

BMDs to use for determining the point of departure must be made by the risk assessor using scientific judgement and principles of risk assessment, as well as the results of the modeling process.

Toxicological Evaluation for AEL Derivation. Benchmark dose modeling was conducted following EPA guidelines. EPA modeled six data sets for liver vacuolation and reduced sperm motility based on results from two studies to identify the lowest BMDL as a point of departure (POD).⁷ EPA selected these endpoints for BMD analysis because they were consistently found to be the most sensitive effect across the many studies that were conducted on the compound. Further, these particular studies provided robust data on these endpoints so that BMD analysis could be conducted. Based on this analysis, sperm motility in the F1 males from the WIL (2001) study was selected as the POD as it would be protective for all effects of nPB. SLR conducted a BMD analysis using data sets for numerous endpoints from 5 studies, including the WIL (2000) and ClinTrials (1997b) studies used by EPA (SLR International Corp., 2001b).⁸ SLR also identified sperm motility in F1 males from the WIL (2001) study as the lowest BMDL. The SLR BMD analysis is discussed further in section IV.A.1.d. The methods used in development of the AEL based on sperm motility are described below. It is important to note that the animals in the 2-generation study were dosed every day for six hours. As such, the dosing scenario used for the testing procedure does not exactly mirror the human exposure scenario in the workplace of 8 hours per day 5 days per week. However, it is still appropriate to consider the data because they address the most sensitive health endpoints, and because the BMDL is adjusted by deriving a HEC to account for workplace exposures. A more complete discussion of EPA's

adjustment of the BMDL is contained in ICF, 2002a.

EPA did not use neurotoxic effects as endpoints for deriving an AEL value since we did not consider this to be one of the most sensitive endpoints. No neurotoxic effects were reported in the 2-generation reproductive toxicity assay (WIL, 2001), and no adverse effects were observed in the functional observational battery analysis, either in an abbreviated form in the 28-day study at exposure concentrations of 400 and 1,000 ppm (ClinTrials, 1997a), nor in the 90-day study at concentrations of 400 and 600 ppm (ClinTrials, 1997b). Although the NIOSH voluntary medical survey performed in 1999 attempted to assess symptoms of neurotoxic effects, no exposure-response trend for headache or other neurological effects could be identified from the data.

The vacuolation of the white brain matter that was observed in the 28-day study at all exposure concentrations was not observed in the 90-day study, indicating that this effect may be a transient response and not adverse. Further, the vacuolation was not dose-dependent and did not correlate with other gross CNS effects observed at 1,600 ppm in the 28-day study. In the 2-generation study, clinical signs were monitored and CNS effects were not observed at any exposure concentration (0, 100, 250, 500, and 750 ppm) in the F0 or F1 animals, nor were histopathologic lesions observed in the brain, spinal cord or peripheral (sciatic) nerve of rats in the 750-ppm group of the F0 generation in the 2-generation study or in the F1 population.

EPA's Benchmark Dose Software (BMDS) was used for model fitting and BMD and BMDL estimation. To derive a BMD and BMDL for reduced sperm motility in the F0 and F1 males from WIL (2001), the data were modeled as continuous effects. Following EPA's Benchmark Dose guidelines, BMDs and BMDLs were defined based on benchmark responses (BMRs) of 10% extra risk—that is, the level at which 10% of the animals would show adverse effects for a particular endpoint. BMDLs were defined as the 95% lower confidence bound on the corresponding BMD estimates. Confidence bounds were calculated by BMDS using a likelihood profile method. The data sets for the reduced sperm motility endpoint were quantitatively summarized by group means and measures of variability (standard errors or standard deviations). The models used to represent the dose-response behavior of these continuous endpoints are those implemented in EPA's Benchmark Dose Software which are the Power model, the Hill model,

and the polynomial model. Goodness-of-fit for each model for a given data set was determined based on a likelihood ratio statistic. In particular, maximized log-likelihoods associated with the modeling were sequentially compared.

Based on the criteria below, the most appropriate mathematical model and its corresponding BMDL was chosen as the best fit for each of the data sets modeled:

1. Models with an unacceptable fit (including consideration of local fit in the low-dose region) were excluded. Visual fit, particularly in the low-dose region, was assessed for models that had acceptable global goodness-of-fit.

2. If the BMDL values for the remaining models for a given endpoint were within a factor of 3, no model dependence was assumed, and the models were considered indistinguishable in the context of the precision of the methods. The models were then ranked according to the Akaike Information Criterion (AIC), which is reported by the BMDS software to aid in comparing the fit of different models. The model with the lowest AIC (within the family of models) was chosen as the basis for the BMDL.

3. If the BMDL values were not within a factor of 3, some model dependence was assumed, and the lowest BMDL was selected as a reasonable conservative estimate, unless it was an outlier compared to the results from all of the other models. Note that when outliers are removed, the remaining BMDLs may then be within a factor of 3, and so the criteria given in item 2 would be applied.

BMDs for reduced sperm motility in F1 and F0 males were 276 ppm and 362 ppm respectively, and BMDLs were 169 ppm and 282 ppm. Consistent with EPA risk assessment guidance, the BMDL of 169 ppm for reduced sperm motility in F1 males (WIL, 2001) was selected as the POD. EPA considered whether a BMDL derived from the F1 generation should be used to determine a workplace exposure limit, particularly in relation to the potential mechanisms by which nPB exerts its effects on the reproductive system. While some mechanistic data are available on this subject, they are inconclusive and limited. The available data do not rule out the possibility that the effects on the F1 generation occurred as a result of effects on parental germ cells (sperm or ova) or effects mediated by changes to the endocrine system. Because of the lack of mechanistic data on developmental and potential transgenerational effects, it is most appropriate and protective, as well as consistent with EPA risk assessment

⁷ Data sets that were modeled from the WIL study include sperm motility and liver vacuolation in the F0 and F1 generations. Data sets modeled from ClinTrials (1997b) were liver vacuolation in both males and females.

⁸ SLR International Corp. (2001b) conducted BMD modeling on the following studies: ClinTrials (1997a), ClinTrials (1997b), Ichihara, *et al.* (2000a and b), and WIL (2001). Reproductive endpoints modeled included sperm count, retained sperm in seminiferous tubules, sperm deformities, sperm motility, epididymal sperm count, fertility index, litter viability, and plasma glucose levels. Other toxicological endpoints modeled included forelimb strength, hind limb strength, motor conduction velocity, distal latency time, plasma creatinine phosphokinase levels, brain cell vacuolation, liver vacuolation in males, and analysis in various parameters associated with effects on blood formation.