

associations with DBP exposure can be found in the Stage 1 DBPR (USEPA 1998c).

2. New Epidemiological Cancer Studies

New studies published since the Stage 1 DBPR continue to support an association between bladder, colon and rectal cancers and exposure to chlorinated surface water (Yang *et al.* 1998; Koivusalo *et al.* 1998; King *et al.* 2000b). Based on the weight of evidence provided by the cancer epidemiology database, EPA has chosen to use the same PAR analysis to estimate the primary benefits from bladder cancer cases potentially avoided as a consequence of reducing the DBP levels from the Stage 2 DBPR (*see* section VII). For the Stage 2 DBPR analysis, EPA updated the 1997 estimate of new bladder cancer cases per year nationally from 54,500 to 56,500 (projected by the American Cancer Society, 2002) and accounted for the reductions in DBP exposure that were projected for the Stage 1 DBPR.

a. New bladder cancer studies.

Bladder cancer and chlorinated DBP exposure has historically been the most strongly supported association of all the possible cancers, based on human evidence. Two new studies (Yang *et al.* 1998 and Koivusalo *et al.* 1998) also suggest an association of DBP exposure with bladder cancer. Yang *et al.* 1998 found a positive association between consumption of chlorinated drinking water and bladder cancer. Koivusalo *et al.* (1998) found evidence of increased risk as a function of increasing DBP exposure duration. Long exposure durations (≥ 45 years for Koivusalo *et al.* 1998) were associated with about a two-fold increase in risk. The new bladder cancer studies continue to support an association and potential for a causal relationship between exposure to chlorination byproducts and risk for bladder cancer.

A new publication by C.M. Villanueva *et al.* (Villanueva *et al.* 2003) reports on their meta-analysis of case-control and cohort studies. This meta-analysis may be useful for improving the estimate of national population attributable risk (fraction of bladder cancer cases in the U.S. that may be attributed to chlorinated drinking water). Compared to EPA's current approach (*i.e.*, providing a range of population attributable risks (PAR)), use of the meta-estimate would provide a more stable result because:

- It provides a single (meta) estimate of the odds ratio from which to calculate the PAR, thereby summarizing the results across studies, thus reducing the

influence of geographic and temporal differences.

- It uses three additional high-quality studies not included in the PAR range analysis conducted by EPA (*i.e.*, studies by Koivusalo *et al.* 1998, Doyle *et al.* 1997, and Vena *et al.* 1993).

- It weights the individual studies according to their precision, so more precise estimates (due principally to greater numbers of cases) carry greater statistical weight and therefore have greater influence on the meta-estimate.

- In addition to the primary analysis, the authors conducted an evaluation of the robustness of their conclusions. They examined the sensitivity of estimates to decisions made with respect to exposure definitions, cut points defining exposure groups, inclusion/exclusion of individual studies, and potential publication bias.

The meta-analysis provided at least two meta-estimates that may be useful for estimating national population attributable risk:

- A combined odds ratio for ever-exposure, with confidence intervals and
- A combined dose-response regression slope coefficient, relating increasing odds ratios to additional years of chlorinated drinking water consumption.

EPA conducted an estimate of the impact of using the meta-analysis to provide a perspective on the national population attributable risk. This estimate is based on the author's correction of a minor transcription error in their published manuscript (the appropriate estimate for the King study yields corrected over-all odds ratio for ever-consumers of 1.2 with 95% confidence interval of 1.091 to 1.320, personal communication from M. Kogevinas to M. Messner, 5/19/2003). Assuming 70% of the U.S. population is in the ever-consumed category (based on the chlorinated surface water exposed population), a point estimate of the population attributable risk using the odds ratio from the meta-analysis is 12% (95% interval 6% to 18%). Although EPA's population attributable risk range (2% to 17%) was not intended to convey a quantified level of confidence, it is not vastly different from the meta-analysis' 95% confidence range of 6% to 18%. EPA regards the meta-range as additional support for EPA's population attributable risk range. The meta-analysis provides continued support for an association between exposure to chlorinated surface water and bladder cancer.

EPA requests comment on the use of a meta-estimated odds ratios to estimate national population attributable risk for the purpose of supporting the benefit

analysis for this rule, either based specifically on the Villanueva *et al.* publication or on the application of a similar approach. EPA also solicits comments and suggestions for use of the combined dose-response regression slope coefficient associated with the increased risk of bladder cancer for each additional year's exposure to DBPs in drinking water for estimating the drop in risk associated with a reduction in DBPs as part of the benefit analysis of this rule. EPA provides further discussion and solicitation of comment on how the slope factor might further be considered in estimating the benefits of this rule in the economic section of this preamble.

b. New colon cancer studies.

Colorectal cancer is the third most common type of new cancer cases and deaths in both men and women in the U.S. It is estimated that 148,300 new colorectal cancer cases will be diagnosed in 2002, with 56,600 resulting in deaths (American Cancer Society, 2002). Human epidemiology studies on chlorinated surface water have reported associations with colorectal cancer. Since the Stage 1 DBPR, two new human epidemiology studies (Yang *et al.* 1998 and King *et al.* 2000b) have been conducted to investigate the relationship between colon cancer and exposure to chlorinated surface water. Yang *et al.* 1998 did not identify an association between consumption of chlorinated drinking water and colon cancer. The King *et al.* (2000b) study found evidence of a DBP association with colon cancer among males, but no association was observed among females.

Similarity of effects reported in animal toxicity and human epidemiology studies strengthen the weight of evidence for an association between DBP exposure and colon cancer. Effects observed in animal studies which included tumors in BDCM exposed rats and mice at several sites (NTP 1987); colon tumors in bromoform exposed rats (NTP 1989); and development of aberrant crypt foci, a preneoplastic lesion of colon cancer in animals exposed to DBP mixtures (DeAngelo *et al.* 2002), are comparable to observations in some cancer epidemiological studies showing an association with colorectal cancer and consumption of chlorinated water (King *et al.* 2000b).

Even with the additional study showing an association, the epidemiological database on colon cancer as a whole is not as strong as that for bladder cancer. However, this new study increases the weight of evidence of an association between DBP exposure