4.0 REFERENCE DATA USED FOR AN ASSESSMENT OF FETAX PERFORMANCE CHARACTERISTICS

4.1 Description of Laboratory Mammal and Human Reference Data Sources

Reference teratogenic data were obtained from several general sources listed below. If teratogenesis and developmental toxicity studies were not listed for a particular substance in these general sources, NICEATM staff searched the Developmental and Reproductive Toxicology (DART) database, available through the TOXNET system (http://sis.nlm.nih.gov/sis1/), a product of the National Library of Medicine (NLM), and the ReproTox® System, produced by the Reproductive Toxicology Center and available on the MICROMEDIX' TOMES CPS™ CD-ROM. Keywords included specific chemical names, synonyms, and Chemical Abstract Service Registry Numbers (CASRN). For substances not located in these two databases, NLM's MEDLINE and TOXLINE databases were also searched for teratogenicity information.

- Friedman, J.M., and J.E. Polifka. 1994. Teratogenic Effects of Drugs. A Resource for Clinicians (TERIS). Johns Hopkins University Press, Baltimore, MD.

- National Institute for Occupational Safety and Health (NIOSH). RTECS® (Registry of Toxic Effects of Chemical Substances). On: the TOXNET® system. Internet Resource Internet Resource (http://sis.nlm.nih.gov/sis1/).

- National Library of Medicine (NLM). HSDB® (Hazardous Substances Data Bank). On: the TOXNET® system. Internet Resource Internet Resource (http://sis.nlm.nih.gov/sis1/).

- Schardein, J.L. 1993. Chemically Induced Birth Defects, 2nd Edition, Marcel Dekker, Inc, New York, NY.

· Shepard, T.H. 1995. Catalog of Teratogenic Agents. 8th Edition. John Hopkins University Press, Baltimore, MD.

· Smith, M.K., G.L. Kimmel, D.M. Kochhar, T.H. Shepard, S.P. Spielberg, and J.G. Wilson. 1983. A selection of candidate compounds for *in vitro* teratogenesis test validation. Teratog. Carcinog. Mutagen. 3:461-480

· Szabo, K.T. 1989. Congenital Malformations in Laboratory and Farm Animals. Academic Press, Inc., New York, NY.

In the reference data collection process conducted by NICEATM, there was no intent to collect all laboratory mammal and human teratogenicity data (i.e., the search strategy was limited to substances tested in FETAX), to obtain original data for the reference studies, to evaluate the appropriateness of the study design, or to critically review the scientific merit of the conclusions of the investigator. In considering the reference data, a weight-of-evidence approach was not used in classifying a substance as a teratogen or non-teratogen. Rather, the presence of at least one positive teratogenic study resulted in the substance being classified as a teratogen for the species evaluated. While potentially resulting in some false positive classifications, this approach was considered by NICEATM to be the most conservative.

4.2. Laboratory Mammal Reference Data

The laboratory mammal reference data are provided by substance in **Appendix 4**. Laboratory mammal (mouse, rat, and rabbit) teratogenicity data were obtained for 90 of the 137 substances evaluated in FETAX plus one environmental sample. These data were entered by individual species. Data on the teratogenicity of these substances in other species, both mammalian and non-mammalian, were included as a separate entry, where identified. Where available, descriptive information on the types of malformations observed was included in the database. In using these data to evaluate the performance characteristics of FETAX against combined laboratory mammal (i.e., rat, mouse, and rabbit) results, positive studies were given weight over negative studies within an individual species and, where multiple species had been evaluated, the

overall teratogenicity classification was made on the basis of a positive response in any single species. In addition, the performance characteristics of FETAX against each of the three primary laboratory mammal species were calculated. Data from the other non-human species were not considered in an evaluation of the performance characteristics of FETAX.

4.3 Availability of Original Laboratory Mammal Reference Test Data

The availability of original test data for the reference mammalian assays is not known.

4.4 Laboratory Mammal Reference Data Quality

Generally, teratogenicity findings for laboratory mammals (e.g., rat, mouse, and rabbit) were obtained from reviews, compilations of data, or individual published reports. The sources used were considered authoritarian for this purpose. However, the quality of the data in terms of accuracy and whether the studies were conducted in compliance with national/international Good Laboratory Practice (GLP) Guidelines is not known.

4.5 Availability and Use of Human Teratogenicity Data

Human teratogenicity data were obtained for 34 chemicals from the sources listed in **Section 4.1**. These data are summarized in **Appendix 4**.

A single positive human study was considered to be definitive for the purpose of classifying a substance as a human teratogen. While potentially resulting in false positive classifications, this approach was considered by NICEATM to be the most conservative for the purpose of analyzing the performance characteristics of FETAX against the human database.

4.6 Section 4 Conclusions

Reference teratogenic data were obtained from general sources; additional information (e.g., research papers, literature reviews, book chapters) were located by searching the DART

database, the ReproTox® System, and the MEDLINE and TOXLINE databases. Studies using humans, rats, mice, rabbits, and other species (both mammalian and non-mammalian) were considered. Sources for human data included case reports, epidemiological studies, case-control studies, literature reviews, and other secondary references. The search was not intended to be comprehensive; only substances tested in FETAX were considered and no effort was made to critically evaluate the conclusions of the investigator. In classifying substances as teratogens or non-teratogens in rats, mice, rabbits, or humans, a single positive study was sufficient to classify the substance as a teratogen. This approach may have resulted in some false-positive classifications within the database. A critical evaluation of the current laboratory mammal (rat, mouse, rabbit) and human teratogenicity databases by appropriate experts would be an important contribution to this field of investigation, and to the development and validation of alternative *in vitro* teratogenicity assays.