



APPLIED PHARMACOLOGY
AND TOXICOLOGY, INC.

Weight of Evidence Determinations for EPA's EDSP

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Many approaches have been developed

- ECETOC, WHO, IPCS, EPA Human Relevance Framework, ILSI WoE Project, etc.
- None provide off-the-shelf approach useful for ESB (T1S).

Two publications review & critique WoE literature

- Weed, 2005
 - WoE approaches; metaphorical, methodological, theoretical.
- Krimsky, 2005 (criticisms)
 - All evidence relevant to the status of an hypothesis is purportedly taken into account - epistemic foundation undefined.
 - Objectives: enhance clarity & transparency; enhance consistency of regulatory decision-making; identifies discretionary assumptions.
 - Objectives of WoE approaches not met because of *a priori* assumptions about the value of different evidentiary modalities based on expert judgments.
 - WoE approaches are subjective, qualitative, reduce continuous data to dichotomous judgments or at best, ordered numeric scale judgments.

House Appropriations Committee FY 2010 Report

- directed EPA to develop and publish criteria by October 30, 2010, for evaluating results of Tier 1 screening and determining whether a chemical should undergo Tier 2 analysis.

EPA Endocrine Disruptor Screening Program; Policies and Procedures for Initial Screening, Federal Register, April 15, 2009 (Volume 74, Number 71), pages 17560 -17579,

- EPA noted that a WoE would be used to determine that a chemical does or does not have the potential to interact with the endocrine system (i.e., specifically the estrogen, androgen, or thyroid hormone systems).

Draft for Public Comment released Nov 4, 2010

Purpose:

- “. . .to set forth some of the general principles, criteria, and considerations EPA generally believes to be relevant” under a WoE approach for evaluating data submitted as part of EPA's two-tiered paradigm for screening and testing chemicals for endocrine activity under the EDSP.
- “. . . to provide guidance to EPA staff and managers who will be reviewing data submitted in response [to] Orders for Tier 1 screening . . .”

Accomplishment (?):

- “. . .provides a transparent scientific approach for broadly evaluating Tier 1 screening data to detect an interaction with E, A, and/or T hormonal systems and determine if additional Tier 2 testing is necessary.”

Synopsis of EPA's WoE Draft

- 9 numbered pages
- 1 page ~ blank
- 1 page table of assays
- 1 page References
- 3.5 pages on Background, description of EDSP, ESB assays & endpoints, etc.
- 2.5 pages on WoE
 - EPA composed 1 page per \$400,000 of screening, per chemical; or 1 page per \$60,000,000 of screening for currently listed chemicals, not counting OSRI, etc.
 - Applies to OSRI as well as ESB
 - Describes some elements to be considered when conducting WoE evaluation;
 - Provides no guidance on how to conduct a WoE evaluation.

A New Approach is Needed to Accommodate T1S Data

- Accounts for T1S Endpoints in a screening context
- Avoids legitimate criticisms of WoE Approaches

OBJECTIVES

1. Clearly articulate the epistemic foundation of data evaluation.
 - Gori's three tenets.
2. Define the hypotheses to be evaluated.
 - consistent with Rhomberg approach.
3. Use rules for Systematic Review to research the literature.
 - not involved in Tier 1, but OSRI and overall EDSP will use literature.
 - Use Klimisch codes to develop weighting for data sources.

Objectives (cont'd)

4. Develop a quantitative “weighting” scheme derived empirically wherever possible.
 - Preserve continuous nature of data whenever possible.
 - Provide rationale for reducing continuous to ordered or dichotomous judgments when necessary.
5. Clearly distinguish weighting based on judgments from those derived empirically.
 - Example: *in vivo* trumps *in vitro*
6. Empirical causality method (Borgert & Gori, in prep)
 - Based on Gori’s three tenets
 - Utilizes Hill’s Aspects of Association
 - Emphasizes counterfactual study designs
 - Crucial when evaluating mode of action aspects

Gori's Three Tenets

1. The identity and authenticity of scientific measurements must be verifiable within a defined range of precision.
2. Measurements and observations must not be confounded by extraneous factors and influences known to corrupt their accuracy and precision.
3. Measurements and observations must be replicable in independent hands.

Klimisch Codes

- “test species, test substances (purity, origin), number of animals evaluated, scope of investigations per animal (e.g., clinical chemistry, organ weights, hematology, histopathology), description of changes or lesions observed, control and historical control groups, test conditions, route of administration, dose schedule and dose concentration (including analytical verification)”
- diets, composition of water bottles and cage materials, bedding, stressors such as handling and manipulation, and any other factors that could affect hormonal systems, as well as details on the mathematical and statistical algorithms used to analyze the data
- GLP; Guideline Studies

Causality (Borgert & Gori, in prep)

- Demonstrating that a specific endocrine mode of action underlies a particular adverse effect requires more than the mere coincidence of a tier 1 screening result with an effect in tier 2 testing.
- David Hume (1748) wrote that a cause is “. . . an object followed by another . . . where, if the first object had not been, the second never had existed.”
- Does R still occur when Q, and only Q, is eliminated or blocked?
- Beyond capability of most epidemiology studies;
- Implicit in pharmacology and clinical medicine.
- Hill's Aspects must be evaluated using data that comport with Gori's three tenets.

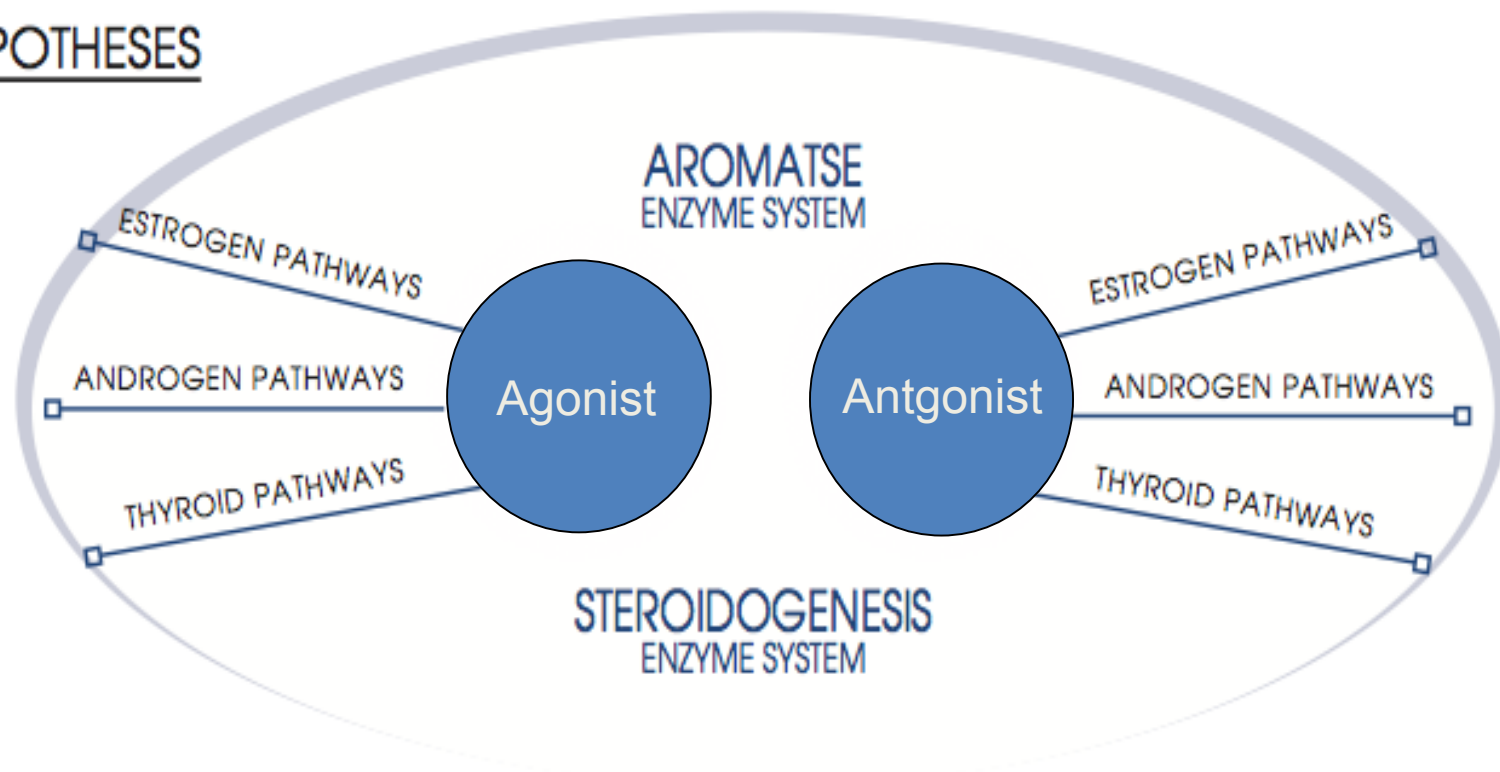
WoE Evaluations Will Be Needed for Determining:

- [a] from Tier 1 ESB and OSRI whether a substance exhibits the potential for interaction with androgen, estrogen, or thyroid pathways in vivo;
- [b] from Tier 1 ESB, OSRI and other information whether the substance should be further evaluated in Tier 2 toxicity tests;
- [c] from Tier 2 toxicity tests whether a substance exhibits adverse effects potentially mediated by androgen, estrogen, or thyroid pathways;
- [d] from Tier 1 ESB, OSRI, Tier 2 toxicity tests, and as necessary, additional mode-of-action experiments, whether the adverse effects observed in Tier 2 toxicity tests are a consequence of endocrine activity, and;
- [e] whether endocrine-mediated adverse effects on humans or wildlife are possible at environmentally relevant exposure levels.

New WoE Approach for ESB

(Borgert et al., in prep.)

TIER 1 HYPOTHESES



Hypothesis 1a: Chemical interacts as an agonist with components of estrogen pathways

Tier 1 Assay	Endpoints*	Prototypical Response of Estrogenic Agonist	Actual Response of Test Agent
Androgen Receptor Binding			
Estrogen Receptor Binding			
Aromatase			
<i>Etc. All Tier 1 Assays + OSRI</i>	<i>Repeat for each assay</i>	<i>Repeat for each assay</i>	<i>Repeat for each assay</i>

* Some assays include multiple endpoints

- 1. Relevancy Weight** for each endpoint / assay based on minimal epistemic status (Gori's tenets)
 - Ideally, the analyst understanding would also include the positive and negative predictive value of each end point in each assay - i.e., its sensitivity and specificity - for predicting adverse endocrine-mediated effects in Tier 2 tests.
 - Based on data, once we have it.
 - May require rank ordering of endpoints until sufficient data are available to provide numerical rankings.
- 2. Result Weight** scores the results obtained with the test substance according to a scale derived from the positive and negative control data for the assay.
 - Preserves continuous nature of data