



UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

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OFFICE OF
RESEARCH AND DEVELOPMENT

MEMORANDUM

SUBJECT: Revised ORD Statement on the Use of ToxCast Data in EDSP

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Background

The Office of Chemical Safety and Pollution Prevention (OCSPP) has requested that the Office of Research and Development (ORD) provide their expert opinion regarding the value of using ToxCast assay data as a replacement for data from the assays in the EDSP Tier 1 Screening Battery.

National Center for Computational Toxicology (NCCT) and National Health and Environmental Effects Research Laboratory (NHEERL) scientists have discussed this issue with OCSPP and the following is the response of ORD scientists from NCCT and NHEERL. This memo clarifies and supersedes ORD's memorandum on the same subject, dated April 20, 2010.

ORD Consensus Statement

Currently, the EDSP T1 S screening battery contains several *in vitro* and *in vivo* assays to detect alterations of estrogen, androgen and thyroid (EAT) hormone pathways including the evaluation of many complementary endpoints to further identify the specific modes of action (MOA) of concern. The MOAs included are those mediated through ER and AR receptor activation, EAT synthesis and metabolism, and alteration of hypothalamic-pituitary gonadal and thyroid functions as they relate to EAT. As required by the Food Quality Protection Act amendments to the Federal Food Drug and Cosmetic Act, each of these assays was validated prior to its inclusion in the Tier 1 battery.

ToxCast is an ORD research project coordinated by NCCT that is developing chemical prioritization methods based on high throughput screening (HTS) and computational tools. With over 500 HTS assays being conducted for each chemical, ToxCast is profiling the bioactivity of hundreds of chemicals and developing computational methods suitable for prioritizing chemicals for further screening and testing. Several ToxCast assays are relevant to EAT hormone pathways. NCCT has completed the first phase of ToxCast testing, and is in the process of a second phase of testing that will expand and validate the performance and predictivity of the ToxCast assays. The combination of data from phases one and two of ToxCast will ultimately confirm the reliability and relevance of ToxCast assays for prioritizing chemicals based on specific toxicity potentials, including endocrine related toxicity potential. However, it is our position that the ToxCast *in vitro* assays cannot at this time be considered as an acceptable alternative to the EDSP T1 S *in vivo* or *in vitro* assays because:

1. The reliability and responsiveness of the ToxCast assays are still being determined and published from the first and second phases of the project. Phases one and two of ToxCast will include positive and negative control compounds in order to adequately confirm assay performance across time, and in multiple laboratories conducting assays for the same biological targets.
2. The relevance of the ToxCast assays is still being determined by collecting, analyzing and publishing data from the first and second phases of the project. This analysis will determine the statistical and biological significance of ToxCast assays results relative to specific targets and toxicity endpoints relevant to the endocrine system.
3. The development of acceptability criteria comparable to what has been published for the current EDSP T1 S *in vitro* assay test guidelines will require completion of the first and second phases of the ToxCast project.
4. The assays presently included in ToxCast do not evaluate all known targets of toxicity of EAT hormonal pathways that are detected with current *in vitro* or *in vivo* screens. These include steroidogenesis, and targets in the hypothalamic-pituitary system. Addressing these additional targets in ToxCast will require additional assays or computational methods.
5. Like EDSP T1 S *in vitro* assays, most of the *in vitro* assays of ToxCast do not account for the absorption, distribution, metabolism or excretion (ADME) of chemicals. Concerns regarding ADME issues are a significant reason for inclusion of *in vivo* assays in the EDSP Tier 1 battery, and the current ToxCast assays are not suitable replacements for EDSP T1 S *in vivo* assays.
6. Until all of the relevant methods, data, analyses and conclusions from phase one and two of ToxCast are appropriately peer-reviewed and published, it is not possible to rigorously and transparently evaluate the application of these results to regulatory decisions.

EPA is working to improve the utility of ToxCast in the EDSP and other screening efforts. At present, ToxCast offers potential for prioritizing the selection of chemicals that enter into future stages of the EDSP effort. With additional data, analysis, peer-review, and application of suitable acceptability criteria, it is possible that ToxCast assays and data could emerge as alternatives to EDSP T1 S *in vitro*.

Should you have any questions regarding this statement, please do not hesitate to contact any one of us.