

data from the two-generation reproductive study (WIL, 2001). In the fall of 2000, Albemarle analyzed preliminary data from the two highest exposure groups in two-generation study, 750 ppm and 500 ppm, and found evidence of reproductive effects. As a proactive measure while completing analysis of the data, Albemarle started with an exposure level of 250 ppm and divided by a safety factor of 10, yielding an exposure guideline of 25 ppm. EPA has not seen the derivation of Great Lakes Chemical Corporation's workplace exposure guideline of 10 ppm or Atofina's guideline of 5 ppm.

The AEL recommended by Enviro Tech International is based on two separate analyses. In the first analysis, Rozman and Doull (2001) recommend an AEL of 60–90 ppm based on the results obtained from a health questionnaire administered as a part of a NIOSH Health Hazard Evaluation at a site where nPB is used as an adhesive (NIOSH, 1999). This AEL derivation was subsequently published in *Applied Occupational Environmental Hygiene*, the ACGIH's journal, in 2002 (Rozman and Doull, 2002).

In their analysis, Rozman and Doull identified the most sensitive endpoint for nPB toxicity as peripheral/central neurotoxicity followed by reproductive toxicity and then liver toxicity. This ranking was based on a subchronic inhalation study by Ichihara (2000b) in which decreased hind limb strength in mice was observed following 4 weeks of exposure at 200 ppm. Rozman and Doull concluded that rats are more sensitive to reproductive effects of nPB than humans based on the NIOSH health survey (NIOSH 2002b), which did not identify any statistically significant reproductive effects in humans exposed to nPB. Based on the NIOSH health survey data, conducted at a facility where nPB was used as an adhesive solvent, Rozman and Doull identified 170 ppm as a no observed effect level (NOEL) in workers who reported having a headache more than once per week. They then applied a safety of 2 to protect nearly all workers, and a safety factor of 3 to provide a larger margin of safety from this adverse effect. This approach resulted in a recommended industrial exposure guideline for nPB of 60–90 ppm.

EPA does not agree with Rozman and Doull's AEL recommendation. First, their ranking of neurotoxicity as the most sensitive toxicological endpoint fails to take into account that in the Ichihara study, rats were dosed 8 hours per day for 12 weeks, while in the two-generation study, animals were exposed

to nPB for 6 hours per day. Therefore, the exposure levels in the Ichihara study must be adjusted by a factor of 0.75 in order to directly compare doses to the 2 generation study. If this adjustment is made, the LOAEL for the Ichihara study becomes 266 ppm, higher than the LOAEL of 250 ppm for reproductive and liver effects identified in the two-generation study. Further, the results of the Ichihara study conflict with the results of the 90-day inhalation study (ClinTrials, 1997b), in which decreases in grip strength were not observed in rats exposed to levels up to 600 ppm nPB for 6 hours/day for 5 days/week. In fact, in the ClinTrials study, there were no consistent treatment-related changes reported in the rats following 4, 8, or 13 weeks of exposure in any parameter evaluated in a full functional observational battery (a suite of tests designed to assess a full spectrum of neurotoxic effects). Because the LOAEL for neurotoxic effects in Ichihara *et al.* (2000b) is actually higher than the LOAEL identified in the two-generation study, and because the findings on neurotoxicity from the Ichihara study conflict with the results of the 90-day ClinTrials (1997b) study, it is erroneous to conclude that neurotoxicity is the most sensitive endpoint for nPB exposure.

Second, the NIOSH medical survey used by Rozman and Doull is not a suitable basis for deriving an AEL. Use of epidemiological data for a quantitative risk assessment requires that the exposures be well-characterized, that the sample size be large enough to allow for the detection of subtle effects in a statistically significant way, and that comparisons to an unexposed control group be made. The data provided in the NIOSH evaluation do not fit these criteria: (1) The sample size in this study was relatively small (46 participants); (2) the health survey was not given to an unexposed control population for comparison; (3) no obvious exposure-response trend for headache was seen, since the low and medium exposure groups had similar prevalence of headache. For each of the neurological symptoms evaluated in the NIOSH health survey, air concentrations of nPB were not statistically different between those employees reporting the symptom compared to those not reporting the symptom (NIOSH 2002).

Finally, EPA disagrees with Rozman and Doull's conclusion that reproductive toxicity did not occur in workers exposed to up to 190 ppm of nPB, which is the basis for their assertion that humans are less sensitive to reproductive health effects of nPB

compared to rats (Rozman and Doull, 2001). The NIOSH report states that 3 workers (2 male and 1 female) who had been exposed to between 110 and 157 ppm of nPB reported difficulty in having a child. However, as noted by the authors of the NIOSH report, due to the small sample size and the personal nature of the questions, there were significant limitations in the ability of the NIOSH medical survey to detect reproductive or fertility problems. The data from the NIOSH medical survey should not be used to conclude that rats are more sensitive than humans to reproductive effects of nPB, or to draw any general conclusions regarding the potential reproductive toxicity of nPB in humans.

In the second analysis submitted by Enviro Tech, SLR International Corporation derived an AEL for nPB of 156 ppm (SLR International, 2001b). We understand that this derivation is currently undergoing peer review for potential publication in a scientific journal. This analysis used benchmark dose-response modeling using data sets for several effects taken from the various animal toxicity tests that have been conducted with nPB. SLR derived a BMDL at a 10% response level of 156 ppm, based on reduced sperm motility in F1 males from the WIL (2001) study. This BMDL is similar to EPA's BMDL for sperm motility of 169 ppm. SLR stated that "Due to the relative completeness of the toxicological database on nPB, including data on human *in vitro* bioassays, use of a UF is likely not considered necessary for this chemical." Thus, SLR's recommended AEL is equivalent to their BMDL. EPA maintains that an uncertainty factor is necessary for protection of sensitive individuals since low sperm count is a condition that can occur in otherwise healthy workers. There are no data indicating that human sperm are less sensitive than rat sperm. In fact, sperm production is less efficient in humans, suggesting that human males are likely to be more susceptible than rats to nPB (Amann, 1986). Further, based on EPA's RfC guidelines, an uncertainty factor of 3 is necessary to account for interspecies differences in pharmacodynamics between rats and humans. Had SLR applied what EPA considers appropriate uncertainty factors, their recommended AEL would have been 17 ppm.

In a memorandum submitted to Poly Systems International, Joel Charm, a certified industrial hygienist, supported the analyses by both SLR and Rozman and Doull. Mr. Charm suggested that establishing an occupational exposure level of 100 ppm as a ceiling value (i.e.,