

Uterotrophic Assay *Validation & Peer-Review*

American
Chemistry
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Uterotrophic Assay *Validation & Peer-Review*

Issues Raised by Others

- 1. Need for additional negative test substances*
- 2. Poor ability to distinguish weak positives from negatives; statistical issues*
- 3. Dose setting procedure has not been addressed*

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Consideration of Additional Negative Test Substances?

- *Assay specificity is good*
 - *Uterotrophic response is very specific; Few mechanisms other than estrogenicity could produce uterotrophic response*
 - *The assay is used as part of a battery; other assays can assist in interpretation.*
- *If additional negatives are needed, biology is well defined; thus, prudent selection of 1-2 compounds sufficient*

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Poor Ability to Distinguish Weak Positives from Negatives ?

- *Statistical vs biological significance; if the signal does not rise above the biological "noise," is it important?*
 - *Concern for estrogenic effects is a receptor-based concern . . . should not be confused with equivocal responses seen at very high doses.*
 - *Protocol can specify multiple doses & data interpretation procedures*
- *The assay is used as part of a battery; other assays can assist in interpretation.*

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Dose Setting Procedure Important - But Doesn't Need to be Addressed As Part of the Method

- *Phase I of EDSP will focus on Pesticide AI's (PAI) and HPV substances that are inerts.*
- *Both PAI and HPV chemicals have more than sufficient toxicological datasets to guide dose setting.*
- *2-3 dose groups can be run to ensure adequate range.*

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Recommendations

- *TG document should be developed, and should:*
 - *Address dose setting issues and use of other data (e.g., PAI, HPV).*
 - *Address equivocal responses: biological vs statistical significance. Data Interpretation Procedures*
 - *Address use of assay within battery & interpretation within context of other data.*
- *Tier 1 Battery should, & will typically be performed in a coordinated manner to leverage GLP test article/dose solution analytical costs; will also ensure availability of complementary data.*