

studies and BMDLs for spermatoc effects and liver effects that were used in developing the AEL. Adjustments were made to account for continuous lifetime exposure and sensitive subpopulations. The lowest BMDL of 110 ppm was based on the incidence of liver effects (centrilobular vacuolation) in the two-generation reproductive study (WIL, 2001). Using EPA's dosimetry guidelines for a category 3 gas (US EPA, 1994), and making adjustments to account for continuous exposure, the human equivalent concentration (HEC) is $110 \text{ ppm} \times (6 \text{ hours}/24 \text{ hours}) = 27.5 \text{ ppm}$. No adjustment for differences in pharmacokinetics was necessary based on EPA's RfC guidelines. EPA applied an UF of 3 for extrapolation from rat to human pharmacodynamics. An additional factor of 10 was applied for intrahuman variability including the protection of sensitive subpopulations (e.g., individuals with liver disease, children, or the elderly). Therefore, the total uncertainty factor was 30 (3 for differences in pharmacodynamics, 10 for sensitive subpopulations). The application of the uncertainty factor of 30 to the HEC of 27.5 ppm results in a community exposure guideline of approximately 1 ppm. EPA requests comment on the appropriate use of uncertainty factors for the community exposure guideline.

The next lowest BMDL (169 ppm) was for the effects on sperm motility in the second generation of male rats in the two generation study. In the derivation of a community exposure guideline RfC for this endpoint, EPA adjusted the BMDL to account for continuous exposure averaged over 24 hours a day, resulting in an HEC of 42 ppm. An uncertainty factor of up to 10 may be applied for animals to human extrapolation in consideration of potential differences in pharmacokinetics and pharmacodynamics. However, for the reasons listed earlier, we did not consider an uncertainty factor necessary to account for differences in pharmacokinetics. The results of the in vitro studies conducted with liver cells do not allow us to draw any conclusions regarding the relative sensitivity of the human and rat spermatocyte to nPB. Consequently, EPA applied a factor of 3 for differences in pharmacodynamics. Finally, an uncertainty factor of 10 was applied for intrahuman variability including the protection of sensitive individuals in the general population (e.g., children whose sex organs are in development, pregnant women, and individuals with low fertility). An overall uncertainty factor of 30 results (3

for differences in pharmacodynamics, and 10 for the protection of sensitive individuals). The application of the overall uncertainty factor (30) to the HEC (42 ppm) results in a community exposure guideline an RfC of approximately 1 ppm. The estimated community exposure guideline values are identical for both liver and reproductive effects. Consequently, EPA estimated that a RfC community exposure guideline of 1 ppm would be protective for all health endpoints—that is, someone exposed to an average of 1 ppm of nPB, 24 hours of every day during a lifetime, would not be at appreciable risk for adverse health effects during their lifetime.

The next step was to determine whether people living close to sites where nPB is used in emissive applications could potentially be exposed to levels above the estimated RfC community exposure guideline of 1 ppm. Data collected from actual facilities (CCPCT, 2001) used to characterize two scenarios: (1) A typical large, high-use adhesive application facility where the closest resident is 100 meters away; and (2) a smaller facility with average-use adhesive application in an urban area, where the nearest resident is only 3 meters away.

EPA's SCREEN3 (US EPA, 1995a) air dispersion model was used to assess the likely maximum-potential concentration of nPB from single sources. This technique is typically used to evaluate air quality impacts of sources pursuant to the requirements of the Clean Air Act, such as New Source Review and air toxic regulations. The approach applied here was the initial-phase approach used to determine if either: (1) The source clearly poses no air quality problem or (2) the potential for an air quality problem exists. If a potential problem exists, then a more refined analysis is necessary.

The results from our screen indicated that modeled exposures in either scenario did not exceed the RfC of 1 ppm. The urban scenario where a facility uses fans to ventilate nPB horizontally (through windows or other openings in the walls as opposed to openings in the roof), modeled exposures of 0.24 ppm at a distance of 3 meters away from the source, 0.19 ppm at 5 meters from the source, and 0.13 ppm at 10 meters from the source. These levels were by far the highest concentrations of nPB exposures modeled. The majority of modeled exposures were at least an order of magnitude lower, and ranged from 0 ppm to 0.08 ppm. Because the community exposure guideline was not exceeded for any of the exposure

scenarios in this conservative screening approach, EPA has concluded that nPB exposure to populations living close to adhesive application sites is not a major concern. A memo describing the risk screen in detail may be found in the public docket (ICF, 2002a).

4. What Limit Is EPA Proposing on Isopropyl Bromide Contamination of nPB as a Condition of Acceptability, and Why?

Isopropyl bromide (iPB or 2-bromopropane), an isomer of nPB (1-bromopropane), is a contaminant that is created to different degrees in the manufacture of some nPB formulations. In reviewing the toxicological risks of iPB, EPA initially was concerned that its molecular structure was similar to chemicals that are potent reproductive toxins and carcinogens. This concern focused on the position of the halogen atom within the compound. There are toxicological data that indicate that when the halogen atom is located on the second carbon, there may be increased potential for the compound to cause cancer when compared to the compound with the halogen atom on carbon number 1. One example of this is the differential toxicity of 1-nitropropane and 2-nitropropane. Inhalation exposure to 2-nitropropane has been linked to liver toxicity in humans and has resulted in liver, and to a lesser extent, lung toxicity in male and female Sprague-Dawley rats (US EPA, 1991); it has also been shown to induce liver cancer in both Sprague-Dawley (IARC, 1992) and Fischer rats (Fiala, 1995). 1-Nitropropane has shown no carcinogenic potential to date.

Direct data on the carcinogenic potential of iPB are limited, although it has been shown to induce reverse mutations in bacteria (Maeng and Yu, 1997). Further, iPB was shown to be more cytotoxic and genotoxic to human liver cells than nPB and other toxins, including methylene chloride and trichloroethylene (SLR, 2001a). The combination of the position of the bromine atom in iPB (and its relationship to the carcinogenic potential of the compound) and the genotoxicity of the compound in bacterial and human cells indicate that caution is necessary when recommending an acceptable exposure concentration for iPB.

In the limited animal testing data available, iPB has been shown to be inherently more toxic than nPB on reproductive and hematopoietic endpoints. In two separate studies, significant disruptions in the estrous cycles and abnormal growth in uterine cells were reported in female rats