PEER REVIEW CHARGES

for

INDEPENDENT PEER REVIEW OF THE 15-DAY INTACT ADULT MALE RAT ASSAY AS A POTENTIAL SCREEN IN THE ENDOCRINE DISRUPTOR SCREENING PROGRAM (EDSP) TIER-1 BATTERY

August 29, 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 15-day intact adult male rat assay. The intact adult male assay consists of multiple endpoints; principally, terminal weights of primary and secondary sex organs and thyroid gland, histology of the testes, epididymides and thyroid, and serum concentrations of reproductive steroids, gonadotropins and thyroid hormones.

According to numerous reports published in peer-reviewed scientific journals, the intact adult male rat assay has the capacity to detect estrogen receptor agonists/antagonists, androgen receptor agonists/antagonists, progesterone receptor agonists/antagonists, steroid biosynthesis inhibitors, gonadotropin and thyroid modulators either directly or indirectly by altering the hypothalamic-pituitary-gonadal or -thyroidal axes, and prolactin modulators through neuroendocrine pathways.

A weight-of-evidence approach among the multiple endpoints within the bioassay combined with biological plausibility is expected to help distinguish endocrine-related effects from spurious effects and to determine whether a chemical substance has a positive or negative effect on the estrogen, androgen or thyroid hormonal systems.

The purpose of this peer review is to review and comment on the intact adult male screening assay for use within the EDSP to detect various MOAs, especially AR agonists/antagonists, steroid biosynthesis inhibitors, gonadotropin and thyroid modulators either directly or indirectly through intact HPG or HPT axes.

Although peer review of the intact adult male assay will be done on an individual basis (i.e., its strengths and limitations evaluated as a stand alone assay), it is noted that this 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).

Each peer reviewer is asked to review the Integrated Summary Report and accompanying support materials and comment on the results of the validation process of the 15-day intact adult male rat assay, especially the inter-laboratory validation exercise. Review and comment shall be directed to each of the following:

1. Clarity of the stated purpose of the assay.

2. Clarity, comprehensiveness and consistency of the data interpretation wit the stated purpose of the assay.

3. Biological and toxicological relevance of the assay as related to its stated purpose.

4. Clarity and conciseness of the protocol in describing the methodology of the assay such 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 results.

5. Strengths and/or limitations of the assay.

6. Impacts of the choice of:
    a. test substances,
    b. analytical methods, and
    c. statistical methods in terms of demonstrating the performance of the assay.

7. Repeatability and reproducibility of the results obtained with the assay, considering the variability inherent in the biological and chemical test methods.