PEER REVIEW CHARGES

for

INDEPENDENT PEER REVIEW OF THE FISH SHORT-TERM REPRODUCTION ASSAY AS A POTENTIAL SCREEN IN THE ENDOCRINE DISRUPTOR SCREENING PROGRAM (EDSP) TIER-1 BATTERY

December 14, 2007

Background:

According to Section 408(p) of the EPA's Federal Food Drug and Cosmetic Act, the purpose of the EDSP is to:

> *develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate [21 U.S.C. 346a(p)].*

Subsequent to passage of the Act, the EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), a panel of scientists and stakeholders that was charged by the EPA to provide recommendations on how to implement the EDSP. Upon recommendations from the EDSTAC, the EPA expanded the EDSP using the Administrator's discretionary authority to include the androgen and thyroid hormone systems as well as wildlife.

One of the test systems recommended by the EDSTAC was the Fish Short-term Reproduction Assay (Fish Assay). Its purpose in the Tier-1 battery is to provide an *in vivo* assay to detect chemicals that may affect the endocrine system through the hypothalamic-pituitary-gonadal (HPG) axes. The fish assay is conducted with fathead minnows and is designed to detect changes in spawning, morphology, and specific biochemical endpoints that reflect disturbances in the HPG axis involving the estrogen and androgen hormonal pathways, and is relevant to wildlife and other animals, including humans.

Although peer review of the fish assay will be conducted on an individual basis (i.e., its strengths and limitations evaluated as a stand-alone assay), it is noted that—pending the outcome of peer review—the fish assay along with other *in vivo* and *in vitro* assays will be proposed for inclusion in the Tier 1 battery of complementary screening assays. A weight-of–evidence approach is also expected to be used among assays within the Tier-1 battery to determine whether a chemical substance has a positive or negative effect on the estrogen, androgen, or thyroid hormonal systems. Peer review of the EPA's recommendations for the Tier-1 battery will be done at a later date by the FIFRA Scientific Advisory Panel (SAP).

This peer review will focus on the scientific work EPA performed to validate the fish assay. Each peer reviewer is asked to focus his/her review on this issue and utilize the Integrated

Summary Report (ISR) as the vehicle for conducting this review. The review is not a critique or peer review of the ISR per se. Laboratory reports of studies supporting validation, and other supporting documents are provided as background information.

Review and comment shall be directed to each of the following questions.

Charge Questions:

1. Is the stated purpose of the assay clear?

2. Is the assay biologically and toxicologically relevant to the stated purpose?

3. Does the protocol describe the methodology of the assay in a clear, and concise manner so that the laboratory can

   - comprehend the objective;
   - conduct the assay;
   - observe and measure prescribed endpoints;
   - compile and prepare data for statistical analyses; and
   - report the results?

   If warranted, please also make suggestions or recommendations for test method improvement.

4. Have the strengths and/or limitations of the assay been adequately addressed?

5. Were the (a) test substances, (b) analytical methods, and (c) statistical methods chosen appropriate to demonstrate the performance of the assay?

6. Considering the variability inherent in biological and chemical test methods, were the results obtained with this assay sufficiently repeatable and reproducible?

7. With respect to performance criteria, were appropriate parameters selected and reasonable values chosen to ensure proper performance of the assay?