Endocrine Disruptor Webinar

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Agenda Topics

- Approach and Actions Taken on Pesticide Chemicals
- Endocrine Disruptors Scientific and Policy Issues
- Approach and Recent Actions Taken on Drinking Water Chemicals
- Discussion/Q&A
EDSP -- A Little History
EDSP Origins

■ Emerging issue in the 1990s
  ➢ Do some environmental agents mimic hormones -- “disrupt” normal hormonal system?
  ➢ Most known example is Diethylstilbestrol (DES) -- synthetic estrogen drug which caused severe birth defects; do other chemicals cause similar problems?
  ➢ Research on wildlife indicates possible risks -- implications for humans (birth defects, fertility impacts)

■ Theo Coburn (Our Stolen Future, 1997) and others conducting research looking at population impacts, specific effects (e.g., hermaphroditic fish)

■ “Silent Sperm” -- New Yorker Magazine, January 1996
EDSP Origins (cont’d)

- Summer 1994, EPA appropriations bill
  - Senator Al D’Amato (R-NY) suggests funding research to “test all chemicals”
    - Chemicals, breast cancer on Long Island controversial issues
  - Expected cost: $50 per chemical
    - Tentative inexpensive protocol
Food Quality Protection Act (FQPA)

- August 1996: FQPA Happens
- Extensive Amendments to FIFRA and FFDCA to ensure safety of pesticides used on food
  - Specific list of “factors” to be considered in making safety determinations, including
    - “such information as the Administrator may require on whether the pesticide chemical may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen or other endocrine effect”
FQPA Testing Program

- FFDCA Section 408(p): Estrogenic Substances Screening Program
  - Develop screening program within two years
  - Implement program within three years

- “In carrying out the screening program, the Administrator
  - Shall provide for the testing of all pesticide chemicals; and
  - May provide for the testing of any other substance that may have an effect that is cumulative to an effect of a pesticide chemical if the Administrator determines that a substantial population may be exposed to such substance”
FQPA Testing Program (cont’d)

- Conscious attempt to fix perceived “failure” and limitations of TSCA
- Emphasis on exposure to drive test requirements
- Chemical industry opposed; pesticide industry sees little likely impact at the time
- Amendments to SDWA enacted in same week
  - Senate Environment Committee ties them together
EDSTAC

- Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC)
  - October 1996 Federal Advisory Committee
  - Many widely known leading scientists
  - “Blue ribbon panel”

- Report Issued August 2008
Son of EDSTAC

- EPA attempts to have informal continuation of “blue ribbon” panel
  - Litigation by animal rights groups over FACA rules
- 2001 EPA officially empanels new FACA, includes animal rights groups
  - Endocrine Disruptor Methods Validation Subcommittee (Subcommittee of NACEPT)
Many Years after 1996 ….

- Process bogs down for many reasons
  - Difficulty of the underlying science
  - FQPA requires any tests be “validated” ones
  - Funding requirements

- Pace improves after 2002
  - December 2002: EPA requests public comment on approach to select first group of chemicals
    - Emphasis on pesticides with wide exposure
  - September 2005: EPA publishes its conceptual approach to first group
    - Similar to 2002 approach

- NGO pressure intensifies as FQPA deadline approaches (2006)
More Recent History

- June 2007: draft of specific chemicals subject to testing
  - 73 pesticides and inert ingredients
- April 2009: First Final List of Chemicals subject to testing requirements
  - 67 pesticides and inert ingredients
  - Ten years late
2010 -- Program Next Phases

- November 17, 2010 -- Draft Policies and Procedures for “SDWA Chemicals”
- November 17, 2010 -- List of 134 Chemicals
  - Expands beyond pesticides
  - More detail in next presentation
Issues

- EPA has most clear authority to require testing of pesticides
  - Industry views screening data as duplicative and more prone to false positives
  - Some belief that in-hand pesticide data will be used to validate EDSP screens
- EPA not clear on what results from Tier 1 will move to require Tier 2 tests
  - Tier 2 test undefined
- Fear of product deselection pressure based on screening test results
  - EPA trying to communicate what results might mean
- Outside of pesticides, rules and procedures for sharing of testing costs becomes more uncertain
- EPA has “order authority” to require these tests in lieu of rulemaking
  - Makes requirements much more sweeping and immediate for many affected parties outside the pesticide industry
Future Prospects

- EPA expected to be aggressive in its utilization of this authority
- Programmatic details unclear (data cost sharing, how results will be interpreted)
- Regulatory implications unclear (when might EPA regulate or otherwise act to mitigate exposure based on EDSP results)
- Can EPA meet its goal of communicating clearly what results do and do not mean?
EPA’s Endocrine Disruptor Screening Program

James C. Lamb  Ph.D., DABT, Fellow ATS
jlamb@exponent.com
What will be discussed?

- Endocrine system and its disruption
- Design and response to the EDSP
- EPA response to Tier 1 submissions
- Interactions of politics and regulation
Hormones and Endocrine Disruption

- Hormones are chemical messengers
  - Move from organ A to B with a biological purpose and control
- Endocrine disruptor is “an exogenous substance which causes adverse effects in an organism, or its progeny, subsequent to changes in the endocrine system.” Weybridge Conference (1996)
- Many possible chemical modes of action are implicated in the definition
Hormonal Activity

- Growth
- Reproduction
- Behavior
  - Mating
  - Migration
- Many other functions

Estradiol-17\(\beta\)

Source: www.3dchem.com/imagesofmolecules/Estradiol.jpg.
Sources and Targets of Hormones

- Brain
- Thyroid
- Gonads
- Pancreas
- Adrenal glands
- Every part of the body is a target of one or more hormones
- EDCs work in various ways
What is EPA looking at?

- Estrogen
- Androgen
- Thyroid
- Tier 1 Screen
  - Priority setting (not for risk assessment or management)
- Tier 2 Testing
  - Develop data that might be used for regulation (studies not defined yet)
Risk Assessment and Risk Management

- Hazard identification and dose response
- Exposure assessment
- Risk characterization

- Regulatory action and communication
Risk Assessment and Regulatory Paradigm

- NOT a simple-minded conclusion about low level hormonal activity
- T1S is NOT sufficient for Risk Assessment or Management (per EDSTAC)
- Must develop T2T within the context of all the data available
EDSP Design and Strategy

- “Validated” assays for E, A and T
- Protocols are quite variable in detail and interpretation
- Diverse set of assays -- What is the theme?
- T2 Testing not yet defined, so how will these assays be weighed?
- Strategic mis-match -- How can you develop T1S if you do not know what the T2 tests will be, or criteria for moving to Tier 2, or risk assessment will look like?
Tier 1 Screens (T1S)

- **In vitro**
  - Estrogen receptor (ER) binding -- rat uterine cytosol
  - Estrogen receptor -- (hERα) transcriptional activation -- Human cell line (HeLa-9903)
  - Androgen receptor (AR) binding -- rat prostate cytosol
  - Steroidogenesis -- Human cell line (H295R)
  - Aromatase -- Human recombinant microsomes

- **In vivo**
  - Uterotrophic (rat)
  - Hershberger (rat)
  - Pubertal female (rat)
  - Pubertal male (rat)
  - Amphibian metamorphosis (frog)
  - Fish short-term reproduction
Registrant and Producer Perspective

- Collection of assays to be conducted
  - Expectation in FQPA was cheap and quick T1S
  - Not cheap
  - Not quick

- 67 chemicals on first list (many pesticides)
  - Responses submitted to EPA
  - Some reviews by EPA have been completed
  - OSRI reviews do not appear even-handed

- Over 100 on the new list (SDWA-driven)
OMB, EPA, and OSRI or Other Scientifically Relevant Information

- OMB encouraged EPA to consider OSRI in deciding whether any Tier 1 assays could be waived
- EPA issued very limited guidance on what would be considered acceptable OSRI
- Functionally equivalent data exist for many Tier 1 assays for pesticides
- Weight of the Evidence (WoE) document ($2^{1/2}$ pages of substance) has been published
Other Scientifically Relevant Information

- OSRI has been submitted
  - In depth review of certain guideline studies
  - Review relevant published literature
  - EPA ToxCast data
  - Develop a WoE approach
  - Develop a response for each assay or hormone
EPA OSRI Evaluation Process Ongoing and Late

- OSRI for **15** chemicals evaluated by EPA to date; responses for some are published
  - [http://www.epa.gov/endo/pubs/EDSP_OSR1_Response_Table.pdf](http://www.epa.gov/endo/pubs/EDSP_OSR1_Response_Table.pdf)
- Many EPA OSRI responses are more than 6 months late; EPA initial estimate 90 days for evaluation from receipt
  - EPA indicated challenges: “the diversity of approaches to OSRI, as well as the volume and frequency of the order/DCI responses and short time frame (90 days). Including OSRI from public.”
- **EPA Data table for OSRI responses incomplete**
  - Some reviews unavailable; no links provided
  - Some link to incorrect chemicals
OSRI Evaluation Process at EPA Ongoing and Changing

- Appears to be improvisational approach to OSRI evaluation and approved options
  - Confusion at EPA?
  - Example: Bypass option (move directly to Tier 2) issued for several chemicals, then withdrawn
- As noted above, still a limited number of OSRI evaluations to draw conclusions from, but some patterns appear to be emerging
Patterns in EPA OSRI Evaluations

• *In vitro* studies:
  • Several published studies have been accepted in lieu of Tier 1 screening assays. In these cases, there is a strong parallel between the Tier 1 assay methodology and that of the published study

• Negative *in vivo* studies:
  • Uniformly rejected if any deviations from Tier 1 guidelines, regardless of their quality, consistency of the findings in multiple studies or commitment to perform other Tier 1 assays evaluating closely related endpoints

• Positive *in vivo* studies:
  • Two accepted as basis for waivers despite poor study quality and/or marked divergence from Tier 1 guidelines
OSRI “Deficiencies” Not Addressed by Tier 2 Mammalian Study

- Thyroid evaluations faulted because a 5 point subjective scale was not used for histopathologic characterization of thyroid lesions, including follicle height and colloid
  - Examination of follicle height and colloid are key components of analyses, regardless of qualitative scale
  - Comparative thyroid studies do not specify subjective scale for evaluation
OSRI “Deficiencies” Not Addressed by Tier 2 Mammalian Study (cont’d)

- Benfluralin and malathion: “organ weight data are inadequate because they were obtained from adult animals whereas in the Tier 1 pubertal studies these weights are obtained in pubertal animals.”
  - 1998 reproductive toxicity guideline requires organ weights and requires histopathological evaluations in weanling and adult animals, not in pubertal animals.
Patterns in OSRI Responses -- ToxCast Data

- EPA ToxCast data uniformly rejected, even in context of extensive other supporting information
- ToxCast assays include *in vitro* ER and AR binding and transactivation; multiplex assay; thyroid activity; aromatase
- ToxCast assays used to screen potential endocrine toxicity of oil dispersants used in the Gulf, though not acceptable for T1S
Patterns in EPA OSRI Evaluations

- No WoE process evident for OSRI evaluation
  - Studies considered individually, without consideration of other studies with the same or closely functionally-related endpoints
  - Without consideration of any Tier 1 assays the registrant has promised to perform
- Weak non-specific positive responses, or responses in poor quality studies, have been used as indications that an EAT pathway may be affected
Patterns in EPA OSRI Evaluations (cont’d)

- Lack of a WoE approach sets a poor precedent for evaluation of Tier 1 screening results
- OSRI evaluations to date predict any positive finding in an *in vivo* Tier 1 or OSRI study will lead to a “potential endocrine pathway activity” finding and likely to Tier 2 testing
CONCLUSIONS:
Political Pressures on EPA re EDSP

- Legislative action to screen on 100 more chemicals quickly

HOWEVER

- Need to look and see whether the battery really works for priority setting or not
- OSRI review process is not consistent or based on a WoE evaluation
- Not just about hormone activity, key is ultimate value in risk assessment and risk management
Safe Drinking Water Act (SDWA) Chemicals under the EDSP

SDWA Section 1457* on the “Endocrine Substances Screening Program” was effective in August 1996 and states as follows:

…the Administrator may provide for testing under the screening program … of any substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance.

*42 U.S.C. § 300j-17
EPA’s initial implementation of this SDWA provision was outlined in two November 2010 Federal Register notices:

- The Second List of chemicals for which EPA intends to issue test orders under the EDSP, including
  - Additional pesticides; and
  - Priority drinking water chemicals

- The policies and procedures that are expected to be followed for the SDWA chemicals on the list
Development of the Second List of Chemicals for EDSP Tier 1 Testing

The “Second List” chemicals include:

- Additional pesticides that are “scheduled for registration review after 2008”; and
- “[O]ther SDWA chemicals”
  - Listing is based on SDWA Section 1457
  - EPA began with an initial candidate list containing:
    - Regulated contaminants with National Primary Drinking Water Regulations (NPDWR); and
    - Unregulated contaminants listed on the “Third Contaminant Candidate List” (CCL 3)
Background Information on Development of CCL 3*

- SDWA directs EPA to publish a CCL every five years
  - “A list of contaminants that are currently not subject to any proposed or promulgated national primary drinking water regulations, that are known or anticipated to occur in public water systems, and which may require regulation under the Safe Drinking Water Act.”

- For CCL 3, EPA used an “improved process” relative to that used for CCL 1 and CCL 2
  - The new process built on the previous CCL evaluations and also included substantial expert input and recommendations from
    - The National Academy of Science’s National Research Council; and
    - The National Drinking Water Advisory Council

- EPA used a multi-step process to select candidates for the draft CCL 3 and then refined the list to include 104 chemicals or chemical groups in the final list

*http://water.epa.gov/scitech/drinkingwater/dws/ccl/ccl3.cfm
The key steps included:

- Identifying a broad universe of potential drinking water contaminants called the “CCL 3 Universe” which contained approximately 7,500 potential chemical and microbial contaminants.
- Applying screening criteria to identify almost 600 contaminants that should be further evaluated (Preliminary CCL or PCCL).
- Selection of 116 PCCL contaminants to include on the CCL based on more detailed evaluation of occurrence and health effects and expert judgment.
- EPA also incorporated information from the public in response to a Federal Register notice on the draft CCL 3 list and process, as well as expert input and review during the CCL process.
Background Information on CCL 3

- In meeting its general obligations under SDWA, EPA will evaluate the CCL 3 contaminants to determine:
  - Those that have sufficient information to allow an EPA “regulatory determination,” versus
  - Contaminants that lack sufficient information
    - EPA will encourage research to provide needed additional information for a regulatory determination

- CCL 3 is an informal listing that does not in and of itself impose any regulatory requirements

- EPA nonetheless used CCL 3 as the source of “other SDWA chemicals” for inclusion in the second list of chemicals for EDSP testing
EPA’s Approach to “Other SDWA Chemicals” in Developing the Second List of Chemicals for EDSP Tier 1 Testing

EPA began with:

- 85 NPDWR regulated contaminants, and
- 116 unregulated contaminants (includes both chemicals and microbes) listed on CCL 3

Contaminants were reviewed to exclude:

- Biological agents or naturally occurring chemicals
- Chemicals for which manufacturers/importers could not be clearly identified
- Chemicals included on the earlier EDSP list
- Hormones with confirmed endocrine effects
- Chemicals judged not likely to be biologically active or which presented testing issues (e.g., gases)
EPA’s Approach to “Other SDWA Chemicals” in Developing the Second List

- Approximately 134 chemicals remained following this process and were included in the Second List of Chemicals for EDSP Tier 1 Screening

- The approximately 84 “other SDWA chemicals” listed included:
  - Over 60 TSCA Inventory listed chemicals
  - Ingredients used in personal care products
  - 3 pharmaceuticals
  - Environmental degradates, etc.

- The full Second List, including 50 pesticides scheduled for registration review after 2008, is available at http://www.epa.gov/endo/pubs/prioritysetting/draftlist2.htm
As a result of their inclusion on the Second List, chemicals would be considered by EPA for development of FFDCA Section 408(p) testing orders:

- Second List pesticides would be handled via “FIFRA/FFDCA orders” whereas
- “Other SDWA chemicals” would be handled via “SDWA/FFDCA orders”
Policies and Procedures for “Other SDWA Chemicals” under the EDSP

- Recognizing the differences in authorities, EPA drafted a supplemental “policy and procedures” document to be used for the “other SDWA chemicals”

- This document is currently open for comment
Policies and Procedures for “Other SDWA Chemicals”

- To identify possible test order recipients, EPA plans to rely on information reported under the TSCA Inventory Update Rule (IUR).
- If no companies are identified, EPA will use the Toxics Release Inventory (TRI) and possibly other sources.
- For chemicals regulated by other agencies, EPA may consult with those agencies (e.g., FDA for pharmaceuticals).
Policies and Procedures for “Other SDWA Chemicals” (cont’d)

- EPA indicates it will focus its efforts on “all significant” manufacturers and importers
  - EPA discusses a *de minimus* exemption for chemicals produced
    - in "grams (as opposed to thousands of pounds)"; and
    - for R&D only
  - “Production for export only” is included, however
    - Since it lacks such information, EPA suggests that entities could “either identify themselves or another person” who falls into this category

- EPA is considering “catch-up orders” for companies that start production within 5 years of issuance of a test order

- Chemicals for which no producers can be identified will be considered “orphans” and EPA is asking for comment on how they should be approached
EPA plans to notify test order recipients by registered mail or electronically

“All test order recipients” would be listed on EPA’s EDSP website

- EPA does not discuss how it will handle “producer identity” that is claimed CBI under IUR

To avoid duplication of testing and assist sharing of test costs, EPA intends to post status information on the EDSP website
Policies and Procedures for “Other SDWA Chemicals” (cont’d)

- EPA identifies and discusses the following set of response options from test order recipients:
  - Testing is planned to be done
  - Existing data or OSRI will be submitted
  - A testing consortium is planned
  - Recipient claims not to be subject to the order
  - Recipient intends to discontinue production
  - Recipient can demonstrate that chemical is:
    - An endocrine disruptor
    - Eligible for exemption as “not anticipated” to cause endocrine disruption
    - Used as a positive control to validate EDSP assays
Policies and Procedures for “Other SDWA Chemicals” (cont’d)

- EPA states that “each recipient” of a test order has a “separate obligation” to satisfy the order

- EPA, since it believes it cannot impose binding arbitration, proposes procedures to facilitate joint data generation/sharing of testing costs

- EPA proposes to allow order recipients to rely on studies submitted by other entities if certain conditions (permission, compensation, etc.) are met
Policies and Procedures for “Other SDWA Chemicals” (cont’d)

■ Under SDWA, protections for CBI are limited to those established under the Trade Secrets Act (TSA)
  ➢ Further, EPA states that the TSCA CBI protections are generally not available in such a proceeding

■ EPA states that a test order is a final agency action subject to judicial review

■ EPA also intends to include an informal “administrative review procedure” whereby order recipients could raise questions or issues
Other Issues for Comment

- Response option to cease manufacture
  - EPA asks for comment on whether it is “generally inappropriate” to allow compliance by agreeing to cease manufacture or import

- Persistence
  - Although SDWA and FFDCA are silent on persistence, EPA asks whether and how to factor this attribute into EDSP policies and procedures

- Catch-up orders and data compensation
  - Is 5 years the appropriate period for catch-up orders and data compensation for “other SDWA chemicals” or, consistent with FIFRA, should it be 15 years, or some other period?
Legal and Policy Considerations

There are many legal and policy considerations in addition to those noted by Jim Lamb, Jim Aidala, and Charlie Auer
Legal and Policy Considerations (cont’d)

Important to focus on the differences derivative of the source of the Second List of Chemicals for Tier 1 testing, i.e., an EDSP2 SDWA chemical will be subject to different test order procedural/substantive requirements than an EDSP1 pesticide active ingredient (PAI) and inert ingredients -- based on the differing statutory and regulatory requirements that exist between FIFRA/FQPA and the SDWA.

- One important distinction is that when EPA issued test orders to substances under the first EDSP that are inert ingredients in pesticide products, manufacturers and importers were allowed to opt out of testing by responding that they would discontinue the sale of the chemical into the pesticide market.

- Substances issued SDWA/FFDCA orders have a much broader prohibition – to cease all manufacture and import of that chemical. Even then, EPA is seeking comments on whether it is appropriate to allow companies that contributed in the past to exposures to drinking water sources to opt out of testing by ceasing manufacture/import.
Legal and Policy Considerations (cont’d)

- Many questions regarding EPA's belief that inclusion on the CCL3 presumptively satisfies the second requirement for identifying SDWA EDSP chemicals -- SDWA Section 1412(b)(1)(C) requirement that a substantial population may be exposed; commenters should review carefully the support EPA offers for this determination and comment accordingly.

- WoE guidance document raises more questions than it answers. A request for an extension of the comment period has been submitted, but presently comments are due January 3. Much more clarity is needed to understand EPA's almost universal rejection of OSRI and how its WoE approach is being applied in practice.
Legal and Policy Considerations (cont’d)

- Difficult issues regarding limited CBI protections afforded to SDWA EDSP chemicals. EPA's view is because chemical identity is public, EPA expects there "would be no need to claim submitted information as confidential." Data submitted under a SDWA test order would only be subject to protections of FOIA and TSA.

- Data compensation issues are many and varied. Under FIFRA, qualifying test data are compensable for a 15-year period. EPA intends to issue catch-up orders for a 15-year period following submission of data under the EDSP. FIFRA provisions for data protection would not apply to SDWA chemicals, however. EPA seeks comment on whether 5 years is the appropriate length of time it should issue SDWA/FFDCA catch-up orders.

- EPA has indicated it does not intend to respond to comments submitted in response to the request for comment on the List 2 chemicals or “reopen” the comment period for any arguments why a chemical should not have been listed on the CCL3. Questionable whether this complies with APA, and the Administration's comment on transparency and process.
Questions & Discussion
Thank you