# Collaborations for Development of EPA's ToxCast™ Program for Predicting Toxicity

## Opportunity:

The EPA is interested in finding partners for collaboration on a Cooperative Research and Development Agreement (CRADA) to facilitate and expand the development and evaluation of its ToxCast™ research program for predicting the toxicity of environmental chemicals. Researchers at the National Center for Computational Toxicology (NCCT) of the Office of Research and Development (ORD) of EPA are developing ToxCast™ as an innovative approach building computational models that forecast toxicity based on data from state-of-the-art high-throughput screening (HTS)[1] bioassays. These hazard predictions should provide EPA's regulatory programs with science-based information helpful in prioritizing chemicals for more detailed toxicological evaluations, and therefore lead to using animal tests more efficiently. Partnering opportunities with EPA exist to expand the breadth of assays involved in Phase 1, and the breadth of chemicals and assays in Phase 2. A description of each Phase is provided below.

**To indicate interest:** Please reply to Kathleen Graham at graham.kathleen@epa.gov or 202-564-2678 by August 31, 2007 if you are interested in a partnering on this CRADA. For more information on CRADAs please see the following website: http://www.epa.gov/osp/ftta.htm

## Overview:

Across EPA programs, there are thousands of environmental chemicals for which limited or insufficient data are available for hazard and risk assessments. These chemicals include antimicrobial agents, inert pesticide ingredients, high-production-volume chemicals, and drinking water contaminant candidates. ToxCast™ is a five-year research program testing the hypothesis that multi-dimensional evaluation of chemical properties and effects across a broad spectrum of information domains will yield signatures predictive of toxicity, which can then be used to prioritize chemicals for more detailed toxicological examination. Information domains include physical-chemical properties, predicted biological activities derived from existing structure-activity models, biochemical and cellular properties from HTS assays[1], genomic analyses of cells, and responses in non-mammalian model organisms. Signatures will be defined and evaluated by their ability to predict outcomes from existing mammalian toxicity assays.

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[1] HTS is a system to rapidly and efficiently test large batches of chemicals for bioactivity utilizing robotics and automation applied to molecular biology and cellular assays.

This five-year effort is divided into three phases. As proof–of-concept, Phase 1 of the program is evaluating more than 300 chemicals in over 400 different bioassays. The HTS assays are available through an initial $6M investment made by EPA in nine extramural contracts awarded in April 2007. The contracts have the capacity to assay up to 10,000 chemicals over the five-year period. In addition, an Interagency Agreement (IAG) was established with the NIH Chemical Genomics Center (NCGC) to provide access to the novel technologies developed by the NIH Molecular Libraries Initiative. All these data types will be used to derive predictive signatures based on the known toxicity of the 300 chemicals. The Phase 1 chemicals are primarily pesticide active ingredients that have been extensively evaluated by traditional toxicity testing, and hence have known properties representative of various phenotypic outcomes (e.g., carcinogenicity; developmental, reproductive and neural toxicity). Results from the ToxCast™ Phase 1 assays are expected in early 2008 and will provide, for the first time, a comprehensive and detailed overview of the impact of environmental chemicals upon key cellular activities. The assays range from characterizing the interactions of chemicals with proteins that regulate and maintain proper cell function, to measuring the response of whole cells, to studying chemical effects in a model organism. To ensure transparency and collaboration, ToxCast™ data will be made publicly available.

Upon completion and evaluation of the proof of concept, the research program will enter Phase 2 which will focus on the confirmation and expansion of ToxCast™ predictive signatures, generating data on up to 1,000 additional chemicals. In Phase 3, ToxCast™ will be applied to the thousands of environmental chemicals requiring prioritization, delivering an affordable, science-based system for categorizing chemicals. As the ToxCast™ database and models develop, so will confidence in predicted toxicity and potential mechanisms useful in refining and reducing the use of animals in toxicity testing.

Readers should refer to the NCCT website (http://www.epa.gov/ncct/) for more information on the ToxCast™ program, or to the article describing “The ToxCast™ program for prioritizing toxicity testing of environmental chemicals” published in *Toxicological Sciences* (Dix et al., 2007, vol. 95, pg. 5-12).

## Specifications:

EPA is seeking CRADA partners interested in collaborating on the ToxCast™ research program by generating additional HTS data with Phase 1 chemicals, or supporting generation of HTS data with Phase 2 chemicals. Phase 2 of ToxCast™ is projected to involve up to 1,000 additional chemicals representing broader chemical structure and use classes, in order to confirm

and expand on the predictive bioactivity signatures developed in Phase 1. The CRADA is expected to involve multiple partners, including but not limited to non-governmental organizations, private sector companies, academic institutions, and companies with expertise in predictive toxicology. EPA is also working with other national agencies and international governments through appropriate vehicles in this collaborative process. Common areas of interest and potential cooperation include: 1) toxicity endpoints of concern; 2) chemicals of concern; 3) toxic modes of action; 4) screening data generation with either a) new assays for common chemicals, or b) new chemicals for common assays; and 5) data management, analysis and sharing.

**Partnership Opportunity:** CRADA