

pharmacokinetics and mechanistic (PK/MECH) data to support the application of the model for the endpoints listed under Tier II of the EDC ECA. Specifically, the PK/MECH testing will develop data to inform:

i. Oral-to-inhalation extrapolation of subchronic toxicity data reported by Daniel, *et al.* (1994; Ref. 9) relevant to corn oil gavage.

ii. Oral-to-inhalation extrapolation of subchronic neurotoxicity data relevant to drinking water exposure of a study to be conducted under Tier II Testing.

iii. Oral-to-inhalation extrapolation of reproductive effects testing conducted under Tier II Testing and each dosing paradigm of studies reported by Alumot *et al.* (1976; Ref. 10), Rao, *et al.* (1980; Ref. 11) and Lane *et al.* (1982; Ref. 12).

In addition, the Companies will provide model simulations with point and uncertainty estimates of internal dose metrics (parent chemical peak and area under the curve (AUC) concentrations in blood and brain, and 24-hour total glutathione-dependent metabolism) in rats and humans to inform quantitative route-to-route extrapolations of dose-response. These simulations will be used to evaluate the acceptability of: Subchronic neurotoxicity testing of oral exposure via drinking water in rats, extant oral subchronic toxicity data of Daniel *et al.*

(1994; Ref. 9) in rats via corn oil gavage, and reproductive toxicity testing of oral exposure via drinking water in rats.

3. *EPA Program Review.* Model development and data from Tier I Program Review Testing are subject to an EPA Program Review. It is essential to the success of the EDC ECA alternative testing program for EPA to ensure that the model and the PK/MECH data used to support the route-to-route extrapolations of dose-response are of the highest quality. The purpose of the EPA Program Review will be to determine:

i. Whether it is feasible and appropriate to apply Tier I Program Review Testing data and data from other studies acceptable to EPA to support computational route-to-route extrapolations of dose-response for endpoints listed in the Tier II Testing segment of the ECA.

ii. Whether the data from the Tier I Program Review Testing segment provide a sufficient basis for conducting the endpoint testing and/or the computational route-to-route extrapolations for the dose-responses specified in the Tier II Testing segment.

iii. The nature and scope of any additional work that may be required before Tier II Testing and application of the EDC model for route-to-route extrapolation of dose-response reporting

(e.g., development of additional PK/MECH data, modification to the EDC model).

4. *Tier II Testing and/or Extrapolation Reporting.* This segment of the EDC ECA alternative testing program consists of endpoint testing by drinking water exposure for subchronic neurotoxicity and reproductive toxicity. The reproductive effects toxicity testing is intended to confirm studies reported by Alumot *et al.* (1976; Ref. 10), Rao *et al.* (1980; Ref. 11), and Lane *et al.* (1982; Ref. 12), and provide data needed on fertility index, gestation index, gross necropsy, organ weight, histopathology, estrous cycle, sperm evaluation, vaginal opening, and preputial separation as described in the ECA.

This segment will also include application of the EDC model for quantitative route-to-route extrapolation reporting (oral to inhalation) for Tier II endpoint testing (subchronic neurotoxicity and reproductive toxicity) and similar computational extrapolation reporting for extant subchronic toxicity reported by Daniel *et al.* (1994; Ref. 9).

Testing conducted under this ECA will allow EPA to characterize certain potential health hazards resulting from inhalation exposure to EDC. The following Table 1 sets forth the required testing, test standard, and reporting requirements under the ECA for EDC.

TABLE 1.—REQUIRED TESTING, TEST STANDARD, AND REPORTING REQUIREMENTS FOR EDC

| Testing Segment | Required testing | Test standard | Deadline for final report ¹ (Months) |
|---|---|---|---|
| Tier I HAPs Testing. | Acute toxicity, with BAL and histopathology (inhalation). | 40 CFR 799.9135 (as annotated in ECA Appendix D.1). | 18 |
| | Acute neurotoxicity (inhalation). | 40 CFR 799.9620 (as annotated in ECA Appendix D.1). | 18 |
| Tier I Program Review Testing. | PK/MECH data to support model validation and verification of oral-to-inhalation extrapolation of dose-response for the following data needs in the F344 rat: a. Subchronic toxicity. b. Subchronic neurotoxicity. c. Reproductive toxicity. PBPK model simulations. | ECA Appendix C (1–4). | 21 |
| | | ECA Appendix C (1–5). | 21 |
| Tier II Testing and/or Extrapolation Reporting. | Subchronic toxicity route-to-route extrapolation of dose-response (oral Tier II Testing to inhalation) of a study reported by Daniel <i>et al.</i> (1994). | ECA Appendix C.2 and C.6. | 36 |
| | Subchronic neurotoxicity (oral). | 40 CFR 799.9620 (as annotated in ECA Appendix D.2). | 42 |
| | Subchronic neurotoxicity route-to-route extrapolation of dose-response (oral Tier II Testing to inhalation). | ECA Appendix C.3 and C.6. | 52 |
| | Reproductive toxicity (oral). | 40 CFR 799.9380 (as annotated in ECA Appendix D.3). | 42 |