9.0 OTHER SCIENTIFIC REPORTS AND REVIEWS

9.1 Availability of Other FETAX Data

The focus of the BRD has thus far been on the use of FETAX, as defined in the ASTM FETAX Guideline (1991, 1998), as a screening assay for identifying substances that may pose a developmental hazard in humans. The sources for the FETAX data evaluated for that purpose included peer-reviewed literature (including studies accepted for publication) and non peer-reviewed book chapters. Information not considered included abstracts, manuscripts not accepted for publication, studies where test substances were not identified, studies not conducted in general compliance with the ASTM FETAX Guideline (1991, 1998), and published reports lacking appropriate quantitative FETAX data. Published information on substances not appropriately identified was excluded to avoid the possibility of duplication of results during an analysis of the performance characteristics of FETAX.

9.2 Conclusions of Other Peer Reviews

No other independent peer reviews of FETAX have been conducted. However, an evaluation of the performance of FETAX was published in 1987 by Sabourin and Faulk, based on FETAX studies conducted in their laboratory. FETAX was evaluated as a candidate *in vitro* teratogenicity assay by testing 35 chemicals listed in a consensus NTP teratogenesis chemical repository. The authors concluded that the most promising endpoints were embryo malformations and growth during the 96-hour test. In FETAX, 17 of 20 *in vivo* laboratory mammal teratogens tested positive, and 12 of 15 negative laboratory mammal teratogens tested negative, for an overall accuracy of 83%. Furthermore, the concordance between the types of malformations (e.g., skeletal, visceral, nervous, optic, osmoregulatory) detected in *Xenopus* and in mammals was 67% for 19 teratogens. The authors concluded that FETAX was a strong candidate for further consideration as a teratogen screen. However, due to the lack of quantitative FETAX malformation data for the substances considered in this review, this information was not considered in the evaluation of FETAX conducted by NICEATM.

The utility of *X. laevis* for identifying human developmental hazards was discussed also in a review by Sakamoto et al. (1992). In this review, based on analysis of seventeen substances tested in-house and a review of the literature, Sakamoto et al. concluded that the *Xenopus* embryo and larva system is a good candidate for a simple and effective test system to evaluate developmental toxicants. Due to significant protocol differences, the data provided in this review were not considered by NICEATM in the evaluation of the performance characteristics of FETAX.

Recently, Fort et al. (2000a) assessed the predictive validity of FETAX, with and without metabolic activation, for identifying the potential developmental toxicity of a group of diverse coded chemicals (fungicides, herbicides, nematocides) by comparison with results from *in vivo* teratogenicity studies in rats. A total of 12 chemicals were evaluated, three of which were classified as teratogenic *in vivo*, four of which were embryolethal but not teratogenic *in vivo*, and five that did not produce any developmental toxicity *in vivo*. The FETAX studies followed the 1991 ASTM FETAX guideline. In this study, each test chemical was judged to have developmental hazard when the TI value was greater than 3.0, the MCIG/LC_{50} ratio was less than 0.30, and/or strong characteristic malformations were induced. If the TI value was between 1.5 and 2.9, the MCIG/LC_{50} ratio was greater than 0.3, but characteristic malformations of moderate severity were induced, the chemical was classified as equivocal. The test chemical was judged not hazardous when all decision criteria fell into the non-hazard category. The investigators concluded that FETAX correctly predicted that three chemicals had strong teratogenic potential (were positive in FETAX), four had low teratogenic hazard potential but were embryolethal (i.e., were equivocal in FETAX), and five posed little if any developmental toxicity hazard (i.e., were negative in FETAX). In addition, the investigators stated that within a family of chemical analogs, the compounds could be ranked according to relative teratogenic hazard and that, for the teratogenic compounds, the types of malformations induced in *Xenopus* mimicked the abnormalities induced *in vivo* in rats. Based on these results, the investigators concluded that the results confirmed that the FETAX assay is predictive and can be useful in an integrated biological hazard assessment for the preliminary screening of chemicals.

Although supportive of a conclusion that FETAX was predictive of rat teratogenicity results, these data could not be used by NICEATM in their evaluation of the performance characteristics of FETAX. First and most importantly, the identity of each test chemical was not available; each test substance was identified by chemical class (e.g., substituted diphenyl ether) only. Furthermore, although tested with and without metabolic activation, only a single set of FETAX data were provided for each compound and information on the metabolic activation status of that data was not provided in the publication. Finally, mortality and malformation rates for the inactivated MAS and CP only negative control dishes are reported to range from 0-25% and 2.5-100%, respectively. These values exceed the 10% mortality and malformation limits that appear to be established by the ASTM FETAX guideline (1991, 1998) as being acceptable.

9.3 Section 9 Conclusions

No other independent peer reviews of FETAX were located. An evaluation of the performance of FETAX was published in 1987 by Sabourin and Faulk, based on FETAX studies conducted in their laboratory. However, due to the lack of quantitative FETAX data for the substances considered in this review, this information was not considered in the evaluation of FETAX conducted by NICEATM. The utility of *X. laevis* for identifying human developmental hazards was discussed also in a review by Sakamoto et al. (1992), in which it was concluded that the *Xenopus* embryo and larva system is a good candidate for a simple and effective test system to evaluate developmental toxicants.