Appendix T

Update to Ethylbenzene Toxicity Reference Values and Risk Values
February 2007

The previously provided (December 12, 2006) risk values for ethylbenzene were based on toxicity reference value derivations that utilized an unpublished version of the mouse PBPK model for ethylbenzene. That model has been updated based on new data (Saghir et al., 2006) and the manuscript revised, resubmitted, and accepted for publication (Nong et al., 2007).

The change in the mouse lung metabolism parameters caused changes in the internal dose estimates. Revised internal dose metrics were calculated for mouse data sets, and BMDS analyses conducted for male mouse lung cancer, male mouse liver noncancer effects, and female mouse liver cancer. The point of departure for derivation of the noncancer RfC (LED10 for liver effects in male mice) was essentially unchanged. The point of departure for the lung cancer RfC/RfD was increased by a factor of 2.7, indicating that the previous evaluation of lung cancer was conservative. The corresponding revised lung cancer RfC and RfD were 3.1 ppm and 4.3 mg/kg-day, respectively. These changes in toxicity reference value have no impact on the risk assessment and are not further discussed here.

The results for female mouse liver cancer benchmark dose analysis indicated a change in the “best fit” dose-response models. In the revised benchmark dose analysis, two dose-response models in BMDS (quantal quadratic--QQ and multistage--MS) were identical in the parameters used to identify the best fit (visual inspection, AIC value, p-value). Previously, QQ was identified as the "best fit" model, and the LED10 value based on this model was used to derive the cancer RfC/RfD. Since both models returned the same fit (the MS model reduces to a quadratic model when only the squared term is significant), they should have returned the same results. However, in the revised analysis, we noticed that the LED10 values for the QQ and MS models were different. We determined that EPA’s BMDS software did not incorporate all sources of error in the LED10 for the QQ model, thus the LED10 reported for the MS model is the appropriate point of departure for the RfC/RfD. This issue with the QQ model was not identified in the earlier analysis since it returned a believable LED10 value, and because at that time the QQ and MS models were not comparable in fit, so there was no need to question the QQ model results.

The point of departure in the revised analysis (LED10, in mg metabolized/kg liver per week) is ~2-fold lower than the previous point of departure (Figure T-1). Due to rounding, the net result is a change of ~3-fold in the cancer RfC and RfD (0.1 ppm and 0.07 mg/kg-day, respectively) and the resulting cancer HIs (Table T-1).

The only revised HIs greater than 1 are for the upperbound production worker, with a cancer HI of 3. The central tendency cancer HI for this group is 0.3. These HIs indicate that only the most highly-exposed prospective parents could potentially be considered at elevated risk for liver cancer from ethylbenzene. We believe the actual risk is minimal to nonexistent because of the lack of relevance of the mouse liver tumors to humans.

Upper-bound children's cancer HIs are 0.1 for bottle-fed and worker's breast fed infants. These HIs indicate that even the most highly-exposed children are not elevated risk for liver cancer from ethylbenzene.

Figure T-1. Fit of Multistage Model to Dose-Response Data for Liver Tumors in Female Mice

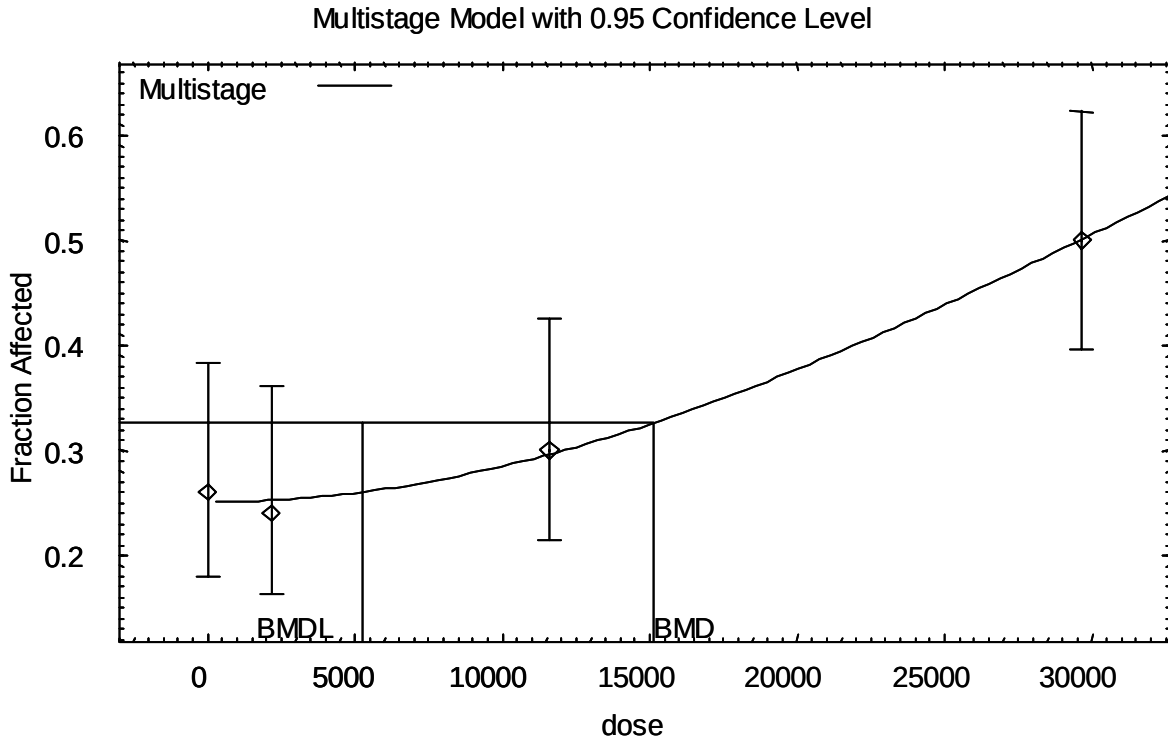

Table T-1. Revised Ethylbenzene Cancer Hazard Characterization

Scenario	Assessment	Route	<1 year (Bottle-fed)	<1 year (Breastfed)	Worker's Child (Breastfed)	1-2 years	3-5 years	6-8 years	9-14 years	15-19 years	At-Home Parent	Office Worker	Production Worker
Urban, Smoking	Central Tendency	Inhalation	4E-02	4E-02	4E-02	4E-02	3E-02	2E-02	2E-02	1E-02	2E-02	1E-02	3E-01
Intake		Oral	1E-02	5E-03	7E-03	9E-03	5E-03	3E-03	1E-03	1E-03	1E-03	1E-03	1E-03
		Total	5E-02	4E-02	4E-02	5E-02	3E-02	3E-02	2E-02	1E-02	2E-02	1E-02	3E-01
	Upper Bound	Inhalation	8E-02	8E-02	8E-02	8E-02	7E-02	5E-02	4E-02	3E-02	4E-02	3E-02	3E+00
		Oral	2E-02	8E-03	3E-02	2E-02	1E-02	7E-03	3E-03	3E-03	2E-03	2E-03	2E-03
		Total	1E-01	9E-02	1E-01	1E-01	8E-02	6E-02	4E-02	3E-02	4E-02	3E-02	3E+00
Urban, Non-Smoking	Central Tendency	Inhalation	3E-02	3E-02	3E-02	3E-02	2E-02	2E-02	1E-02	9E-03	1E-02	9E-03	3E-01
		Oral	1E-02	5E-03	7E-03	9E-03	5E-03	3E-03	1E-03	1E-03	1E-03	1E-03	1E-03
		Total	4E-02	3E-02	3E-02	3E-02	3E-02	2E-02	1E-02	1E-02	1E-02	1E-02	3E-01
	Upper Bound	Inhalation	6E-02	6E-02	6E-02	6E-02	5E-02	4E-02	3E-02	2E-02	2E-02	2E-02	3E+00
		Oral	2E-02	8E-03	3E-02	2E-02	1E-02	7E-03	3E-03	3E-03	2E-03	2E-03	2E-03
		Total	8E-02	6E-02	9E-02	7E-02	6E-02	4E-02	3E-02	2E-02	3E-02	2E-02	3E+00
Rural/Suburban, Smoking	Central Tendency	Inhalation	2E-02	2E-02	2E-02	2E-02	2E-02	1E-02	1E-02	7E-03	9E-03	8E-03	3E-01
		Oral	1E-02	5E-03	7E-03	9E-03	5E-03	3E-03	1E-03	1E-03	1E-03	1E-03	1E-03
		Total	3E-02	2E-02	3E-02	3E-02	2E-02	2E-02	1E-02	9E-03	1E-02	9E-03	3E-01
	Upper Bound	Inhalation	5E-02	5E-02	5E-02	5E-02	4E-02	3E-02	3E-02	2E-02	2E-02	2E-02	3E+00
		Oral	2E-02	8E-03	3E-02	2E-02	1E-02	7E-03	3E-03	3E-03	2E-03	2E-03	2E-03
		Total	7E-02	6E-02	9E-02	7E-02	5E-02	4E-02	3E-02	2E-02	2E-02	2E-02	3E+00
Rural/Suburban, Non-Smoking	Central Tendency	Inhalation	1E-02	1E-02	1E-02	1E-02	1E-02	9E-03	7E-03	5E-03	6E-03	5E-03	3E-01
		Oral	1E-02	5E-03	7E-03	9E-03	5E-03	3E-03	1E-03	1E-03	1E-03	1E-03	1E-03
		Total	3E-02	2E-02	2E-02	2E-02	2E-02	1E-02	8E-03	7E-03	7E-03	6E-03	3E-01
	Upper Bound	Inhalation	4E-02	4E-02	4E-02	4E-02	3E-02	2E-02	2E-02	1E-02	1E-02	1E-02	3E+00
		Oral	2E-02	8E-03	3E-02	2E-02	1E-02	7E-03	3E-03	3E-03	2E-03	2E-03	2E-03
		Total	6E-02	4E-02	7E-02	5E-02	4E-02	3E-02	2E-02	2E-02	2E-02	2E-02	3E+00