# APPENDIX F

# TCE Noncancer Dose-Response Analyses

**CONTENTS—Appendix F: TCE Noncancer Dose-Response Analyses**

**CONTENTS (continued)**

## LIST OF TABLES

## LIST OF FIGURES

## LIST OF FIGURES (continued)

# APPENDIX F: TCE NONCANCER DOSE-RESPONSE ANALYSES

## F.1. DATA SOURCES

Data sources are cited in the body of this report in the section describing dose-response analyses (see Chapter 5).

## F.2. DOSIMETRY

This section describes some of the more detailed dosimetry calculations and adjustments used in Section 5.1.

### F.2.1. Estimates of Trichlorethylene (TCE) in Air From Urinary Metabolite Data Using Ikeda et al. (1972)

#### F.2.1.1. *Results for Chia et al. (1996)*

Chia et al. (1996) demonstrated a dose-related effect on hyperzoospermia in male workers exposed to trichloroethylene (TCE), lumping subjects into four groups based on range of trichloroacetic acid (TCA) in urine (see Table F-1).

**Table F-1. Dose-response data from Chia et al. (1996)**

| TCA, mg per g creatinine | No. of subjects | No. with hyperzoospermia |
|---|---|---|
| 0.8 to <25 | 37 | 6 |
| 50 to <75 | 18 | 8 |
| 75 to <100 | 8 | 4 |
| ≥100 to 136.4 | 5 | 3 |

Minimum and maximum TCA levels are reported in the text of Chia et al. (1996), the other data, in their Table 5.

Data from Ikeda et al. (1972) were used to estimate the TCE exposure concentrations corresponding to the urinary TCA levels reported by Chia et al. (1996). Ikeda et al. (1972) studied 10 workshops, in each of which TCE vapor concentration was "relatively constant." They measured atmospheric concentrations of TCE and concentrations in workers' urine of total trichloro compounds (TTC), TCA, and creatinine, and demonstrated a linear relation between TTC/creatinine (mg/g) in urine and TCE in the work atmosphere. Their data are tabulated as geometric means (the last column was calculated by us, as described in Table F-2).

**Table F-2. Data on TCE in air (ppm) and urinary metabolite concentrations in workers reported by Ikeda et al. (1972)**

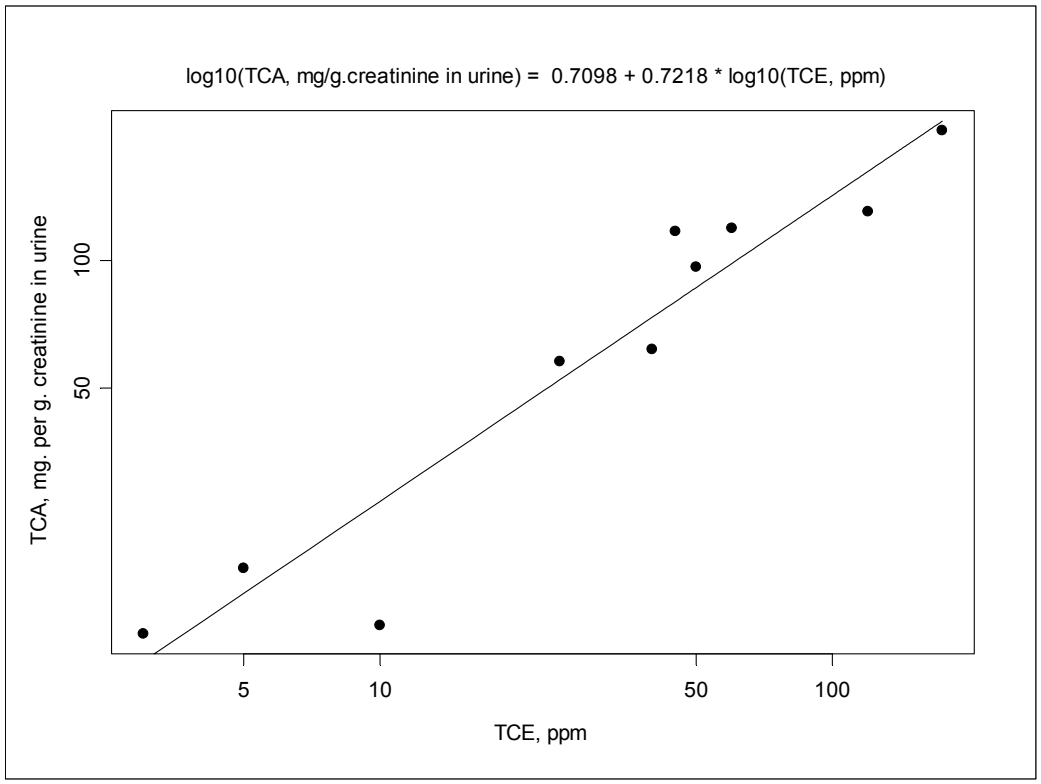
| *n* | TCE (ppm) | TTC (mg/L) | TCA (mg/L) | TTC (mg/g creatinine) | TCA (mg/g creatinine) |
|---|---|---|---|---|---|
| 9 | 3 | 39.4 | 12.7 | 40.8 | 13.15127 |
| 5 | 5 | 45.6 | 20.2 | 42.4 | 18.78246 |
| 6 | 10 | 60.5 | 17.6 | 47.3 | 13.76 |
| 4 | 25 | 164.3 | 77.2 | 122.9 | 57.74729 |
| 4 | 40 | 324.9 | 90.6 | 221.2 | 61.68273 |
| 5 | 45 | 399 | 138.4 | 337.7 | 117.137 |
| 5 | 50 | 418.9 | 146.6 | 275.8 | 96.52012 |
| 5 | 60 | 468 | 155.4 | 359 | 119.2064 |
| 4 | 120 | 915.3 | 230.1 | 518.9 | 130.4478 |
| 4 | 175 | 1210.9 | 235.8 | 1040.1 | 202.5399 |

These data were used to construct the last column "TCA.cr.mg.g" (mg TCA/g creatinine), as follows: TCA (mg/g creatinine) = TCA (mg/L) × TTC (mg/g creatinine)/TTC (mg/L). The regression relation between TCE (ppm) and TCA (mg/g creatinine) was evaluated using these data. Ikeda et al. (1972) reported that the measured values are lognormally distributed and exhibit heterogeneity of variance, and that the reported data (above) are geometric means. Thus, the regression relation between log10(TCA [mg/g creatinine]) and log10(TCE [ppm]) was used, assuming constant variances and using number of subjects "*n*" as weights. Figure F-1 shows the results.

Next, a Berkson setting for linear calibration was assumed, in which one wants to predict *X* (TCE, ppm) from means for *Y* (TCA, mg/g creatinine), with substantial error in *Y* (Snedecor and Cochran, 1980). Thus, the inverse prediction for the data of Chia et al. (1996) was used to infer their mean TCE exposures. The relation based on data from Ikeda et al. (1972) is

$$\log10(\text{TCA, mg/g creatinine}) = 0.7098 + 0.7218*\log10(\text{TCE, ppm}) \qquad \text{(Eq. F-1)}$$

and the inverse prediction is




```
Coefficients:
                Value Std. Error t value Pr(>|t|)
   (Intercept) 0.7098 0.1132     6.2688  0.0002
log10(TCE.ppm) 0.7218 0.0771     9.3578  0.0000

Residual standard error: 0.3206 on 8 degrees of freedom
Multiple R-Squared: 0.9163
F-statistic: 87.57 on 1 and 8 degrees of freedom, the p-value
is 0.0000139
```

**Figure F-1. Regression of TCE in air (ppm) and TCA in urine (mg/g creatinine) based on data from Ikeda et al. (1972).**

$$\log10(\text{TCE}) = [\log10(\text{TCA}) - 0.7098]/0.7218 \qquad \text{(Eq. F-2)}$$

$$\text{TCE, ppm} = 10\text{^}( [\log10(\text{TCA}) - 0.7098]/0.7218)$$

Because of the lognormality of data reported by Ikeda et al. (1972), the means of the logarithms of the ranges for TCA (mg/g creatinine) in Chia et al. (1996), which are estimates of the median for the group, were used. The results are shown in Table F-3.

**Table F-3. Estimated urinary metabolite and TCE air concentrations in dose groups from Chia et al. (1996)**

| TCA, mg per g Creatinine | Estim. TCA median[a] | Log10(TCA median) | Estim. ppm TCE[b] |
|---|---|---|---|
| 0.8 to <25 | 4.47 | 0.650515 | 0.827685 |
| 50 to <75 | 61.2 | 1.787016 | 31.074370 |
| 75 to <100 | 86.6 | 1.937531 | 50.226119 |
| ≥100 to 136.4 | 117 | 2.067407 | 76.008668 |

[a] 10^(mean[log10(TCA limits in first column)] ).
[b] 10^([log10(TCA median)] − 0.7098)/0.7218.

Dose-response relations for the data of Chia et al. (1996) were modeled using both the estimated medians for TCA (mg/g creatinine) in urine and estimated TCE (ppm in air) as doses. The TCE-TCA-TTC relations are linear up to about 75 ppm TCE (Figure 1 of Ikeda et al. 1972), and certainly in the range of the benchmark dose (BMD). As noted below (see Section F.2.2), the occupational exposure levels are further adjusted to equivalent continuous exposure for deriving the point of departure (POD).

#### F.2.1.2. *Results for Mhiri et al. (2004)*

The lowest-observed-adverse-effect level (LOAEL) group for abnormal trigeminal nerve somatosensory evoked potential reported in Mhiri et al. (2004) had a urinary TCA concentration of 32.6 mg TCA/mg creatinine. Using Eq. F-2, above gives an occupational exposure level = 10^([log10(32.6) − 0.7098]/0.7218) = 12.97404 ppm. As noted below (see Section F.2.2), the occupational exposure levels are further adjusted to equivalent continuous exposure for deriving the POD.

### F.2.2. Dose Adjustments to Applied Doses for Intermittent Exposure

The nominal applied dose was adjusted for exposure discontinuity (e.g., exposure for 5 days per week and 6 hours per day reduced the dose by the factor [5/7]*[6/24]). The physiologically based pharmacokinetic (PBPK) dose metrics took into account the daily and weekly discontinuity to produce an equivalent average dose for continuous exposure. No dose adjustments were made for duration of exposure or a less-than-lifetime study, as is typically done for cancer risk estimates, though in deriving the candidate reference values, an uncertainty factor for subchronic-to-chronic exposure was applied where appropriate.

For human occupational studies, inhalation exposures (air concentrations) were adjusted by the number of work (vs. nonwork) days and the amount of air intake during working hours as a fraction of the entire day (10 $m^3$ during work/20 $m^3$ for entire day). For the TCE ppm in air converted from urinary metabolite data using Ikeda et al. (1972), the work week was 6 days, so the adjustment for number of work days is 6/7.

### F.2.3. Physiologically Based Pharmacokinetic (PBPK) Model-Based Internal Dose Metrics

PBPK modeling was used to estimate levels of dose metrics corresponding to different exposure scenarios in rodents and humans (see Section 3.5). The selection of dose metrics for specific organs and endpoints is discussed under Section 5.1.

The PBPK model requires an average body weight. For most of the studies, averages specific to each species, strain, and sex were used. Where these were not reported in the text of an article, data were obtained by digitizing the body weight graphics (Maltoni et al., 1986) or by finding the median of weekly averages from graphs (National Cancer Institute [NCI], 1976; National Toxicology Program [NTP], 1990, 1988). Where necessary, default adult body weights specific to the strain were used (U.S. EPA, 1994).

## F.3. DOSE-RESPONSE MODELING PROCEDURES

Where adequate dose-response data were available, models were fitted with the BenchMark Dose Software (BMDS) (http://www.epa.gov/ncea/bmds) using the applicable applied doses or PBPK model-based dose metrics for each combination of study, species, strain, sex, endpoints, and benchmark response (BMR) under consideration.

### F.3.1. Models for Dichotomous Response Data

#### F.3.1.1. *Quantal Models*

For dichotomous responses, the log-logistic, multistage, and Weibull models were fitted. These models adequately describe the dose-response relationship for the great majority of data sets, specifically in past TCE studies (Filipsson and Victorin, 2003). If the slope parameter of the log-logistic model was less than 1, indicating a supralinear dose-response shape, the model with the slope constrained to 1 was also fitted for comparison. For the multistage model, an order one less than the number of dose groups was used, in addition to the $2^{nd}$-order multistage model if it differed from the preceding model, and the first-order ('linear') multistage model (which is identical to a Weibull model with power parameter equal to 1). The Weibull model with the power parameter unconstrained was also fitted t.

#### F.3.1.2. *Nested Dichotomous Models*

In addition, nested dichotomous models were used for developmental effects in rodent studies to account for possible litter effects, such maternal covariates or intralitter correlation. The available nested models in BMDS are the nested log-logistic model, the Rai-VanRyzin models, and the NCTR model. Candidates for litter-specific covariates (LSC) were identified from the studies and considered legitimate for analysis if they were not significantly dose-related (determined via regression, analysis of variance). The need for a LSC was indicated by a difference of at least 3 in the Akaike Information Criteria (AIC) for models with and without a LSC. The need to estimate intralitter correlations (IC) was determined by presence of a high correlation coefficient for at least one dose group and by AIC. The fits for nested models were also compared with the results from quantal models.

### F.3.2. Models for Continuous Response Data

For continuous responses, the distinct models available in BMDS were fitted: power model (power parameter unconstrained and constrained to $\geq 1$), polynomial model, and Hill model. Both constant variance and modeled variance models were fit; but constant variance models were used for model parsimony unless the *p*-value for the test of homogenous variance was <0.10, in which case the modeled variance models were considered. For the polynomial model, model order was selected as follows. A model of order 1 was fitted first. The next higher order model (up to order $n-1$) was accepted if AIC decreased more than 3 units and the *p*-value for the mean did not decrease.

### F.3.3. Model Selection

After fitting these models to the data sets, the recommendations for model selection set out in U.S. Environmental Protection Agency (U.S. EPA)'s *Benchmark Dose Technical Guidance Document* (Inter-Agency Review Draft, U.S. EPA, 2008b) were applied. First, models were generally rejected if the *p*-value for goodness of fit was <0.10. In a few cases in which none of the models fit the data with $p > 0.10$, linear models were selected on the basis of an adequate visual fit overall. Second, models were rejected if they did not appear to adequately fit the low-dose region of the dose-response relationship, based on an examination of graphical displays of the data and scaled residuals. If the benchmark dose lower bound (BMDL) estimates from the remaining models were "sufficiently close" (a criterion of within 2-fold for "sufficiently close" was used), then the model with the lowest AIC was selected. The AIC is a measure of information loss from a dose-response model that can be used to compare a set of models. Among a specified set of models, the model with the lowest AIC is considered the "best." If two

or more models share the lowest AIC, the BMD *Technical Guidance Document* (U.S. EPA, 2008b) suggests that an average of the BMDLs could be used, but averaging was not used in this assessment (for the one occasion in which models shared the lowest AIC, a selection was made based on visual fit). If the BMDL estimates from the remaining models are not sufficiently close, some model dependence is assumed. With no clear biological or statistical basis to choose among them, the lowest BMDL was chosen as a reasonable conservative estimate, as suggested in the *Benchmark Dose Technical Guidance Document*, unless the lowest BMDL appeared to be an outlier, in which case further judgments were made.

### F.3.4. Additional Adjustments for Selected Data Sets

In a few cases, the dose-response data necessitated further adjustments in order to improve model fits.

The behavioral/neurological endpoint "number of rears" from Moser et al. (1995) consisted of counts, measured at five doses and four measurement times (with eight observations each). The high dose for this endpoint was dropped because the mean was zero, and no monotone model could fit that well. Analysis of means and standard deviations for these counts suggested a Box-Cox power transform (Box et al., 1978) of ½ (i.e., square root) to stabilize variances (i.e., the slope of the regression of log[standard deviation (SD)] on log[mean] was 0.46, and the relation was linear and highly significant). This information was helpful in selecting a suitable variance model with high confidence (i.e., variance constant, for square-root transformed data). Thus, the square root was taken of the original individual count data, and the mean and variance of the transformed count data were used in the BMD modeling.

The high-dose group was dropped due to supra-linear dose-response shapes in two cases: fetal cardiac malformations from Johnson et al. (2003) and decreased PFC response from Woolhiser et al. (2006). Johnson et al. (2003) is discussed in more detail below (see Section F.4.2.1). For Woolhiser et al. (2006), model fit near the BMD and the lower doses as well as the model fit to the variance were improved by dropping the highest dose (a procedure suggested in U.S. EPA (2008b).

In some cases, the supralinear dose-response shape could not be accommodated by these measures, and a LOAEL or no-observed-adverse-effect level (NOAEL) was used instead. These include NCI (1976) (toxic nephrosis, >90% response at lowest dose), Keil et al. (2009) (autoimmune markers and decreased thymus weight, only two dose groups in addition to controls), and Peden-Adams et al. (2006) (developmental immunotoxicity, only two dose groups in addition to controls).

## F.4. DOSE-RESPONSE MODELING RESULTS

### F.4.1. Quantal Dichotomous and Continuous Modeling Results

The documents Appendix.linked.files\AppF.Non-cancer.Plots.TCE.contin.DRAFT.pdf and Appendix.linked.files\AppF.Non-cancer.Plots.TCE.dichot.DRAFT.pdf show the fitted model curves. The graphics include observations (group means or proportions), the estimated model curve (solid red line) and estimated BMD, with a BMDL. Vertical bars show 95% confidence intervals for the observed means. Printed above each plot are some key statistics (necessarily rounded) for model goodness of fit and estimated parameters. Printed in the plots in the upper left are the BMD and BMDL for the rodent data, in the same units as the rodent dose.

More detailed results, including alternative BMRs, alternative dose metrics, quantal analyses for endpoints for which nested analyses were performed, etc. are documented in the several spreadsheets. Input data for the analyses are in the following documents: Appendix.linked.files\AppF.Non-cancer.Input.Data.TCE.contin.DRAFT.pdf and Appendix.linked.files\AppF.Non-cancer.Input.Data.TCE.dichot.DRAFT.pdf. The documents Appendix.linked.files\AppF.Non-cancer.Results.TCE.contin.DRAFT.pdf and Appendix.linked.files\AppF.Non-cancer.Results.TCE.dichot.DRAFT.pdf present the data and model summary statistics, including goodness-of-fit measures (Chi-square goodness-of-fit *p*-value, AIC), parameter estimates, BMD, and BMDL. The group numbers "GRP" are arbitrary and are the same as GRP in the plots. Finally, note that not all plots are shown in the documents above, since these spreadsheets include many "alternative" analyses.

### F.4.2. Nested Dichotomous Modeling Results

#### F.4.2.1. *Johnson et al. (2003) Fetal Cardiac Defects*

**F.4.2.1.1.** ***Results using applied dose.*** The biological endpoint was frequency of rat fetuses having cardiac defects, as shown in Table F-4. Individual animal data were kindly provided by Dr. Johnson (personal communication from Paula Johnson, University of Arizona, to Susan Makris, U.S. EPA, 26 August 2009). Cochran-Armitage trend tests using number of fetuses and number of litters indicated significant increases in response with dose (with or without including the highest dose).

One suitable candidate for a LSC was available: female weight gain during pregnancy. Based on goodness of fit, this covariate did not contribute to better fit and was not used. Some ICs were significant and these parameters were included in the model.

**Table F-4. Data on fetuses and litters with abnormal hearts from Johnson et al. (2003)**

| Dose group (mg/kg/d): | 0 | 0.00045 | 0.048 | 0.218 | 129 |
|---|---|---|---|---|---|
| Fetuses | | | | | |
| Number of pups: | 606 | 144 | 110 | 181 | 105 |
| Abnormal heart: | 13 | 0 | 5 | 9 | 11 |
| Litters | | | | | |
| Number of litters: | 55 | 12 | 9 | 13 | 9 |
| Abnormal heart: | 9 | 0 | 4 | 5 | 6 |

With the high dose included, the chi-square goodness of fit was acceptable, but some residuals were large (1.5 to 2) for the control and two lower doses. Therefore, models were also fitted after dropping the highest dose. For these, goodness of fit was adequate, and scaled residuals were smaller for the low doses and control. Predicted expected response values were closer to observed when the high dose was dropped, as shown in Table F-5:

**Table F-5. Comparison of observed and predicted numbers of fetuses with abnormal hearts from Johnson et al. (2003), with and without the high-dose group, using a nested model**

| Dose group (mg/kg/d): | Abnormal hearts (pups) | | | | |
|---|---|---|---|---|---|
| | 0 | 0.00045 | 0.048 | 0.218 | 129 |
| Observed: | 13 | 0 | 5 | 9 | 11 |
| Predicted expected: | | | | | |
| With high dose | 19.3 | 4.5 | 3.5 | 5.7 | 11 |
| Without high dose | 13.9 | 3.3 | 3.4 | 10 | -- |

Accuracy in the low-dose range is especially important because the BMD is based upon the predicted responses at the control and the lower doses. Based on the foregoing measures of goodness of fit, the model based on dropping the high dose was used.

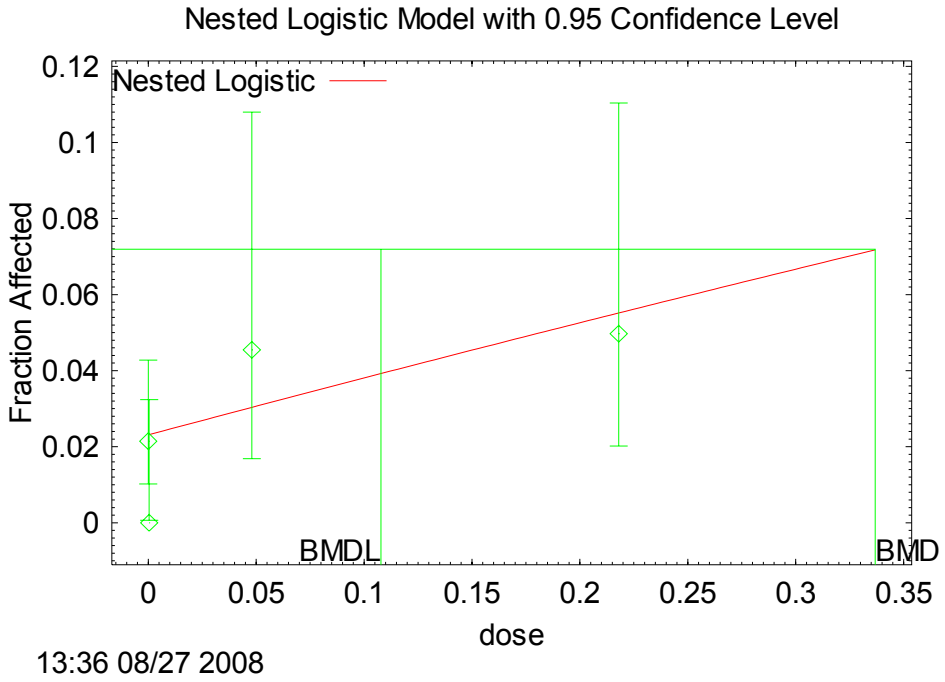
The nested log-logistic and Rai-VanRyzin models were fitted; these gave essentially the same predicted responses and POD. The former model was used as the basis for a POD; results are in Table F-6 and Figure F-2.

**Table F-6. Results of nested log-logistic model for fetal cardiac anomalies from Johnson et al. (2003) without the high-dose group, on the basis of applied dose (mg/kg/d in drinking water)**

| Model | LSC? | IC? | AIC | Pval | BMR | BMD | BMDL |
|---|---|---|---|---|---|---|---|
| NLOG | Y | Y | 246.877 | NA (df = 0) | 0.01 | 0.252433 | 0.03776 |
| NLOG | Y | N | 251.203 | 0.0112 | 0.01 | 0.238776 | 0.039285 |
| NLOG | N | N | 248.853 | 0.0098 | 0.01 | 0.057807 | 0.028977 |
| NLOG | N | Y | 243.815 | 0.0128 | 0.1 | 0.71114 | 0.227675 |
| NLOG | N | Y | 243.815 | 0.0128 | 0.05 | 0.336856 | 0.107846 |
| **NLOG*** | **N** | **Y** | **243.815** | **0.0128** | **0.01** | **0.064649** | **0.020698** |

* Indicates model selected (Rai-VanRyzin model fits are essentially the same).

NLOG = "nested log-logistic" model.
LSC analyzed was female weight gain during pregnancy.



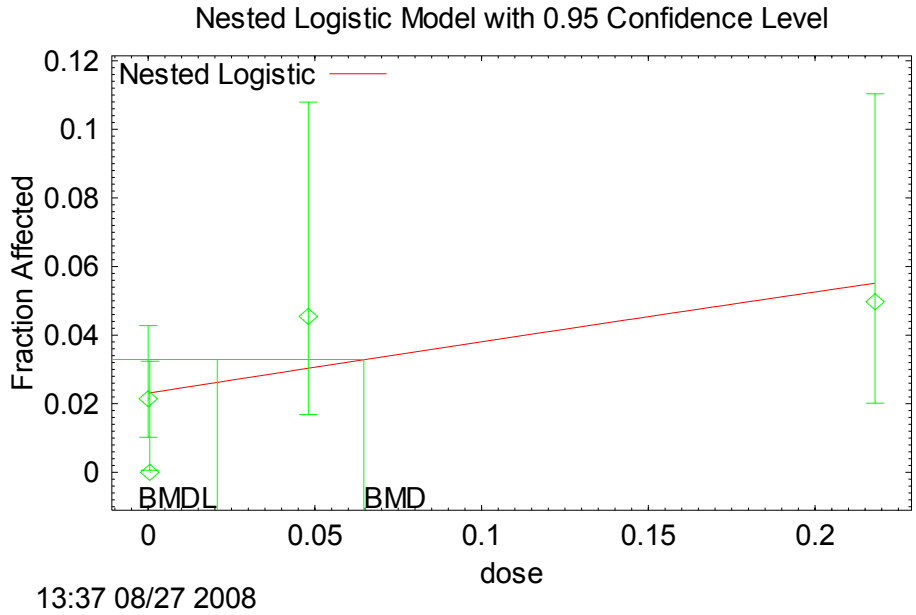




**Figure F-2. BMD modeling of Johnson et al. (2003) using nested log-logistic model, with applied dose, without LSC, with IC, and without the high-dose group, using a BMR of 0.05 extra risk (top panel) or 0.01 extra risk (bottom panel).**

**F.4.2.1.2.** ***Chi-square Goodness of Fit Test for nested log-logistic.*** The BMDS choice of subgroups did not seem appropriate given the data. The high-dose group of 13 litters was subdivided into three subgroups having sums of expected counts 3, 3, and 2. However, the control group of 55 litters could have been subdivided because expected response rates for controls were relatively high. There was also concern that the goodness of fit might change with alternative choices of subgroupings.

An R program was written to read the BMDS output, reading parameters and the table of litter-specific results (dose, covariate, estimated probability of response, litter size, expected response count, observed response count, scaled chi-square residual). The control group of 55 litters was subdivided into three subgroups of 18, 18, and 19 litters. Control litters were sampled randomly without replacement 100 times, each time creating 3 subgroups—i.e., 100 random assignments of the 55 control litters to three subgroups were made. For each of these, the goodness-of-fit calculation was made and the *p*-value saved. Within these 100 *p*-values, ≥75% were ≥0.05, and ≥50% had *p*-values ≥0.11, this indicated that the model is acceptable based on goodness-of-fit criteria.

**F.4.2.1.3.** ***Results using physiologically based pharmacokinetic (PBPK) model-based dose metrics.*** The nested log-logistic model was also run using the dose metrics in the dams of total oxidative metabolism scaled by body weight to the ¾-power (TotOxMetabBW34) and the area-under-the-curve of TCE in blood (AUCCBld). As with the applied dose modeling, LSC (maternal weight gain) was not included, but IC was included, based on the criteria outlined previously (see Section F.3.1.2). The results are summarized in Table F-7 and Figure F-3 for TotOxMetabBW34 and Table F-8 and Figure F-4 for AUCCBld.

**F.4.2.2.** ***Narotsky et al. (1995)***

Data were combined for the high doses in the single-agent experiment and the lower doses in the 'five-cube' experiment. Individual animal data were kindly provided by Dr. Narotsky (personal communications from Michael Narotsky, U.S. EPA, to John Fox, U.S. EPA, 19 June 2008, and to Jennifer Jinot, U.S. EPA, 10 June 2008). Two endpoints were examined: frequency of eye defects in rat pups and prenatal loss (number of implantation sites minus number of live pups on postnatal day 1).

**Table F-7. Results of nested log-logistic model for fetal cardiac anomalies from Johnson et al. (2003) without the high-dose group, using the TotOxMetabBW34 dose metric**

| Model | LSC? | IC? | AIC | Pval | BMR | BMD | BMDL |
|---|---|---|---|---|---|---|---|
| NLOG | Y | Y | 246.877 | NA (df = 0) | 0.01 | 0.174253 | 0.0259884 |
| NLOG | Y | N | 251.203 | 0.0112 | 0.01 | 0.164902 | 0.0270378 |
| NLOG | N | Y | 243.815 | 0.0128 | 0.1 | 0.489442 | 0.156698 |
| **NLOG*** | **N** | **Y** | **243.815** | **0.0128** | **0.01** | **0.0444948** | **0.0142453** |
| NLOG | N | N | 248.853 | 0.0098 | 0.01 | 0.0397876 | 0.0199438 |

* Indicates model selected. BMDS failed with the Rai-VanRyzin and NCTR models.

NLOG = "nested log-logistic" model.
LSC analyzed was female weight gain during pregnancy.

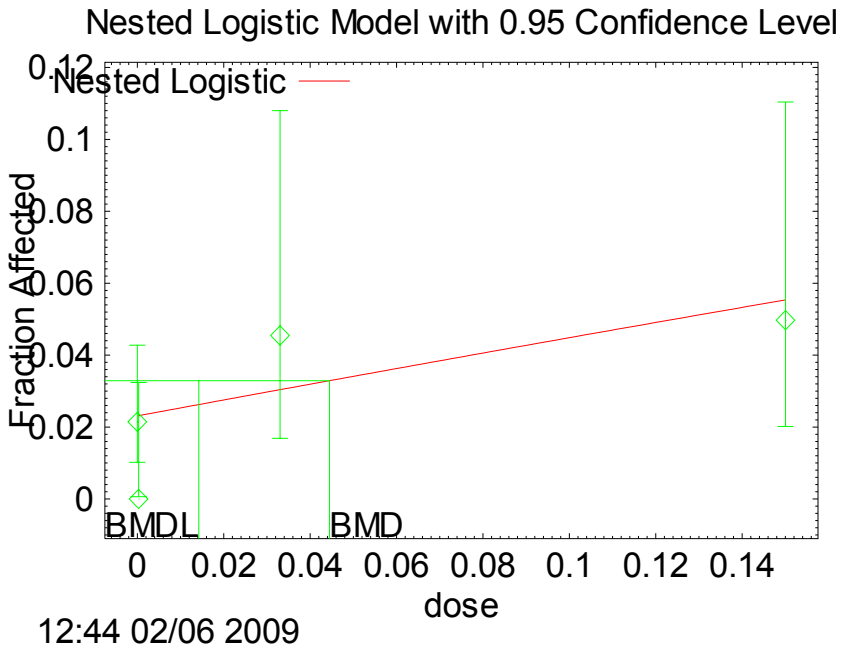



**Figure F-3. BMD modeling of Johnson et al. (2003) using nested log-logistic model, with TotOxMetabBW34 dose metric, without LSC, with IC, and without the high-dose group, using a BMR of 0.01 extra risk.**

**Table F-8. Results of nested log-logistic model for fetal cardiac anomalies from Johnson et al. (2003) without the high-dose group, using the AUCCBld dose metric**

| Model | LSC? | IC? | AIC | Pval | BMR | BMD | BMDL |
|---|---|---|---|---|---|---|---|
| NLOG | Y | Y | 246.877 | NA (df = 0) | 0.01 | 0.00793783 | 0.00118286 |
| NLOG | Y | N | 251.203 | 0.0112 | 0.01 | 0.00750874 | 0.00123047 |
| NLOG* | N | Y | 243.816 | 0.0128 | 0.1 | 0.0222789 | 0.00712997 |
| **NLOG*** | **N** | **Y** | **243.816** | **0.0128** | **0.01** | **0.00202535** | **0.000648179** |
| NLOG | N | N | 248.853 | 0.0098 | 0.01 | 0.00181058 | 0.000907513 |

* Indicates model selected. BMDS failed with the Rai-VanRyzin and NCTR models.

NLOG = "nested log-logistic" model.
LSC analyzed was female weight gain during pregnancy.

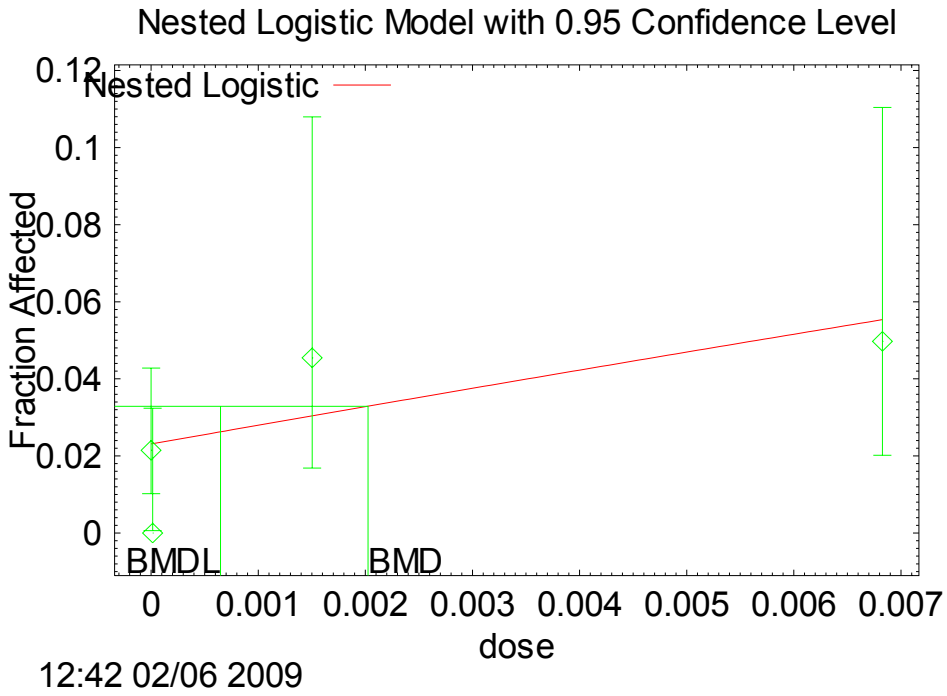



**Figure F-4. BMD modeling of Johnson et al. (2003) using nested log-logistic model, with AUCCBld dose metric, without LSC, with IC, and without the high-dose group, using a BMR of 0.01 extra risk.**

Two LSCs were considered, with analyses summarized in Table F-9. The number of implants is unrelated to dose, as inferred from regression and analysis of variance, and was considered as a LSC for eye defects. As number of implants is part of the definition for the endpoint of prenatal loss, it is not considered as a LSC for prenatal loss. A second LSC, the dam body weight on gestation day (GD) 6 (damBW6) was significantly related to dose and is unsuitable as a litter-specific covariate.

**Table F-9. Analysis of LSCs with respect to dose from Narotsky et al. (1995)**

| Relation of litter-specific covariates to dose | | | |
|---|---|---|---|
| Implants: | none | | |
| damBW6: | significant | | |
| | | Mean | Mean |
| | TCE | Implants | damBW6 |
| | 0 | 9.5 | 176.0 |
| | 10.1 | 10.1 | 180.9 |
| | 32 | 9.1 | 174.9 |
| | 101 | 7.8 | 170.1 |
| | 320 | 10.4 | 174.5 |
| | 475 | 9.7 | 182.4 |
| | 633 | 9.6 | 185.3 |
| | 844 | 8.9 | 182.9 |
| | 1,125 | 9.6 | 184.2 |
| Using expt as covariate, e.g., damBW6 ~ TCE.mg.kgd + expt | | | |
| Linear regression | | $p = 0.7486$ | $p = 0.0069$ |
| AoV (ordered factor) | | $p = 0.1782$ | $p = 0.0927$ |

Two LSCs were considered, with analyses summarized in Table F-9. The number of implants is unrelated to dose, as inferred from regression and analysis of variance, and was considered as a LSC for eye defects. As number of implants is part of the definition for the endpoint of prenatal loss, it is not considered as a LSC for prenatal loss. A second LSC, the dam body weight on GD 6 (damBW6) was significantly related to dose and is unsuitable as a litter-specific covariate.

**F.4.2.2.1.** ***Fetal eye defects.*** The nested log-logistic and Rai-VanRyzin models were fitted to the number of pups with eye defects reported by Narotsky et al. (1995), with the results summarized in Table F-10.

**Table F-10. Results of nested log-logistic and Rai-VanRyzin model for fetal eye defects from Narotsky et al. (1995), on the basis of applied dose (mg/kg/d in drinking water)**

| Model | LSC? | IC? | AIC | Pval | BMR | BMD | BMDL |
|---|---|---|---|---|---|---|---|
| NLOG | Y | Y | 255.771 | 0.3489 | 0.05 | 875.347 | 737.328[a] |
| NLOG | Y | N | 259.024 | 0.0445 | 0.05 | 830.511 | 661.629 |
| NLOG | N | Y | 270.407 | 0.2281 | 0.05 | 622.342 | 206.460 |
| NLOG | N | N | 262.784 | 0.0529 | 0.10 | 691.93 | 542.101 |
| NLOG | N | N | 262.784 | 0.0529 | 0.05 | 427.389 | 264.386 |
| NLOG | N | N | 262.784 | 0.0529 | 0.01 | 147.41 | 38.7117[b] |
| RAI | Y | Y | 274.339 | 0.1047 | 0.05 | 619.849 | 309.925 |
| RAI | Y | N | 264.899 | 0.0577 | 0.05 | 404.788 | 354.961 |
| RAI | N | Y | 270.339 | 0.2309 | 0.05 | 619.882 | 309.941 |
| RAI | N | N | 262.481 | 0.0619 | 0.10 | 693.04 | 346.52 |
| RAI | N | N | 262.481 | 0.0619 | 0.05 | 429.686 | 214.843 |
| RAI | N | N | 262.481 | 0.0619 | 0.01 | 145.563 | 130.938 [b] |

[a] Graphical fit at the origin exceeds observed control and low dose responses and slope is quite flat (see Figure F-5), fitted curve does not represent the data well.
[b] Indicates model selected.

NLOG = "nested log-logistic" model; RAI = Rai-VanRyzin model.
LSC analyzed was implants.

Results for the nested log-logistic model suggested a better model fit with the inclusion of the LSC and IC, based on AIC. However, the graphical fit (see Figure F-5) is strongly sublinear and high at the origin where the fitted response exceeds the observed low-dose responses for the control group and two low-dose groups. An alternative nested log-logistic model without either LSC or IC (see Figure F-6), which fits the low-dose responses better, was selected. Given that this model had no LSC and no IC, the nested log-logistic model reduces to a quantal log-logistic model. Parameter estimates and the *p*-values were essentially the same for the two models (see

Table F-11). A similar model selection can be justified for the Rai-Van Ryzin model (see Figure F-7). Because no LSC and no IC were needed, this endpoint was modeled with quantal models, using totals of implants and losses for each dose group, which allowed choice from a wider range of models (those results appear with quantal model results in this appendix).

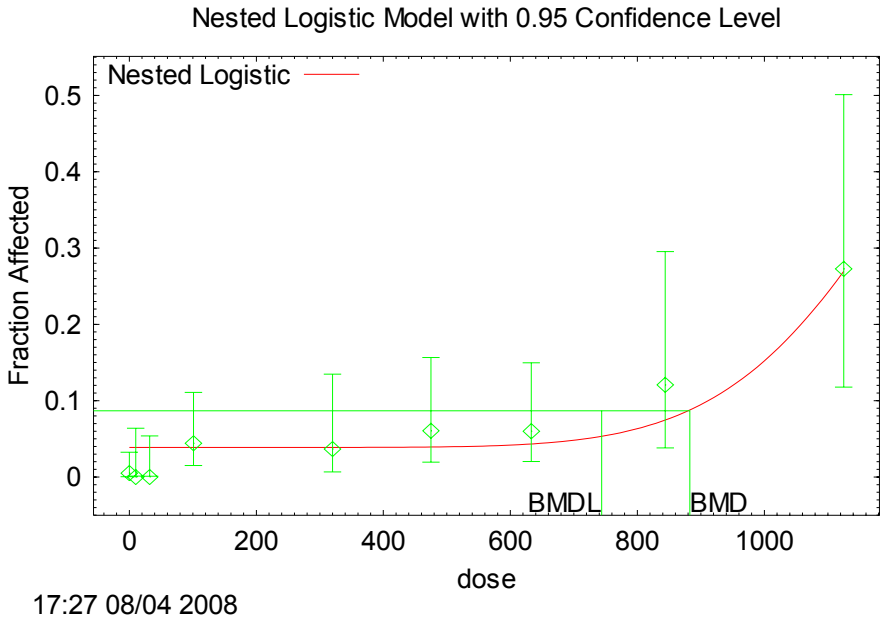



**Figure F-5. BMD modeling of fetal eye defects from Narotsky et al. (1995) using nested log-logistic model, with applied dose, with both LSC and IC, using a BMR of 0.05 extra risk.**

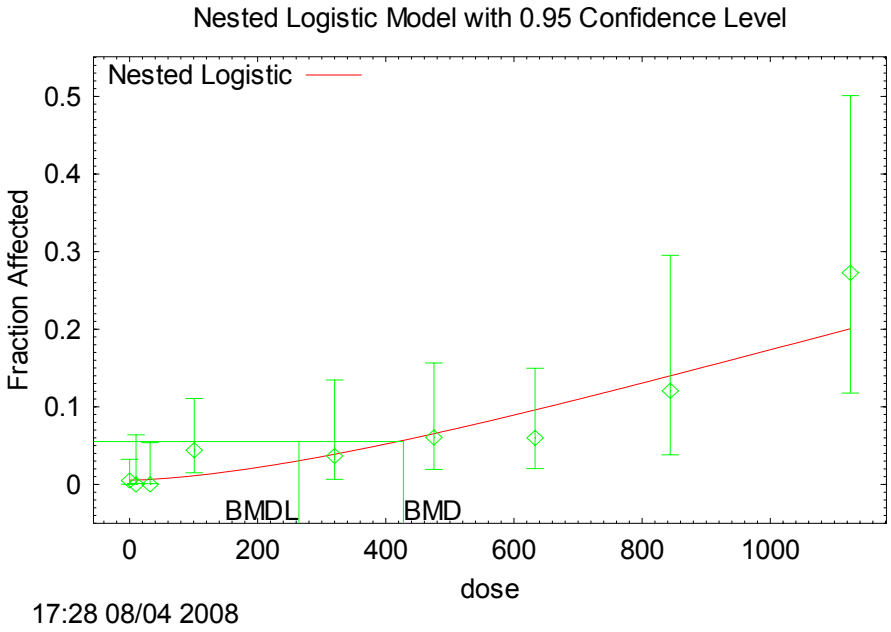



**Figure F-6. BMD modeling of fetal eye defects from Narotsky et al. (1995) using nested log-logistic model, with applied dose, without either LSC or IC, using a BMR of 0.05 extra risk.**

**Table F-11. Comparison of results of nested log-logistic (without LSC or IC) and quantal log-logistic model for fetal eye defects from Narotsky et al. (1995)**

| Model | Parameter | | | $BMD_{05}$ | $BMDL_{05}$ |
|---|---|---|---|---|---|
| | Alpha | Beta | Rho | | |
| Nested | 0.00550062 | -12.3392 | 1.55088 | 427.4 | 264.4 |
| Quantal | 0.00549976 | -12.3386 | 1.55079 | 427.4 | 260.2 |

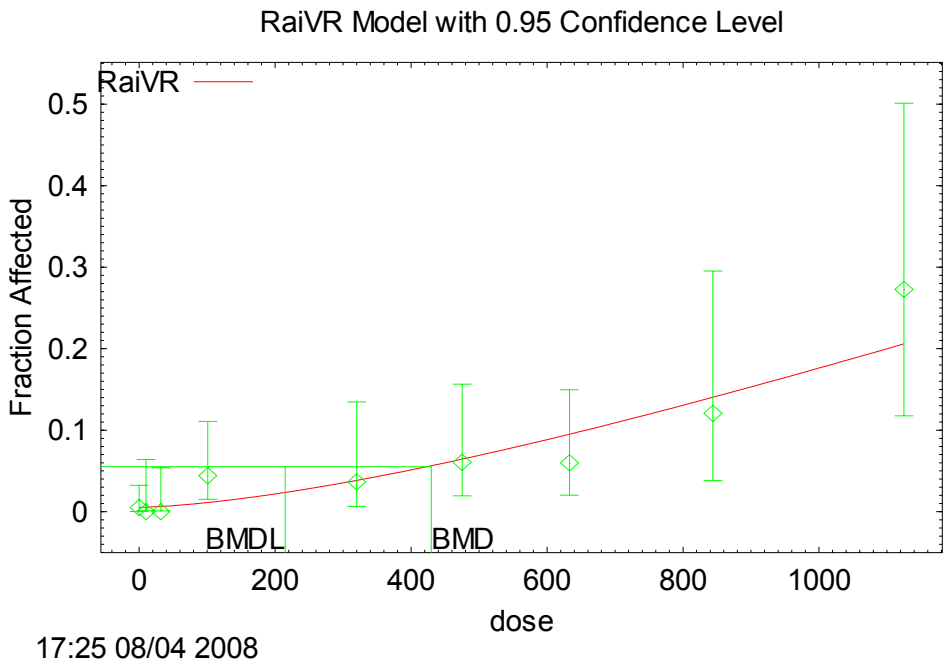



**Figure F-7. BMD modeling of fetal eye defects from Narotsky et al. (1995) using nested Rai-VanRyzin model, with applied dose, without either LSC or IC, using a BMR of 0.05 extra risk.**

**F.4.2.2.2.** ***Narotsky et al. (1995) prenatal loss.*** The nested log-logistic and Rai-VanRyzin models were fitted to prenatal loss reported by Narotsky et al. (1995), with the results summarized in Table F-12.

The BMDS nested models require a LSC, so dam body weight on GD6 ("damBW6") was used as the LSC. However, damBW6 is significantly related to dose and, so, is not a reliable LSC. Number of implants could not be used as a LSC because it was identified as number at risk in the BMDS models. These issues were obviated because the model selected did not employ the LSC.

**Table F-12. Results of nested log-logistic and Rai-VanRyzin model for prenatal loss from Narotsky et al. (1995), on the basis of applied dose (mg/kg/d in drinking water)**

| Model | LSC? | IC? | AIC | Pval | BMR | BMD | BMDL |
|---|---|---|---|---|---|---|---|
| NLOG | Y | Y | 494.489 | 0.2314 | 0.10 | 799.723 | 539.094 |
| NLOG | Y | N | 627.341 | 0.0000 | 0.10 | 790.96 | 694.673 |
| NLOG | N | N | 628.158 | 0.0000 | 0.10 | 812.92 | 725.928 |
| NLOG | N | Y | 490.766 | 0.2509 | 0.10 | 814.781 | 572.057 |
| NLOG | N | Y | 490.766 | 0.2509 | 0.05 | 738.749 | 447.077 |
| **NLOG** | **N** | **Y** | **490.766** | **0.2509** | **0.01** | **594.995** | **252.437 *** |
| RAI | Y | Y | 491.859 | 0.3044 | 0.10 | 802.871 | 669.059 |
| RAI | Y | N | 626.776 | 0.0000 | 0.10 | 819.972 | 683.31 |
| RAI | N | N | 626.456 | 0.0000 | 0.10 | 814.98 | 424.469 |
| RAI | N | Y | 488.856 | 0.2983 | 0.10 | 814.048 | 678.373 |
| RAI | N | Y | 488.856 | 0.2983 | 0.05 | 726.882 | 605.735 |
| **RAI** | **N** | **Y** | **488.856** | **0.2983** | **0.01** | **562.455** | **468.713 *** |

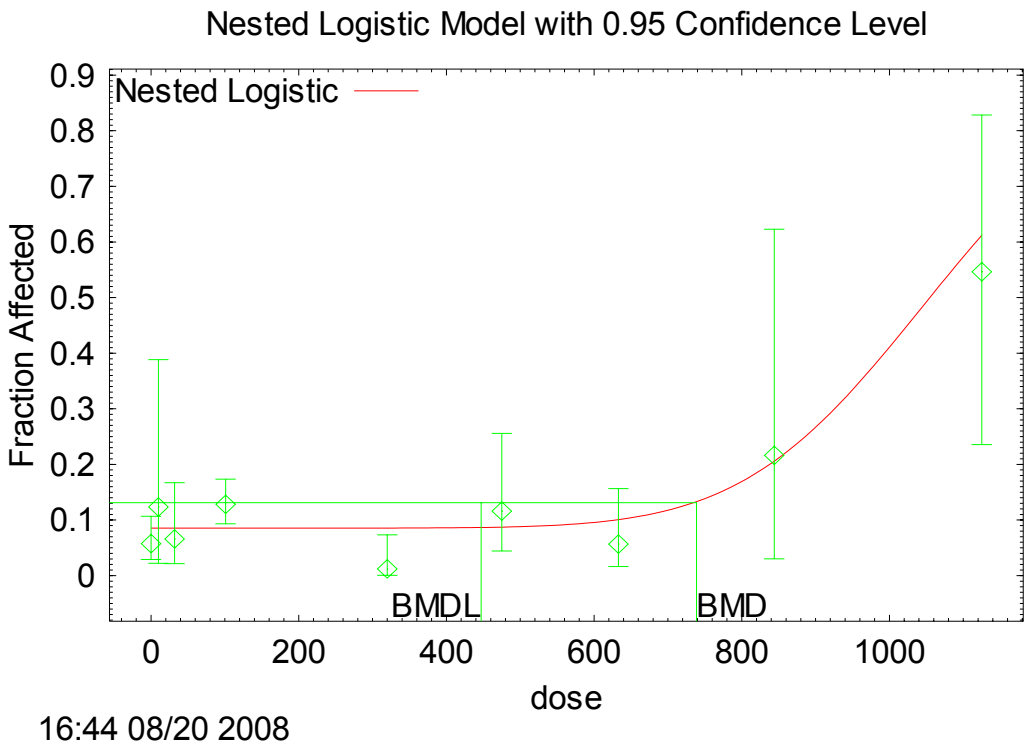
* Indicates model selected.

NLOG = "nested log-logistic" model; RAI = Rai-VanRyzin model.
LSC analyzed was dam body weight on GD6.

For the nested log-logistic models, the AIC is much larger when the IC is dropped, so the IC is needed in the model. The LSC can be dropped (and is also suspect because it is correlated with dose). The model with IC and without LSC was selected on the basis of AIC (shown in Figure F-8). For the Rai-VanRyzin models, the model selection was similar to that for the nested log-logistic, leading to a model with IC and without LSC, which had the lowest AIC (shown in Figure F-9).

### F.4.3. Model Selections and Results

The final model selections and results for noncancer dose-response modeling are presented in Table F-13.



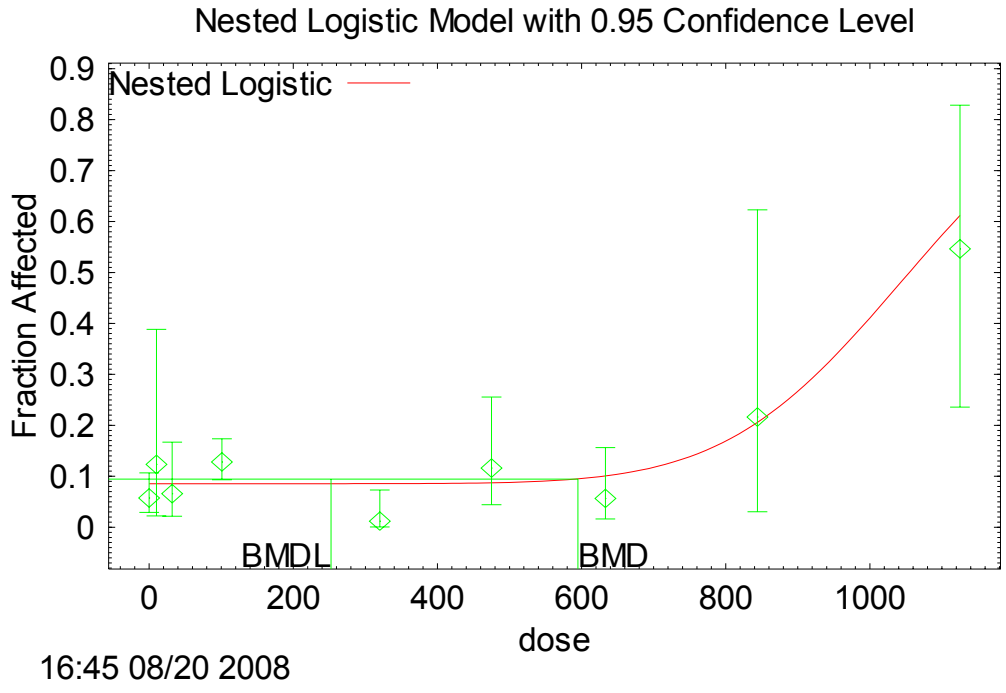
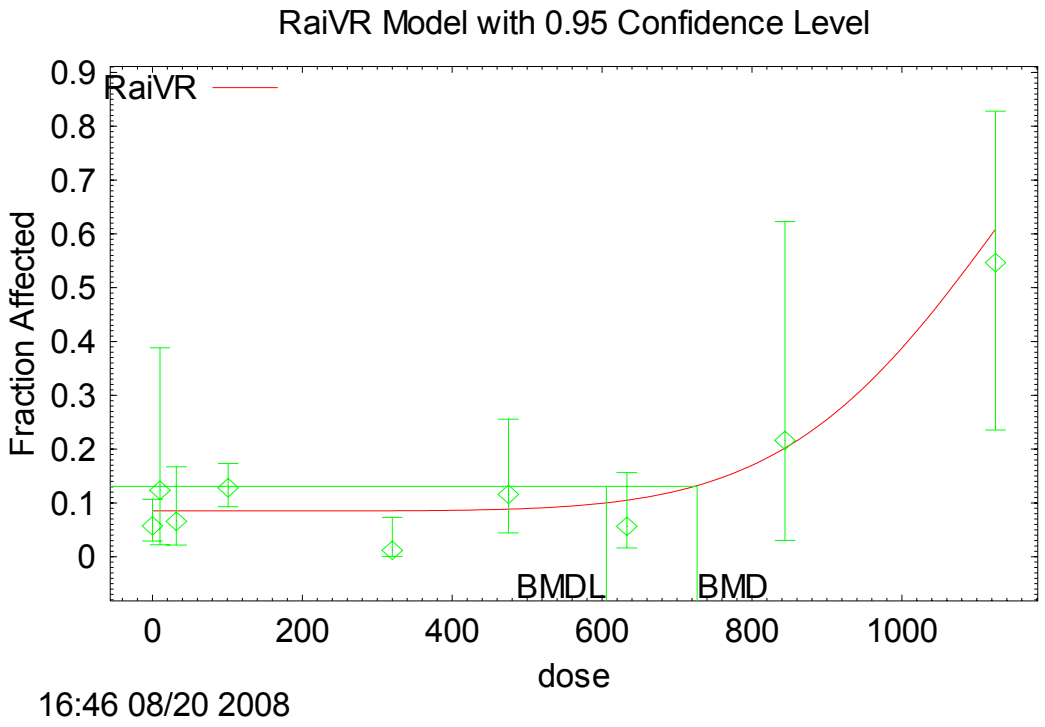




**Figure F-8. BMD modeling of prenatal loss reported in Narotsky et al. (1995) using nested log-logistic model, with applied dose, without LSC, with IC, using a BMR of 0.05 extra risk (top panel) or 0.01 extra risk (bottom panel).**



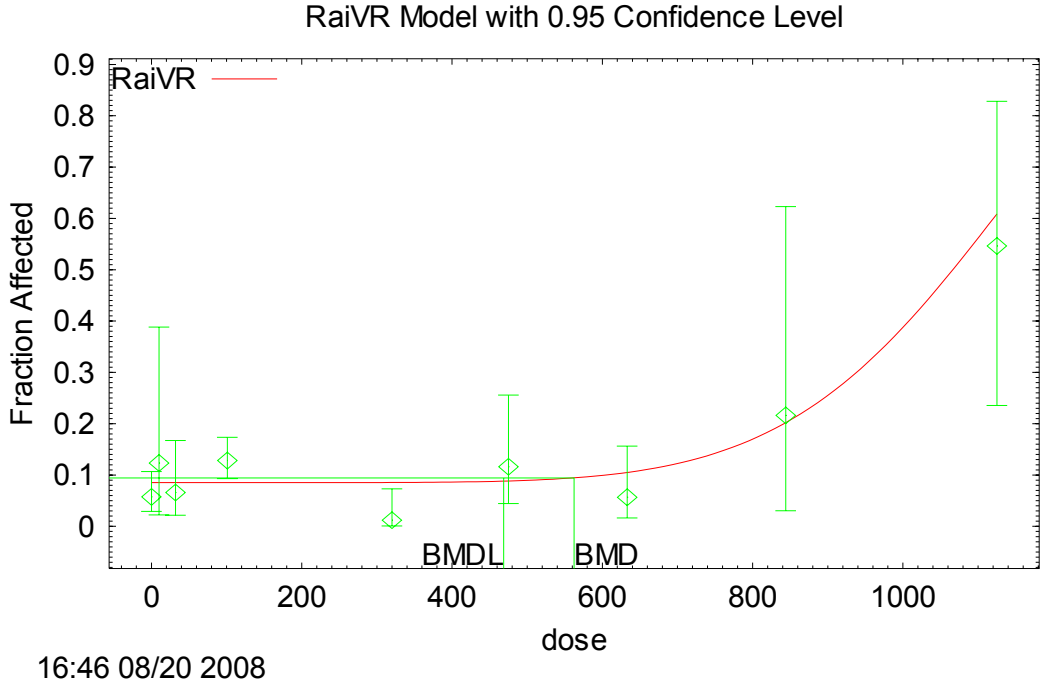




**Figure F-9. BMD modeling of prenatal loss reported in Narotsky et al. (1995) using nested Rai-VanRyzin model, with applied dose, without LSC, with IC, using a BMR of 0.05 extra risk (top panel) or 0.01 extra risk (bottom panel).**

## Table F-13. Model selections and results for noncancer dose-response analyses

| GRP | Study/run abbrev. | Species | Sex | Strain | Exp. route | Endpoint | Dose metric | BMR type | BMR | BMD/ BMDL | BMDL | Model | Rep. BMD | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Dichotomous models** | | | | | | | | | | | | | | |
| 3 | Chia et al., 1996 | human | M | workers.elec.factory | inhal | N.hyperzoospermia | appl.dose | extra | 0.1 | 2.14 | 1.43 | loglogistic.1 | 3.06 | |
| 7 | Narotsky et al., 1995 | rat | F | F344 | oral.gav | N.pups.eye.defects | appl.dose | extra | 0.01 | 1.46 | 60.1 | multistage | 806 | a |
| 13 | Narotsky et al., 1995.sa | rat | F | F344 | oral.gav | N.dams.w.resorbed.litters | appl.dose | extra | 0.01 | 5.47 | 32.2 | multistage.2 | 570 | |
| 13 | Narotsky et al., 1995.sa | rat | F | F344 | oral.gav | N.dams.w.resorbed.litters | AUCCBld | extra | 0.01 | 5.77 | 17.5 | multistage.2 | 327 | |
| 13 | Narotsky et al., 1995.sa | rat | F | F344 | oral.gav | N.dams.w.resorbed.litters | TotMetabBW34 | extra | 0.01 | 1.77 | 77.5 | weibull | 156 | |
| 14 | Johnson et al., 2003.drophi | rat | F | Sprague.Dawley | oral.dw | N.litters.abnormal.hearts | appl.dose | extra | 0.1 | 2.78 | 0.0146 | loglogistic.1 | 0.0406 | b |
| 36 | Griffin et al., 2000 | mice | F | MRL++ | oral.dw | portal.infiltration | appl.dose | extra | 0.1 | 2.67 | 13.4 | loglogistic.1 | 35.8 | |
| 38 | Maltoni et al., 1986 | rat | M | Sprague.Dawley | inhal | megalonucleocytosis | appl.dose | extra | 0.1 | 1.22 | 40.2 | multistage | 49.2 | c |
| 38 | Maltoni et al., 1986 | rat | M | Sprague.Dawley | inhal | megalonucleocytosis | ABioactDCVCBW34 | extra | 0.1 | 1.18 | 0.0888 | loglogistic | 0.105 | |
| 38 | Maltoni et al., 1986 | rat | M | Sprague.Dawley | inhal | megalonucleocytosis | AMetGSHBW34 | extra | 0.1 | 1.19 | 0.086 | loglogistic | 0.102 | |
| 38 | Maltoni et al., 1986 | rat | M | Sprague.Dawley | inhal | megalonucleocytosis | TotMetabBW34 | extra | 0.1 | 1.13 | 53.8 | weibull | 61 | d |
| 39 | Maltoni et al., 1986 | rat | M | Sprague.Dawley | oral.gav | megalonucleocytosis | appl.dose | extra | 0.1 | 1.53 | 33.8 | multistage.2 | 51.8 | e |
| 49 | NTP, 1988 | rat | F | Marshall | oral.gav | toxic nephropathy | appl.dose | extra | 0.05 | 1.45 | 9.45 | loglogistic.1 | 28.9 | |
| 49 | NTP, 1988 | rat | F | Marshall | oral.gav | toxic nephropathy | ABioactDCVCBW34 | extra | 0.05 | 1.45 | 0.0132 | loglogistic.1 | 0.0404 | |
| 49 | NTP, 1988 | rat | F | Marshall | oral.gav | toxic nephropathy | AMetGSHBW34 | extra | 0.05 | 1.46 | 0.0129 | loglogistic.1 | 0.0397 | |
| 49 | NTP, 1988 | rat | F | Marshall | oral.gav | toxic nephropathy | TotMetabBW34 | extra | 0.05 | 1.45 | 2.13 | loglogistic.1 | 6.5 | |

## Table F-13. Model selections and results for noncancer dose-response analyses (continued)

| GRP | Study/run abbrev. | Species | Sex | Strain | Exp. route | Endpoint | Dose metric | BMR type | BMR | BMD/ BMDL | BMDL | Model | Rep. BMD | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Nested dichotomous models** | | | | | | | | | | | | | | |
| NA | Johnson et al., 2003.drophi | rat | F | Sprague.Dawley | oral.dw | N.pups.abnormal.hearts | appl.dose | extra | 0.01 | 3.12 | 0.0207 | loglogistic.IC | 0.711 | b |
| NA | Johnson et al., 2003.drophi | rat | F | Sprague.Dawley | oral.dw | N.pups.abnormal.hearts | TotOxMetabBW34 | extra | 0.01 | 3.12 | 0.0142 | loglogistic.IC | | b |
| NA | Johnson et al., 2003.drophi | rat | F | Sprague.Dawley | oral.dw | N.pups.abnormal.hearts | AUCCBld | extra | 0.01 | 3.12 | 0.000648 | loglogistic.IC | | b |
| NA | Narotsky et al., 1995 | rat | F | F344 | oral.gav | N.prenatal.loss | appl.dose | extra | 0.01 | 1.2 | 469 | RAI.IC | 814 | |
| **Continuous models** | | | | | | | | | | | | | | |
| 2 | Land et al., 1981 | mouse | M | (C57B1xC3H)F1 | inhal | pct.abnormal.sperm | appl.dose | standard | 0.5 | 1.33 | 46.9 | polynomial.constvar | 125 | |
| 6 | Carney et al., 2006 | rat | F | Sprague-Dawley (Crl:CD) | inhal | gm.wgt.gain.GD6.9 | appl.dose | relative | 0.1 | 2.5 | 10.5 | hill | 62.3 | |
| 8 | Narotsky et al., 1995 | rat | F | F344 | oral.gav | gm.wgt.gain.GD6.20 | appl.dose | relative | 0.1 | 1.11 | 108 | polynomial.constvar | 312 | |
| 19 | Crofton and Zhao. 1997 | rat | M | Long-Evans | inhal | dB.auditory.threshold(16kHz) | appl.dose | absolute | 10 | 1.11 | 274 | polynomial.constvar | 330 | |
| 21 | George et al., 1986 | rat | F | F344 | oral.food | litters | appl.dose | standard | 0.5 | 1.69 | 179 | polynomial.constvar | 604 | |
| 23 | George et al., 1986 | rat | F | F344 | oral.food | live.pups | appl.dose | standard | 0.5 | 1.55 | 152 | polynomial.constvar | 470 | |
| 26 | George et al., 1986 | rat | F | F344 | oral.food | Foffspring.BWgm.day21 | appl.dose | relative | 0.05 | 1.41 | 79.7 | polynomial.constvar | 225 | |
| 34sq | Moser et al., 1995+perscom | rat | F | F344 | oral.gav | no.rears | appl.dose | standard | 1 | 1.64 | 248 | polynomial.constvar | 406 | b,f |
| 49 | George et al., 1986 | rat | F | F344 | oral.food | traverse.time.21do | appl.dose | relative | 1 | 1.98 | 72.6 | power | 84.9 | |
| 51 | Buben and O'Flaherty, 1985 | mouse | M | SwissCox | oral.gav | Liverwt.pctBW | appl.dose | relative | 0.1 | 1.26 | 81.5 | hill.constvar | 92.8 | |

**Table F-13. Model selections and results for noncancer dose-response analyses (continued)**

| GRP | Study/run abbrev. | Species | Sex | Strain | Exp. route | Endpoint | Dose metric | BMR type | BMR | BMD/ BMDL | BMDL | Model | Rep. BMD | Notes |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 51 | Buben and O'Flaherty, 1985 | mouse | M | SwissCox | oral.gav | Liverwt.pctBW | AMetLiv1BW34 | relative | 0.1 | 1.08 | 28.6 | polynomial.constvar | 28.4 | |
| 51 | Buben and O'Flaherty, 1985 | mouse | M | SwissCox | oral.gav | Liverwt.pctBW | TotOxMetabBW34 | relative | 0.1 | 1.08 | 37 | polynomial.constvar | 36.7 | |
| 58 | Kjellstrand et al, 1983b | mouse | M | NMRI | inhal | Liverwt.pctBW | appl.dose | relative | 0.1 | 1.36 | 21.6 | hill | 30.4 | |
| 58 | Kjellstrand et al, 1983b | mouse | M | NMRI | inhal | Liverwt.pctBW | AMetLiv1BW34 | relative | 0.1 | 1.4 | 22.7 | hill | 32.9 | |
| 58 | Kjellstrand et al, 1983b | mouse | M | NMRI | inhal | Liverwt.pctBW | TotOxMetabBW34 | relative | 0.1 | 1.3 | 73.4 | hill | 97.7 | |
| 60.Rp | Kjellstrand et al, 1983b | mouse | M | NMRI | inhal | Kidneywt.pctBW | appl.dose | relative | 0.1 | 1.17 | 34.7 | polynomial | 47.1 | |
| 60.Rp | Kjellstrand et al, 1983b | mouse | M | NMRI | inhal | Kidneywt.pctBW | AMetGSHBW34 | relative | 0.1 | 1.18 | 0.17 | polynomial | 0.236 | |
| 60.Rp | Kjellstrand et al, 1983b | mouse | M | NMRI | inhal | Kidneywt.pctBW | TotMetabBW34 | relative | 0.1 | 1.17 | 71 | polynomial | 95.2 | |
| 63 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | Antibody.Forming Cells | appl.dose | standard | 1 | 1.94 | 31.2 | power.constvar | 60.6 | b |
| 62 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | Antibody.Forming Cells | AUCCBld | standard | 1 | 1.44 | 149 | polynomial | 214 | |
| 62 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | Antibody.Forming Cells | TotMetabBW34 | standard | 1 | 1.5 | 40.8 | polynomial | 61.3 | |
| 65 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | kidney.wt.per100gm | appl.dose | relative | 0.1 | 4.29 | 15.7 | hill.constvar | 54.3 | |
| 65 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | kidney.wt.per100gm | ABioactDCVCBW34 | relative | 0.1 | 4.27 | 0.0309 | hill.constvar | 0.103 | |
| 65 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | kidney.wt.per100gm | AMetGSHBW34 | relative | 0.1 | 4.28 | 0.032 | hill.constvar | 0.107 | |
| 65 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | kidney.wt.per100gm | TotMetabBW34 | relative | 0.1 | 1.47 | 40.8 | polynomial.constvar | 52.3 | |
| 67 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | liver.wt.per100gm | appl.dose | relative | 0.1 | 4.13 | 25.2 | hill.constvar | 70.3 | |
| 67 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | liver.wt.per100gm | AMetLiv1BW34 | relative | 0.1 | 1.53 | 46 | polynomial.constvar | 56.1 | |
| 67 | Woolhiser et al, 2006 | rat | F | CD (Sprague-Dawley) | inhal | liver.wt.per100gm | TotOxMetabBW34 | relative | 0.1 | 1.53 | 48.9 | polynomial.constvar | 59.8 | |

## Table F-13. Model selections and results for noncancer dose-response analyses (continued)

[a]Eight-stage multistage model.
[b]Dropped highest dose.
[c]Three-stage multistage model.
[d]Weibull selected over log-logistic with the same AIC on basis of visual fit (less extreme curvature).
[e]Second-order MS selected on basis of visual fit (less extreme curvature).
[f]Square-root transformation of original individual count data.

Applied dose BMDLs are in units of ppm in air for inhalation exposures and mg/kg/d for oral exposures. Internal dose BMDLs are in dose metric units. Reporting BMD is BMD using a BMR of 0.1 extra risk for dichotomous models, and 1 control SD for continuous models.
Log-logistic = unconstrained log-logistic; log-logistic.1 = constrained log-logistic; multistage = multistage with #stages=dose groups-1; multistage.n = n-stage multistage; log-logistic.IC = nested log-logistic with IC, without LSC; RAI.IC = Rai-VanRyzin model with IC, without LSC; zzz.constvar = continuous model zzz with constant variance (otherwise variance is modeled).
Rep. = reporting, Exp. = exposure, Abbrev. = abbreviation.

## F.5. DERIVATION OF POINTS OF DEPARTURE

### F.5.1. Applied Dose Points of Departure

For oral studies in rodents, the POD on the basis of applied dose in mg/kg/d was taken to be the BMDL, NOAEL, or LOAEL. NOAELs and LOAELs were adjusted for intermittent exposure to their equivalent continuous average daily exposure (for BMDLs, the adjustments were already performed prior to BMD modeling).

For inhalation studies in rodents, the POD on the basis of applied dose in ppm was taken to be the BMDL, NOAEL, or LOAEL. NOAELs and LOAELs were adjusted for intermittent exposure to their equivalent continuous average daily exposure (for BMDLs, the adjustments were already performed prior to BMD modeling). These adjusted concentrations are considered human equivalent concentrations, in accordance with U.S. EPA (1994), as TCE is considered a Category 3 gas (systemically acting) and has a blood-air partition coefficient in rodents greater than that in humans (see Section 3.1).

### F.5.2. Physiologically Based Pharmacokinetic (PBPK) Model-Based Human Points of Departure

As discussed in Section 5.1.3, the PBPK model was used for simultaneous interspecies (for endpoints in rodent studies), intraspecies, and route-to-route extrapolation based on the estimates from the PBPK model of the internal dose points of departure (idPOD) for each candidate critical study/endpoints. The following documents contain figures showing the derivation of the human equivalent doses and concentrations (human equivalent doses [HEDs] and human equivalent concentrations [HECs]) for the median ($50^{th}$ percentile) and sensitive ($99^{th}$ percentile) individual from the (rodent or human) study idPOD. In each case, for a specific study/endpoint(s)/sex/species (in the figure main title), and for a particular dose metric (Y-axis label), the horizontal line shows the original study idPOD (a BMDL, NOAEL, or LOAEL as noted) and where it intersects with the human $99^{th}$ percentile (open square) or median (closed square) exposure-internal-dose relationship:

Appendix.linked.files\AppF.Non-cancer.HECs.Plots.human.inhalation.studies.TCE.DRAFT.pdf
Appendix.linked.files\AppF.Non-cancer.HECs.Plots.rodent.inhalation.studies.TCE.DRAFT.pdf
Appendix.linked.files\AppF.Non-cancer.HECs.Plots.rodent.oral.studies.TCE.DRAFT.pdf
Appendix.linked.files\AppF.Non-cancer.HEDs.Plots.human.inhalation.studies.TCE.DRAFT.pdf
Appendix.linked.files\AppF.Non-cancer.HEDs.Plots.rodent.inhalation.studies.TCE.DRAFT.pdf
Appendix.linked.files\AppF.Non-cancer.HEDs.Plots.rodent.oral.studies.TCE.DRAFT.pdf

The original study internal doses are based on the median estimates from about 2,000 "study groups" (for rodent studies) or "individuals" (for human studies), and corresponding

exposures for the human median and 99$^{th}$ percentiles were derived from a distribution of 2,000 "individuals." In both cases, the distributions reflect combined uncertainty (in the population means and variances) and population variability.

In addition, as part of the uncertainty/variability analysis described in Section 5.1.4.2, the POD for studies/endpoints for which BMD modeling was done was replaced by the LOAEL or NOAEL. This was done to because there was no available tested software for performing BMD modeling in such a context and because of limitations in time and resources to develop such software. However, the relative degree of uncertainty/variability should be adequately captured in the use of the LOAEL or NOAEL. The graphical depiction of the $HEC_{99}$ or $HED_{99}$ using these alternative PODs is shown in the following files:

Appendix.linked.files\AppF.Non-cancer.HECs.AltPOD.Plots.rodent.inhalation.studies.TCE.DRAFT.pdf

Appendix.linked.files\AppF.Non-cancer.HECs.AltPOD.Plots.rodent.oral.studies.TCE.DRAFT.pdf

Appendix.linked.files\AppF.Non-cancer.HEDs.AltPOD.Plots.rodent.inhalation.studies.TCE.DRAFT.pdf

Appendix.linked.files\AppF.Non-cancer.HEDs.AltPOD.Plots.rodent.oral.studies.TCE.DRAFT.pdf.

## F.6. SUMMARY OF POINTS OF DEPARTURE (PODs) FOR CRITICAL STUDIES AND EFFECTS SUPPORTING THE INHALATION REFERENCE CONCENTRATION (RfC) AND ORAL REFERENCE DOSE (RfD)

This section summarizes the selection and/or derivation of PODs from the critical studies and effects that support the inhalation reference concentration (RfC) and oral reference dose (RfD). In particular, for each endpoint, the following are described the dosimetry (adjustments of continuous exposure, PBPK dose metrics), selection of BMR and BMD model (if BMD modeling was performed), and derivation of the human equivalent concentration or dose for a sensitive individual (if PBPK modeling was used). Section 5.1.3.1 discusses the dose metric selection for different endpoints.

### F.6.1. National Toxicology Program (NTP, 1988)—Benchmark Dose (BMD) Modeling of Toxic Nephropathy in Rats

The critical endpoint here is toxic nephropathy in female Marshall rats (NTP, 1988), which was the most sensitive sex/strain in this study, although the differences among different sex/strain combinations was not large (BMDLs differed by ≤3-fold).

#### F.6.1.1. *Dosimetry and Benchmark Dose (BMD) Modeling*

Rats were exposed to 500 or 1,000 day, 5 days/week, for 104 weeks. The primary dose metric was selected to be average amount of dichlorovinyl cysteine (DCVC) bioactivated/$kg^{3/4}$/day, with median estimates from the PBPK model for the female Marshall rats in this study of 0.47 and 1.1.

Figure F-10 shows BMD modeling for the dichotomous models used (see Section F.5.1, above). The log-logistic model with slope constrained to ≥1 was selected because (1) the log-logistic model with unconstrained slope yielded a slope estimate <1 and (2) it had the lowest AIC.

The idPOD of 0.0132 mg DCVC bioactivated/$kg^{3/4}$/day was a BMDL for a BMR of 5% extra risk. This BMR was selected because toxic nephropathy is a clear toxic effect. This BMR required substantial extrapolation below the observed responses (about 60%); however, the response level seemed warranted for this type of effect and the ratio of the BMD to the BMDL was not large (1.56 for the selected model).

#### F.6.1.2. *Derivation of $HEC_{99}$ and $HED_{99}$*

The $HEC_{99}$ and $HED_{99}$ are the lower 99$^{th}$ percentiles for the continuous human exposure concentration and continuous human ingestion dose that lead to a human internal dose equal to the rodent idPOD. The derivation of the $HEC_{99}$ of 0.0056 ppm and $HED_{99}$ of 0.00338 mg/kg/d for the 99$^{th}$ percentile for uncertainty and variability are shown in Figure F-11. These values are used as this critical effect's POD to which additional uncertainty factors (UFs) are applied.

### F.6.2. National Cancer Institute (NCI, 1976)—Lowest-Observed-Adverse-Effect Level (LOAEL) for Toxic Nephrosis in Mice

The critical endpoint here is toxic nephrosis in female B6C3F1 mice (NCI, 1976), which was the most sensitive sex in this study, although the LOAEL for males differed by less than 50%.

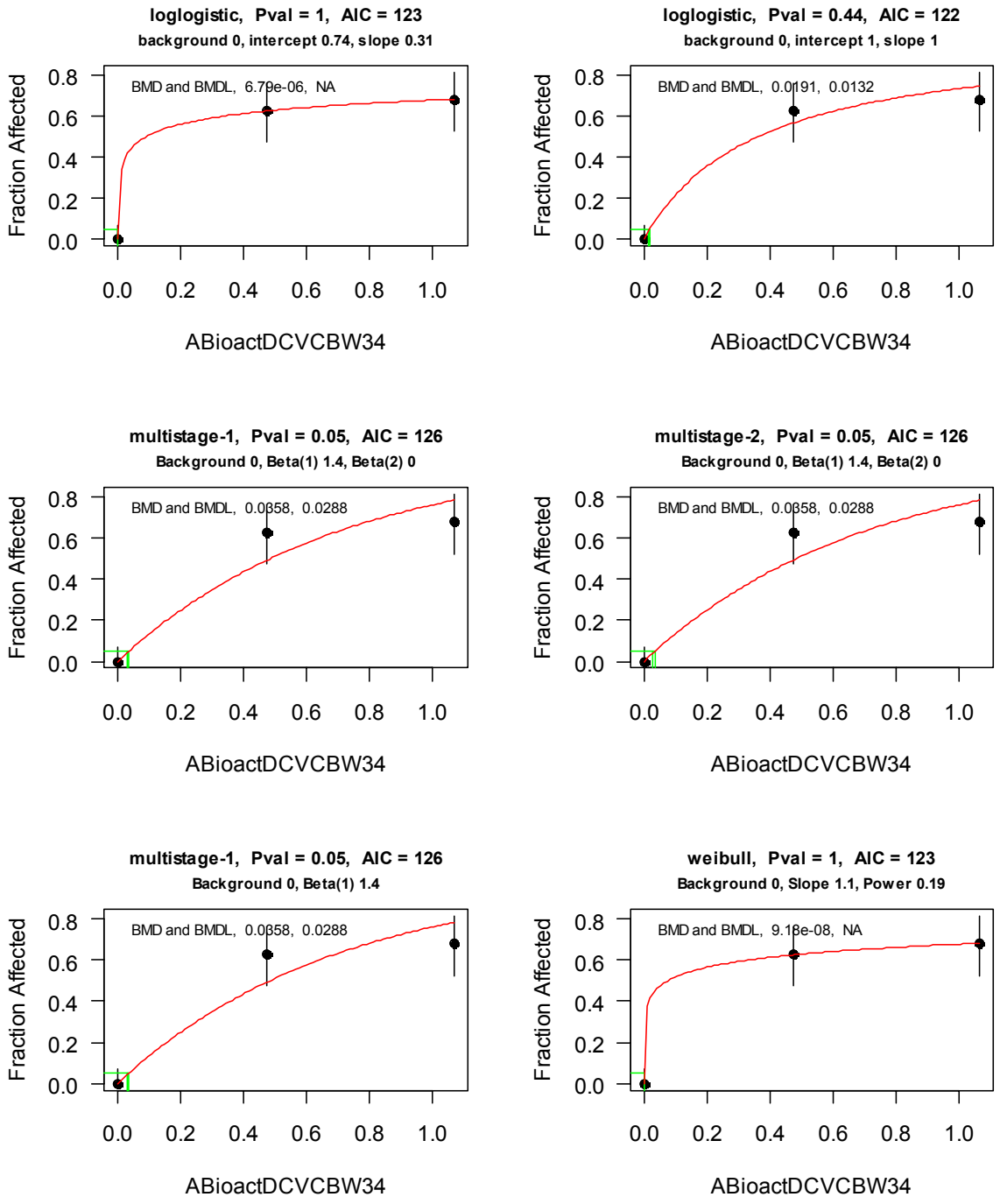



**Figure F-10. BMD modeling of NTP (1988) toxic nephropathy in female Marshall rats.**

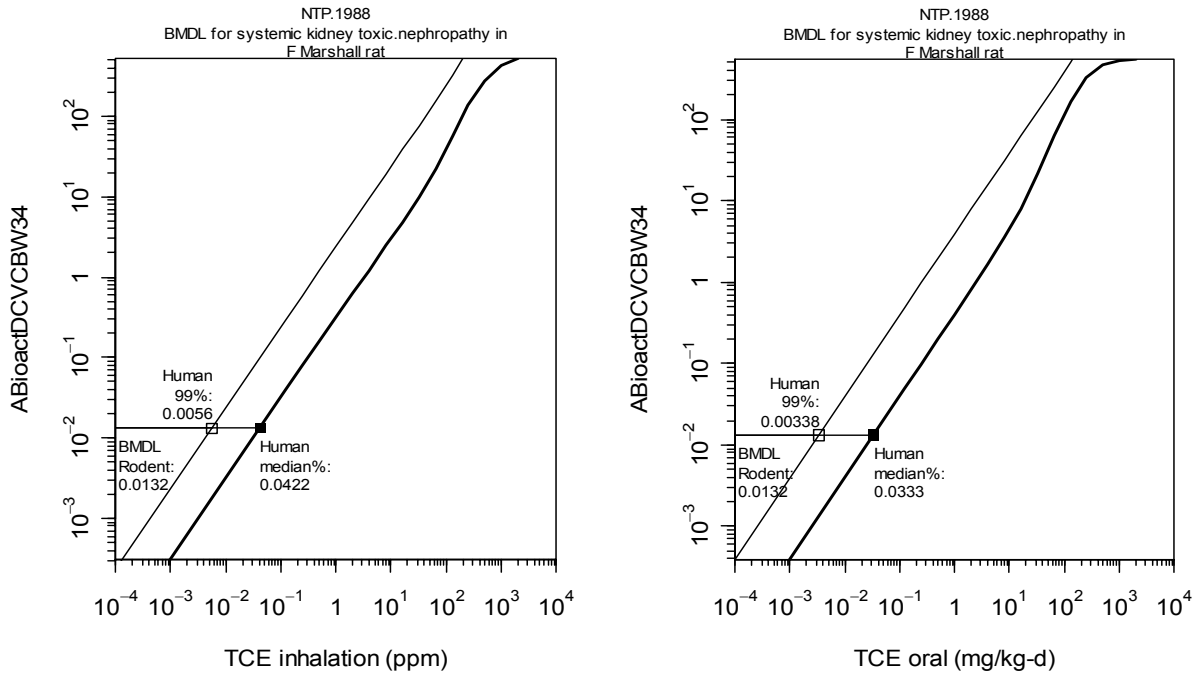



**Figure F-11. Derivation of $HEC_{99}$ and $HED_{99}$ corresponding to the rodent idPOD from NTP (1988) toxic nephropathy in rats.**

### F.6.2.1. *Dosimetry*

Mice were exposed to a time-weighted average of 869 and 1,739 mg/kg/d, 5 days/week, for 78 weeks. BMD modeling was not performed because the response at the LOAEL was >90%. The primary dose metric was selected to be average amount of TCE conjugated with glutathione (GSH)/$kg^{3/4}$/d. In this study, the lower dose group was exposed to two different dose levels (700 mg/kg/d for 12 weeks and 900 mg/kg/d for 66 weeks). The median estimates from the PBPK model for the two dose levels were 0.583 and 0.762 mg TCE conjugation with GSH/$kg^{3/4}$/d. Applying the same time-weighted averaging gives an idPOD LOAEL of 0.735 mg TCE conjugation with GSH/$kg^{3/4}$/d.

### F.6.2.2. *Derivation of $HEC_{99}$ and $HED_{99}$*

The $HEC_{99}$ and $HED_{99}$ are the lower 99$^{th}$ percentiles for the continuous human exposure concentration and continuous human ingestion dose that lead to a human internal dose equal to the rodent idPOD. The derivation of the $HEC_{99}$ of 0.50 ppm and $HED_{99}$ of 0.30 mg/kg/d for the

99th percentile for uncertainty and variability are shown in Figure F-12. These values are used as this critical effect's POD to which additional UFs are applied.

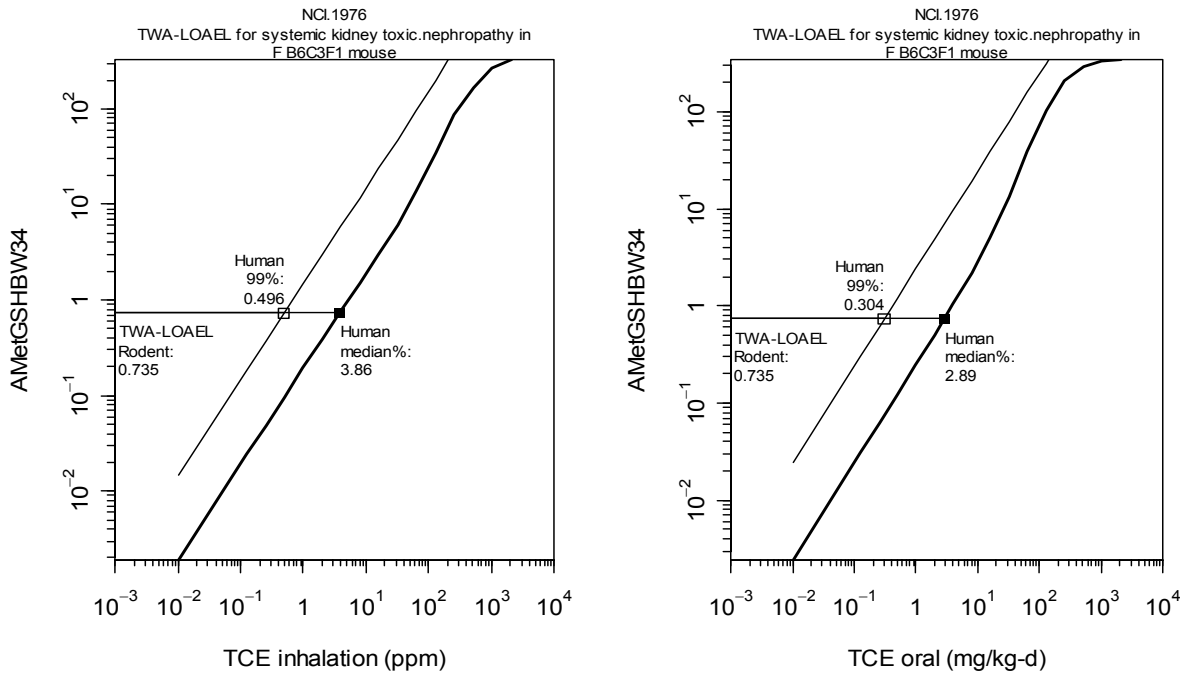



**Figure F-12. Derivation of $HEC_{99}$ and $HED_{99}$ corresponding to the rodent idPOD from NTP (1988) toxic nephrosis in mice.**

### F.6.3. Woolhiser et al. (2006)—Benchmark Dose (BMD) Modeling of Increased Kidney Weight in Rats

The critical endpoint here is increased kidney weights in female Sprague-Dawley (S-D) rats (Woolhiser et al., 2006).

#### F.6.3.1. *Dosimetry and Benchmark Dose (BMD) Modeling*

Rats were exposed to 100, 300, and 1000, 6 hours/day, 5 days/week, for 4 weeks. The primary dose metric was selected to be average amount of DCVC bioactivated/$kg^{3/4}$/day, with median estimates from the PBPK model for this study of 0.038, 0.10, and 0.51.

Figure F-13 shows BMD modeling for the continuous models used (see Section F.5.2, above). The Hill model with constant variance was selected because it had the lowest AIC and because other models with the same AIC either were a power model with power parameter <1 or had poor fits to the control data set.

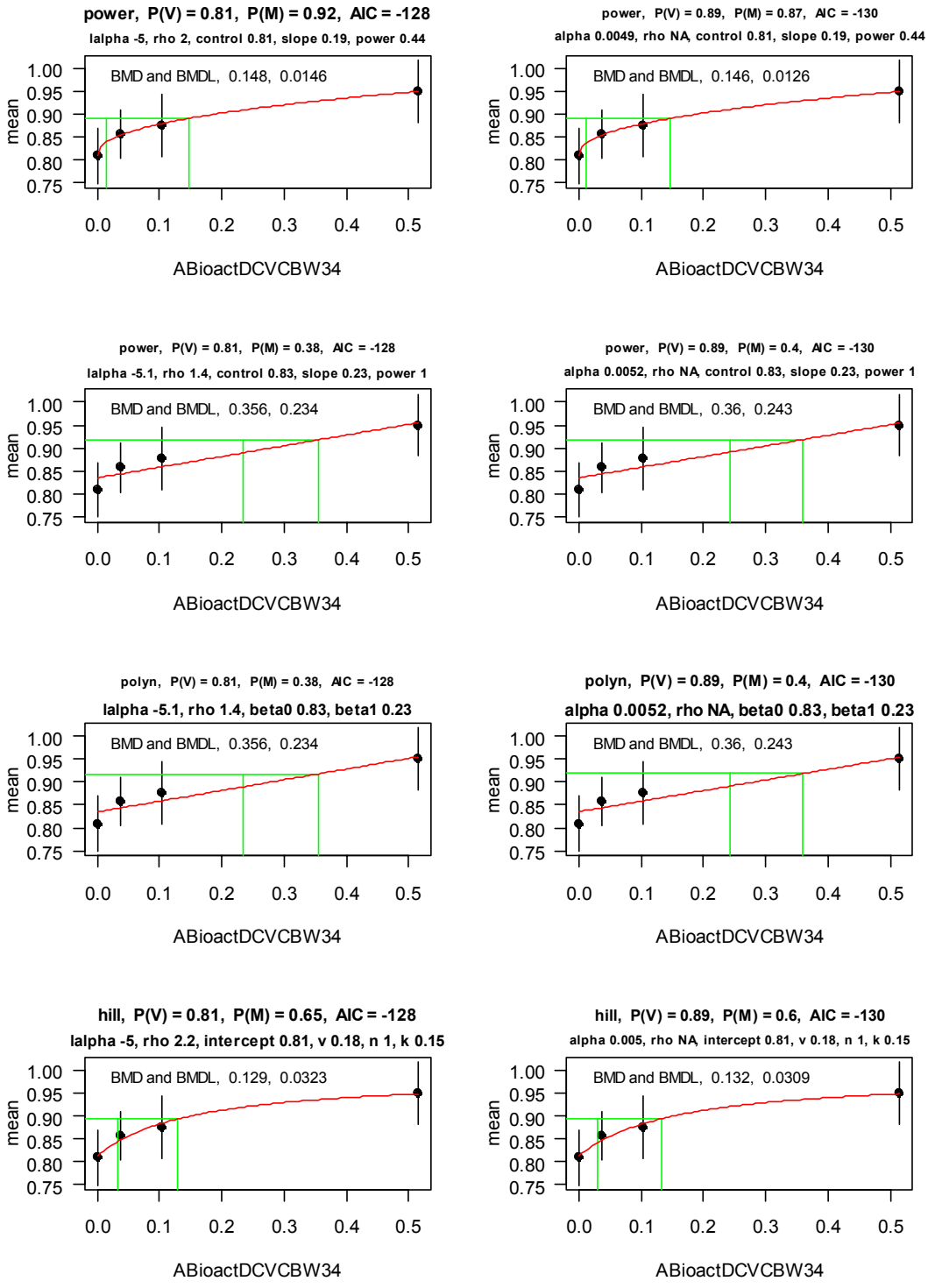



**Figure F-13. BMD modeling of Woolhiser et al. (2006) for increased kidney weight in female S-D rats.**

The idPOD of 0.0309 mg DCVC bioactivated/kg$^{3/4}$/day was a BMDL for a BMR of 10% weight change, which is the BMR typically used by U.S. EPA for body weight and organ weight changes. The response used in each case was the organ weight as a percentage of body weight, to account for any commensurate decreases in body weight, although the results did not differ much when absolute weights were used instead.

#### F.6.3.2. *Derivation of $HEC_{99}$ and $HED_{99}$*

The $HEC_{99}$ and $HED_{99}$ are the lower 99$^{th}$ percentiles for the continuous human exposure concentration and continuous human ingestion dose that lead to a human internal dose equal to the rodent idPOD. The derivation of the $HEC_{99}$ of 0.0131 ppm and $HED_{99}$ of 0.00791 mg/kg/d for the 99$^{th}$ percentile for uncertainty and variability are shown in Figure F-14. These values are used as this critical effect's POD to which additional UFs are applied.

### F.6.4. Keil et al. (2009)—Lowest-Observed-Adverse-Effect Level (LOAEL) for Decreased Thymus Weight and Increased Anti-dsDNA and Anti-ssDNA Antibodies in Mice

The critical endpoints here are decreased thymus weight and increased anti-dsDNA and anti-ssDNA antibodies in female B6C3F1 mice (Keil et al., 2009).

### F.6.5. Keil et al. (2009)—Lowest-Observed-Adverse-Effect Level (LOAEL) for Decreased Thymus Weight and Increased Anti-dsDNA and Anti-ssDNA Antibodies in Mice

The critical endpoints here are decreased thymus weight and increased anti-dsDNA and anti-ssDNA antibodies in female B6C3F1 mice (Keil et al., 2009).

#### F.6.5.1. *Dosimetry*

Mice were exposed to 1400 and 14000 ppb of TCE in drinking water, with an average dose estimated by the authors to be 0.35 and 3.5 mg/kg/d, for 30 weeks. The dose-response relationships were sufficiently supralinear that BMD modeling failed to produce an adequate fit. The primary dose metric was selected to be the average amount of TCE metabolized/kg$^{3/4}$/day. The lower dose group was the LOAEL for both effects, and the median estimate from the PBPK model at that exposure level was 0.139 mg TCE metabolized/kg$^{3/4}$/day, which is used as the rodent idPOD.

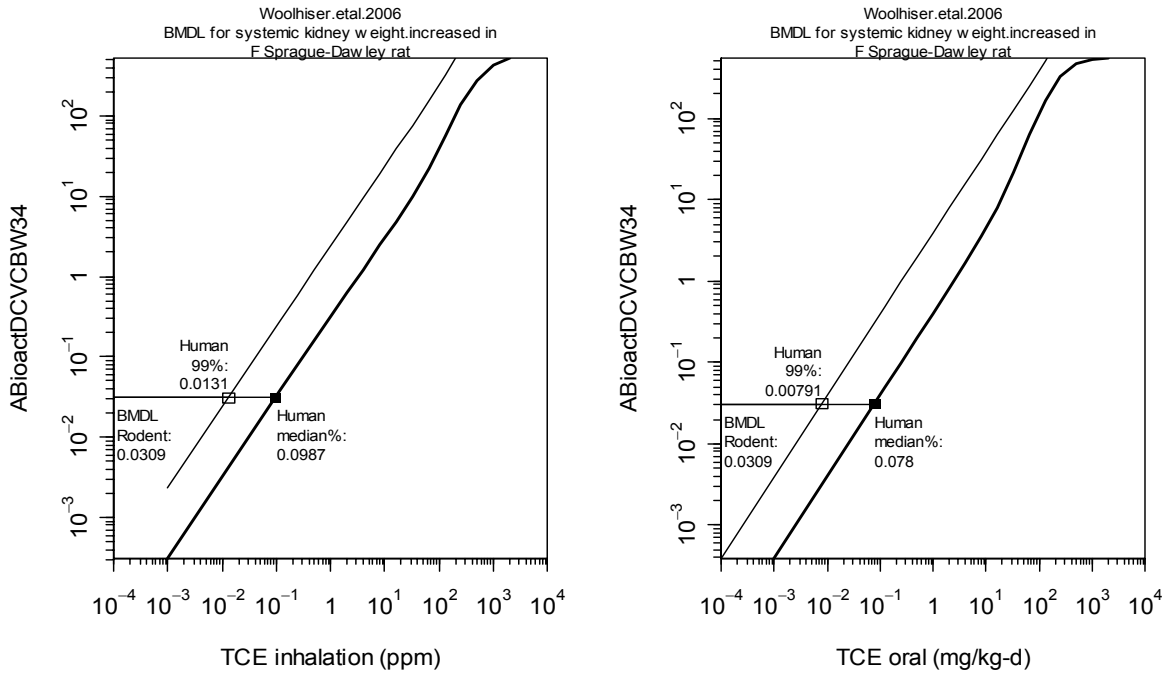



**Figure F-14. Derivation of $HEC_{99}$ and $HED_{99}$ corresponding to the rodent idPOD from Woolhiser et al. (2006) for increased kidney weight in rats.**

### F.6.5.2. *Derivation of $HEC_{99}$ and $HED_{99}$*

The $HEC_{99}$ and $HED_{99}$ are the lower 99$^{th}$ percentiles for the continuous human exposure concentration and continuous human ingestion dose that lead to a human internal dose equal to the rodent idPOD. The derivation of the $HEC_{99}$ of 0.0332 ppm and $HED_{99}$ of 0.0482 mg/kg/d for the 99$^{th}$ percentile for uncertainty and variability are shown in Figure F-15. These values are used as this critical effect's POD to which additional UFs are applied.

## F.6.6. Johnson et al. (2003)—Benchmark Dose (BMD) Modeling of Fetal Heart Malformations in Rats

The critical endpoint here is increased fetal heart malformations in female S-D rats (Johnson et al., 2003).

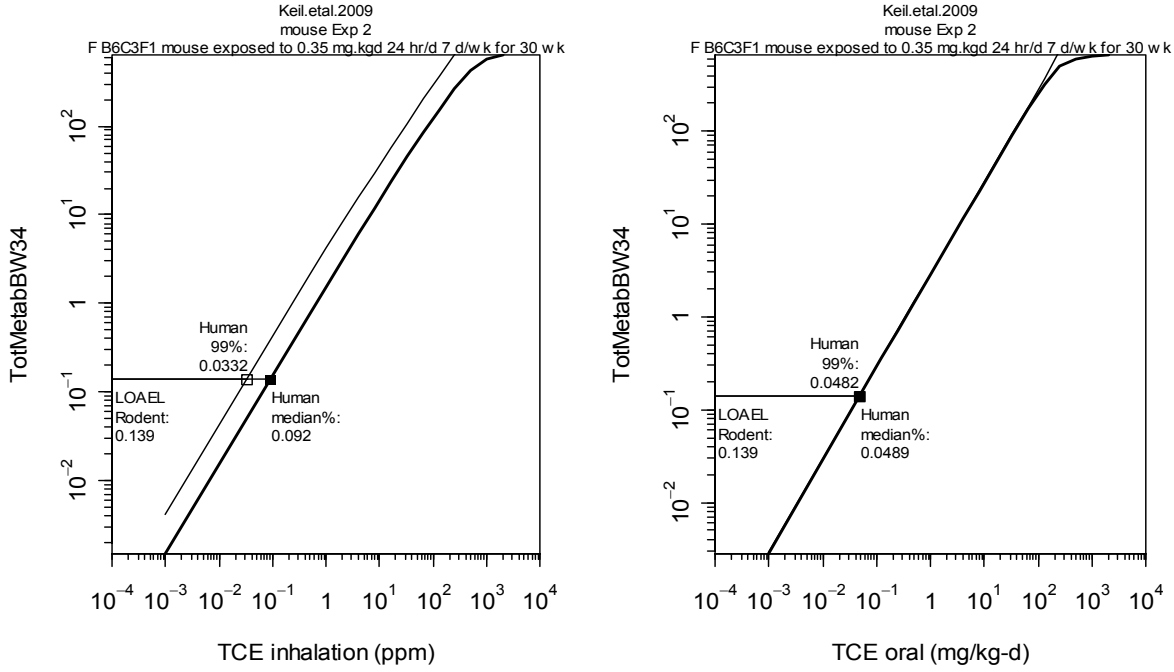



**Figure F-15. Derivation of $HEC_{99}$ and $HED_{99}$ corresponding to the rodent idPOD from Keil et al. (2009) for decreased thymus weight and increased anti-dsDNA and anti-ssDNA antibodies in mice.**

### F.6.6.1. *Dosimetry and Benchmark Dose (BMD) Modeling*

Rats were exposed to 2.5, 250, 1.5, or 1,100 ppm TCE in drinking water for 22 days (GD 1−22). The primary dose metric was selected to be average amount of TCE metabolized by oxidation/$kg^{3/4}$/day, with median estimates from the PBPK model for this study of 0.00031, 0.033, 0.15, and 88.

As discussed previously in Section F.4.2.1, from results of nested log-logistic modeling of these data, with the highest dose group dropped, the idPOD of 0.0142 mg TCE metabolized by oxidation/$kg^{3/4}$/day was a BMDL for a BMR of 1% increased in incidence in pups. A 1% extra risk of a pup having a heart malformation was used as the BMR because of the severity of the effect; some of the types of malformations observed could have been fatal.

### F.6.6.2. *Derivation of $HEC_{99}$ and $HED_{99}$*

The $HEC_{99}$ and $HED_{99}$ are the lower 99$^{th}$ percentiles for the continuous human exposure concentration and continuous human ingestion dose that lead to a human internal dose equal to the rodent idPOD. The derivation of the $HEC_{99}$ of 0.00365 ppm and $HED_{99}$ of 0.00515 mg/kg/d

for the 99th percentile for uncertainty and variability are shown in Figure F-16. These values are used as this critical effect's POD to which additional UFs are applied.

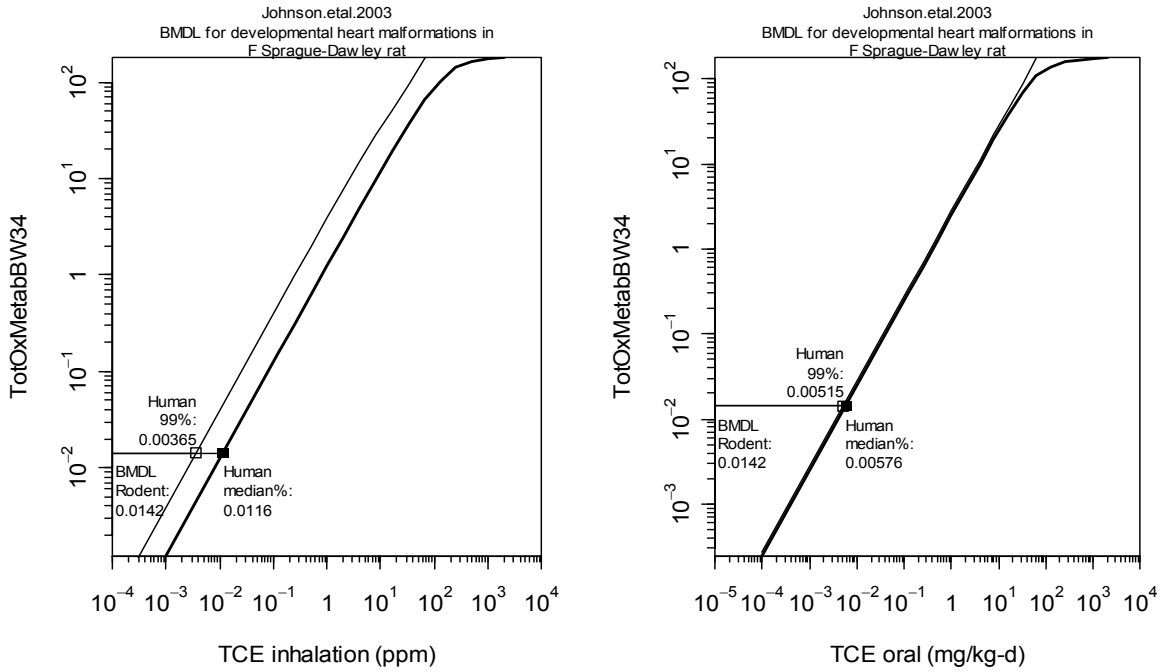



**Figure F-16. Derivation of $HEC_{99}$ and $HED_{99}$ corresponding to the rodent idPOD from Johnson et al. (2003) for increased fetal cardiac malformations in female S-D rats using the total oxidative metabolism dose metric.**

### F.6.7. Peden-Adams et al. (2006)—Lowest-Observed-Adverse-Effect Level (LOAEL) for Decreased PFC Response and Increased Delayed-Type Hypersensitivity in Mice

The critical endpoints here are decreased PFC response and increased delayed-type hypersensitivity in mice exposed pre- and postnatally (Peden-Adams et al., 2006).

Mice were exposed to 1400 and 14,000 ppb in drinking water, with an average dose in the dams estimated by the authors to be 0.37 and 3.7 mg/kg/d, from GD0 to postnatal ages of 3 or 8 weeks. The dose-response relationships were sufficiently supralinear that BMD modeling failed to produce an adequate fit. In addition, because of the lack of an appropriate PBPK model and parameters to estimate internal doses given the complex exposure pattern (placental and lactational transfer, and pup ingestion postweaning), no internal dose estimates were made. Therefore, the LOAEL of 0.37 mg/kg/d on the basis of applied dose was used as the critical effect's POD to which additional UFs are applied.

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