoferrin mRNA, an estrogen-responsive gene in the uterus, while ERKO females showed no detectable response. Progesterone receptor mRNA was detected but not stimulated by estrogen in the uterus, mammary gland, and ovary, indicating an estrogen-dependent and -independent regulation. Both male and female animals survive to adulthood with normal gross external phenotypes. ERKO females have elevated ovarian gonadotropin receptor levels (6-8 fold) as well as elevated serum estrogen (10-15x) and LH (8x), compared to wild type. The influence of ER activity on mammary tumorigenicity was evaluated by crossing WNT-1 transgenic mice having an increased incidence of mammary tumors onto the ERKO background. Mice exhibiting wild type ER and WNT-1 transgene show 98% tumor incidence at 26 weeks of age. ERKO/WNT-1 mice show a reduced tumor incidence (58%) and delayed onset (54 weeks). Both sexes show an effect on the skeleton and shortened bone length supporting a direct role for ER action in bone.

12:15 p.m. Discussion

12:30 p.m. Buffet Lunch, Faculty Club (Please return registration form by April 6, 1998 for reservations. Cost \$10.00 to be paid at registration.)

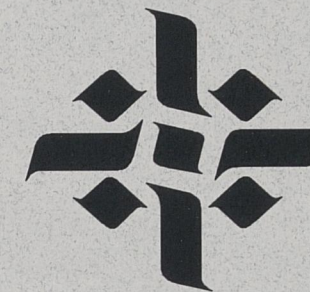
2:30 p.m. Discussion with Graduate Students, Room 137, Chemistry-Physics Building

  
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### Toxicology of Environmental Chemicals that Act as Hormones

SPEAKERS  
Louis J. Guillette, Jr.  
Kenneth S. Korach  
Stephen H. Safe

Monday, April 13, 1998

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