

# **APPENDIX F**

## **TCE Noncancer Dose-Response Analyses**

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10/20/09

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1                   **APPENDIX F: TCE NONCANCER DOSE-RESPONSE ANALYSES**

2  
3  
4   **F.1. DATA SOURCES**

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

7  
8   **F.2. DOSIMETRY**

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

11  
12 **F.2.1. Estimates of Trichloroethylene (TCE) in Air From Urinary Metabolite Data Using**  
13 **Ikeda et al. (1972)**

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

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

18  
19           **Table F-1. Dose-response data from Chia et al. (1996)**

20

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

21  
22           Minimum and maximum TCA levels are reported in the text of Chia et al. (1996), the other data, in their  
23 Table 5.

24  
25  
26           Data from Ikeda et al. (1972) were used to estimate the TCE exposure concentrations  
27 corresponding to the urinary TCA levels reported by Chia et al. (1996). Ikeda et al. (1972)  
28 studied 10 workshops, in each of which TCE vapor concentration was “relatively constant.”  
29 They measured atmospheric concentrations of TCE and concentrations in workers’ urine of total  
30 trichloro compounds (TTC), TCA, and creatinine, and demonstrated a linear relation between  
31 TTC/creatinine (mg/g) in urine and TCE in the work atmosphere. Their data are tabulated as  
32 geometric means (the last column was calculated by us, as described in Table F-2).

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1 **Table F-2. Data on TCE in air (ppm) and urinary metabolite concentrations**  
 2 **in workers reported by Ikeda et al. (1972)**  
 3

| <i>n</i> | 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              |

4  
 5  
 6 These data were used to construct the last column “TCA.cr.mg.g” (mg TCA/g creatinine),  
 7 as follows: TCA (mg/g creatinine) = TCA (mg/L) × TTC (mg/g creatinine)/TTC (mg/L). The  
 8 regression relation between TCE (ppm) and TCA (mg/g creatinine) was evaluated using these  
 9 data. Ikeda et al. (1972) reported that the measured values are lognormally distributed and  
 10 exhibit heterogeneity of variance, and that the reported data (above) are geometric means. Thus,  
 11 the regression relation between log<sub>10</sub>(TCA [mg/g creatinine]) and log<sub>10</sub>(TCE [ppm]) was used,  
 12 assuming constant variances and using number of subjects “*n*” as weights. Figure F-1 shows the  
 13 results.

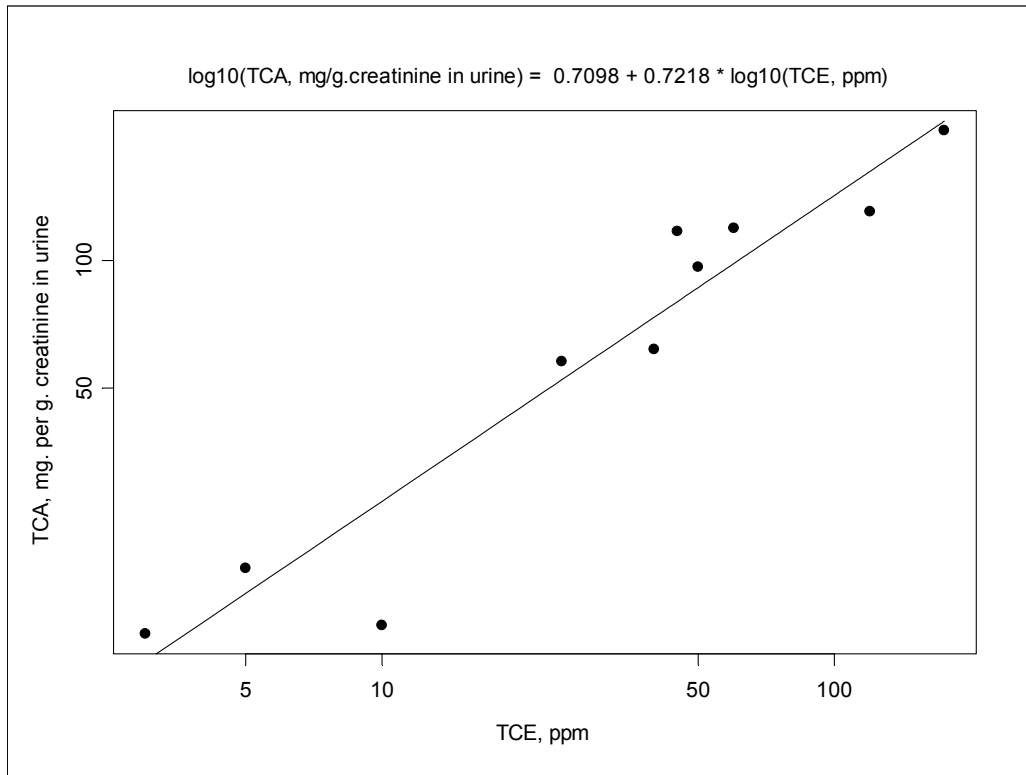
14 Next, a Berkson setting for linear calibration was assumed, in which one wants to predict  
 15 *X* (TCE, ppm) from means for *Y* (TCA, mg/g creatinine), with substantial error in *Y* (Snedecor  
 16 and Cochran, 1980). Thus, the inverse prediction for the data of Chia et al. (1996) was used to  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

$$\log_{10}(\text{TCA, mg/g creatinine}) = 0.7098 + 0.7218 \cdot \log_{10}(\text{TCE, ppm}) \quad (\text{Eq. F-1})$$

18  
 19  
 20  
 21 and the inverse prediction is



1



2

| 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

3

4

5

6

7

8

9

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

10

$$\log_{10}(\text{TCE}) = [\log_{10}(\text{TCA}) - 0.7098]/0.7218 \quad (\text{Eq. F-2})$$

11

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

12

13

14

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.

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

| TCA, mg per g Creatinine | Estim. TCA median <sup>a</sup> | Log10(TCA median) | Estim. ppm TCE <sup>b</sup> |
|--------------------------|--------------------------------|-------------------|-----------------------------|
| 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                   |

4  
 5 <sup>a</sup>  $10^{(\text{mean}[\log_{10}(\text{TCA limits in first column})])}$ .

6 <sup>b</sup>  $10^{([\log_{10}(\text{TCA median})] - 0.7098)/0.7218}$ .

7  
 8  
 9 Dose-response relations for the data of Chia et al. (1996) were modeled using both the  
 10 estimated medians for TCA (mg/g creatinine) in urine and estimated TCE (ppm in air) as doses.  
 11 The TCE-TCA-TTC relations are linear up to about 75 ppm TCE (Figure 1 of Ikeda et al. 1972),  
 12 and certainly in the range of the benchmark dose (BMD). As noted below (see Section F.2.2),  
 13 the occupational exposure levels are further adjusted to equivalent continuous exposure for  
 14 deriving the point of departure (POD).

15  
 16 **F.2.1.2. Results for Mhiri et al. (2004)**

17 The lowest-observed-adverse-effect level (LOAEL) group for abnormal trigeminal nerve  
 18 somatosensory evoked potential reported in Mhiri et al. (2004) had a urinary TCA concentration  
 19 of 32.6 mg TCA/mg creatinine. Using Eq. F-2, above gives an occupational exposure level =  
 20  $10^{([\log_{10}(32.6) - 0.7098]/0.7218)} = 12.97404$  ppm. As noted below (see Section F.2.2), the  
 21 occupational exposure levels are further adjusted to equivalent continuous exposure for deriving  
 22 the POD.

23  
 24 **F.2.2. Dose Adjustments to Applied Doses for Intermittent Exposure**

25 The nominal applied dose was adjusted for exposure discontinuity (e.g., exposure for  
 26 5 days per week and 6 hours per day reduced the dose by the factor  $[5/7]*[6/24]$ ). The  
 27 physiologically based pharmacokinetic (PBPK) dose metrics took into account the daily and  
 28 weekly discontinuity to produce an equivalent average dose for continuous exposure. No dose  
 29 adjustments were made for duration of exposure or a less-than-lifetime study, as is typically done  
 30 for cancer risk estimates, though in deriving the candidate reference values, an uncertainty factor  
 31 for subchronic-to-chronic exposure was applied where appropriate.

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

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

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

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

## 17 **F.3. DOSE-RESPONSE MODELING PROCEDURES**

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

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

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

24 For dichotomous responses, the log-logistic, multistage, and Weibull models were fitted.  
25 These models adequately describe the dose-response relationship for the great majority of data  
26 sets, specifically in past TCE studies (Filipsson and Victorin, 2003). If the slope parameter of  
27 the log-logistic model was less than 1, indicating a supralinear dose-response shape, the model  
28 with the slope constrained to 1 was also fitted for comparison. For the multistage model, an  
29 order one less than the number of dose groups was used, in addition to the 2<sup>nd</sup>-order multistage  
30 model if it differed from the preceding model, and the first-order ('linear') multistage model  
31 (which is identical to a Weibull model with power parameter equal to 1). The Weibull model  
32 with the power parameter unconstrained was also fitted t.  
33  
34  
35

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

2 In addition, nested dichotomous models were used for developmental effects in rodent  
3 studies to account for possible litter effects, such maternal covariates or intralitter correlation.  
4 The available nested models in BMDS are the nested log-logistic model, the Rai-VanRyzin  
5 models, and the NCTR model. Candidates for litter-specific covariates (LSC) were identified  
6 from the studies and considered legitimate for analysis if they were not significantly dose-related  
7 (determined via regression, analysis of variance). The need for a LSC was indicated by a  
8 difference of at least 3 in the Akaike Information Criteria (AIC) for models with and without a  
9 LSC. The need to estimate intralitter correlations (IC) was determined by presence of a high  
10 correlation coefficient for at least one dose group and by AIC. The fits for nested models were  
11 also compared with the results from quantal models.  
12

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

14 For continuous responses, the distinct models available in BMDS were fitted: power  
15 model (power parameter unconstrained and constrained to  $\geq 1$ ), polynomial model, and Hill  
16 model. Both constant variance and modeled variance models were fit; but constant variance  
17 models were used for model parsimony unless the  $p$ -value for the test of homogenous variance  
18 was  $< 0.10$ , in which case the modeled variance models were considered. For the polynomial  
19 model, model order was selected as follows. A model of order 1 was fitted first. The next higher  
20 order model (up to order  $n-1$ ) was accepted if AIC decreased more than 3 units and the  $p$ -value  
21 for the mean did not decrease.  
22

### 23 **F.3.3. Model Selection**

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

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1 or more models share the lowest AIC, the BMD *Technical Guidance Document* (U.S. EPA,  
2 2008b) suggests that an average of the BMDLs could be used, but averaging was not used in this  
3 assessment (for the one occasion in which models shared the lowest AIC, a selection was made  
4 based on visual fit). If the BMDL estimates from the remaining models are not sufficiently  
5 close, some model dependence is assumed. With no clear biological or statistical basis to choose  
6 among them, the lowest BMDL was chosen as a reasonable conservative estimate, as suggested  
7 in the *Benchmark Dose Technical Guidance Document*, unless the lowest BMDL appeared to be  
8 an outlier, in which case further judgments were made.

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

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

13 The behavioral/neurological endpoint “number of rears” from Moser et al. (1995)  
14 consisted of counts, measured at five doses and four measurement times (with eight observations  
15 each). The high dose for this endpoint was dropped because the mean was zero, and no  
16 monotone model could fit that well. Analysis of means and standard deviations for these counts  
17 suggested a Box-Cox power transform (Box et al., 1978) of  $\frac{1}{2}$  (i.e., square root) to stabilize  
18 variances (i.e., the slope of the regression of  $\log[\text{standard deviation (SD)}]$  on  $\log[\text{mean}]$  was  
19 0.46, and the relation was linear and highly significant). This information was helpful in  
20 selecting a suitable variance model with high confidence (i.e., variance constant, for square-root  
21 transformed data). Thus, the square root was taken of the original individual count data, and the  
22 mean and variance of the transformed count data were used in the BMD modeling.

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

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

1 **F.4. DOSE-RESPONSE MODELING RESULTS**

2 **F.4.1. Quantal Dichotomous and Continuous Modeling Results**

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

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

21

22 **F.4.2. Nested Dichotomous Modeling Results**

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

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

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

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1 **Table F-4. Data on fetuses and litters with abnormal hearts from Johnson et**  
 2 **al. (2003)**  
 3

| <b>Dose group (mg/kg/d):</b> | <b>0</b> | <b>0.00045</b> | <b>0.048</b> | <b>0.218</b> | <b>129</b> |
|------------------------------|----------|----------------|--------------|--------------|------------|
| 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          |

4  
 5  
 6 With the high dose included, the chi-square goodness of fit was acceptable, but some  
 7 residuals were large (1.5 to 2) for the control and two lower doses. Therefore, models were also  
 8 fitted after dropping the highest dose. For these, goodness of fit was adequate, and scaled  
 9 residuals were smaller for the low doses and control. Predicted expected response values were  
 10 closer to observed when the high dose was dropped, as shown in Table F-5:  
 11

12 **Table F-5. Comparison of observed and predicted numbers of fetuses with**  
 13 **abnormal hearts from Johnson et al. (2003), with and without the high-dose**  
 14 **group, using a nested model**  
 15

| <b>Dose group (mg/kg/d):</b> | <b>Abnormal hearts (pups)</b> |                |              |              |            |
|------------------------------|-------------------------------|----------------|--------------|--------------|------------|
|                              | <b>0</b>                      | <b>0.00045</b> | <b>0.048</b> | <b>0.218</b> | <b>129</b> |
| 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           | --         |

16  
 17  
 18 Accuracy in the low-dose range is especially important because the BMD is based upon  
 19 the predicted responses at the control and the lower doses. Based on the foregoing measures of  
 20 goodness of fit, the model based on dropping the high dose was used.

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

4  
 5 **Table F-6. Results of nested log-logistic model for fetal cardiac anomalies**  
 6 **from Johnson et al. (2003) without the high-dose group, on the basis of**  
 7 **applied dose (mg/kg/d in drinking water)**  
 8

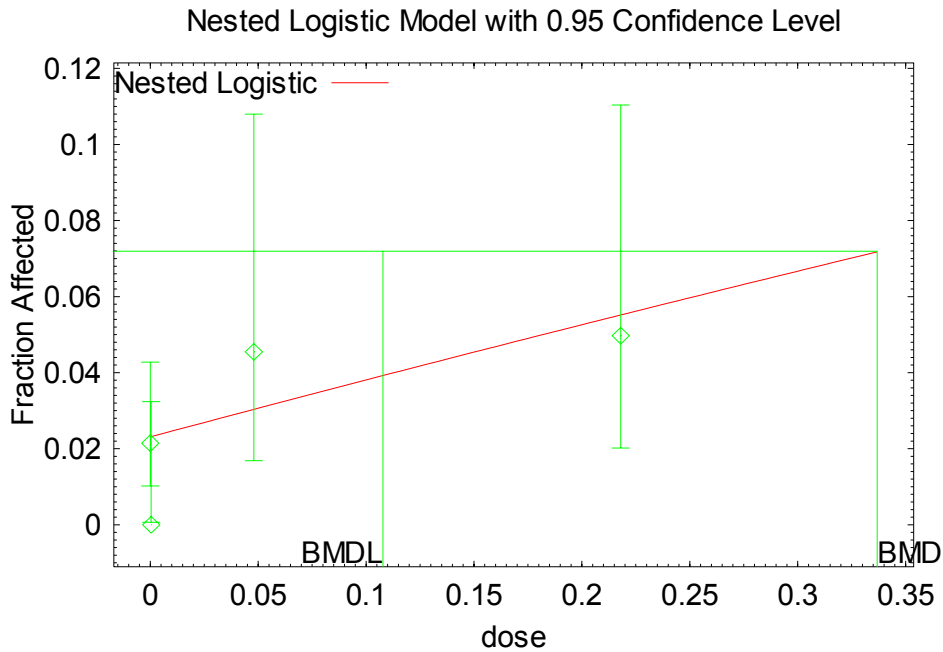
| Model        | LSC?     | IC?      | AIC            | Pval          | BMR         | BMD             | BMDL            |
|--------------|----------|----------|----------------|---------------|-------------|-----------------|-----------------|
| NLOG         | Y        | Y        | 246.877        | NA (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        |
| <b>NLOG*</b> | <b>N</b> | <b>Y</b> | <b>243.815</b> | <b>0.0128</b> | <b>0.01</b> | <b>0.064649</b> | <b>0.020698</b> |

9  
 10 \* Indicates model selected (Rai-VanRyzin model fits are essentially the same).

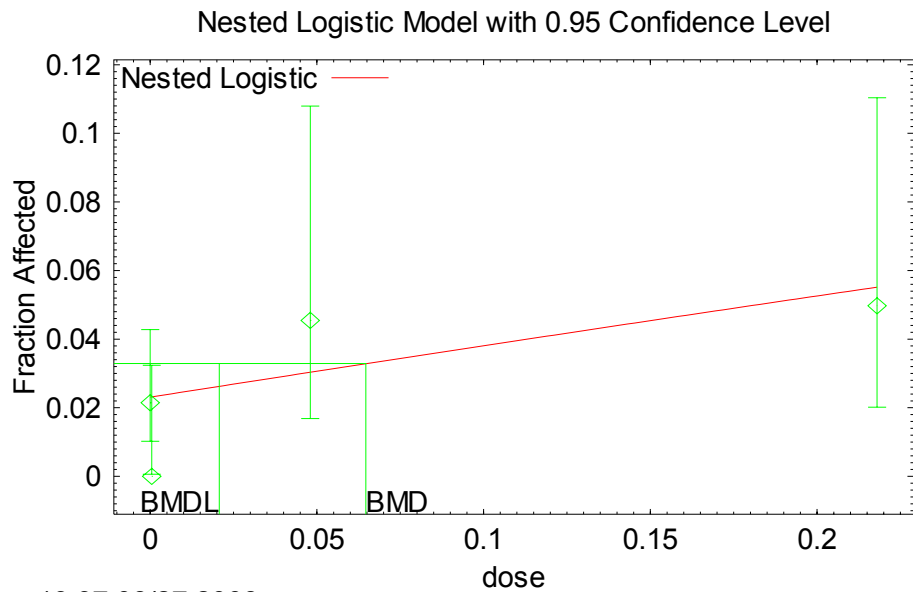
11 NLOG = “nested log-logistic” model.

12 LSC analyzed was female weight gain during pregnancy.  
 13





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**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).**

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

7 An R program was written to read the BMDS output, reading parameters and the table of  
8 litter-specific results (dose, covariate, estimated probability of response, litter size, expected  
9 response count, observed response count, scaled chi-square residual). The control group of  
10 55 litters was subdivided into three subgroups of 18, 18, and 19 litters. Control litters were  
11 sampled randomly without replacement 100 times, each time creating 3 subgroups—i.e.,  
12 100 random assignments of the 55 control litters to three subgroups were made. For each of  
13 these, the goodness-of-fit calculation was made and the *p*-value saved. Within these  
14 100 *p*-values,  $\geq 75\%$  were  $\geq 0.05$ , and  $\geq 50\%$  had *p*-values  $\geq 0.11$ , this indicated that the model is  
15 acceptable based on goodness-of-fit criteria.

16  
17 **F.4.2.1.3. Results using physiologically based pharmacokinetic (PBPK) model-based dose**  
18 **metrics.** The nested log-logistic model was also run using the dose metrics in the dams of total  
19 oxidative metabolism scaled by body weight to the  $3/4$ -power (TotOxMetabBW<sup>3/4</sup>) and the area-  
20 under-the-curve of TCE in blood (AUCCBld). As with the applied dose modeling, LSC  
21 (maternal weight gain) was not included, but IC was included, based on the criteria outlined  
22 previously (see Section F.3.1.2). The results are summarized in Table F-7 and Figure F-3 for  
23 TotOxMetabBW<sup>3/4</sup> and Table F-8 and Figure F-4 for AUCCBld.

#### 24 25 **F.4.2.2. Narotsky et al. (1995)**

26 Data were combined for the high doses in the single-agent experiment and the lower  
27 doses in the ‘five-cube’ experiment. Individual animal data were kindly provided by Dr.  
28 Narotsky (personal communications from Michael Narotsky, U.S. EPA, to John Fox, U.S. EPA,  
29 19 June 2008, and to Jennifer Jinot, U.S. EPA, 10 June 2008). Two endpoints were examined:  
30 frequency of eye defects in rat pups and prenatal loss (number of implantation sites minus  
31 number of live pups on postnatal day 1).

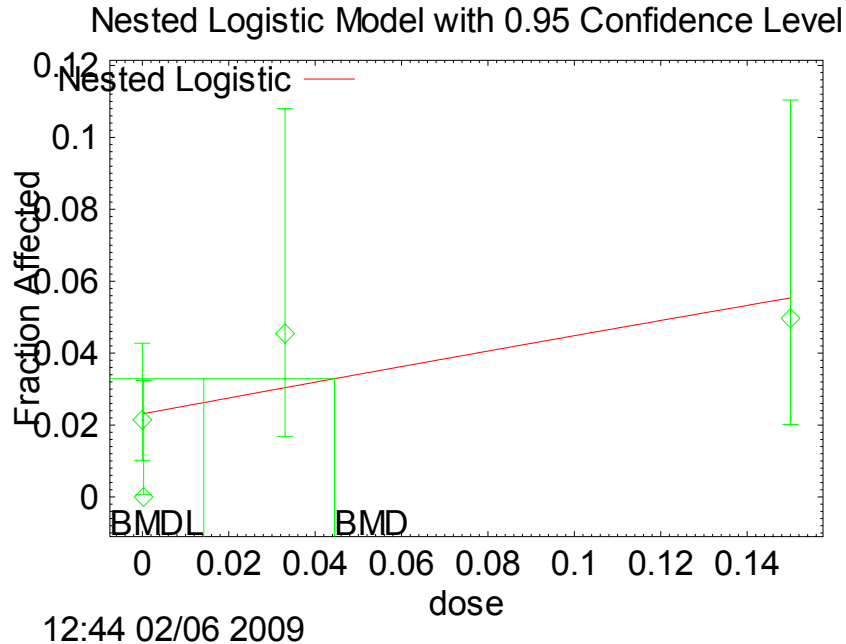
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**Table F-7. Results of nested log-logistic model for fetal cardiac anomalies from Johnson et al. (2003) without the high-dose group, using the TotOxMetabBW34 dose metric**

| 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         |
| <b>NLOG*</b> | <b>N</b> | <b>Y</b> | <b>243.815</b> | <b>0.0128</b> | <b>0.01</b> | <b>0.0444948</b> | <b>0.0142453</b> |
| NLOG         | N        | N        | 248.853        | 0.0098        | 0.01        | 0.0397876        | 0.0199438        |

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\* 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.



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**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.**

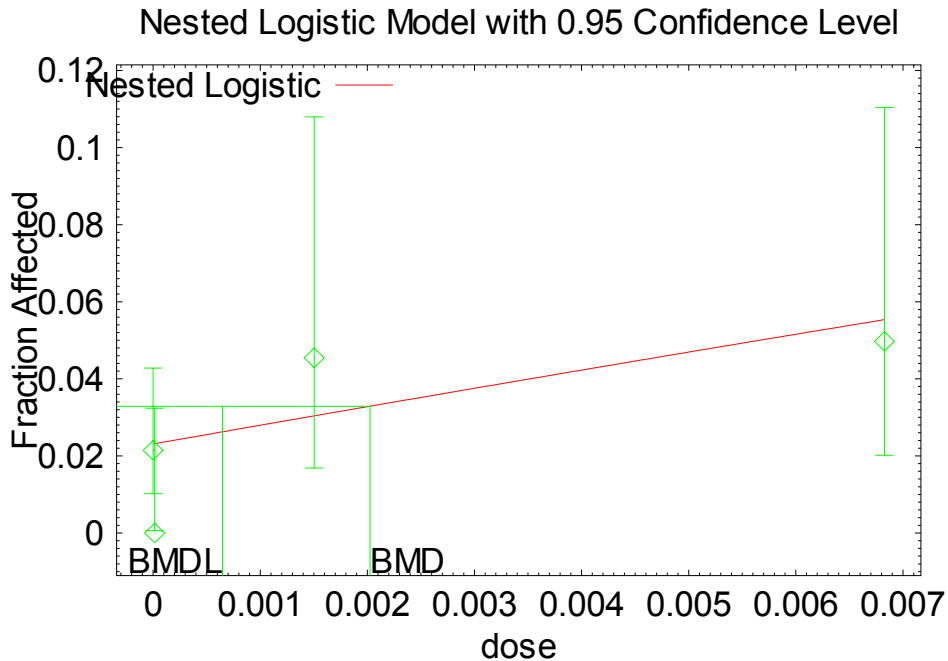
1 **Table F-8. Results of nested log-logistic model for fetal cardiac anomalies**  
 2 **from Johnson et al. (2003) without the high-dose group, using the AUCCBld**  
 3 **dose metric**  
 4

| 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         |
| <b>NLOG*</b> | <b>N</b> | <b>Y</b> | <b>243.816</b> | <b>0.0128</b> | <b>0.01</b> | <b>0.00202535</b> | <b>0.000648179</b> |
| NLOG         | N        | N        | 248.853        | 0.0098        | 0.01        | 0.00181058        | 0.000907513        |

5 \* Indicates model selected. BMDs failed with the Rai-VanRyzin and NCTR models.  
 6

7 NLOG = “nested log-logistic” model.  
 8

9 LSC analyzed was female weight gain during pregnancy.  
 10  
 11



12 **Figure F-4. BMD modeling of Johnson et al. (2003) using nested log-logistic**  
 13 **model, with AUCCBld dose metric, without LSC, with IC, and without the**  
 14 **high-dose group, using a BMR of 0.01 extra risk.**  
 15

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

7  
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**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., $\text{damBW6} \sim \text{TCE.mg.kgd} + \text{expt}$ |             |              |              |
| Linear regression   |             | $p = 0.7486$ | $p = 0.0069$ |
| AoV (ordered factor)  |             | $p = 0.1782$ | $p = 0.0927$ |

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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.

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

4  
 5 **Table F-10. Results of nested log-logistic and Rai-VanRyzin model for fetal**  
 6 **eye defects from Narotsky et al. (1995), on the basis of applied dose (mg/kg/d**  
 7 **in drinking water)**  
 8

| Model | LSC? | IC? | AIC     | Pval   | BMR  | BMD     | BMDL                 |
|-------|------|-----|---------|--------|------|---------|----------------------|
| NLOG  | Y    | Y   | 255.771 | 0.3489 | 0.05 | 875.347 | 737.328 <sup>a</sup> |
| 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 <sup>b</sup> |
| 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 <sup>b</sup> |

9  
 10 <sup>a</sup> Graphical fit at the origin exceeds observed control and low dose responses and slope is quite flat (see Figure F-5),  
 11 fitted curve does not represent the data well.

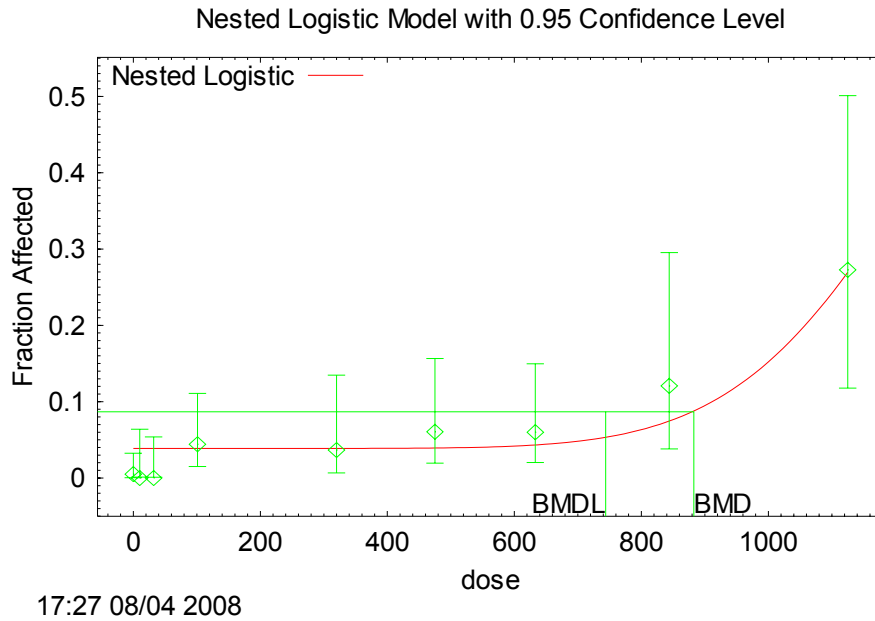
12 <sup>b</sup> Indicates model selected.

13  
 14 NLOG = “nested log-logistic” model; RAI = Rai-VanRyzin model.  
 15 LSC analyzed was implants.

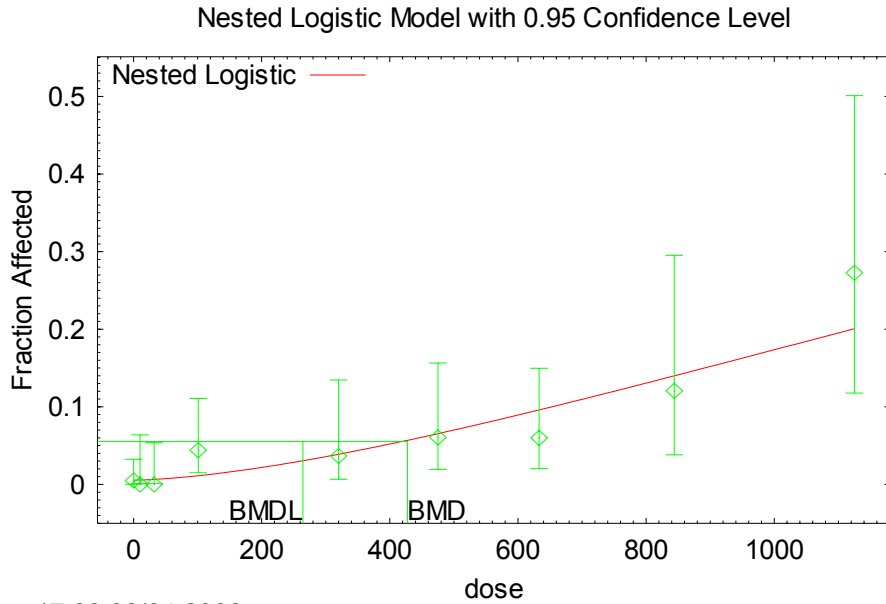
16  
 17  
 18 Results for the nested log-logistic model suggested a better model fit with the inclusion of  
 19 the LSC and IC, based on AIC. However, the graphical fit (see Figure F-5) is strongly sublinear  
 20 and high at the origin where the fitted response exceeds the observed low-dose responses for the  
 21 control group and two low-dose groups. An alternative nested log-logistic model without either  
 22 LSC or IC (see Figure F-6), which fits the low-dose responses better, was selected. Given that  
 23 this model had no LSC and no IC, the nested log-logistic model reduces to a quantal log-logistic  
 24 model. Parameter estimates and the *p*-values were essentially the same for the two models (see

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1 Table F-11). A similar model selection can be justified for the Rai-Van Ryzin model (see  
2 Figure F-7). Because no LSC and no IC were needed, this endpoint was modeled with quantal  
3 models, using totals of implants and losses for each dose group, which allowed choice from a  
4 wider range of models (those results appear with quantal model results in this appendix).  
5



6  
7 **Figure F-5. BMD modeling of fetal eye defects from Narotsky et al. (1995)**  
8 **using nested log-logistic model, with applied dose, with both LSC and IC,**  
9 **using a BMR of 0.05 extra risk.**



1  
2 **Figure F-6. BMD modeling of fetal eye defects from Narotsky et al. (1995)**  
3 **using nested log-logistic model, with applied dose, without either LSC or IC,**  
4 **using a BMR of 0.05 extra risk.**  
5  
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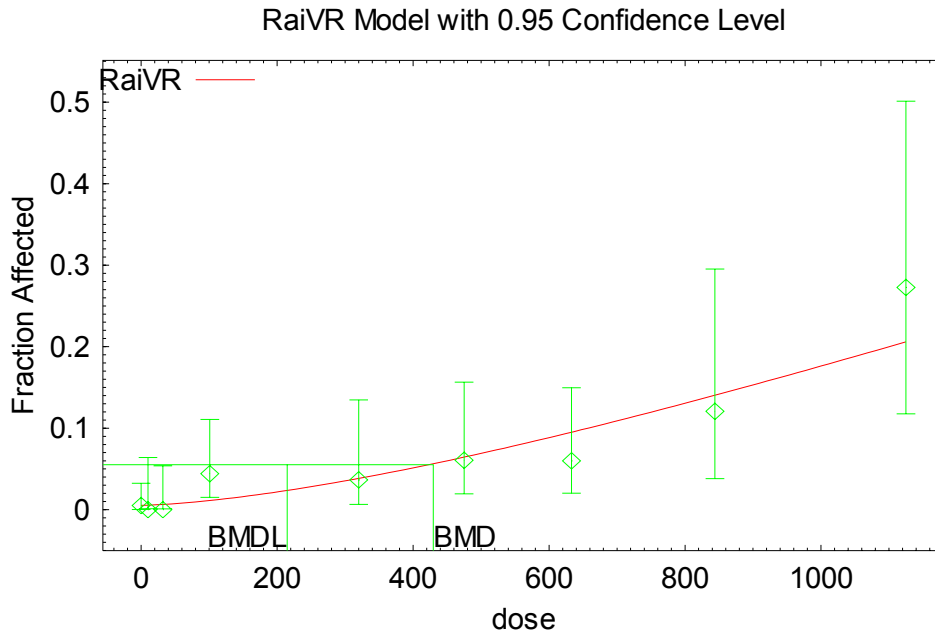
7 **Table F-11. Comparison of results of nested log-logistic (without LSC or IC)**  
8 **and quantal log-logistic model for fetal eye defects from Narotsky et al.**  
9 **(1995)**  
10

| Model   | Parameter  |          |         | BMD <sub>05</sub> | BMDL <sub>05</sub> |
|---------|------------|----------|---------|-------------------|--------------------|
|         | 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              |

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2  
3 **Figure F-7. BMD modeling of fetal eye defects from Narotsky et al. (1995)**  
4 **using nested Rai-VanRyzin model, with applied dose, without either LSC or**  
5 **IC, using a BMR of 0.05 extra risk.**  
6  
7

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

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

1 **Table F-12. Results of nested log-logistic and Rai-VanRyzin model for**  
 2 **prenatal loss from Narotsky et al. (1995), on the basis of applied dose**  
 3 **(mg/kg/d in drinking water)**  
 4

| 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          |
| <b>NLOG</b> | <b>N</b> | <b>Y</b> | <b>490.766</b> | <b>0.2509</b> | <b>0.01</b> | <b>594.995</b> | <b>252.437 *</b> |
| 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          |
| <b>RAI</b>  | <b>N</b> | <b>Y</b> | <b>488.856</b> | <b>0.2983</b> | <b>0.01</b> | <b>562.455</b> | <b>468.713 *</b> |

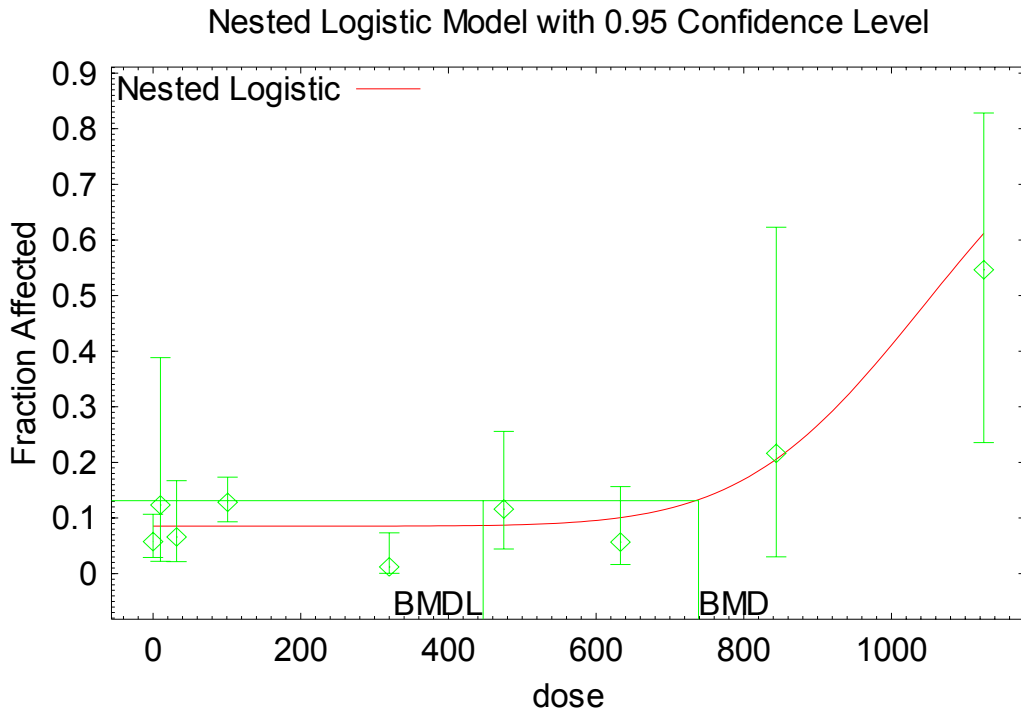
5 \* Indicates model selected.

6  
 7  
 8 NLOG = “nested log-logistic” model; RAI = Rai-VanRyzin model.  
 9 LSC analyzed was dam body weight on GD6.

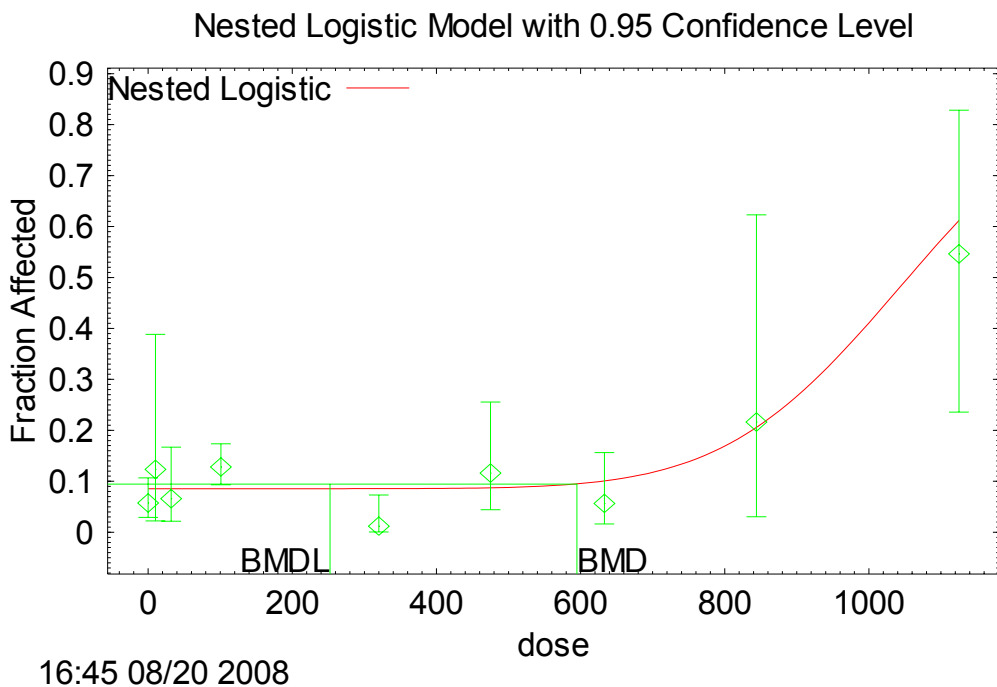
10  
 11  
 12 For the nested log-logistic models, the AIC is much larger when the IC is dropped, so the  
 13 IC is needed in the model. The LSC can be dropped (and is also suspect because it is correlated  
 14 with dose). The model with IC and without LSC was selected on the basis of AIC (shown in  
 15 Figure F-8). For the Rai-VanRyzin models, the model selection was similar to that for the nested  
 16 log-logistic, leading to a model with IC and without LSC, which had the lowest AIC (shown in  
 17 Figure F-9).

18  
 19 **F.4.3. Model Selections and Results**

20 The final model selections and results for noncancer dose-response modeling are  
 21 presented in Table F-13.  
 22



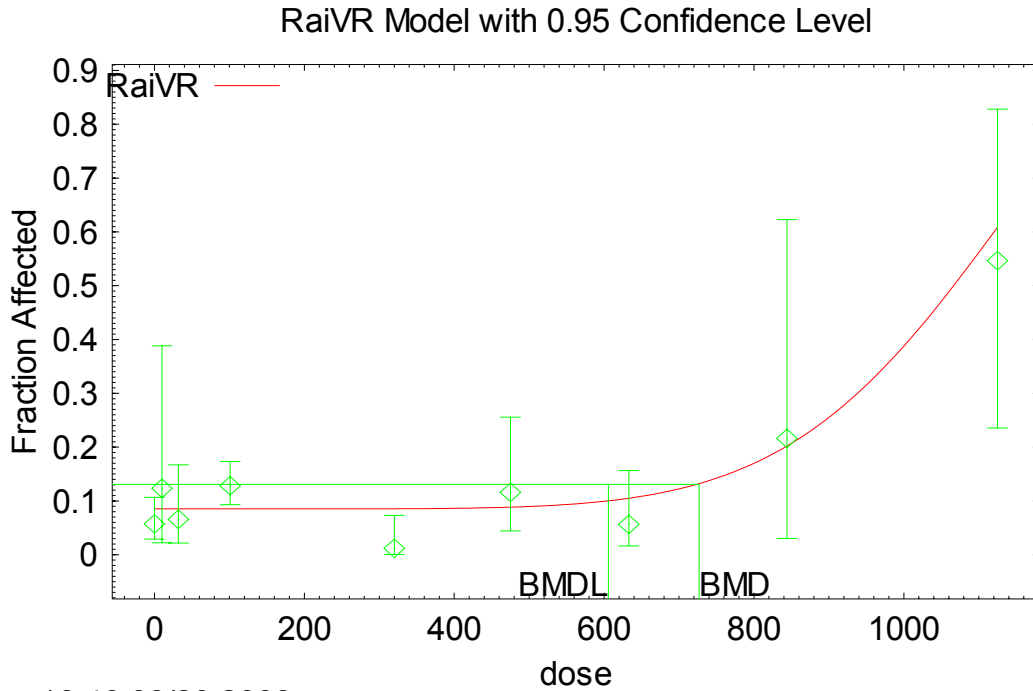
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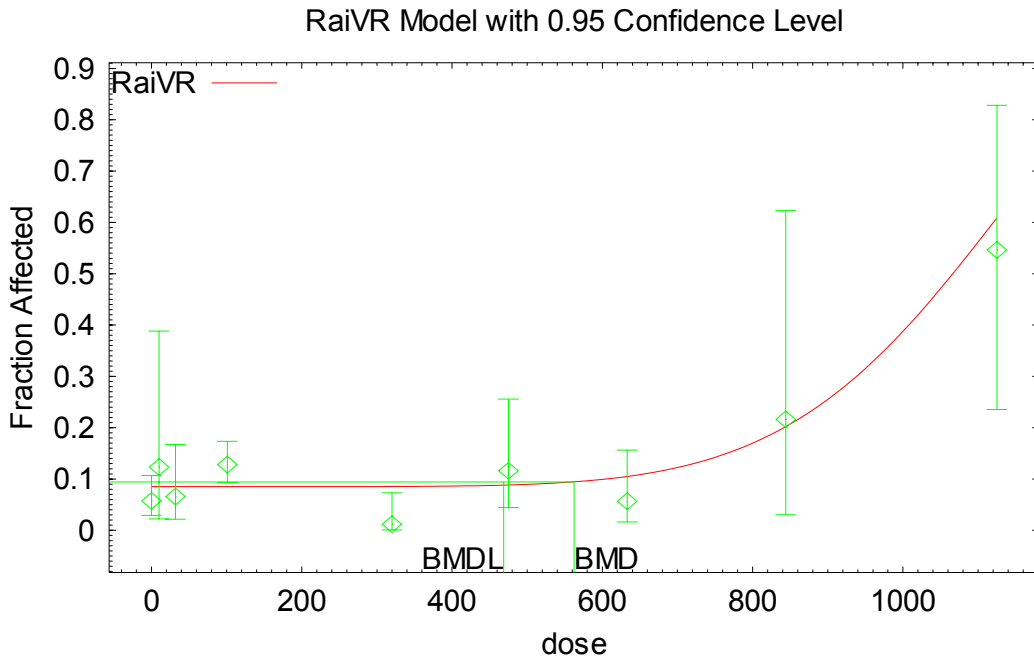
**Figure F-8. BMD modeling of prenatal loss reported in Narotsky et al. (1995) using nested log-logistic model, with applied dose, without LSC, with IC, using a BMR of 0.05 extra risk (top panel) or 0.01 extra risk (bottom panel).**

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**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 |
|---------------------------|-----------------------------|---------|-----|----------------------|------------|---------------------------|-----------------|----------|------|----------|--------|---------------|----------|-------|
| <b>Dichotomous models</b> |                             |         |     |                      |            |                           |                 |          |      |          |        |               |          |       |
| 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      |       |

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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 |
|----------------------------------|-----------------------------|---------|-----|-------------------------|------------|------------------------------|----------------|----------|------|----------|----------|---------------------|----------|-------|
| <b>Nested dichotomous models</b> |                             |         |     |                         |            |                              |                |          |      |          |          |                     |          |       |
| 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       | AUCCBid        | 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      |       |
| <b>Continuous models</b>         |                             |         |     |                         |            |                              |                |          |      |          |          |                     |          |       |
| 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 (CrI: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 | AUCCBid         | 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)

<sup>a</sup>Eight-stage multistage model.

<sup>b</sup>Dropped highest dose.

<sup>c</sup>Three-stage multistage model.

<sup>d</sup>Weibull selected over log-logistic with the same AIC on basis of visual fit (less extreme curvature).

<sup>e</sup>Second-order MS selected on basis of visual fit (less extreme curvature).

<sup>f</sup>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.

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1 **F.5. DERIVATION OF POINTS OF DEPARTURE**

2 **F.5.1. Applied Dose Points of Departure**

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

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

14

15 **F.5.2. Physiologically Based Pharmacokinetic (PBPK) Model-Based Human Points of**  
16 **Departure**

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

28 [Appendix.linked.files\AppF.Non-cancer.HECs.Plots.human.inhalation.studies.TCE.DRAFT.pdf](#)

29 [Appendix.linked.files\AppF.Non-cancer.HECs.Plots.rodent.inhalation.studies.TCE.DRAFT.pdf](#)

30 [Appendix.linked.files\AppF.Non-cancer.HECs.Plots.rodent.oral.studies.TCE.DRAFT.pdf](#)

31 [Appendix.linked.files\AppF.Non-cancer.HEDs.Plots.human.inhalation.studies.TCE.DRAFT.pdf](#)

32 [Appendix.linked.files\AppF.Non-cancer.HEDs.Plots.rodent.inhalation.studies.TCE.DRAFT.pdf](#)

33 [Appendix.linked.files\AppF.Non-cancer.HEDs.Plots.rodent.oral.studies.TCE.DRAFT.pdf](#)

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

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1 exposures for the human median and 99<sup>th</sup> percentiles were derived from a distribution of 2,000  
2 “individuals.” In both cases, the distributions reflect combined uncertainty (in the population  
3 means and variances) and population variability.

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

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

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

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

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

## 20 **F.6. SUMMARY OF POINTS OF DEPARTURE (PODs) FOR CRITICAL STUDIES** 21 **AND EFFECTS SUPPORTING THE INHALATION REFERENCE CONCENTRATION** 22 **(RfC) AND ORAL REFERENCE DOSE (RfD)**

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

### 31 **F.6.1. National Toxicology Program (NTP, 1988)—Benchmark Dose (BMD) Modeling of** 32 **Toxic Nephropathy in Rats**

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

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

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

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

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

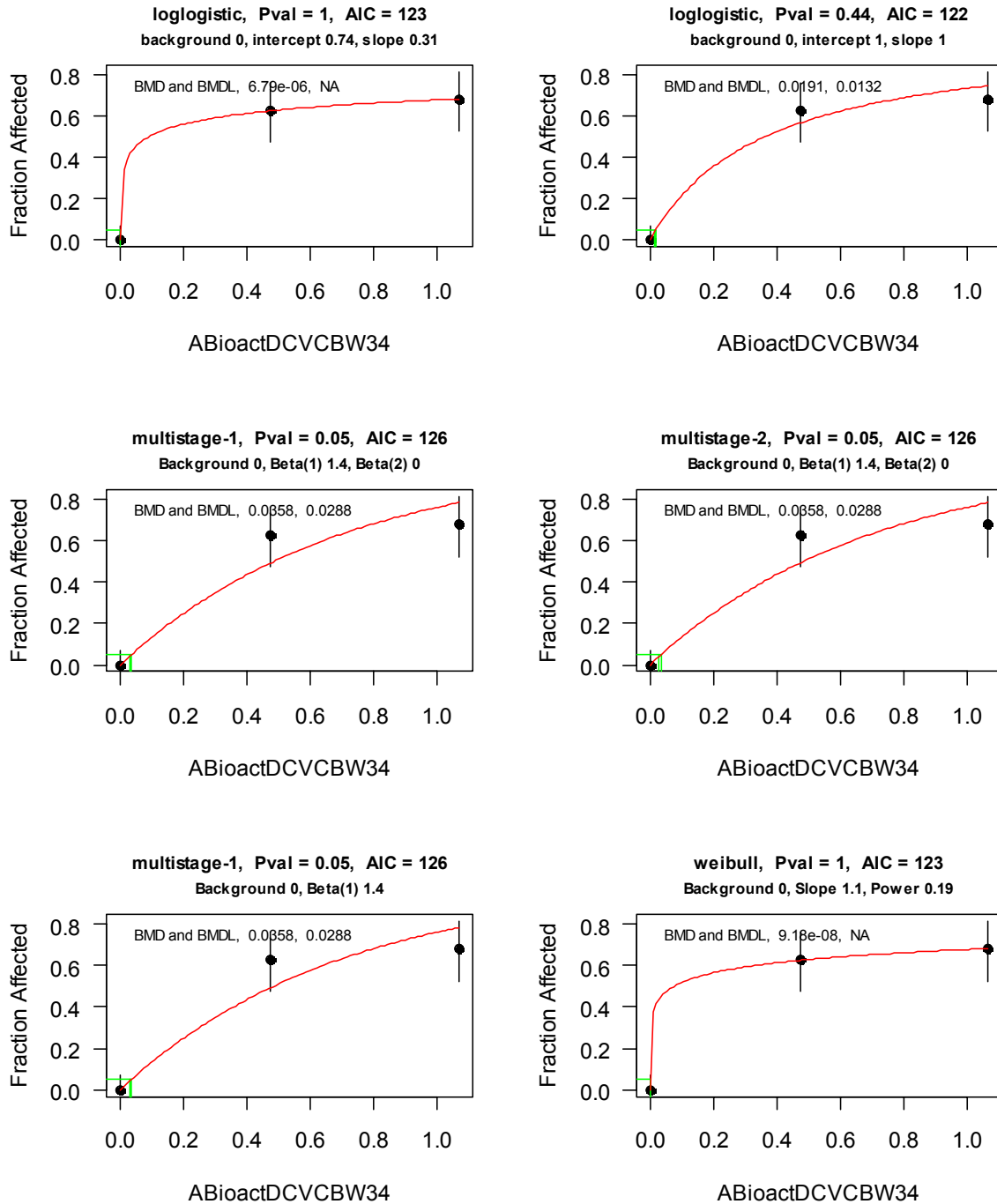
15  
16 **F.6.1.2. Derivation of HEC<sub>99</sub> and HED<sub>99</sub>**

17 The HEC<sub>99</sub> and HED<sub>99</sub> are the lower 99<sup>th</sup> percentiles for the continuous human exposure  
18 concentration and continuous human ingestion dose that lead to a human internal dose equal to  
19 the rodent idPOD. The derivation of the HEC<sub>99</sub> of 0.0056 ppm and HED<sub>99</sub> of 0.00338 mg/kg/d  
20 for the 99<sup>th</sup> percentile for uncertainty and variability are shown in Figure F-11. These values are  
21 used as this critical effect's POD to which additional uncertainty factors (UFs) are applied.

22  
23 **F.6.2. National Cancer Institute (NCI, 1976)—Lowest-Observed-Adverse-Effect Level**  
24 **(LOAEL) for Toxic Nephrosis in Mice**

25 The critical endpoint here is toxic nephrosis in female B6C3F1 mice (NCI, 1976), which  
26 was the most sensitive sex in this study, although the LOAEL for males differed by less than  
27 50%.

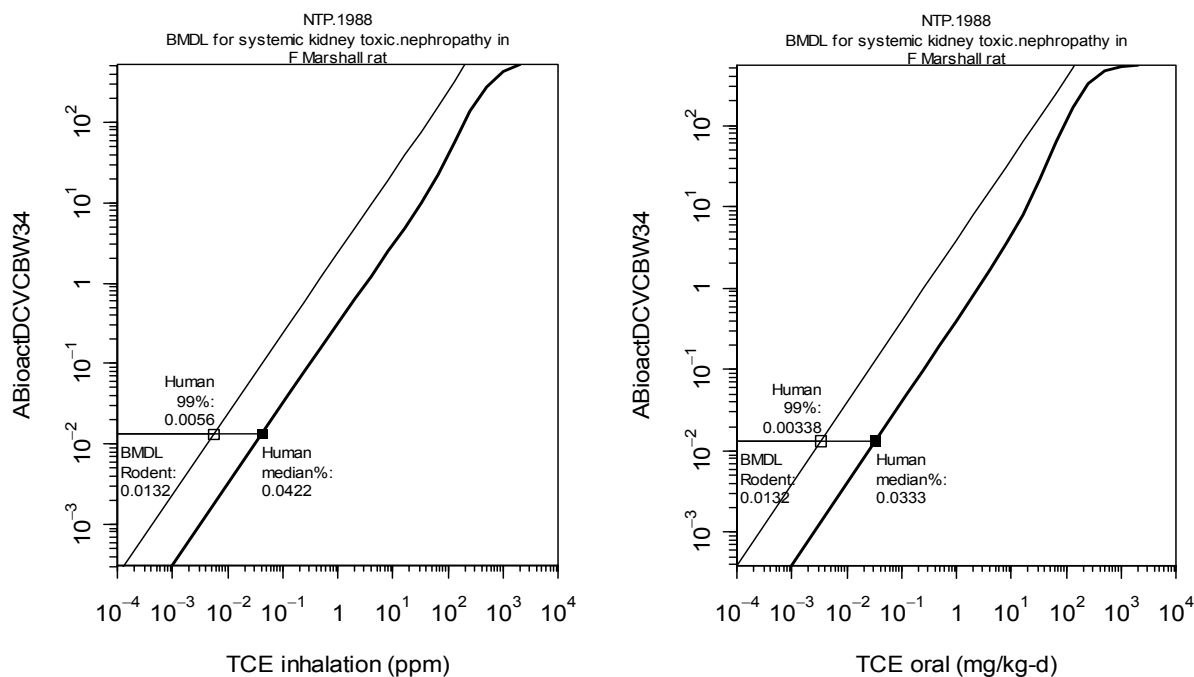
NTP.1988 kidney toxic nephropathy rat Marshall F oral.gav (GRP 49)  
 BMR: 0.05 extra



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

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1  
2  
3 **Figure F-11. Derivation of HEC<sub>99</sub> and HED<sub>99</sub> corresponding to the rodent**  
4 **idPOD from NTP (1988) toxic nephropathy in rats.**  
5  
6

7 **F.6.2.1. Dosimetry**

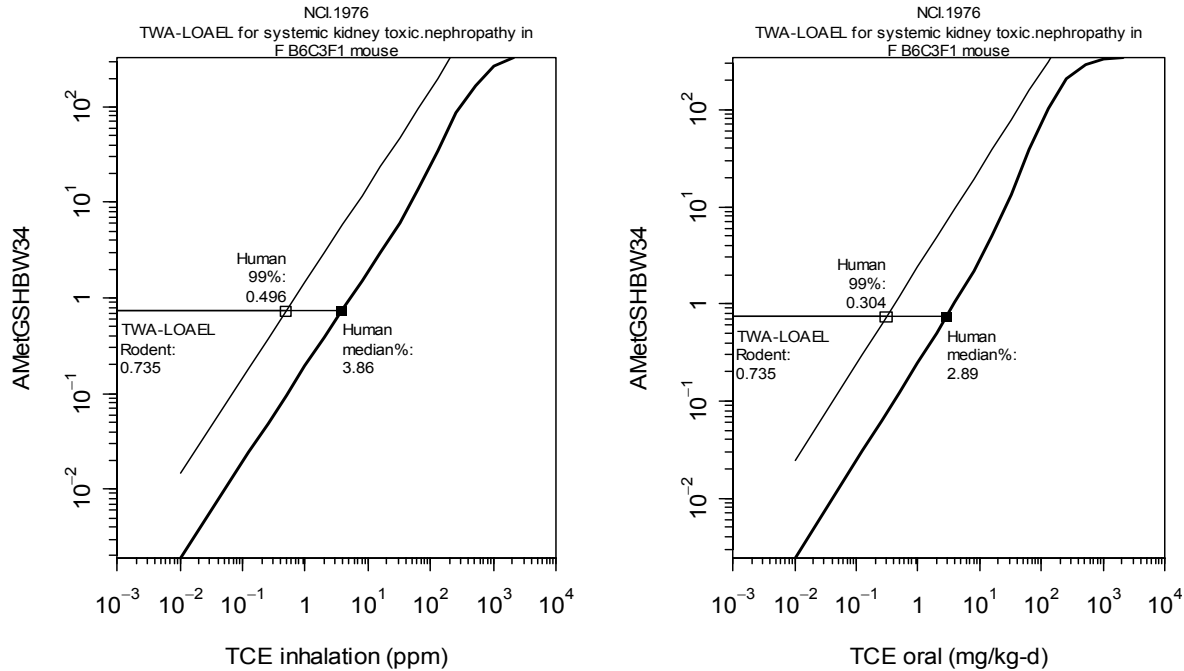
8 Mice were exposed to a time-weighted average of 869 and 1,739 mg/kg/d, 5 days/week,  
9 for 78 weeks. BMD modeling was not performed because the response at the LOAEL was  
10 >90%. The primary dose metric was selected to be average amount of TCE conjugated with  
11 glutathione (GSH)/kg<sup>3/4</sup>/d. In this study, the lower dose group was exposed to two different dose  
12 levels (700 mg/kg/d for 12 weeks and 900 mg/kg/d for 66 weeks). The median estimates from  
13 the PBPK model for the two dose levels were 0.583 and 0.762 mg TCE conjugation with  
14 GSH/kg<sup>3/4</sup>/d. Applying the same time-weighted averaging gives an idPOD LOAEL of 0.735 mg  
15 TCE conjugation with GSH/kg<sup>3/4</sup>/d.  
16

17 **F.6.2.2. Derivation of HEC<sub>99</sub> and HED<sub>99</sub>**

18 The HEC<sub>99</sub> and HED<sub>99</sub> are the lower 99<sup>th</sup> percentiles for the continuous human exposure  
19 concentration and continuous human ingestion dose that lead to a human internal dose equal to  
20 the rodent idPOD. The derivation of the HEC<sub>99</sub> of 0.50 ppm and HED<sub>99</sub> of 0.30 mg/kg/d for the

1 99<sup>th</sup> percentile for uncertainty and variability are shown in Figure F-12. These values are used as  
2 this critical effect's POD to which additional UFs are applied.

3



4

5

6 **Figure F-12. Derivation of HEC<sub>99</sub> and HED<sub>99</sub> corresponding to the rodent**  
7 **idPOD from NTP (1988) toxic nephrosis in mice.**

8

9

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

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

14

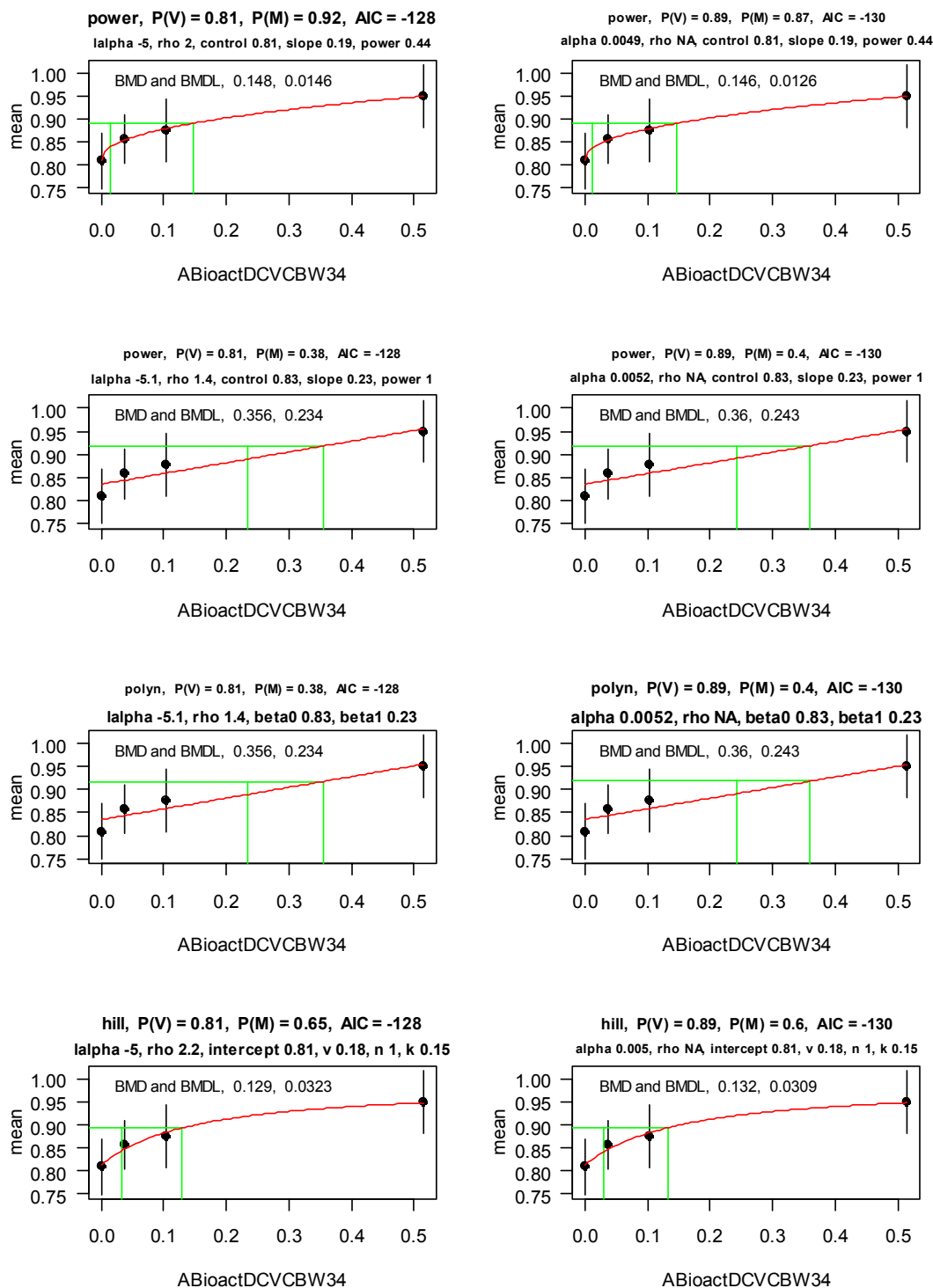
15 **F.6.3.1. Dosimetry and Benchmark Dose (BMD) Modeling**

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

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

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Woolhiser.etal.2006 Kidney kidney.wt.per100gm rat CD (Sprague-Dawley) F inhal (GRP 65)  
 BMR: 0.1 relative



1  
 2  
 3

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

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1 The idPOD of 0.0309 mg DCVC bioactivated/kg<sup>3/4</sup>/day was a BMDL for a BMR of 10%  
2 weight change, which is the BMR typically used by U.S. EPA for body weight and organ weight  
3 changes. The response used in each case was the organ weight as a percentage of body weight,  
4 to account for any commensurate decreases in body weight, although the results did not differ  
5 much when absolute weights were used instead.  
6

#### 7 **F.6.3.2. Derivation of HEC<sub>99</sub> and HED<sub>99</sub>**

8 The HEC<sub>99</sub> and HED<sub>99</sub> are the lower 99<sup>th</sup> percentiles for the continuous human exposure  
9 concentration and continuous human ingestion dose that lead to a human internal dose equal to  
10 the rodent idPOD. The derivation of the HEC<sub>99</sub> of 0.0131 ppm and HED<sub>99</sub> of 0.00791 mg/kg/d  
11 for the 99<sup>th</sup> percentile for uncertainty and variability are shown in Figure F-14. These values are  
12 used as this critical effect's POD to which additional UFs are applied.  
13

#### 14 **F.6.4. Keil et al. (2009)—Lowest-Observed-Adverse-Effect Level (LOAEL) for Decreased 15 Thymus Weight and Increased Anti-dsDNA and Anti-ssDNA Antibodies in Mice**

16 The critical endpoints here are decreased thymus weight and increased anti-dsDNA and  
17 anti-ssDNA antibodies in female B6C3F1 mice (Keil et al., 2009).  
18

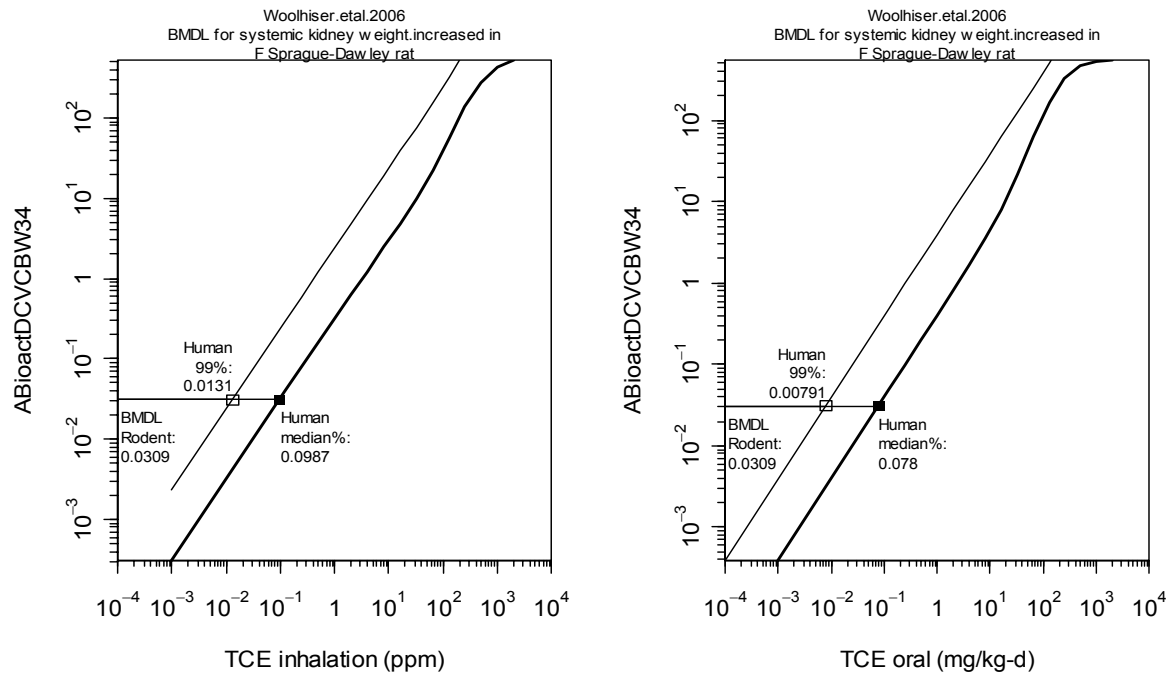
#### 19 **F.6.5. Keil et al. (2009)—Lowest-Observed-Adverse-Effect Level (LOAEL) for Decreased 20 Thymus Weight and Increased Anti-dsDNA and Anti-ssDNA Antibodies in Mice**

21 The critical endpoints here are decreased thymus weight and increased anti-dsDNA and  
22 anti-ssDNA antibodies in female B6C3F1 mice (Keil et al., 2009).  
23

#### 24 **F.6.5.1. Dosimetry**

25 Mice were exposed to 1400 and 14000 ppb of TCE in drinking water, with an average  
26 dose estimated by the authors to be 0.35 and 3.5 mg/kg/d, for 30 weeks. The dose-response  
27 relationships were sufficiently supralinear that BMD modeling failed to produce an adequate fit.  
28 The primary dose metric was selected to be the average amount of TCE metabolized/kg<sup>3/4</sup>/day.  
29 The lower dose group was the LOAEL for both effects, and the median estimate from the PBPK  
30 model at that exposure level was 0.139 mg TCE metabolized/kg<sup>3/4</sup>/day, which is used as the  
31 rodent idPOD.  
32





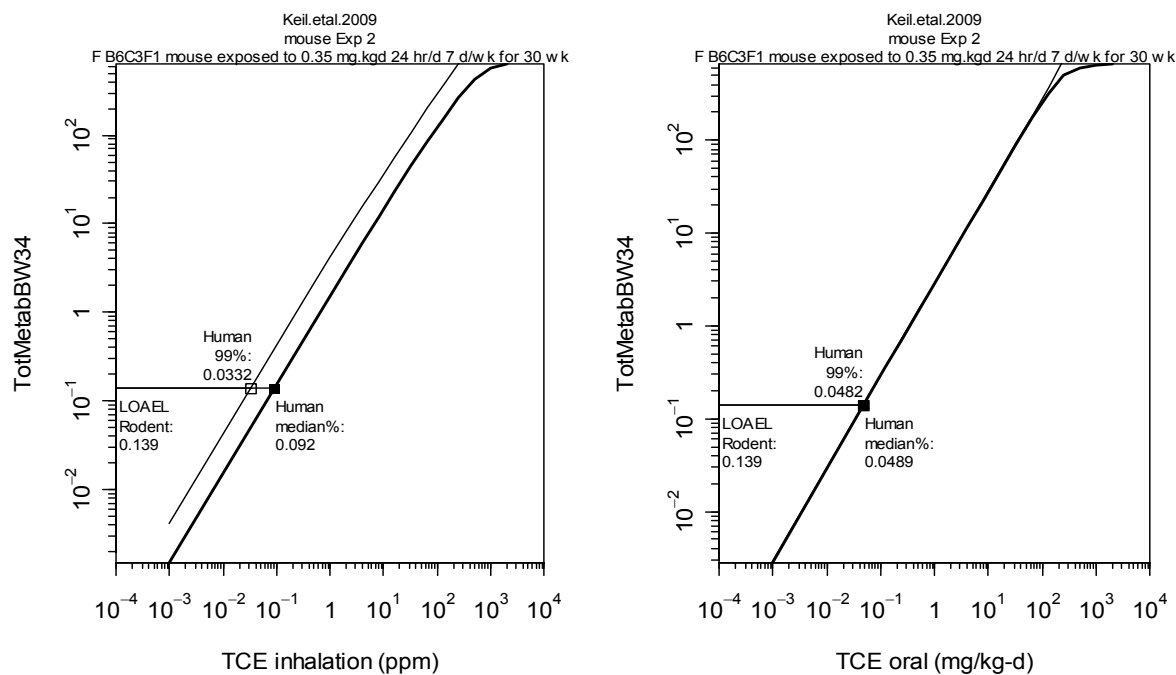
1  
2  
3 **Figure F-14. Derivation of HEC<sub>99</sub> and HED<sub>99</sub> corresponding to the rodent**  
4 **idPOD from Woolhiser et al. (2006) for increased kidney weight in rats.**  
5  
6

7 **F.6.5.2. Derivation of HEC<sub>99</sub> and HED<sub>99</sub>**

8 The HEC<sub>99</sub> and HED<sub>99</sub> are the lower 99<sup>th</sup> percentiles for the continuous human exposure  
9 concentration and continuous human ingestion dose that lead to a human internal dose equal to  
10 the rodent idPOD. The derivation of the HEC<sub>99</sub> of 0.0332 ppm and HED<sub>99</sub> of 0.0482 mg/kg/d for  
11 the 99<sup>th</sup> percentile for uncertainty and variability are shown in Figure F-15. These values are  
12 used as this critical effect's POD to which additional UFs are applied.  
13

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

16 The critical endpoint here is increased fetal heart malformations in female S-D rats  
17 (Johnson et al., 2003).  
18



1  
2  
3 **Figure F-15. Derivation of HEC<sub>99</sub> and HED<sub>99</sub> corresponding to the rodent**  
4 **idPOD from Keil et al. (2009) for decreased thymus weight and increased**  
5 **anti-dsDNA and anti-ssDNA antibodies in mice.**

6  
7  
8 **F.6.6.1. Dosimetry and Benchmark Dose (BMD) Modeling**

9 Rats were exposed to 2.5, 250, 1.5, or 1,100 ppm TCE in drinking water for 22 days  
10 (GD 1–22). The primary dose metric was selected to be average amount of TCE metabolized by  
11 oxidation/kg<sup>3/4</sup>/day, with median estimates from the PBPK model for this study of 0.00031, 0.033,  
12 0.15, and 88.

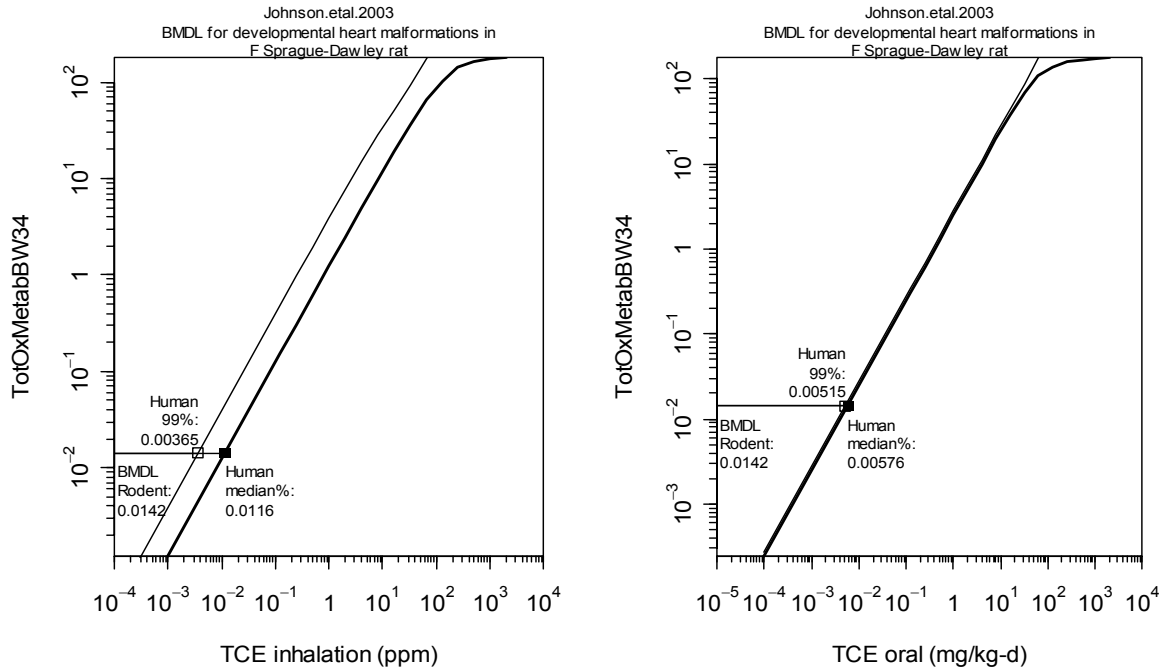
13 As discussed previously in Section F.4.2.1, from results of nested log-logistic modeling  
14 of these data, with the highest dose group dropped, the idPOD of 0.0142 mg TCE metabolized  
15 by oxidation/kg<sup>3/4</sup>/day was a BMDL for a BMR of 1% increased in incidence in pups. A 1%  
16 extra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

18  
19 **F.6.6.2. Derivation of HEC<sub>99</sub> and HED<sub>99</sub>**

20 The HEC<sub>99</sub> and HED<sub>99</sub> are the lower 99<sup>th</sup> percentiles for the continuous human exposure  
21 concentration and continuous human ingestion dose that lead to a human internal dose equal to  
22 the rodent idPOD. The derivation of the HEC<sub>99</sub> of 0.00365 ppm and HED<sub>99</sub> of 0.00515 mg/kg/d

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

3



4

5

6 **Figure F-16. Derivation of HEC<sub>99</sub> and HED<sub>99</sub> corresponding to the rodent**  
7 **idPOD from Johnson et al. (2003) for increased fetal cardiac malformations**  
8 **in female S-D rats using the total oxidative metabolism dose metric.**

9

10

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

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

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

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