Toxicity Testing in the 21st Century and reforming the science of EPA's Endocrine Disruptor Screening Program

Introduction
In light of recent developments in biotechnology and toxicological computation, there is an unprecedented opportunity to improve the efficiency of and decision-making by modernizing scientific testing methods that continue to consume time, human, and financial resources. Traditional animal-based studies that are of questionable relevance to humans. At the behest of the President's Office of Science and Technology Policy (OSTP) and the National Academy of Sciences (NAS), the NAS has developed a new approach to toxicity testing that recognizes the impact of these scientific developments. The result of this effort, NAS's 2007 publication, "Toxicity Testing in the 21st Century: A Vision and A Strategy," outlines a transformative paradigm shift in toxicology from an observational to a predictive science. Based largely on non-animal test methods, this shift learns high-throughput methods capable of managing large amounts of data and chemicals at relatively low cost. Consistent with NAS’s recommendations, we present an integrated approach of testing methods (ITs) applied to the Endocrine Disruptor Screening Program (EDSP) that would result in more efficient screening and characterization of the endocrine-disrupting potential of manufactured chemicals while reducing testing costs.

EPA EDSP / Proposed Integrated Testing Strategies (ITS)
Created in 1988 through a resolution to the Federal Insecticides, Fungicides and Rodenticide Act (FIRAA), the EDSP is organized into two tiers of test batteries that aim to characterize the risks posed by endocrine, androgenic and thyroid (EAT) chemicals to human and environmental health. The first battery (in vitro and in vivo assays) aims to identify chemicals that have the potential to interact with the EAT hormonal systems by discerning mechanistic information about test chemicals. Although EDSP has not defined how this change will take place, this strategy aims to reduce the number of proteins that would proceed to Tier 2 testing based on a weight-of-evidence assessment of the results of Tier 1 assays. The proposed Tier 2 battery, integrated testing methods (ITs) applied to the EDSP, would include a number of dose-response relationships for any adverse endocrine-related effects. It is unclear what combination of Tier 1 results will trigger Tier 2 testing. It is unknown whether this new Tier 2 testing scheme will stimulate the Agency to revise the current test order to obtain other Scientifically Relevant Information (OSRI) in lieu of performing some of the Tier 2 assays. This is not to suggest that EDSP testing is redundant, but it is unclear how new testing data will be used to weed out portions of Tier 2 and Tier 2 testing. For Phase I of the EDSP test orders have been placed for 27 chemical substances (rodent and avian species) and nine high production volume (HPV) chemicals as used in pesticide inert ingredients) based on their exposure potential.

Evaluation of existing data for atrazine, Phase I chemicals
Atrazine is a paraquat that has been on the market for more than 50 years and is one of the most widely used agricultural products worldwide. As a result, atrazine has been thoroughly tested in a wide range of vertebrate species using a variety of methods, including protocols similar if not identical to those required under both the Tier 1 and Tier 2 testing of the EDSP (such as reproductive and/or toxicity testing in rodents, fish, and birds, as well as a range of metabolic and pharmacokinetic studies). The Tier 1 atrazine test, for instance, uses mouse uterine growth in vivo or in vitro exposure to test chemicals by evaluating two endpoints, body weight and uterine weight, to determine the lowest observed adverse effect level (LOAEL) for atrazine’s potential estrogenic activity. As shown in the table below, information on many of the endocrine-related endpoints examined in Tier 1 and Tier 2 tests already exist in the EDSP database.

Summary
Three available data sources for the EDSP for Phase I chemicals, atrazine, an integrated scheme incorporating existing data from in vivo and in vitro tests is capable of fulfilling information requirements in place of new Tier 1 and Tier 2 tests. Since EPA issued the first EDSP test orders in December 2003, PETA and FCMI have submitted reviews of the EDSP’s current toxicity testing for each of the 67 Phase I chemicals. Consistent with the example provided here for atrazine, many of these Phase I chemicals have already been evaluated for endpoints that would be caught by Tier 2 testing, eliminating the need for further testing and reducing the cost of regulatory decision-making.

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Weight of evidence analysis
Phase I atrazine does not exhibit estrogen-like response, even at doses levels up to a million-fold greater than the minimally effective concentration. Atrazine does not appear to be an estrogen receptor agonist.

Weight of evidence analysis
Phase I atrazine does not exhibit anti-androgenic effects of gestational exposure. Although a number of adverse effects do occur at doses that are unlikely to be experienced in endocrine assessments, no reduction in reproductive potential has been reported.

Weight of evidence analysis
Phase I atrazine does not interact with thyroid and endocrine pathways.