

guidelines, to use the endpoint observed at the lowest effect level to derive the AEL. In this case, that endpoint is decreased sperm motility in the F1 generation.

The BMDL was multiplied by 6/8 and 7/5 in order to derive the HEC, which accounts for temporal differences between the exposure duration used in the study (6 hours per day, 7 days per week) and an 8-hour per day, 5-day work week. This results in a HEC for spermatogenic effects of 177 ppm.

Uncertainty factors were then applied to the HEC, taking into account the following considerations listed below.

(1) An uncertainty factor is needed to account for physiological differences between humans and rats. EPA reference concentration (RfC) guidelines describe the factors that must be considered and state that an uncertainty factor 10 may be used for potential differences between study animals and humans. This factor of 10 is often thought to consist of two uncertainty factors of 3—the first to account for differences in pharmacokinetics⁹ and another uncertainty factor to account for differences in pharmacodynamics¹⁰ between the study animal and humans. (The value of 3 is the closest whole number to the square root of 10.) According to EPA RfC guidelines, no adjustment for differences in pharmacokinetics is necessary in this case since the blood/air partition coefficient¹¹ for nPB in the human (7.1) is less than in the rat (11.7), indicating that the delivered dose of nPB into the bloodstream in rats is slightly higher than in humans.

However, EPA recognizes that the lack of an uncertainty adjustment for pharmacokinetic differences between animals and humans rests on a default approach applied to category 3 gases described in Appendix J of its guidelines for deriving an inhalation RfC. This default approach assumes that the pharmacokinetics of nPB conform to a model that requires several assumptions, in particular: (1) The toxicity is directly related to the inhaled parent compound in the arterial blood, and (2) the critical metabolic pathways scale across species, with respect to body weight, in the same way as the ventilation rate (e.g., BW^{3/4}). Given the hypothesized metabolic pathways for

nPB (ICF, 2002a; CERHR, 2002a), it is plausible that toxicity in rats may be related to a reactive metabolite in the target tissue rather than the blood level of the parent compound. EPA is not aware of any quantitative data on nPB metabolism in humans, or evidence implicating the biologically active agent or mode of action. EPA requests additional data and comment from the public on nPB pharmacokinetics, metabolism, and mode of action that will help determine whether an interspecies uncertainty factor greater than 1 is appropriate to account for pharmacokinetics. If data become available indicating that nPB does not conform to the constraints assumed by the default pharmacokinetic model in the RfC guidelines, EPA would refine its risk assessment for nPB as necessary, and apply an uncertainty factor for pharmacokinetics in extrapolating from animal to humans. We would also revise our acceptability determinations accordingly.

With regard to the UF for pharmacodynamics, no data exist to compare the effect of nPB on human spermatocytes and rat spermatocytes. EPA does not have data suggesting that the default of 3 for pharmacodynamics should not be used. Thus, the full uncertainty factor of 3 for differences in pharmacodynamics was applied. EPA also requests comments and data on this uncertainty factor.

(2) Although workers employed in the types of industrial sectors that are part of this SNAP review likely represent a generally healthy population, pre-existing reproductive conditions as well as general variability in fertility would not impact a worker's overt health or employment status, and would be largely unobserved. It is estimated that 6% of adult males are infertile (Purves, 1992), and that 40%–90% of these cases are due to deficient sperm production of unidentifiable origin (Griffin, 1994). Given this information, EPA concludes that a significant portion of the male population has pre-existing reproductive deficits. EPA's risk guidelines for deriving community-based reference concentrations recommend a factor of 10 in accounting for intraspecies variability. EPA believes that in the case of nPB, a lower uncertainty factor is appropriate to account for variability within the worker population. This UF is intended to protect for potential "unobserved" reproductive medical conditions (e.g., decreased sperm motility, aberrant sperm formation) that are known to exist among otherwise healthy males of working age. Because we are concerned about exposures in the workplace, not

exposures to the full population, and because exposures would not be continuous, such as would be expected when developing an RfC, we employed an UF of three as an upper bound instead of the full uncertainty factor of 10 for intrahuman variability.

The following equation describes how EPA derives 18 ppm as a starting point in the development of a recommended AEL using a UF of 3 for variations in the human population, and 3 for pharmacodynamics:

$$169 \text{ ppm} * \frac{6}{8} * \frac{7}{5} * \frac{1}{3} * \frac{1}{3} = 18 \text{ ppm}$$

This derivation rests on assumptions that some may consider conservative, including the use of the F1 generation as the point of departure for workplace exposure, and the fact that reduced sperm motility may be a particularly sensitive endpoint for male reproductive effects. For a further discussion, see the next section below, "AEL adjustment based on risk management principles."

AEL adjustment based on risk management principles. Risk management uses risk characterization, along with directives of the enabling regulatory legislation and other factors, to decide whether to control exposure to the suspected agent and the level of control. Risk management decisions also consider socioeconomic, technical, and political factors (EPA Reproductive Risk Assessment Guidelines, 1996). Unlike many other chemicals being reviewed by SNAP, nPB is already in use. Therefore, a decision on the AEL that incorporates risk management considerations may be appropriate. Doing so is consistent with one of the original "Guiding Principles" of the SNAP program (59 FR 13046, March 18, 1994):

EPA does not intend to restrict a substitute if it poses only marginally greater risk than another substitute. Drawing fine distinctions concerning the acceptability of substitutes would be extremely difficult given the variability in how each substitute can be used within a specific application and the resulting uncertainties surrounding potential health and environmental effects. The Agency also does not want to intercede in the market's choice of available substitutes, unless a substitute has been proposed or is being used that is clearly more harmful to human health and the environment than other alternatives.

If EPA adopted 18 ppm as the AEL, we would likely propose that use of nPB be listed as unacceptable in adhesives applications, based on data indicating that exposure to nPB in such uses regularly exceed 18 ppm on average. However, EPA has determined that adhesive operations can meet an AEL of 25 ppm with proper ventilation and

⁹ Pharmacokinetics refers to the activity or fate of chemicals in the body, including the processes of absorption, distribution, localization in tissues, biotransformation, and excretion.

¹⁰ Pharmacodynamics refers to the biochemical and physiological effects of chemicals in the body and the mechanisms of their actions.

¹¹ A ratio of a chemical's concentration between blood and air when at equilibrium.