Endocrine Disruptor Screening Program meeting with the White House Office of Management & Budget

2 June 2009

Detailed Agenda

I. Introductions, review of the agenda (*all; 5 minutes*)

II. Center for Regulatory Effectiveness Concerns: (*Scott Slaughter, 15 minutes*)
   a. The public record demonstrates that eight (8) Tier 1 tests do not have practical utility and do not meet IQA guidelines

III. Chemical Industry Concerns:
   a. CropLife America (*Erik Janus, 15 minutes*)
      i. Tier 1 data has no actual practical utility and imposes a superfluous burden
      ii. EPA has not evaluated existing data to minimize duplication
   b. American Chemistry Council (*Rick Becker, 15 minutes*)
      i. Concerns regarding EDSP and requirements of TSCA 8(e) and FIFRA 6(a)(2)
      ii. Concerns regarding specific Tier 1 Battery test methods
   c. Chemical Producers & Distributors Association (*Sue Ferenc, 15 minutes)*
      i. EPA has presented an incorrect estimation and scope of burden
      ii. OMB should return the ICR to EPA to demonstrate actual practical utility of the information collection
   d. Consumer Specialty Products Association *(Doug Fratz and Susan Little, 15 minutes*)
      i. EPA failure to establish actual practical utility also presents problems for member companies seeking to respond to test orders
      ii. EPA has presented incorrect costs for consortia start-up and operation

IV. Animal Welfare Community Concerns (*Kate Willett, People for the Ethical Treatment of Animals; Chad Sandusky, Physicians Committee for Responsible Medicine, 15 minutes*)
   a. The EDSP in general and the Phase I in particular is unlikely to produce any useful regulatory information and therefore fails regarding "practical utility" and is an unwarranted massive use of animals and resources
   b. Alternative strategies for EDSP testing and implementation

Rostker, David

From: scott slaughter [slaughterenator@gmail.com]
Sent: Friday, May 29, 2009 5:06 PM
To: Rostker, David
Cc: Erik Janus; Becker, Rick; Susan Ferenc; Susan Little; Beth Law; Doug Fratz; Chad Sandusky; Kate Willett; Kristie Sullivan; Scott Slaughter
Subject: Attendance list for meeting with OMB on the EDSP Tier 1

The following persons will be attending the meeting with OMB on June 2 at 10:00 am. We will send you an agenda. Please let me know if you need anything else before the meeting.

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May 22, 2009

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Re: **Information Collection Request (EPA ICR No. 2249.01) EPA-HQ-OPPT-2007-1081**

Dear Mr. Rostker and Dr. Wooge:

These comments are submitted on behalf of the Alternatives Research and Development Foundation, the American Anti-Vivisection Society, Humane Society Legislative Fund, The Humane Society of the United States, People for the Ethical Treatment of Animals and the Physicians Committee for Responsible Medicine. The parties to this submission are national animal protection, health, and scientific advocacy organizations with a combined constituency of more than 12 million Americans who share the common goal of promoting reliable and relevant regulatory testing methods and strategies that protect human health and the environment while reducing, and ultimately eliminating, the use of animals.

On April 15, 2009, the Environmental Protection Agency (EPA; hereafter known as the Agency) submitted a new information collection request (ICR) to the Office of Management and Budget (OMB) regarding information collection activities associated with Phase I of its Endocrine Disruptor Screening Program (EDSP). At the same time, EPA published in the Federal Register its final Policies and Procedures for Initial Screening (74 FR 17560).

It is our understanding that these comments should not address the EDSP directly, but rather "to comment on the Agency's practical utility justification of the collection activities and its related burden and cost estimates as they presented in the ICR."[1] Therefore our comments are directed at the utility and cost of Phase I of the EDSP.

[1] Response to Comments on the Public Review Draft of the Information Collection Request (ECR) entitled "Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)", available in Docket ID no. EPA-HQ-OPPT-2007-1081, page 6.

I. Utility of Phase I of the EDSP: The EDSP Phase I is not likely to provide new regulatory information

A. Reliability and reproducibility of the assays to be used

We and others have pointed out on a number of occasions that the Tier 1 assays listed in the ICR have not been shown to be reproducible or sufficiently specific to adequately identify chemicals that are capable of interacting with estrogen, androgen or thyroid hormone receptors or systems.[2,3,4] In response, the EPA has merely described the process it had taken to review the assays and concluded that the majority of the assays "had indeed completed the validation process."[5] Completing a validation process is not the same as having been validated. Our comments and those of others do not argue that many of the assays have not gone through a validation process; rather, we are arguing that the evaluations of these assays were not as unequivocally positive as the EPA has publically represented.

Since our specific concerns have been detailed elsewhere, we will not repeat them here. The EPA has provided a response to some of these concerns;[6] however, several of the EPA's responses highlight, rather than mitigate, our concerns. For example, in response to our concerns about inter-laboratory variability (reproducibility) of the amphibian metamorphosis assay and the male and female pubertal assays, the EPA acknowledged that, while different labs did indeed obtain different results, "the overall trend was consistent among laboratories." This admission is disconcerting since for many Phase I chemicals, this will be the first time they have been run in the Tier 1 assays and, unless recipients of test orders all use the same few contract laboratories with experience running these assays, it is likely this will be the first time these assays will be run in some labs. In other words, the Phase I testing will likely not be performed in multiple, experienced labs, there will be no "overall trends" available for comparison, and consequently, interpretation of results is likely to be extremely difficult or impossible.

In response to our concerns about specificity (ability to distinguish true negatives from true positives) of several of the assays, the EPA argued that, "(b)ecause the Tier 1 assays will operate in a battery and will only identify a chemical's potential to interact with the endocrine system, rather than to predict actual effects, the rate of false positives and negatives for individual assays in the battery is not an essential part of validation." This reasoning is deeply flawed. Logically, if a battery consists of multiple assays of low specificity, the combined results will be heavily skewed toward false positives. For several of the assays, chemicals tested in the validation studies resulted in NO negatives (not even the negative controls were negative for some endpoints). What is the

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[2] Comments submitted by People for the Ethical Treatment of Animals et al., Crop Life America, the American Chemistry Council, the Center for Regulatory Effectiveness, available in Docket ID no. EPA-HQ-OPP-2008-0012.
[3] Comment document entitled: "EPA Response to the Center for Regulatory Effectiveness (CRE) Information Quality Act Request for Correction Regarding the Amphibian Metamorphosis Assay, available in Docket ID no. EPA-HQ-OPPT-2007-1080.
[4] Physicians Committee for Responsible Medicine (PCRM) Comments to OMB on the Endocrine Disruptor Screening Program (EDSP), available in Docket ID nol. EPA-HQ-OPPT-2007-1080.
[5] Response to Comments on the Public Review Draft of the Information Collection Request (ECR) entitled "Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)", contained in Docket ID no. EPA-HQ-OPPT-2007-1081, pages 5 and 6.
[6] Draft Response to Comment document entitled: "Physicians Committee for Responsible Medicine's Comments to OMB and EPA's Responses," available in Docket ID no. EPA-HQ-OPPT-2007-1080.

conceivable value of a collection of assays that are not capable of distinguishing positives from negatives?

Furthermore, it is disconcerting that the EPA has offered no discussion or guidance on interpretation. In response to a concern expressed regarding the draft ICR that "the agency has yet to provide guidance on how results of the individual assays will be interpreted...,"[7] the EPA states that "the current [lack of] availability of final SEPs and WOEs for EDSP related determinations does not preclude the Agency form evaluating the potential interaction of a chemical with the endocrine system". The EPA cites its extensive experience with WOE approaches in other assessment areas and suggests that this experience will translate to the EDSP, yet no one, including the Agency itself, has experience interpreting the result of the Tier 1 assays as a battery.

The ICR states that the EPA has "considered data from prototypes of the assays included in the current EDSP Tier 1 screen, along with other existing data in preparing the risk assessments of procymidone[8] and vinclozolin;[9]" however, in the Tolerance Reassessment Progress and Risk Management Decision (TRED) for procymidone, no mention is made of data from a Tier 1-like assay. In fact, the TRED states: "In several studies, a number of testicular effects were observed at one or more dose levels in the developmental, multi-generation, and chronic toxicity studies in rats. When additional appropriate screening and/or testing protocols currently being considered under the Agency's Endocrine Disruptor Screening Program (EDSP) have been developed, procymidone may be subjected to further screening and/or testing to better characterize effects related to endocrine disruption." In other words, Tier 2 testing has already been performed for procymidone and did not contribute to the tolerance-setting decision, which was based primarily on carcinogenicity considerations. Vinclozolin, on the other hand, is a known modulator of androgen activity and has been thoroughly assessed in detailed studies resembling both Tier 1 and Tier 2 assays. Interestingly, the TRED for vinclozolin states "(h)owever, the human consequence of many of the low dose effects in male rats such as reduced ano-genital distance, areola and nipple development, and reduced prostate weight is unknown." Ultimately, vinclozolin (and its primary active metabolite, 3,5-dichloroaniline) is also regulated based on its potential carcinogenicity (which is believed to be related to its anti-estrogenic activity) and not directly on data obtained from Tier 1- or Tier 2-like assays. Additionally, the EPA has never evaluated Tier 1 data for its intended purpose: to determine what, if any Tier 2 testing is needed for risk assessment.

The ICR states that "(c)hemicals that go through Tier 1 screening and are found to have the potential to interact with the estrogen, androgen, or thyroid hormone systems will proceed to the next stage of the EDSP where EPA will determine, which if any of the Tier 2 tests are necessary based on the available data." As described above, many of these assays have demonstrated low selectivity and high variability, which, combined with a lack of experience or guidance for interpretation of combined results, is very likely to lead to a large number of false positive determinations, and therefore a large number of chemicals unnecessarily progressing to Tier 2 testing, which is extremely animal-intensive and expensive (one standard 2-generation reproductive toxicity test uses 2,600 rats

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[7] [7] Response to Comments on the Public Review Draft of the Information Collection Request (ECR) entitled "Tier 1 Screening of Certain Chemicals Under the Endocrine Disruptor Screening Program (EDSP)", contained in Docket ID no. EPA-HQ-OPPT-2007-1081, page 16.

[8] www.epa.gov/pesticides/reregistration/procymidone/

[9] www.epa.gov/pesticides/reregistration/vinclozolin/

and costs $380,000; one developmental toxicity study in two species uses 1,300 rats, 660 rabbits and costs $127,000).

B. The chemicals to be tested in Phase I of the EDSP are already among the most data rich chemicals in existence.

Of the 67 chemicals on the final list for Phase I testing, 58 are pesticide active ingredients and 9 are High Production Volume (HPV) pesticide inert chemicals.[10] For registration, pesticides currently are often subject to dozens of separate animal tests, including reproductive and chronic/lifecycle studies in rodents, fish and birds, as well as metabolism and pharmacokinetics studies.[11] These tests kill thousands of animals and include many of the same endpoints addressed in the presumptive EDSP Tier 2 tests. Similarly, EPA's HPV and ChAMP programs also provide for the collection of data which may be germane to the assessment of potential reproductive toxicity.[12]

For example, Reproduction and Fertility effects (OPPTS 870.3880) and Prenatal Developmental Toxicity (OPPTS 870.3700) tests are required for both food-use and non-food-use pesticide Technical Grade of the Active Ingredients (TGAI). The simple mechanistic data produced by the Hershberger, Uterotrophic, the male and female pubertal assays will not provide additional regulatory information; indeed, chemicals tested according to the current OPPTS 870.3880 have, in effect, already been subject to EDSP Tier 2 mammalian testing. Thus, with the possible exception of mechanistic screening for thyroid effects, ***EDSP Tier 1 screens would appear to provide little or no value-added for pesticide chemicals.***

In addition, four of the chemicals included on this draft list (atrazine, butylbenzyl phthalate, di-*n*-butyl phthalate and linuron) are included in the Revised ICCVAM List of Recommended ED Reference Substances. Atrazine has been well characterized in terms of its endocrine activity in numerous *in vitro* and *in vivo studies*, including *in vivo* studies and risk assessments already conducted by the EPA.[13] Similarly, butyl benzyl phthalate (BBP) has been shown to possess endocrine activity in *vitro* and *in vivo* in numerous animal studies, including those already conducted by the EPA.[14,15] The anti-androgenic activity of di-*n*-butyl phthalate (DBP) has been studied in detail.[16,17] Both BBP and DBP have been associated with endocrine-related effects in humans.[18] Linuron is a well-characterized weak anti-androgen, and was used as a control in OECD validation

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[10] 74 FR 17579. April 15, 2009; EPA Final List of Initial Pesticide Active Ingredients and Pesticide Inert Ingredients to be Screened Under the Federal Food, Drug, and Cosmetic Act.

[11] 72 FR 60934, October 26, 2007: EPA 40 CFR Parts 9 and 158: Pesticides; Data Requirements for Conventional Chemicals.

[12] 65 FR 81657, December 26, 2000; EPA 40 CFR Part 799: Testing of Certain High Production Volume Chemicals

[13] Gammon, D.W, et al., 2005. A risk assessment of Atrazine use in California: human health and ecological aspects. Pest. Manag. Sci. 61: 331-55.

[14] Gray, et al., 2000. Perinatal exposure to the phthalates DEHP, BBP and DINP, but no DEP, DMP, or DOTP alters sexual differentiation I of the male rat. Toxicol. Sci. 58: 350-65

[15] Aso, et al., 2005. A two-generation reproductive toxicity study of butyl benzyl phthalate in rats. J. Toxicol. Sci. 30 Spec No.:39-58.

[16] Bredhult, C. et al., 2007. Effects of some endocrine disruptors on the proliferation and viability of human endometrial endothelial cells. Reprod. Toxicol. 23:550-9.

[17] Wang Y.B., et al. 2007 Monobutyl phthalate inhibits steroidogenesis by down-regulating steroidogenic acute regulatory protein expression in mouse Leydic tumor cells (MLTC-1). Toxicol. Environ, Health. A. 70:947-55.

[18] Marsee, K. et al., 2006. Estimated daily phthalate exposures in a population of mothers of male infants exhibiting reduced anogenital distance. Environ. Health. Perspect. 114: 805-9.

exercises for the Hershberger assay[19,20] and as a control in the EPA's own evaluation of the 15-day intact male assay.[21] ***Due to the abundance of existing endocrine-related data, it is unlikely that further testing using the presumptive Tier 1 or Tier 2 EDSP assays will provide any additional information regarding the endocrine activity of these chemicals.***

We have previously brought this to the attention of both EPA[22] and OMB[23]. EPA responded that it "recognizes that several of the chemicals on the initial list have been studied in detail for endocrine disrupting effects…" and goes on to explain that "…registrants will have the option of citing to existing data to satisfy part or all of the Tier 1 Orders in addition to the option of conducting testing." Under the final Policies and Procedures for Initial Screening, the EPA will now accept existing data and "(o)ther scientifically relevant information may either be functionally equivalent to information obtained from the Tier 1 assays—that is, data from assays that perform the same function as EDSP Tier 1 assays—or may include data that provide information on a potential consequence or effect that could be due to effects on the estrogen, androgen or thyroid systems,"[24] suggesting that, for many pesticides, data from reproductive, fertility and developmental studies will suffice, since these address the "potential consequence" of endocrine disruption and in fact will comprise the EDSP Tier 2. In addition, ***the purpose of the Tier 1 is to identify chemicals for testing in Tier 2; therefore it is unnecessary to test chemicals for which Tier 2 data are available in the Tier 1 battery.***

However, in the final Policies and Procedures, EPA significantly mitigates the notion that it will accept such existing data by stating: "EPA generally expects that if the chemical was used by EPA as a ''positive control'' to validate one or more of the screening assays, only the data submitted related to those assays for which the chemical was used to complete the testing as part of the validation effort would be sufficient to satisfy the Tier 1 Order," indicating that the EPA intends to collect all data for the Tier 1 battery for each of the chemicals, regardless of whether the chemical has demonstrated estrogen, androgen *or* thyroid activity. ***In its Phase I exercise, EPA is requesting the testing of chemicals in a large battery of assays that are unlikely to yield any new information that will be useful in regulating those substances.***

II. Cost and Practicality of the Tier 1 battery assays

EPA cost estimates in the ICR, while apparently thorough, are difficult to interpret in terms of actual impact, and appear to be at odds with other estimates (see Appendix). For example, Policies and Procedures for Initial Screening give a deadline of 24 months from issuance of the Order for a recipient to submission of the data and a final report, yet the annual burden calculated in the ICR assumes a "3 year duration of equal annual effort." The current cost estimates for running the assays have been revised in the current ICR (Supplement F) and are closer to estimates that have been made

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[19] Owens, et al., 2007. The OECD program to validate the rat Hershberger bioassay to screen compounds for in vivo androgen and anti-androgen responses: phase 2 dose-response studies. Environ. Health. Perspect. 115:671-8.

[20] Tinwell, H., et al., 2007. Evaluation of the anti-androgenic effects of flutamide, dDE, and Linuron in the weanling rat assay using organ weight, hispathological and proteomic approaches. Toxicol. Sci. 100:54-65.

[21] http://www.epa.gov/scipoly/oscpendo/pubs/adult_male_peer_review_final.pdf

[22] Comment submitted by People for the Ethical Treatment of Animals (PETA), et al., available in Docket ID no. EPA–HQ–OPPT–2004–0109.

[23] [23] Physicians Committee for Responsible Medicine (PCRM) Comments to OMB on the Endocrine Disruptor Screening Program (EDSP), available in Docket ID nol. EPA-HQ-OPPT-2007-1080.

[24] 74 FR 17560. April 15, 2009; EPA Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening.

elsewhere (**Appendix, Table 1**), which estimate a cost as high as $938,000 per chemical. In addition, each chemical requires a minimal use of approximately 600 animals (**Appendix, Table 2**). However, given the uncertainties involved in generating these estimates and that most of these studies will require pilot studies in most of the labs (since the methodology is new), it is likely that the actual cost for running these assays, in terms of both dollars and animal lives, will be much higher.

The ICR assumes that "data generation will not be directly performed by the Order recipient. Instead, EPA assumes that data generation will be performed by a contract laboratory at the request of the order recipient" and that this will result in some reduction of cost. However, several of the tests require unique expertise or equipment (those requiring hormone or histopathological examination, e.g., the amphibian and fish tests) that only a very few (one or two) contract facilities possess. Logistically, it is difficult to see how 67 chemicals will be tested in these assays in the few available contract labs within the two- to three-year time frame.

Part 3(3)(a) of the ICR (Non-duplication) cites the use of harmonized test guidelines as a sign of the EPA's "strong commitment to avoiding potential duplication." Yet several of the methods used by the EDSP are expressly not harmonized test guidelines. For example, the EDSP protocol for androgen receptor uses rat prostate cytosol, while other protocols in development (including those at the OECD) use human androgen receptor, even though the isolation of the receptor is a major contributing factor to variability of the assay and the use of rat receptor contributes requires interspecies extrapolation. The same is true for the proposed estrogen receptor-binding assay in validation exercises at the EPA, which uses rat uterine cytosol. It is very likely that these methods will not be used internationally. An attempt to harmonize the EPA's Fish Reproduction Assay with the Fish Screen in development at the OECD was rejected, in a large part due to stakeholders' objections to the high variability of the fecundity and gonadal histopathology endpoints. Thus far, the male and female pubertal assays are used exclusively in the EDSP. Although a harmonized test guideline for the amphibian metamorphosis assays is in development at the OECD, agreement has not been reached on draft test guideline. The only harmonized test guidelines currently in the EDSP are the Uterotrophic, Hershberger, and ER transcriptional activation assays.

This section of the ICR also mentions that the EPA is a charter member of the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM). It is implied that this involvement will lead to the incorporation of methods that reduce, refine or replace the use of animals, and that this is related to reducing duplicative testing; however, these contentions are unsubstantiated since none of the methods in the current EDSP Tier 1 were validated by ICCVAM.

In that it is unlikely to yield any new regulatory information, the EDSP Phase I is an inappropriate use of resources and waste of a large number of animal lives.

III. The current Tier 1 battery should be replaced by a more considered, step-wise approach

While we agree with EPA's use of a tiered screening program, we do not believe the EPA's choice of assays for a Tier 1 battery is appropriate. Recognizing the need for a faster, more accurate, valid screening battery, we propose an alternative tiered strategy. The preliminary tier includes physical and chemical data, existing toxicological data including metabolism and pharmacokinetics information, and *in vitro* and (Q)SAR methods that are either validated or nearly validated. The results of this alternative Tier 1 can be used in a weight-of-evidence approach to 1) identify priority

chemicals and 2) design an intelligent, chemical-specific strategy for further screening or testing. Such a strategy would greatly reduce the use of animal testing for identification and classification of endocrine disrupting chemicals.

This strategy is reflected in the Organization for Economic Cooperation and Development (OECD) Conceptual Framework for the Testing and Assessment of Endocrine Disrupting Chemicals (framework), which is organized into 5 levels (**Appendix, Table 3**). While the framework is not intended as a tiered system, it nevertheless suggests a logical approach to the sequential and targeted gathering of data. Level 1 assays sort and prioritize chemicals for testing based on existing information. Level 2 consists entirely of *in vitro* assays that address possible mechanisms of action. Not until Level 3 are animal tests involved as *in vivo* mechanistic tests. Chemicals can be screened and prioritized using the fastest, least expensive methods, and the number of animal tests performed overall is greatly reduced.

A strategy similar to the OECD framework that includes preliminary tiers that first assess physiochemical and pre-existing toxicological data, plus *in silico* and a much broader range of *in vitro* mechanistic assays would be more logical, efficient, economical, and use fewer animals. Most of the Phase I chemicals have already been tested in ToxCast screens that include a large number of ER and AR binding and transcriptional activation assays, and nearly half of these showed no evidence of endocrine activity (Appendix, Figure 1).[25] This and similar information must be evaluated for indications of the pathway with which a chemical is capable of interacting before any animal testing is performed, and any subsequent testing must be tailored appropriately.

Thank you for considering our comments.

Sincerely,

Catherine Willett, PhD
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Regulatory Testing Division
People for the Ethical Treatment of Animals

Troy Seidle
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[25] Kavlock, RJ, Dix, D, Houck, K, Judson, R, Knudsen, T, Reif, D. and M Martin. 2009. Biological Profiling of Endocrine Related Effects of Chemicals in ToxCastTM, Presented at the 48th Annual Meeting of the Society of Toxicology, March 15–19, 2009, Baltimore, Maryland.

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Appendix

Table 1: Cost Estimates of the EDSP Tier 1 from various sources[26]

EDSP Tier 1 assay cost estimates (USD)	APT 1998[1] (median)	APT 2003[2] (median)	EPA 2008[3]	Other estimates 2008 - 2009	Low	High
In vitro:						
ER Transcriptional Activation: human ERα	4,900			2,500 - 7,500[4]	2,500	7,500
AR binding: rat cytosol	4,200	7,500	7,066	1,500 - 8,000[4]	1,500	8,000
Steroidogenesis: rat testes	7,500	6,850	11,717	22,200 - 36,300[6]	6,850	36,300
Aromatase - human placental and recombinant		8,175	19,808	37,600 - 61,400[6]	8,175	61,400
In vivo:						
Uterotrophic	26,000 - 67,500*	14,500	20,068	38,000 – 47,000[5]	14,500	67,500
Hershberger	34,400 - 105,000*	23,880	27,579	52,400 - 85,500[6]	27,579	105,000
Pubertal female plus thyroid function	34,700 - 81,000*	44,700	56,725	107,800 - 175,800[6]	34,700	175,800
Pubertal male plus thyroid function		44,000	56,680	107,700 - 175,700[6]	44,000	175,700
Adult male 15-day	68,000	67,900	67,900	165,000 – 212,000[5]	67,900	212,000
Amphibian metamorphosis	17,000		34,894	89,000 - 105,000[5]	34,894	105,000
21-day fish (reproduction) screen	40,000		52,340	76,000 – 97,000[5]	76,000	97,000
					$318,598	**$938,000**

[1]EDSTAC Final Report, August 1998. EPA, Endocrine Disruptor Screening Program. http://www.epa.gov/endo/pubs/edspoverview/finalrpt.htm (accessed March 9, 2009).

*mandatory vs. optional endpoints

[2]Applied Pharmacology and Toxicology, Inc. May 23, 2003 (http://www.apt-pharmatox.com/pdf/2003EDSP-CostReport.final.pdf, accessed March 12, 2009).

[3]According to the Chemicals Producers and Distributers Association, presented at the AIC Annual Conference, San Antonio, TX, May 6 - 8, 2008.

[4]Jeff Pregenzer, CeeTox, personal communication, 2009: cost estimates per chemical are based on number of chemicals assayed: ERα binding: 1 chemical = $6,845, 16 or more chemicals = $1050; AR binding: 1 chemical = $7665, 16 or more chemicals = 1500; ER or AR transactivation: 1 chemical = 7,760, 16 or more = $2,550.

[5] Applied Pharmacology and Toxicology, Inc., March 10, 2008 Comments on EPA's Information Collection Request ("the ICR") developed for the Agency's Endocrine Disruptor Screening Program; Draft Policies and Procedures for Initial Screening, 72 Fed. Reg. 70861 (December 13, 2007).

[6] Estimated from the EPA 2008 estimates using the multipliers determined by APT in the March Comments referenced above. APT determined that the EPA underestimated assay costs by between 1.9- and 3.1-fold.

[26] **Willett, C.E.** and K. Sullivan. Application of an intelligent testing strategy to the US EPA Endocrine Disruptor Screening Program. Presented at the 48th Annual Meeting of the Society of Toxicology, March 15–19, 2009, Baltimore, Maryland.

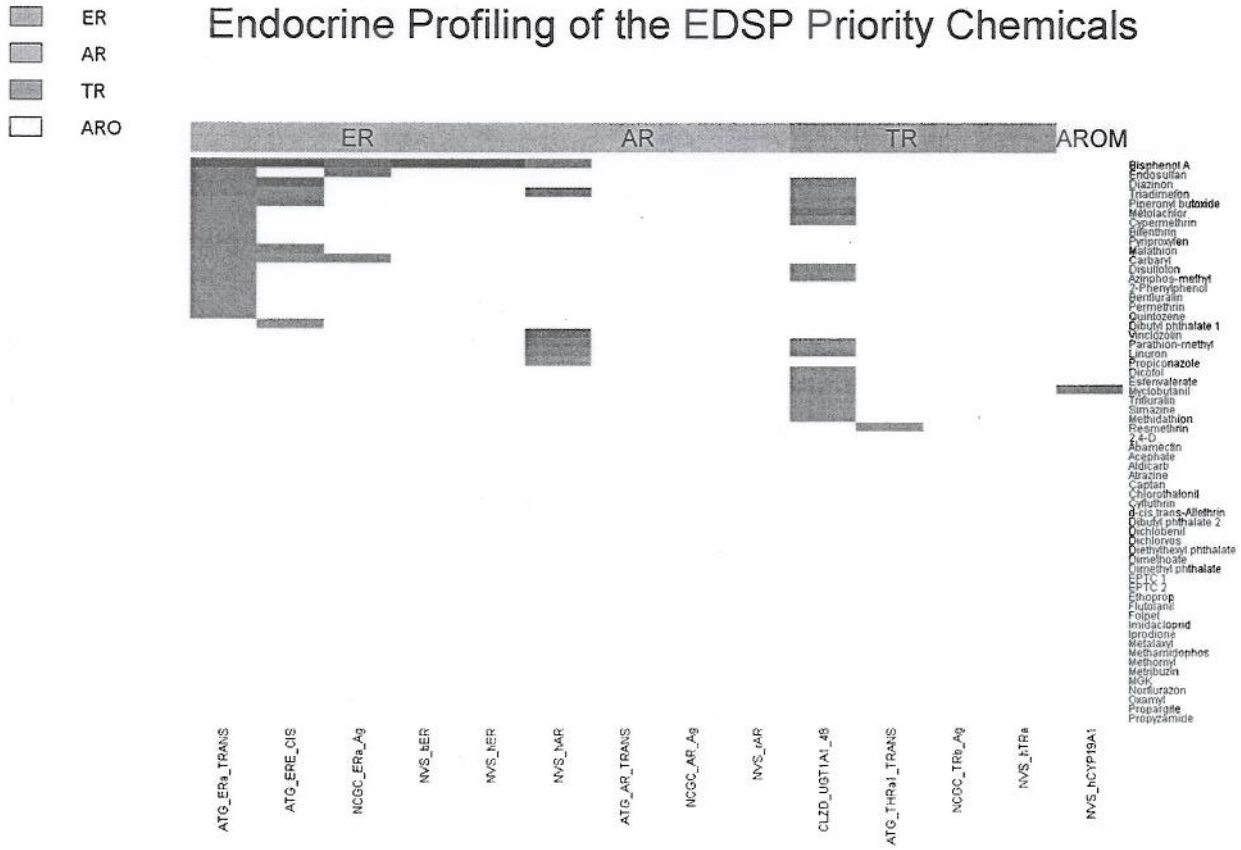
Table 2: Animals used in the Proposed Tier 1 Assays

According to EPA as of Dec 2008	Animals used per chemical	Species	Theoretical mechanism
In vitro:			
ER TA: CERI version (OECD TG 455)		endogenous human ER*a*	Estrogen agonists
AR binding: rat cytosol	?	rat prostate cytosol	Androgen agonists, antagonists
Steroidogenesis - H295R		human	Steroid synthesis (estrogen and testosterone)
Aromatase - human placental and recombinant		human	Steroid synthesis (estrogen)
In vivo:			
Uterotrophic (OECD TG 440)	18	rat, mouse	Estrogen agonists, antagonists
Hershberger	18 - 36	rat, mouse	Androgen agonists, antagonists
Pubertal female plus thyroid function	45	rat	Estrogen agonists, antagonists, synthesis; HPG axis, HPT axis
Pubertal male plus thyroid function	45	rat	Androgen agonists, antagonists, testosterone synthesis; HPG, HPT axes
Adult male 15-day	60	rat	Androgen agonists, antagonists, testosterone synthesis; HPG, HPT axes
Amphibian metamorphosis	320	*Xenopus laevis*	HPT axis
Fish 21 day fish screen	72	fathead minnow	Estrogen and androgen agonists and antagonists, steroid synthesis, HPG, HPT axes
Total	**578 - 596**		

Table 3: The OECD Conceptual Framework for Endocrine Disruptor Screening

Level 1	Physical and chemical properties Human and environmental exposure Hazard (available toxicological data)
Level 2	***In vitro:*** Estrogen and androgen receptor binding Thyroid hormone receptor binding Transcriptional activation Aromatase Steroidogenesis Arylhydrocarbon receptor binding QSARs High-throughput screens Thyroid function Fish hepatocyte vitellogenin
Level 3	***In vivo:*** Uterotrophic Hershberger Fish VTG
Level 4	Enhanced 407 Male and female pubertal assays Adult intact male
Level 5	1 and 2 generation reproduction

Figure 1: Preliminary Data on 55 Phase I Chemicals from 14 ToxCast Endocrine Assays



HTS results from 14 ToxCast assays directly related to E/A/T activity. Assay are grouped left to right as androgen (4 assays), estrogen (5 assays), thyroid (4 assays) and aromatase (1 assay) related. The black bars on the left side designate occurrence of a few selected endocrinopathies seen in multi-generation studies.

From: [1] Kavlock, RJ, Dix, D, Houck, K, Judson, R, Knudsen, T, Reif, D. and M Martin. 2009. Biological Profiling of Endocrine Related Effects of Chemicals in ToxCastTM, Presented at the 48th Annual Meeting of the Society of Toxicology, March 15–19, 2009, Baltimore, Maryland.

Organisation de Coopération et de Développement Économiques
Organisation for Economic Co-operation and Development

24-Jul-2008

English - Or. English

ENVIRONMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

SERIES ON TESTING AND ASSESSMENT
Number 92

REPORT OF THE VALIDATION PEER REVIEW FOR THE AMPHIBIAN METAMORPHOSIS ASSAY AND AGREEMENT OF THE WORKING GROUP OF THE NATIONAL COORDINATORS OF THE TEST GUIDELINES PROGRAMME ON THE FOLLOW-UP OF THIS REPORT

JT03249176

ENV/JM/MONO(2008)19
Unclassified

English - Or. Engl

Report of the Validation Peer Review for the Amphibian Metamorphosis Assay and Agreement of the Working Group of National Coordinators of the Test Guidelines Programme on the Follow-up of this Report

The Peer Review Report of the Amphibian Metamorphosis Assay was submitted for information to the Working Group of National Coordinators of the Test Guidelines Programme (WNT) in February 2008. Following the recommendations from the report, the WNT agreed that:

i) based on the available validation data, intra- and inter-laboratory variability should be documented in the draft Test Guideline, and performance criteria should be identified and included in the draft Test Guideline;

ii) additional guidance and details on the test conditions, exposure system, endpoint measurement, data interpretation and reference to the OECD guidance document on thyroid histopathology should be included in the draft Test Guideline to improve repeatability of the assay,

The WNT requested that the VMG-eco and its Amphibian Expert Group address technical issues identified by the Peer Review Panel or by the WNT and propose solutions to solve them, as appropriate.

Provided that the recommendations of the Peer Review Panel are addressed and considering the benefit of the Amphibian Metamorphosis Assay for the detection of substances that have thyroid agonist or antagonist activity, the WNT noted that it could provide useful information on the vertebrate thyroid system but that extrapolation from frogs to mammals is yet uncertain, and agreed to proceed to the development and finalization of the draft Test Guideline in a reasonable timeframe.

Business and Industry Advisory Committee to the OECD – Comité Consultatif Economique et Industriel Auprès de l'OCDE

BIAC

OECD Guidelines for Multinational Enterprises - BUSINESS BRIEF

AUGUST 2003 Vol. I, Number 2

GUIDELINES: CONFIDENTIALITY OF PROCEEDINGS

BASICS

- Confidentiality of the Guidelines procedure is a core principle for guaranteeing effective implementation of the Guidelines.
- BIAC continuously asks all participants of the Guidelines procedures, namely the governmental National Contact Points (NCPs), NGOs and the companies, to strictly observe the confidentiality requirements agreed upon.
- If the Guidelines would evolve into a campaigning instrument for the benefit of some interested parties - they would lose their credibility with companies.
- The formula agreed upon is: Filing notice of a Guidelines issue with an NCP *is public information*; discussion/deliberations with the NCP *are confidential*; conclusion of deliberations *is public information*.
- This refers to the behaviour of the NCPs as well as to interested parties (NGOs, Trade Unions): Public statements only at the beginning and at the end of a procedure.

CONTEXT

- Besides international agreements, the only legally binding instrument of the OECD are "Decisions". The Decision of the OECD Council from June 2000 obliged adhering countries to set up National Contact Points [NCP], ... "so that they can contribute to the solution of problems which may arise in this connection, *taking due account of the attached Procedural Guidance"*. Thus, the provision of the "Procedural Guidance" and all its confidentiality requirements *are legally binding* for adhering countries.
- In addition, national administrative law may have further confidentiality requirements (e.g. from data protection laws). Infringements of these requirements may give rise to claims of affected companies before national courts/fora.
- **Public statements on specific instances do infringe the principle of confidentiality as long as these instances are pending with NCPs. This affects both, companies' business secrets and the content of deliberations between interested parties as long as a specific instance is pending.**

"The spirit of the confidentiality requirement in the Guidelines procedures does indeed refer to the integrity of the process as a whole, and not only to the area of company secrets." (Chairman of the 24 June 2003 Consultations with NCPs)

CONFIDENTIALITY IN PRACTICE

- In the past, there were a view occasions where Trade Unions and NGOs published lists of specific instances and their state of deliberations, which were already raised with National Contact Points. Also, NGOs were using instances in their campaigns and in public discussion foras while they were pending.
- *However, most National Contact Points and the OECD's Investment Committee are proactively enforcing the confidentiality requirement and helping to keep interested parties within the boundaries of the principle.*

TEXT REFERENCES

Procedural Guidance

"C. Implementation in Specific Instances .....In providing this assistance, the NCP will:

4. a) In order to facilitate resolution of the issues raised, take appropriate steps to protect sensitive business and other information. While the procedures under paragraph 2 are underway, confidentiality of the proceedings will be maintained. At the conclusion of the procedures, if the parties involved have not agreed on a resolution of the issues raised, they are free to communicate about and discuss these issues. However, information and views provided during the proceedings by another party involved will remain confidential, unless that other party agrees to their disclosure.

b) After consultation with the parties involved, make publicly available the results of these procedures unless preserving confidentiality would be in the best interests of effective implementation of the Guidelines."

Commentary on the Implementation Procedures of the OECD Guidelines for Multinational Enterprises

Paragraph 19:

"Transparency is recognised as a general principle for the conduct of NCPs in their dealings with the public. However, paragraph C-4 recognises that there are specific circumstances where confidentiality is important. The NCP will take appropriate steps to protect sensitive business information. Equally, other information, such as the identity of individuals involved in the procedures, should be kept confidential in the interests of the effective implementation of the Guidelines. It is understood that proceedings include the facts and arguments brought forward by the parties. Nonetheless, it remains important to strike a balance between transparency and confidentiality in order to build confidence in the Guidelines procedures and to promote their effective implementation. Thus, while para. C-4 broadly outlines that the proceedings associated with implementation will normally be confidential, the results will normally be transparent."

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EDSP meeting with OIRA/OMB

Erik R. Janus

CropLife America

2 June 2009

CLA issues for today:

- ESDP Tier 1 data has not been shown to have actual practical utility for its intended purpose

- EPA has not evaluated existing data to determine if they are sufficient to meet the EDSP Tier 1 requirements (i.e. to minimize duplication)

The EDSP Tier 1 data must have actual practical utility

- Per 5 CFR § 1320.3(l)
- Requires clear, objectively interpretable standards and/or guidelines for:
  - T1 testing and laboratory protocols
  - Data acceptance
  - Determining compliance with T1 Test Orders
  - Interpretation of data to allow "bright line" to be drawn between compounds that **may** or **may not** interact with the endocrine system

This above info is crucial to assist companies in their response to T1 test orders, in addition to info on scale and scope of Tier 2 testing.

… must have actual practical utility

- Only "theoretical" practical utility will be demonstrated via the EPA's intended "learn as you go" approach to T1 data interpretation
  - What is the actual practical utility in determining how T2 will be triggered?
  - ICR Supporting Statement only provides a vague notion of practical utility based on the statutory purpose – **may** or **may not** interact

EPA is uncertain of practical utility of T1 data

- ICR Supporting Statement (p. 7): "T1 screening data may also be used to determine what kind of Tier 2 data is [sic] appropriate…"
  - This is admission that these data may not be useful at all
  - Could T1 ***increase*** uncertainty in how to design and require Tier 2 testing?
- Downstream effects of this current uncertainty impact the Registration Review process in addition to mandated FIFRA § 6(a)(2) adverse effect reporting

SUMMARY # 1

- If T1 data cannot be sufficiently "binned" (may vs. may not) using a transparent and reproducible weight-of-evidence approach where the "bright line" is determined using the most up-to-date sound science then these data cannot have actual practical utility
  - Substances on screening list that are known to interact with the endocrine system have no informational value for setting this "bright line" and are superfluous to "may vs. may not"

EPA has not evaluated existing data to minimize duplication

- Per 5 CFR § 1320.5(d): "Agency shall demonstrate it has taken every reasonable step to ensure … is not duplicative of information otherwise accessible …"
  - EPA avoids the duplication issue by allowing companies to form data consortia; however, this is not equivalent to prohibition of duplication under this ICR pursuant to PRA
  - FFDCA § 346a(p)(5)(B) restricts EPA in duplicating **new** data; however PRA requires EPA to avoid duplicating **existing** data

EPA has not evaluated existing data to minimize duplication

- Existing test data have not been evaluated to determine whether they are functionally equivalent for T1 purposes (again, to draw "bright line" between compounds that *may* or *may not*)
  - "existing" data extends to other sources of sufficient test data (TSCA; FDA, NIH, EPA NCCT)
  - EPA may have substituted its own ad hoc definition for the one found in PRA

EPA is shifting duty under PRA to the public

- This allows EPA to avoid duplication by asking data submitters to identify & justify use of existing data to satisfy T1
  - In response to CLA petition: FIFRA/FFDCA "clearly indicate it is the responsibility of manufacturer and/or registrant to demonstrate their substance and/or product can be used safely"
  - Purpose of T1 is to separate ***may*** from ***may not***
  - Purpose of T2 is to generate dose-response data for a risk assessment that helps determine safe use conditions

SUMMARY # 2

- EPA is only allowing T1 Test Order recipients to do what is already required under FFDCA § 408(p)
  - According to the present ICR, EPA has done nothing to determine whether any "existing data" can be used to perform the T1 screening purpose
- This ICR shifts the burden - identifying & justifying use of existing data - from EPA to the public
  - PRA does not permit EPA to make this shift as it is intended to manage the government's demands for info from the public

THE PUBLIC RECORD DEMONSTRATES THAT EIGHT TIER 1 TESTS DO NOT HAVE PRACTICAL UTILITY AND DO NOT MEET IQA GUIDELINES

	Summary of Problem
Test 1: Uterotrophic	ICCVAM formally notified EPA that the test is not validated. ICCVAM implied EPA is biased for claiming that the test is validated. ECVAM denounced the OECD peer review process as unscientific and biased. The test had a negative OECD peer review anyway. CRE comments page 16
Test 2: H295R Steroidogenesis	Peer review raised numerous unanswered questions about the accuracy and reliability of this test. In response to peer review, EPA admits that the test is incomplete and needs work, despite asserting elsewhere that it's validated. CRE comments page 14
Test 3: Fish Reproductive Screen (short term)	Peer review found that the test is not adequately reproducible, nor are the test protocols sufficiently clear and detailed. The current OECD proceedings are closed and not transparent. CRE comments page 23
Test 4: Amphibian Metamorphosis	The peer review report made clear that the test is not reproducible. The current OECD proceedings are closed and not transparent. OECD (2008b) does not mention OECD (2008a) or any peer review at all. Impossible to tell whether OECD (2008a) changes were actually made. CRE comments page 33
Tests 5 and 6: Pubertal Rat Assays (Male and Female)	These tests lack specificity and sensitivity and are not reproducible. CRE comments page 25
Test 7: AR Binding	Peer reviewers say that this test has reproducibility problems and is of questionable value "as a screening tool." CRE comments page 32

Summary of Problem	
Test 8: Estrogen Receptor Binding	EPA won't publicly release the peer review report for this test. The public record is incomplete and inadequate for public comment. CRE comments page 10