

abortions associated with TTHMs in California. On the other hand, Savitz *et al.* (1995) found little evidence of an association using either the concentration of TTHM ≥ 81 $\mu\text{g/L}$ or a dose estimate based on the amount of tap water consumed. An increased risk of stillbirth was reported for women in Nova Scotia by Dodds *et al.* 1999, but in New Jersey, Bove *et al.* (1992, 1995) found little evidence of an association with TTHM at 80 $\mu\text{g/L}$, but did report a weak association between stillbirth and use of surface water systems. Aschengrau *et al.* (1993) found an association between stillbirth and the use of a chlorinated vs. chloraminated surface water supply, but not for exposure to surface water.

c. *Fetal malformations and other developmental anomalies.* Reif *et al.* (2000) considered the data for congenital anomalies to be inconsistent across the six studies that have explored these outcomes. For example, two of the four studies on neural tube defects (Bove *et al.* 1995; Magnus *et al.* 1999) reported significant excess risks, but the remaining two studies (Dodds *et al.* 1999; Klotz and Pyrch *et al.* 1999) did not. These studies found lower risks or no evidence of an association with TTHM. However, those studies were conducted in locations with either very low or high concentrations of DBPs which may have limited the contrast in exposures, thereby reducing the ability to detect increased risks. An assessment of congenital anomalies is also difficult due to the relatively small number of cases available for evaluation.

Overall, Reif *et al.* (2000) conclude that the weight of evidence from the epidemiological studies suggest that "DBPs are likely to be reproductive toxicants in humans under appropriate exposure conditions." Reif *et al.* comment that data from animal studies of individual DBPs provide biological plausibility for the effects observed in epidemiological studies. Although the authors recognize that the "data are primarily at the stage of hazard identification," they conclude that "measures aimed at reducing the concentrations of byproducts could have a positive impact on public health."

2. Bove *et al.* 2002

Bove *et al.* (2002) conducted a qualitative review of 14 epidemiological studies that evaluated possible developmental and reproductive endpoints associated with exposure to chlorination byproducts in drinking water. Similar to Reif *et al.*, Bove *et al.* evaluated associations between DBP exposure and outcomes grouped as

effects on (1) fetal growth—small for gestational age (SGA) as defined in each study (usually defined as the fifth or tenth percentile weight by gestational week of birth); (2) fetal viability—spontaneous abortion and stillbirth; and (3) fetal malformations (neural tube defects, oral clefts, and cardiac defects).

a. *Fetal growth.* Bove *et al.* found that, although the studies that evaluated SGA had several limitations, three studies out of eight (Kramer *et al.* 1992, Bove *et al.* 1995, and Gallagher *et al.* 1998) "provided moderate evidence for a causal relationship between a narrow definition of SGA * * * and TTHM levels that could be found currently in some U.S. public water systems." They also concluded that the study with the best exposure assessment found the strongest association between SGA and TTHM exposure (Gallagher *et al.* 1998). One study found a very weak association (Dodds *et al.* 1999) and the other four did not observe an association (Yang *et al.* 2000, Kanitz *et al.* 1996, Kallen *et al.* 2000, and Jaakkola *et al.* 2001).

b. *Fetal viability.* Bove *et al.* evaluated three studies on spontaneous abortion and three studies on stillbirth. Again, Bove *et al.* found that the study employing the best methods found the strongest association between TTHM exposure and spontaneous abortions (Waller *et al.* 1998). The other two studies (Savitz *et al.* 1995 and Aschengrau *et al.* 1989) found weak associations. Two of the studies investigating stillbirths found an association between stillbirths and chlorinated surface water (Dodds *et al.* 2001 and Aschengrau *et al.* 1993). The third study (Bove *et al.* 1995) found no association, however this study did not evaluate individual THM levels or cause of death information.

c. *Fetal malformations.* Bove *et al.* evaluated seven studies that investigated the relationship between birth defects and DBP exposure. This evaluation found "consistency among these studies in the findings for neural tube defects and oral cleft defects, but not for cardiac defects. Associations were found for neural tube defects in all three studies that examined neural tube defects. These studies also evaluated levels of THM exposure (Bove *et al.* 1995; Dodds *et al.* 1999; Klotz *et al.* 1999)." Two studies evaluated oral cleft defects and levels of THMs; one found an association with TTHM (Bove *et al.* 1995) and the other found an association with chloroform (Dodds *et al.* 2001). A third study that did not evaluate THM levels did not identify an association with oral cleft defects (Jaakkola *et al.* 2001). Bove *et al.* 1995

found an association between cardiac defects and TTHM, but Dodds *et al.* 1999, 2001 and Shaw *et al.* 1991 did not. An association between chlorination and urinary tract defects was found in the three studies that evaluated that endpoint (Källén *et al.* 2000; Magnus *et al.* 1999; Aschengrau *et al.* 1993).

Bove *et al.* (2002) concluded that the current reproductive and developmental epidemiological database for exposure to chlorinated byproducts in drinking water presents moderate evidence for associations between DBP exposure and SGA, neural tube defects and spontaneous abortion. The authors acknowledged the difficulties in assessing exposure with any precision in the studies reviewed, but held the opinion that misclassification of exposure would tend to underestimate rather than overestimate the risk.

3. Nieuwenhuijsen *et al.* 2000

Nieuwenhuijsen *et al.* (2000) reviewed the toxicological and epidemiological literature and evaluated the potential risk of chlorination DBPs on human reproductive health. The authors state that "some studies have shown associations for DBPs and other outcomes such as spontaneous abortions, stillbirths and birth defects, and although the evidence for these associations is weaker it is gaining weight." Nieuwenhuijsen *et al.* also concluded that, "although studies report small risks that are difficult to interpret, the large number of people exposed to chlorinated water supplies constitutes a public health concern."

4. Additional Epidemiology Studies

Three new reproductive and developmental epidemiological studies were completed that were not included in the Reif *et al.* 2000, Bove *et al.* 2002, or Nieuwenhuijsen *et al.* 2000 literature reviews.

Waller *et al.* 2001, recalculated the total trihalomethane exposures from their original publication (Waller *et al.* 1998) to evaluate two exposure assessment methods (closest site and utility-wide average). The new calculations were intended to reduce exposure misclassification by employing weighting factors and subset analyses. As in the 1998 publication, the new methods found a relationship between spontaneous abortion and THM exposure, although the unweighted utility-wide point estimate was lower than reported in the original manuscript.

Hwang *et al.* 2002, assessed the effect of water chlorination byproducts on specific birth defects in Norway by