

demonstrated statistically significant delays in both vaginal opening and preputial separation using the body weight on the day of acquisition (postnatal day 45) as the co-variant. This was not found by Christian *et al.* (2002a) using the body weight at weaning as the statistical covariant. However, the authors analyzed the data for preputial separation and vaginal opening with body weight on the day of weaning as a co-variant rather than body weight on the day of acquisition, *i.e.*, the day that the prepuce separates or the day the vagina opens. It is likely that there was an increase in body weight from postnatal day 21 (weaning) until preputial separation (day 45) that was independent of the delay in sexual maturation.

Although the Christian *et al.* (2002a) study was conducted in accordance with EPA's 1998 testing guidelines, EPA has incorporated newer, more sophisticated measures into recent intramural and extramural studies that have not yet been incorporated into the testing guidelines. Such measures include measuring changes in specific proteins in the sperm membrane proteome and fertility assessments via in utero insemination. EPA believes that additional research is needed, utilizing these newer toxicological measures, to clarify the extent to which DBA poses human reproductive or developmental risk. The database on male reproductive effects from exposure to DBA is incomplete and is not suitable for quantitative risk assessment at this time. It does, however, identify reproductive effects as an area of concern.

C. Conclusions Drawn From the Reproductive and Developmental Health Effects Data

EPA believes that the weight of evidence of the best available science, in conjunction with the widespread exposure, supports regulatory changes that target peak DBP exposures specifically through the Stage 2 DBPR. Several epidemiology studies found statistically significant associations between exposure to chlorinated drinking water and fetal growth, spontaneous abortion, stillbirth, and neural tube defects. Although uncertainties remain and the current database does not support a quantitative reproductive and developmental risk assessment for most of the DBPs, the weight of evidence provides an indication of a hazard concern that warrants additional regulatory action beyond the Stage 1 DBPR.

Biological plausibility for the effects observed in epidemiological studies has been demonstrated through various

toxicological studies. Tyl 2000 states that "effects observed in animal studies included embryonic heart and neural tube defects from haloacetic acids in vitro and in vivo, and full litter resorption, reduced numbers of implants per litter, and reduced fetal body weight per litter were also observed from exposure to specific trihalomethanes. Comparable effects were also observed in children in some (but not all) epidemiological studies, with exposure to trihalomethanes (THMs) usually used as a surrogate for specific DBP classes or individual DBPs, as follows: increased incidences of cardiac defects (Bove *et al.* 1995) and of neural tube defects in children (Bove *et al.* 1995; Dodds *et al.* 1999; Klotz and Pyrch 1998) were reported. Intrauterine growth retardation (IUGR, approximately equivalent to reduced fetal body weights per litter) was reported to be associated with waterborne chloroform (Kramer *et al.* 1992; Bove *et al.* 1995; Gallagher *et al.* 1998). Miscarriage or spontaneous abortion, or stillbirth (approximately equivalent to whole litter resorption, reduced numbers of total and/or live implants per litter, and increased resorptions per litter) were observed by Waller *et al.*, 1998; Dodds *et al.*, 1999; and Bove *et al.*, 1995."

Similarity of effects between animals and humans lends credence to and strengthens the weight of evidence for an association between adverse reproductive and developmental health effects and exposure to chlorinated surface water. EPA believes that the weight of evidence of both the reproductive and developmental toxicological and epidemiological databases suggests that exposure to DBPs may induce potential adverse health effects on reproduction and fetal development at some DBP exposures. However, additional toxicological work is necessary to identify the mode of action for the effects observed.

D. Cancer Epidemiology

Epidemiological studies on cancer provide valuable information that contributes to the overall evidence on the potential human health hazards from exposure to chlorinated drinking water. In the area of epidemiology, a number of studies have been conducted to investigate the relationship between exposure to chlorinated surface water and cancer. While EPA cannot conclude there is a causal link between exposure to chlorinated surface water and cancer, some studies have found an association between bladder, rectal and colon cancer and exposure to chlorinated surface water.

1. Population Attributable Risk Analysis

Some epidemiological studies have linked the consumption of chlorinated surface waters to an increased risk of two major causes of human mortality in the United States, colorectal and bladder cancers (Cantor 1998). Bladder cancer was chosen as the primary endpoint of concern in the Stage 1 DBPR (USEPA 1998f) economic analysis because it had the most consistent database for a possible association to chlorinated surface water exposure. More studies have considered bladder cancer than any other cancer. EPA used the published mean risk estimates from five studies to quantify the potential range of risk for bladder cancer from DBP exposure. These risks were expressed as a range of population attributable risks (PAR) of 2–17% (USEPA 1998f). This means that if the associations reported in the studies turn out to reflect a causal link, between 2 and 17% of new bladder cancer cases could be attributable to DBPs. This PAR range also represents that portion of the bladder cancer cases that would not have occurred if the exposure to chlorinated drinking water were absent. A complete discussion of the Stage 1 DBPR bladder cancer PAR evaluation, including uncertainties and assumptions, can be found in the Stage 2 DBPR Economic Analysis (USEPA 2003i).

While EPA recognized the limitations of the epidemiological database for making risk estimates, the Agency believed that it was useful for developing an estimate of bladder cancer risk. The PARs were derived from measured risks (Odds Ratios and Relative Risk) based on the number of years exposed to chlorinated surface water. The uncertainties associated with these PAR estimates are largely due to the common prevalence of both the disease (bladder cancer) and exposure (chlorinated drinking water). EPA recognizes that risks from chlorinated drinking water may be lower or higher than those estimated from the epidemiological literature, and that the PAR range could include zero or be higher than 17%.

Using the PARs of 2% and 17%, EPA estimated that the number of possible bladder cancer cases per year potentially associated with exposures to DBPs in chlorinated drinking water could range from 1,100 to 9,300 cases. This was based on the estimate of 54,500 new bladder cancer cases per year nationally, as projected by the National Cancer Institute for 1997. A thorough discussion of cancer studies published prior to 1998 and possible