

disrupting chemicals, it is reasonable to conclude that the effects of [nPB] are elicited in both sexes via their exposure as adults." They also noted that "the modest degree of change in the 250 ppm F1 sperm motility endpoint (and lack of significance in the F0 at this dose) compared to the collective more robust changes at 500 ppm, in both the F0 and F1, indicates that 250 ppm could reasonably be considered a NOAEL for nPB, with 500 ppm being a LOAEL." Finally, ORD noted that "even if the F1 data may not be directly applicable for occupational exposures in males, it certainly is applicable to occupational exposures of pregnant women." They conclude with suggestions for further research (Klinefelter and Darney, 2002).

EPA asked William Brock to review the draft AEL report from a general toxicological point of view. Dr. Brock is currently a senior manager with Environ Corporation. In his review, Dr. Brock noted that several subchronic studies in rats have been conducted with nPB with concentrations ranging from approximately 100 ppm to 1800 ppm. Biological effects have been on liver, male reproductive tissue, and, to some extent, hematological parameters. Although some of the studies have not been conducted according to GLP, this fact does not necessarily limit the usefulness of the studies to recommend an exposure limit. Overall, the sperm effect observed at 400 ppm and the effects on fertility at 500 ppm with hepatic vacuolation at 250 represent the PODs for setting exposure limits for nPB. The NOAEL for these effects would be 200 ppm. Dr. Brock notes that "exposure limits that have historically been established are generally, but not always, an order of magnitude below the NOAEL. Taking this approach would result in an occupational limit of 20 ppm (200/10). Although the ICF report could be improved by being more specific on effects and concentrations, the logic provided in the report and the end result, *i.e.*, a 25 ppm exposure limit, is certainly justified" (Brock, 2002).

EPA asked Darol Dodd to review and comment on the draft AEL report (ICF, 2000a). Dr. Dodd is currently the Laboratory Director for ManTech Environmental Technology, Inc. In his comments, Dr. Dodd stated that the ICF report provided logical and consistent explanations for selection of the BMDL and uncertainty factors. He noted that several of the studies show LOAEL or NOAEL values at 200 ppm to 250 ppm. In his opinion, "a recommended AEL value that is about one order of magnitude lower than LOAELs/NOAELs in a number of laboratory rodent studies

does not appear to be overly protective" (Dodd, 2002).

HESIS provided comments on the AEL derivation for nPB that focused on the available studies useful for low-dose risk assessment, identifying the LOAELs and NOAELs from these studies, and identifying their disagreements with the ICF evaluation. Overall, HESIS took issue with the approach used by ICF to derive an AEL: "ICF repeatedly ignores or discounts effects seen with low-level exposures. At most points where a decision based on professional judgment must be made, ICF makes the choice that leads to the highest possible AEL." HESIS states that, contrary to the ICF approach, an appropriate risk assessment methodology would take a NOAEL, LOAEL or appropriate BMDL, and apply uncertainty factors of 10 for each of the following conditions: (1) Interspecies variation, (2) intraspecies variation, (3) reliance on a LOAEL rather than a NOAEL where necessary, and (4) extrapolation from acute or subchronic exposure to chronic exposure. The total uncertainty factor would be between 1,000 and 10,000. HESIS stated that appropriate endpoints and points of departure would be reduced pup weight seen in the Huntingdon (2001) study at 103 ppm, the neurotoxicity seen in Ichihara (2000a) at 200 ppm, reduced seminal vesicle weight and increase in tailless sperm seen at 200 ppm in Ichihara (2001a), reduced sperm motility at 200 ppm in Wang (1999), CNS pathology (vacuolation of white matter) at 400 ppm seen in ClinTrials (1997a), and from the WIL (2001) study, reduced fertility observed at 100 ppm and other adverse reproductive and kidney effects observed at 250 ppm or the lowest BMDL calculated from all studies. Using any of these points of departure, HESIS suggests that a reasonable AEL could range from less than 0.05 ppm to less than 5 ppm, and recommends an AEL of 1 ppm.

HESIS stated that, in deriving the AEL for the liver vacuolation, ICF used no uncertainty factor for interspecies pharmacokinetic variation, assuming "without any basis, that gas exchange within the lung constitutes the entire pharmacokinetic variation between the species, simply because the blood-air partition coefficient is lower in humans than in rats." HESIS also disagreed with the use of no uncertainty factor for intraspecies variation for liver vacuolation. With regard to ICF's derivation of an AEL for sperm motility, HESIS disagreed with ICF's use of no uncertainty factor for interspecies pharmacokinetic variation for the same reason given for liver vacuolation.

HESIS also stated that there "is no data base at all on which to determine the likelihood and degree of interhuman variability in sensitivity to the spermatotoxic effect of [nPB] \* \* \* ." Finally, HESIS stated that nPB "is an organic solvent that is probably well absorbed through the skin and should be listed with a skin notation \* \* \* ."

A response from ICF Consultants to HESIS's comments is included in the docket (ICF 2002c). EPA concluded that the issues HESIS raises are, in fact, questioning EPA's risk assessment guidelines that were the basis for the AEL report, rather than comments unique to the AEL for nPB. For example, EPA's risk assessment guidelines allow use of a default uncertainty factor of 1 instead of 3 for pharmacokinetics for nPB and other inhaled gases where the toxicity is from the parent compound, rather than metabolites. As discussed above in section IV.A.1.b, we request comment and data that would confirm or refute the appropriateness of the assumptions in Appendix J of EPA's risk assessment guidelines. In addition, EPA disagrees that the uncertainty factor for variability in the worker population should be the same as that for variability in the general population (10). Because the working population does not include children or the elderly, as is the case for the general population, we do not believe that a full UF of 10 for sensitive subpopulations is necessary. Further, workers are only potentially exposed during a 40-hour workweek and not continuously, as would be expected for the general population. Finally, because of the length of the WIL Laboratories study, we do not believe that it is necessary to add an uncertainty factor to extrapolate from subchronic to chronic exposures.

Various chemical manufacturers and solvent formulators have derived their own recommended industrial exposure limits. Albemarle Corporation and Dead Sea Bromine Group, both of whom continue to produce nPB, recommend an AEL of 25 ppm in their Material Data Safety Sheets. Great Lakes Chemical and Atofina recommended AELs of 10 ppm and 5 ppm respectively, although neither of these companies currently sells nPB. Petroferm produces nPB formulations and recommends an exposure limit of 25 ppm. Finally, Enviro Tech International, Poly Systems International, TULSTAR Products, and Amity International, all of whom produce nPB formulations, recommend an exposure limit of 100 ppm.

In a November 6, 2000, meeting with EPA, Albemarle explained that its derivation of a workplace exposure guideline of 25 ppm is based upon raw