Incorporating Tox21/ToxCast Endocrine-Related Data Into GreenScreen® Chemical Hazard Assessments
Zach Guerreire1, Kathleen Woods1, and Margaret H. Whittaker1
1ToxServices LLC, Washington D.C., U.S.A.

Introduction
Endocrine active chemicals have an inherent ability to interact with the endocrine system resulting in biological, but not necessarily adverse, effects. GreenScreen for Safer Chemicals hazard assessments (GSCA) (CPR 2011) include the evaluation of endocrine activity. Most chemicals currently used in commerce have extensive endocrine activity, and GreenScreen hazard assessments often report data gaps for this endpoint due to the lack of data. In this paper, we present data that support new hazard classifications for the following chemicals of concern: trimethylbenzenes, ethyltoluenes, tetrasiloxane, octamethylcyclo (dimethyl)silane, Silica (ethylacetoacetate), Diisopropoxytitanium bis (1,2,4-), 1,2,4,5-trimethoxybenzene, 20-chlorophenol, propylene glycol, and ethylbenzene. The resulting classifications are based on both traditional and high throughput screening (HTS) methods for endocrine activity.

GreenScreen® for Safer Chemicals Hazard Assessments
GreenScreen® for Safer Chemicals (GS) is a high-throughput screening method developed by the Clean Production Action (CPA). Its primary objective is to evaluate chemicals and their potential transformation products against a suite of toxicological, environmental, and human health effects. The ensuing GS hazard scores inform the development of risk-based decision making regarding the safety and/or use of chemicals. GS hazard score results are based on GS assessments, which are conducted as follows: (1) Chemicals are assessed for a range of chemical properties that may influence their bioavailability, as reported in the database, reproduction, toxicity, and developmental toxicity using in vitro cell-based screening data; (2) GS hazard scores are calculated as the sum of GS assessments, and GS classifications are determined using a GS hazard score threshold; and (3) GS Benchmark Scoring criteria (BM) are used to evaluate chemicals in GS classification categories and determine if a chemical is reassessed.

Endocrine Activity GS Scores Based on Traditional Data
Tox21/ToxCast chemical hazard assessments for 16 chemicals, 15 of which are classified as GS benchmark chemicals, were included in the Tox21/ToxCast initiative and have in vitro data for endocrine-related assays. For comparison, Tox21/ToxCast chemical hazard assessments were reviewed for their potential to identify developmental toxicity and endocrine activity. GS hazard scores for developmental toxicity and endocrine activity are presented in Figure 4 and Table 1, respectively.

Endocrine Activity GS Scores Derived from HTS Data
Tox21/ToxCast assay results for 8 of the 16 chemicals were obtained using the approach materials published by Fisher et al. (2014). GS Benchmark Scoring criteria (BM) are used to evaluate chemicals in GS classification categories and determine if a chemical is reassessed. Tox21/ToxCast assay results for 8 of the 16 chemicals were obtained using the approach materials published by Fisher et al. (2014).

Summary of Endocrine Activity Data
A summary of the GS classifications for reproductive toxicity, developmental toxicity, and endocrine activity and the Tox21 and ToxCast results for the 16 chemicals is presented in the table below.

Results
• Of the 16 chemicals identified as having HTS in vitro data, we identified cytochrome (CAS #57860-70-7), testosterone/methylene, and phytoestrogen receptor binding (ER agonist and antagonist) were identified using the ToxCast database.
• For the 16 chemicals, GS hazard scores did not produce active assays in either database.

Conclusions
• The results from the Tox21 and ToxCast databases indicate that all but one chemical was active in estrogen, androgen, and thyroid-stimulating hormone receptor assays.
• These chemicals may only exert endocrine activity following metabolism in the body and the conditions of the HTS assay may not accurately predict in vivo behavior.

Selected References