

8.0 QUALITY OF DATA REVIEWED

8.1 Extent of Adherence to GLP Guidelines

Ideally, all data supporting the validity of a test method should be obtained and reported in accordance with GLP guidelines, which are nationally and internationally recognized rules designed to produce high-quality laboratory records. GLPs provide a standardized approach to report and archive laboratory data and records, and information about the test protocol, to ensure the integrity, reliability, and accountability of a study (U.S. EPA, 2001, 2002; FDA, 2002).

Based on the available information, none of the published *in vitro* ER binding studies identified for this BRD appear to have been conducted in compliance with national or international GLP guidelines.

8.2 Assessment of Data Quality

Formal assessments of data quality, such as a quality assurance (QA) audit, generally involve a systematic and critical comparison of the data provided in a study report or published paper to the laboratory records generated for a study. No attempt was made to formally assess the quality of the *in vitro* ER binding data included in this BRD. The published data on the competitive binding of substances to the ER were limited to RBA and, to a lesser extent, IC₅₀ and K_i values. Auditing these reported values would require obtaining the original data for each ER binding experiment, which is not readily available.

An informal assessment of the ER binding publications revealed limitations that complicate interpretation of the *in vitro* ER binding assay data (**Appendix D**):

- *Insufficient methods information*: A relatively large number of publications contained limited details about the methods used to conduct the studies. In some cases, publications reported that the methods were “performed as previously described,” and in many of these cases the cited publication referenced another publication for experimental details. Following this trail of references made it difficult to determine the actual protocol used to produce the data reported in the publication being abstracted.
- *Inconsistent nomenclature of test substances*: Most publications did not provide CASRNs for the substances tested, which in some cases made an unequivocal identification difficult. For

example, 19 publications reported results for a hydroxylated form of tamoxifen. Most laboratories reported testing “4-hydroxytamoxifen”; however, a few publications used less specific substance names, such as “monohydroxytamoxifen” and “hydroxytamoxifen,” which do not specify the location of the hydroxy group on the parent molecule. As a result, it is not possible to conclude definitively that these three names referred to same substance.

- *Data reporting:* A few publications calculated the RBA value of a test substance using the IC₅₀ value of 17 β -estradiol reported in another publication. Thus, it could not be determined whether the test substance and 17 β -estradiol were evaluated concurrently in the same experiment. Additionally, much of the data reported in the publications were RBA values only, with no accompanying error term provided to assess the quality of the estimate. Thus, the variability of the experimental data could not be assessed.
- *High number of unreplicated studies:* A majority of the substances tested in ER binding studies have not been tested in multiple laboratories, and thus, the results are unconfirmed. Of the 638 substances included in this BRD, 376 (59%) were tested by one laboratory only.
- *Graphical presentation of data:* Some publications presented the results of ER binding experiments in graphical format only. A majority of these publications presented IC_x data in a semi-log plot (e.g., % [³H]17 β -estradiol vs. log concentration of competitor). In these cases, IC₅₀ values were estimated from the graphs, and used to calculate the corresponding RBA values. These estimations might contribute to some of the variability seen in the RBA values in **Appendix D**.

8.3 Quality Control Audit

NICEATM staff conducted a quality control (QC) audit of the ER binding database provided in **Appendix D**. In conducting this audit, data input into the database was checked against the original sources and corrected if an entry error had been made.

8.4 Need for Data Quality

Data quality is a critical component of the test method validation process. To ensure data quality, ICCVAM recommends that all of the data supporting validation of a test method be available with the detailed protocol under which the data were produced. Original data should be

available for examination, as should supporting documentation, such as laboratory notebooks. Ideally, the data should adhere to national or international GLP guidelines (ICCVAM, 1997).

All of the *in vitro* ER binding assay data included in this BRD were obtained from peer-reviewed scientific articles reporting the results of studies conducted at facilities that do not typically perform studies in compliance with GLP guidelines. It should be noted that a majority of these studies were performed in response to basic research questions and/or to evaluate the binding affinities of estrogen analogs or new drugs, not to support prevalidation or validation of the test method, or the formal submission of data to regulatory agencies. Because these studies span three decades and a multitude of laboratories, verifying the integrity of the data via a formal audit process was not possible.

An informal assessment of the *in vitro* ER binding assay data showed that the test substances and data were not consistently represented in the same format. In addition, the methods were presented in varying levels of detail and completeness. Since the published data were not verified for their accuracy against the original experimental data, caution must be exercised when interpreting the quantitative and qualitative analyses performed in **Section 6**.

An important step towards acceptance of *in vitro* ER binding assay methods into a regulatory screening program is production of high quality data. To achieve this goal, it is recommended that any future prevalidation and validation studies on *in vitro* ER binding assays be conducted with coded substances and in compliance with national and international GLP guidelines. Ideally, the substances should be obtained from a common source, and distributed from a central location. Laboratories not able to perform studies in compliance with GLP guidelines should perform studies in the spirit of GLP. At a minimum, this would require detailed, accurate documentation of laboratory protocols, experiment-related notes, and data entries.

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