

NOAEL of 100 ppm was identified based on decreases in prostate weight observed at 250 ppm in WIL (2001).

- A LOAEL of 250 ppm, and a NOAEL of 100 ppm for female reproduction based on increased estrous cycle length in WIL (2001).

- A LOAEL of 250 ppm and a NOAEL of 100 ppm for mineralization of the kidney pelvis in both F0 and F1 generations, based on WIL (2001).

EPA agrees with the panel's conclusions that the available human data are insufficient to draw conclusions on the reproductive or developmental toxicity of nPB and that the mechanisms that lead to reproductive or developmental toxicity are unknown. EPA also agrees with the panel that a NOAEL for reproductive effects (male) would be considered to be 100 ppm under a traditional risk assessment analysis. However, based on the criteria described previously for selecting endpoints for BMDL analysis, we believe the CERHR endpoints are not appropriate for developing the AEL for nPB, as explained below.

Reduced seminal vesicle weight. EPA did not conduct BMD analysis for reduced seminal vesicle weight observed in the Ichihara (2000b) study because there is no consistency of effect across available studies for this endpoint. Reduced seminal vesicle weight was not found to be a sensitive endpoint in WIL (2001). In fact, a statistically significant reduction in seminal vesicle weight was only seen in the 750 ppm group in the F0 generation, and there were no statistically significant effects on seminal vesicle weight in the F1 generation. Because there were other endpoints that were more sensitive in the WIL study, we regard those endpoints to be of greater toxicological importance. Further, EPA believes that because the Ichihara study was not performed according to GLP guidelines, and there were conflicting reports regarding the exposure regime and the number of animals used, it is not appropriate to use this study in quantitative risk assessment.

Reduced absolute prostate weight. Based on the WIL study, the CERHR Expert Panel identified a NOAEL of 100 (with a LOAEL of 250) for reduced absolute prostate weight in the F0 males. The toxicological relevance of absolute prostate weight reduction is questionable since this endpoint may be associated with reduction in overall weight gain. To assess the significance of this particular endpoint, EPA calculated the mean relative prostate weights for exposed dose groups from the WIL (2001) study. Relative prostate weights (organ weight/body weight) in

F0 males were 0.0040, 0.0039, 0.0036, 0.0035, and 0.0035 at 0, 100, 250, 500, and 750 ppm respectively, revealing that relative prostate weight at exposures greater than or equal to 250 ppm decreased only 10% relative to controls. Because the dose-response relationship in other endpoints was more pronounced, EPA did not conduct BMD modeling on this endpoint.

Increased estrous cycle length. The Expert Panel identified 250 ppm as a LOAEL for females based on increased estrous cycle length in the F1 generation of the WIL (2001) study. EPA agrees that the slight increase in estrous cycle length may be a result of nPB exposure. However, because the estrous cycle length of 4.9 days at 250 ppm is within the range of historical controls, the effect cannot be conclusively attributed to exposure without statistical analysis. The study report also notes lack of cycling in some females, which may have caused difficulty in accurately determining the average estrous cycle length for each affected group. Because these data are lacking, this endpoint should not be used for developing the AEL.

Mineralization of the kidney pelvis. The Expert Panel concluded that mineralization of the pelvis of the kidneys at 250 ppm was an adverse effect. EPA notes that mineralization of the kidney was not consistently associated with nPB exposure across different studies, and that in WIL (2001) the severity of mineralization did not increase above a category of minimal except at 750 ppm where it was mild. Therefore, EPA did not consider using this endpoint as useful for developing the AEL.

Sperm Motility. The Expert Panel identified 500 ppm as the LOAEL for reduced sperm motility. The Panel agreed with the WIL (2001) study authors that the slight but statistically significant reduction in the percentage of motile sperm in the F1 males at 250 ppm (85% vs. 89% in concurrent control animals) could not be attributed to nPB exposure since the percentage of motile sperm in this dose group slightly exceeded that of historic controls (83%). The data indicate that the small changes observed at 250 ppm are consistent with larger changes in sperm motility observed at 500 and 750 ppm. Thus, results for sperm motility in F0 and F1 males exhibited dose-related trends, and conformed to other principles for the selection of endpoints for BMD analysis (See earlier discussion in section IV.A.1.b.). Thus, regardless of whether a LOAEL of 500 ppm or 250 ppm is assigned to this particular endpoint, the Agency determined that reduction in

the percentage of motile sperm in the F1 males is a good candidate for BMD analysis. In addition, it is important to note that the Panel did not have access to either the ICF or SLR International benchmark dose analyses. As discussed in section IV.A.1.b, benchmark dose modeling overcomes the issue of drawing a "bright line" in the form of a LOAEL or NOAEL and instead uses the full set of data across all exposure levels (ICF, Inc., 2002a; SLR International, 2001b). Using the results of benchmark dose modeling, it becomes clear that sperm motility is a sensitive effect, and is an appropriate effect upon which to base an AEL.

d. AELs suggested by other reviewers and outside parties. In the draft final nPB risk screen conducted for EPA in preparation for today's proposal, ICF Consulting states that "Given the strength of the data base and the extrapolation of the data to occupational exposures, a range of uncertainty factors to account for variability in the human population of 2 to 3 is considered appropriate." (ICF, 2002a). EPA recognizes that the choice of UF relates to a wide range of considerations including the strength of the data base. Applying a range of UFs between 2 and 3 to account for intrahuman variability would yield a range of occupational exposure limits between 18 and 30 ppm. ICF suggested that the midpoint of this range, 25 ppm, was an appropriate occupational limit value for the purposes of the risk screen for nPB. EPA requests comment on this recommended approach in deriving an occupational exposure limit, including the application of uncertainty factors.

EPA's Office of Atmospheric Programs solicited comments regarding ICF Consulting's analysis and derivation of a recommended AEL from EPA's Office of Research and Development (ORD), external toxicologist William Brock, external toxicologist Darol Dodd, and the State of California, Department of Health Services, Hazard Evaluation System & Information Service (HESIS). The comments are available in docket A-2001-07.

ORD's comments focused on the WIL Research Laboratories two-generation study and its use in identifying sensitive endpoints. ORD noted that the study's results indicated dose-related trends, that a number of endpoints were significantly affected at 500 ppm in both generations, and there were slight—though in most cases not statistically significant—decreases at 250 ppm and even 100 ppm for some endpoints. They also stated that "[i]n the absence of evidence of dominant lethality or trans-generational effects typical of endocrine