CHARGE TO PEER REVIEWERS

for

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

December 10, 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 placental aromatase assay. Its purpose in the Tier-1 battery is to provide a sensitive *in vitro* assay to detect chemicals that may affect the endocrine system by inhibiting aromatase, the enzyme responsible for the conversion of androgens to estrogens. Alterations in the amount of aromatase present or in the catalytic activity of the enzyme will alter the levels of estrogens in tissues and dramatically disrupt estrogen hormone action. EPA has chosen to validate two versions of the aromatase assay. The first version uses microsomes isolated from the human placenta. The other uses a human recombinant microsome.

Although peer review of aromatase assay will be done on an individual basis (i.e., its strengths and limitations evaluated as a stand alone assay), it is noted that the aromatase assay along with a number of other *in vitro* and *in vivo* assays will potentially constitute a 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 assays. 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 the studies supporting validation and the Detailed Review Paper on aromatase are provided as background information.

Charge Questions:

Your review and comments shall be directed to each of the following 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:

   a) comprehend the objective;
   b) conduct the assay;
   c) observe and measure prescribed endpoints;
   d) compile and prepare data for statistical analyses; and
   e) report the results?

   What additional advice, if any, can be given regarding the protocol?

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?

8. Are the data interpretation criteria clear, comprehensive, and consistent with the stated purpose?

9. Please comment on the overall utility of the assay as a screening tool described in the introduction of the ISR to be used by the EPA to identify chemicals that have the potential to interact with the endocrine system.