

ACC's Perspectives on EPA's Implementation of the Endocrine Disruptor Screening Program (EDSP)

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March 2008





Historical Perspective

- ACC has been engaged on this issue since mid-90's
- We have strongly supported adoption of EPA's tiered, hierarchical screening & testing EDSP framework
 - Tier 1 screening battery to ID substances with potential to interact with component(s) of endocrine system
 - Tier 2 tests to develop dose response, adverse effects data for use in risk assessment
- We support scientific validation of test methods & have contributed to the datasets needed to develop, standardize & validate EDSP methods



Components of EDSP Implementation

- Priority Setting & Chemical Selection
- Adoption of Implementation Policies and Procedures to Require Testing
- Information Collection Request (draft)
- Validation of Tier 1 Assays & Determination of the Tier 1 Battery
 - Laws require EPA to use valid test methods



Priority Setting & Chemical Selection

- Substances selected by EPA for Phase 1 of EDSP match Congressional mandates
- EPA used “exposure potential” as chief selection criteria, therefore limiting possible misunderstanding / miscommunication / product de-selection
- “Pesticide chemicals” as defined in law
 - 64 Pesticide Actives and 9 Inerts/HPVs



Priority Setting & Chemical Selection (continued)

ACC's Comments (comment period ended Feb. 11, 2008):

- Need for continued EPA communications to prevent product deselection of chemicals identified for EDSP Phase 1
- Certain sources of exposure info / databases are less robust than others & need critical review before EDSP phase 2
- EPA needs to develop a transparent, scientifically based process for determining “functional equivalence” so that testing can truly be focused on actual needs
 - Animal welfare concerns
 - Costs



Priority Setting & Chemical Selection (continued)

ACC's Comments cont. (comment period ended Feb. 11, 2008):

- We suggest Agency conduct a “reality check” and a “quality check” looking at all available tox info - are these the right substances to focus on?
- Anticipate and build into the EDSP procedures to incorporate new methods as they become validated
- EPA needs to develop Agency-wide guidance on use of weight of evidence for evaluating results of the Tier1 battery and for the appropriate use of of Tier1 screening results



EPA's Proposed Implementation Policies and Procedures (P&P)

- New Agency authority – to be exercised for the first time (“FQPA Test Orders”)
 - Test Order authority granted by Congress in the 1996 laws
- Possibly precedent setting – and important - as applies to commodity (TSCA) chemicals
 - TSCA substances that are used as inerts
 - Drinking water contaminants / potential water contaminants



Implementation – Who is Responsible to Test?

- Pesticide Active Ingredients
 - Technical Registrants will be responsible
 - FFDCA §408(p) orders
 - FIFRA §3(c)(2)(B) DCI notices
- Inert Ingredients that are also HPV chemicals
 - Manufacturers and Importers will be responsible
 - May include non-registrants
 - FFDCA §408(p) orders
 - TSCA penalties apply
- Agency has indicated intention to apply these P&P only to EDSP⁸ Phase 1- But ???





Data Compensation and CBI

- **Pesticide Active Ingredients and Food Use Inserts that are HPVs**
 - There are existing procedures - EPA will rely on FIFRA §3(c)(2)(B) and FFDCA §408(f) and (i) (tolerance)
- **Non-food Use Inserts that are HPV chemicals**
 - Not covered by FFDCA §408(f) and (i)
 - Would only be covered if submitted by a registrant or consortium with at least one registrant



ACC's Comments on EDSP Implementation Policy and Procedures

ACC's Comments Filed March 12, 2008

- Insufficient time to consider and comment on all aspects of EPA's Draft Implementation Policies
- ACC agrees with limiting the applicability of implementation policies and procedures to EDSP Phase 1 screening
 - Should not create precedent for future implementation
 - EPA should develop cost sharing process & CBI protections applicable to all testing and data incl. inerts/HPVs
- EPA should interpret “minimize duplicative testing” as a prohibition against unnecessary testing



ACC's Comments on EDSP Implementation Policy and Procedures

- EPA must develop guidance on conducting Weight of Evidence for Tier 1 Battery results to avoid inconsistencies and arbitrary decisions
- EPA should ensure communications are balanced & accurate & the use of Tier 1 data is consistent Agency-wide
- “Opt Out” mechanism needed for Manufacturers and Importers for selling inerts/HPV not intended for use in pesticide products
- Testing Orders – all of them - should be judicially reviewable when issued and EPA Should Promulgate Implementation Rule at a Later Date



ACC's Comments on EPA's Draft Information Collection Request

- EPA relied on a 2003 cost survey report from APT (commissioned by ACC) for their Dec. 2007 ICR estimates
- ACC's conclusions re: draft ICR (comments filed March 10, 2008): Serious shortcomings with accuracy of the draft ICR
 - Number & complexity of Tier 1 assays have increased since 2003, but EPA did not account for this
 - EPA has not made final determination of the Tier 1 Battery design (# of assays that will be required/exact protocols required etc.)
 - APT's 2003 report didn't include costs associated with:
 - the Tier 1 amphibian metamorphosis or the Tier 1 fish r screening assays
 - analytical chemistry requirements under Good Laboratory



ACC's Comments on EPA's Draft Information Collection Request

- Continued - ACC's conclusions re: draft ICR: Serious shortcomings with the accuracy of the draft ICR
 - Draft ICR assumes some may conduct less than the entire Tier 1 Battery of assays; but no policy/scientific rationale by EPA for this yet
 - Lack of interpretation procedures for evaluating Tier 1 battery results means it is likely that ambiguous results may necessitate repeating one or more screening tests
 - Lab capacity issue not addressed - some of the screening assays are sufficiently new and specialized that only one or a very few laboratories are able to perform them.



ACC's Comments on EPA's Draft Information Collection Request

- EPA's ICR underestimates costs by 1.5 – 3x. Total cost for EDSP Tier 1 battery could reach \$500K per chemical
- Deficiencies/inaccuracies in ICR must be addressed before test orders are issued
- Instead of updating APT's 2003 estimate with questionable assumptions, the Agency should develop its own, up to date, cost study by surveying test facilities with the final study protocols



Validation of Test Methods and the Tier1 Battery

- EPA has spent > 10 years on research & lab studies to develop, standardize & validate EDSP screens & tests
- EPA Endocrine Research + EDSP Validation and Implementation = total EPA expenditure > \$100 million
- Screens are currently going thru peer review one method at a time (almost all Tier 1 screens completed)
- Tier 1 Battery – EPA will get advice from SAP March 25-28, 2008



Have the Tier 1 Screening Assays Been Validated?

- In preparation for commenting at the upcoming EPA SAP meeting, industry scientists are analyzing the test method validation datasets

Questions for the Analyses:

- **Is the basic design of the assay scientifically sound and suitable for its intended purpose as a Tier 1 screen?**
(Relevance of the assay)
 - Rapid & cost effective? Mechanistically focused on EAT?
 - Robust endpoints & results straight forward to interpret?
 - address 3 Rs concerns?



Have the Tier 1 Screening Assays Been Validated? (continued)

Questions for Analyses (continued):

- Has each test method been standardized? (can any lab take the protocol and use it?)
- Have the validation studies shown that, for its intended purpose, each test method is:
 - sensitive? specific? predictive? reproducible across labs?

(ICCVAM definitions: http://iccvam.niehs.nih.gov/docs/about_docs/validate.pdf)

Sensitivity is defined as the proportion of active substances that are correctly identified by the new test. **Specificity** is defined as the proportion of inactive substances that are correctly identified.



Have the Tier 1 Screening Assays Been Validated? (continued)

Questions for Analyses (continued):

- What are the strengths of each assay as envisioned for EDSP Tier 1?
- What are the limitations of each assay as envisioned for EDSP Tier 1?
- We will try to arrive at overall conclusion as to whether the lab datasets are sufficient to deem a method valid for its intended purpose
 - If we don't think an assay has achieved this required level, we will attempt to provide recommendations



www.isrtp.org

IS RTP Workshop (February 19-20, 2008)

Conducting and Assessing the Results of Endocrine Screening

SESSION I – Background & Current Status of Endocrine Screening: EPA's Endocrine Disruptor Screening Program (EDSP) Tier I

SESSION II – Challenges Faced in Interpreting EDSP Assays & the Tier 1 Battery; Applying Weight of Evidence for Triggering Tier 2 Testing

SESSION III - Using the EDSP Screening Results in Risk Assessment

SESSION IV- Implementation of EPA's EDSP

Presentations will be posted on www.isrtp.org

EDSP Tier I Assay Report Card

	Utero-trophic	Hersh-berger	Pubertal Female	Pubertal Male	Intact Male	Fish Repro
Types MOA detected	limited	limited	multiple	multiple	multiple	multiple
Sensitivity	high	high	high	high	medium	high
Specificity	high	high	low	low	high	low
Neg. Control	yes	yes	no	no	yes	no
Bwt Effects	*	?	possible	possible	no	?
Determines MOA	yes	yes	no	no	yes	no

From S. Marty (ISRTP Workshop, Feb 19-20, 2008)*Marked bwt effects in 3 days indicate MTD exceeded. **Assays must be interpreted as part of a battery!**



ACC's Perspective on the EDSP Tier 1 Battery

- We have strongly supported adoption of EPA's tiered, hierarchical screening & testing EDSP framework
 - Tier 1 screening battery to ID substances with potential to interact with component(s) of endocrine system
 - Tier 2 tests to develop dose response, adverse effects data for use in risk assessment
- BUT – not all the proposed assays have been validated; some may never be



ACC's Perspective on the EDSP Tier 1 Battery

Industry will file detailed written comments & present oral comments at March 25-28, 2008 SAP mtng

- Only valid test methods can be included in T1 Battery
- At present the ER binding assay – a key assay & component of T1 Battery – has not been validated
- The pubertal assays are very problematic – every chemical that will be tested at MTD will likely be positive even if not endocrine active (refer to EPA's negative control)
- The Intact Male Assay is superior to pubertals



ACC's Perspective on the EDSP Tier 1 Battery

- EPA needs to develop procedures for Weight of Evidence determination of Tier 1 Battery results – BEFORE data is collected
- EPA needs to have clear Agency-wide (program offices & regional offices) policy & practices for interpretation & use of screening information ASAP
 - Appropriate use: for priority setting & use in determining if Tier 2 testing is needed
 - Inappropriate: should not be used for risk assessment as stand alone info (not for NOAELs, etc.), not for hazard classification, not for labeling as ED etc.



Conclusions

- Endocrine Testing is mandated by law
- For subsequent EDSP phases:
 - All pesticide chemicals (actives and inerts) are in bounds
 - Commodity and specialty chemicals - any substance that may be found in sources of drinking water with potential for substantial exposure
- Initial EDSP activities will set precedents:
 - Test orders for commodity chemicals
 - Interpreting screening assay results & applying weight of evidence process for deciding what substances need further testing



Conclusions

- Numerous issues are of concern
 - Policy and Procedures - ICR
 - Test method validation & Tier 1 Battery
- Significant implementation challenges will need to be overcome in order for the Agency to meet its announced August 2008 deadline for issuing EDSP Test Orders
- Congressional appropriations language (FY2008 budget) indicates high concern by legislators that EPA implement EDSP testing in 2008



Web Sites and Dockets for More Information

- **EPA EDSP:** <http://www.epa.gov/scipoly/oscpendo/index.htm>
- **EPA SAP:** http://www.epa.gov/scipoly/sap/meetings/2008/032508_mtg.htm
- **Implementation Policies & Procedures:** EPA-HQ-OPPT-2007-1080
- **Candidate List:** EPA-HQ-OPPT-2004-0109
- **ICR:** EPA-HQ-OPPT-2007-1081
- **SAP:** EPA-HQ-OPP-2008-0012