

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460



OFFICE OF CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

Date: March 15, 2011

SUBJECT: Response to Technical Questions from Integrated Laboratory Systems
Regarding Conduct of the *in vivo* Mammalian Studies

PC Code: NA

Decision No.: NA

Petition No.: NA

Risk Assessment Type: N/A

TXR No.: NA

MRID No.: NA

DP Barcode: NA


Registration No.: NA



Regulatory Action: NA

Case No.: NA

CAS No.: NA

40 CFR: NA

FROM: Greg Akerman, Ph.D. 
Executive Secretary
Endocrine Disruptor Review Team

THROUGH: Karen Whitby, Ph.D., Co-Chair 
Endocrine Disruptor Review Team
Office of Pesticide Programs
And
Les Touart Ph.D., Co-Chair 
Endocrine Disruptor Review Team
Office of Science Coordination and Policy

TO: Richard Keigwin, Director
Pesticide Re-Evaluation Division
Office of Pesticide Programs

CONCLUSION

The Endocrine Disruptor Review Team (EDRT) recommends that the standard panels of clinical chemistry parameters required in the 90-day oral toxicity study (870.3100) under the Subdivision F Part 158 toxicology data requirements be the blood panel conducted for the *in vivo* male and female pubertal assays. EDRT concurs with the request that if excessive toxicity at the high dose is clearly demonstrated and documented, it is appropriate to issue amendments to the protocol and make corrections to the high dose for the remainder of the study with the goal of conducting

a valid study. Acceptance of such a study, however, will depend on the overall quality, conduct and confidence of the study as well as the interpretation of the study results.

I. ACTION REQUESTED

Review generic technical questions from Integrated Laboratory Systems (ILS) regarding the conduct of the Tier 1 *in vivo* mammalian assays (Male/Female Pubertal Assays and the Hershberger Assay) and the appropriateness of dose level corrections.

II. BACKGROUND

The Agency formed the Endocrine Disruptor Review Team (EDRT) to support OCSPP scientists and the regulated community in the review and conduct of the EDSP Tier 1 battery and requests for the use of alternate test protocols that may be made by Test Order recipients or the public in response to EDSP Tier 1 test orders.

III. AGENCY'S RESPONSE TO TECHNICAL QUESTIONS

In an e-mail dated February 25, 2011, Dr. Leah Zorrilla of ILS identified the following two issues that needed clarifications from the Agency:

- 1) The Male and Female Pubertal Assays ask for a standard blood panel that includes creatinine and BUN. Is there a specific "standard panel" that the EPA has in mind or prefers?
- 2) In addition, if a high dose in a study produces clinical signs, would it be appropriate to issue an amendment and reduce the dose for the remainder of the study (Hershberger, Male/Female Pubertals) so the study can be completed and would this study still be accepted by the Agency?

IV. AGENCY'S RESPONSE

- 1) Standard blood panel: Clinical chemistry parameters that have historically been part of the Agency's guideline requirements are electrolyte balance, carbohydrate metabolism, and liver and kidney functions. The selection of specific tests will be influenced by the mode of action of the test substance and signs of clinical toxicity (e.g., cholinesterase inhibition for organophosphates). Clinical chemistry parameters required for the 90-Day oral toxicity study in rodents (OPPTS 870.3100) under the Subdivision F Part 158 toxicology data requirements are recommended for the male and female pubertal assays. The parameters include the following:

Electrolytes: calcium, chloride, phosphorous, potassium, and sodium

Enzymes: alkaline phosphatase, alanine amino-transferase, aspartate amino-transferase, sorbitol dehydrogenase, and gamma glutamyl transferase.

Other: albumin, creatinine, urea nitrogen, total cholesterol, glucose, total bilirubin, and total protein.

- 2) Dose level corrections: Signs of treatment-related toxicity associated with an excessive high dose may include but not be limited to: (a) increased mortality, (b) significant reduction of bodyweight gain, (c) marked increases in abnormal behavioral and clinical signs, (d) significant changes in clinical chemistry parameters, and/or (e) saturation of absorption and detoxification mechanisms. If such excessive toxicity is clearly demonstrated and documented at the high dose, it is appropriate to issue amendments to the protocol and make corrections to the high dose for the remainder of the study with the goal of conducting a valid study.

V. EDRT's CONCLUSION

The Endocrine Disruptor Review Team (EDRT) recommends that the standard panel of clinical chemistry parameters required in the 90-day oral toxicity study (870.3100) under the Subdivision F Part 158 toxicology data requirements be measured in the *in vivo* male and female pubertal assays. EDRT concurs with the request that if excessive toxicity at the high dose is clearly demonstrated and documented, it is appropriate to issue amendments to the protocol and make corrections to the high dose for the remainder of the study with the goal of conducting a valid study. Acceptance of the study, however, will depend on the overall quality, conduct and confidence of the study as well as the Agency's interpretation of the study results.

