

9.0 OTHER SCIENTIFIC REPORTS AND REVIEWS

9.1 Availability of Other *In Vitro* ER Binding Data

A number of the peer-reviewed publications identified during the initial literature search that contained ER binding data were not abstracted for inclusion in this BRD. These include:

- Studies lacking either appropriate quantitative data (i.e., RBA or IC₅₀ values) or the necessary information to calculate IC₅₀ values;
- Studies for which test substances were not adequately identified;
- Studies containing data from unique procedures (e.g., use of T47D cells or bovine uterine cytosol); and
- Publications reporting results for only a few substances that had not been tested by any other investigator.

Recognizing that unpublished ER binding data may be available, a formal request was published in the *Federal Register* (Vol. 66, No. 57, pp.16278 - 16279) for data and/or information from completed studies using or evaluating ER binding assays. No information was received in response to this request.

It is known that some companies involved in the development of pharmaceuticals routinely use *in vitro* ER binding assays to screen substances for their potential estrogenic activity. However, these data are unpublished and have not been provided to NICEATM for consideration.

The U.S. EPA has a contract with Battelle Pacific Northwest National Laboratory (Richland, WA) to generate *in vitro* ER binding data to evaluate two QSAR ER binding models developed by scientists at the U.S. Food and Drug Administration National Center for Toxicological Research (FDA NCTR) and by Dr. Ovanes Mekenyan (Mekenyan et al., 2000). Initially, Battelle will test 25 substances in an *in vitro* ER binding RUC assay. The ultimate goal is to test a total of 300 substances for evaluation in the two QSAR models, which the U.S. EPA plans to use for priority setting of substances for the U.S. EPA EDSP. In addition, the American Chemistry Council (ACC) is sponsoring *in vitro* ER binding studies, using the RUC assay, at two laboratories that will be testing approximately 25 substances. Neither the U.S. EPA nor the ACC test results are available at this time.

While every effort was made to include all available, pertinent *in vitro* ER binding assay data in this BRD, some data may have been excluded inadvertently.

9.2 Conclusions of Other Scientific Reviews of *In Vitro* ER Binding Methods

To date, no independent peer reviews of *in vitro* ER binding assays have been conducted. However, two workshops addressed the use of these assays as potential endocrine disruptor screening methods. Although the strengths and limitations of these assays were discussed at both workshops, no effort was made to evaluate the reliability or performance of these assays. Some of the conclusions from these workshops are summarized below.

9.2.1 1996 Endocrine Disruptor Screening Methods Workshop

In vitro ER binding assays were discussed extensively at an Endocrine Disruptor Screening Methods Workshop held in July 1996 at Duke University in Durham, North Carolina. Gray et al. (1997) edited the proceedings of this workshop, which was cosponsored by the U.S. EPA, the Chemical Manufacturer's Association (CMA), and the World Wildlife Fund (WWF).

The major strengths of *in vitro* cytosolic ER binding assays cited by the authors include:

- Sensitivity (can detect ER binding with as low as 50 fmol ER/mg protein);
- Specificity of response;
- Relatively short duration of the test;
- Fairly inexpensive;
- Well-documented; and
- Can be standardized.

The major limitations cited by the authors include:

- Do not distinguish between estrogen agonists and antagonists;
- Substances requiring metabolic activation would produce false negative results;
- Insolubility of test substance in assay buffer could produce a false negative result; and
- Denaturation effects of a test substance could produce false positive results.

In addition, the authors briefly discussed the major advantages and disadvantages of cell-free and whole-cell binding assays using hER. The major strength of these assays is their potential relevance to humans, while their major limitation is that they are relatively new methods with little published data.

9.2.2 1997 Workshop on Screening Methods for Detecting Potential (Anti-) Estrogenic/Androgenic Chemicals in Wildlife

In March 1997, the U.S. EPA, the CMA, and the WWF cosponsored a workshop in Kansas City, Missouri, that addressed the use of ER binding assays as screening methods for detecting potential (anti-) estrogenic chemicals in wildlife. Proceedings of this workshop were published by Ankley et al. (1998).

The major advantages cited by the authors of using ER binding assays as endocrine disruptor screens for wildlife include:

- Widespread acceptance and use; and
- Can be conducted with ER from various mammalian and nonmammalian species, including fish, reptiles and birds.

The major disadvantages include:

- Do not distinguish between agonists and antagonists; and
- Uncertainties regarding extrapolation across species.

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