Cross-Species Conservation of Endocrine Pathways Provides a Basis for Reevaluation of EDSP Tiered Testing Paradigm. Gerald T. Ankley[1], L. Earl Gray[2]; [1]US Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Mid-Continent Ecology Division, Duluth, MN, USA; [2]US Environmental Protection Agency, Office of Research and Development, National Health and Environmental Effects Research Laboratory, Toxicity Assessment Division, RTP, NC, USA.

Many structural and functional aspects of the vertebrate hypothalamic-pituitary-gonadal (HPG) axis are known to be highly conserved, but the relative significance of this from a regulatory toxicology perspective has received comparatively little attention. High-quality data generated through development and validation of Tier 1 tests for the USEPA Endocrine Disruptor Screening Program (EDSP) offer a unique opportunity to compare responses of mammals versus fish to chemicals that may affect shared pathways within the HPG axis. Our analysis focused on data generated with model chemicals that act (primarily) as estrogen receptor agonists (17α-ethynylestradiol, methoxychlor, bisphenol A), androgen receptor agonists (methyltestosterone, 17β-trenbolone), androgen receptor antagonists (flutamide, vincolozolin, p,p'-DDE) or inhibitors of different steroidogenic enzymes (ketoconazole, fadrozole, fenarimol, prochloraz). All 12 chemicals had been tested in the EDSP fish short-term reproduction assay (FSTRA) and in one or more of the four *in vivo* Tier 1 screens with rats (Uterotrophic, Hershberger, male and female pubertal assays). In most cases there was high concordance between the fish and rat assays with respect to identifying chemicals that impacted specific HPG pathways of concern, with the test chemicals producing positive results in the fish and one or more of the rat tests. However, some assays were clearly superior to others in terms of detecting specific pathways; for example, the effects of inhibitors of steroid hormone synthesis were most obvious in the FSTRA, whereas the activity of androgen receptor antagonists were clearest in the Hershberger and male pubertal assays. Based on our analysis it may be possible to use just two of the current Tier 1 tests, the FSTRA and the male pubertal assay, to ensure full coverage of HPG axis pathways of concern. Based on this, we propose that these two tests could serve as initial "gate keeper" assays, following which unknown chemicals may be exempted from further testing (negatives) or (when positive) subjected to additional, confirmatory analyses with other existing Tier 1 assays. This would greatly enhance throughput of chemicals through initial testing, both in terms of resource utilization and timing. *This abstract does not represent the views of the USEPA.*