

data needs identified in the proposed HAPs rulemaking.

Under the TCE ECA testing program, the data needs for TCE are being addressed via an informed testing program that utilizes, wherever possible, extant data from acceptable studies performed by routes other than inhalation, testing by inhalation and the oral route, and development of pharmacokinetics and mechanistic (PK/MECH) data to support a computational dosimetry model to perform route-to-route extrapolations. Since this is a new approach, EPA and the companies included a program review step within the testing program. The testing program consists of Tier I HAPs Testing; Tier I Program Review Testing; EPA Program Review; and Tier II Testing.

Tier I HAPs Testing consisted of endpoint testing conducted by inhalation exposure for acute and subchronic toxicity. The Tier I Program Review Testing included: (1) Development of a computational dosimetry model specific for TCE in rats and mice; (2) simulation testing of the predictive capability of the model against an inhalation test data set; and (3) demonstration of the model's utility in supporting quantitative route-to-route dosimetry extrapolations. The test sponsors also developed PK/MECH data to support the application of the model to oral-to-inhalation extrapolations of dose-response for extant and Tier II Testing endpoint studies. Tier I HAPs Testing and Tier I Program Review Testing results are available in the legacy docket (OPPTS-42198C) and electronically in the e-Docket (OPPT-2002-0056).

The purpose of the program review was to determine:

1. 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 for endpoints listed in the Tier II testing segment of the ECA.

2. 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 specified in the Tier II testing segment.

3. The nature and scope of any additional work that may be required before Tier II testing and the application of the TCE model for route-to-route extrapolation reporting (e.g., development of additional PK/MECH data, modification to the TCE model).

B. What were the Public Comments on the Tier I Program Review Testing?

EPA received one public comment from the People for the Ethical Treatment of Animals (PETA). The comment was submitted by PETA and on behalf of themselves, the Physicians Committee for Responsible Medicine, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. PETA's comments were favorable on the use of the alternative approach to address data needs utilizing PBPK modeling which could result in a reduction in the number of animals used in toxicity testing to meet EPA's data needs. Although, PETA also stated their belief that the presently available data base for TCE is sufficiently extensive to characterize the toxicity of TCE, and that no additional testing is necessary, PETA did not include comments regarding the scientific merit of the PK/MECH data or PBPK model development for TCE.

EPA appreciates the expressed support for the application of alternative approaches that incorporate PBPK modeling as a means to address data needs for HAP chemicals. Although, computational approaches are an increasingly important tool for EPA to use in addressing data needs, they must be scientifically defensible and rely on the development of PK/MECH data relevant to the modeling approach. Computational dosimetry modeling approaches need critical empirical data from toxicity studies conducted in a scientifically adequate manner. EPA has concluded that the Tier II testing is necessary in this case. EPA's basis for this decision is presented in previous **Federal Register** notices, cited in Unit II.A.

C. What are the Conclusions of the EPA Program Review?

EPA has determined that the Tier I Program Review testing and data from other studies acceptable to EPA can support computational route-to-route dosimetry extrapolations for the endpoints listed in the Tier II testing segment of the ECA. More specifically, EPA has concluded that:

1. The PK/MECH data report and Tier I toxicity studies appear to have been conducted in accordance with the protocols and specifications as described in Appendix C of the ECA.

2. The available study records are sufficient to allow an evaluation of the quality of the studies performed.

3. The TCE PBPK model is appropriately chemical-specific, and suitably based on the current understanding of the kinetics of TCE.

4. The species, dose level, exposure regimens, and vehicles used are relevant for the toxicity data that are the object of the Tier II extrapolations.

5. The Tier I Program Review PK/MECH data demonstrated that periodicity was achieved in the studies that support the model.

EPA has also concluded, that the choice of dose metrics for Tier II computational route dosimetry extrapolations should be revised to correlate with Tier I study findings, and that selection of the dosing regimens for Tier II testing could benefit from predictions derived from the PBPK model for TCE. These changes to the original testing and extrapolation reporting are described in the revised Table 1 (Table 1. (amended)) of this **Federal Register** notice, and will be incorporated into protocol development under Tier II activities. EPA's program review activity, including the findings and conclusions, are described in a report titled: "Program Review Report on the Enforceable Consent Agreement for 1,1,2-Trichloroethane" (U.S. EPA, April 21, 2003). This report is available electronically from the e-Docket OPPT-2002-0056.

It is EPA's decision that the HAP Task Force can proceed with Tier II Testing under the schedule set forth in Table 1. of this **Federal Register** notice. The testing schedule corresponds to that originally set forth in the **Federal Register** notice announcing the ECA and Order for TCE, but is modified to include the additional time needed to complete the Program Review segment of the ECA for TCE, which was longer than originally anticipated, plus additional time for Tier II protocol development. Table 1. also identifies additional modifications to Tier II activities to correlate with Tier I study findings. EPA does not consider these modifications of the test schedules or Tier II activities to be significant.

D. What are the Modifications to the ECA for TCE?

This **Federal Register** notice incorporates modifications to the ECA for the TCE test schedule for Tier II ECA activities, clarifies protocol development for Tier II testing, expands consideration for dose metrics to be applied in the Tier II route dosimetry extrapolations and reporting, and identifies a change in signatory companies to the ECA. The testing schedule corresponds to that originally set forth in the **Federal Register** notice announcing the ECA and Order for TCE, but is modified to allow for the time needed to perform the EPA Program Review, which was longer than