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Updated weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products

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Abstract

Disinfection by-products (DBP) are produced when water is treated with chemical disinfectants. Some toxicological and epidemiological studies suggest an association between DBP exposure and adverse reproductive and developmental effects. In a previous critical review, [Graves, C.G., Matanoski, G.M., Tardiff, R.G., 2001. Weight of evidence for an association between adverse reproductive and developmental effects and exposure to disinfection by-products: a critical review. Regul. Toxicol. Pharmacol. 34, (2) 103–124] evaluated the weight of evidence for this exposure and these effects. This investigation updates the previous evaluation and considers all toxicological and epidemiological evidence since the earlier review and reassesses the weight-of-evidence for all of the data on the various effects, outcome by outcome. The updated toxicity weight of evidence found little indication of previously unreported reproductive or developmental toxicity. In particular, the recently published findings of an exceptionally well conducted cohort study of broad scope found no impact of chlorination by-products on the highly controversial outcome of spontaneous abortion, unlike predecessor studies of more limited methodology, leading the authors to recommend no further epidemiologic pursuit for this hypothesis since the cohort was scrutinized very closely and dispelled any concern of such an association. The updated epidemiologic weight of evidence demonstrated that no association with DBP exposure exists for over a dozen outcomes including low and very low birth weight, preterm delivery, some specific congenital anomalies, and neonatal death. The analysis found inconsistent or very weak results for all congenital anomalies/birth defects, all central nervous system anomalies, neural tube defects, and spontaneous abortion. As in the previous article, the updated weight of evidence suggested a positive association with DBP exposure and some measure of growth retardation such as intrauterine growth retardation, small for gestational age, term low birth weight, and small body length or head circumference. Exposure assessment in most epidemiological studies remains inadequate to definitively demonstrate any association of small magnitude.

Keywords: Birth defects; Chlorination; DBP; Developmental effects; Disinfection by-products; Reproductive effects; THM; Trihalomethanes

1. Introduction

Chlorination of public water supplies was introduced in Britain and the United States in the first decade of the 20th century. This public health advance virtually eliminated water borne diseases such as cholera, typhoid, and dysentery in developed countries. However, concomitant with drinking water disinfection is the formation of disinfection by-products (DBP), the result of reaction of chemical disinfectants with naturally occurring organic matter (i.e., vegetable and plant material) primarily in surface water. This paper focuses on the by-products of chlorination, the most widely practiced method of water disinfection. The first articles investigating the potential for adverse reproductive and developmental effects of DBP exposure in animals appeared in 1974; the first investigation of these effects in humans appeared in 1989.

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The 1996 amendments to the Safe Drinking Water Act directed the U.S. Environmental Protection Agency (EPA) to develop rules balancing the risks between microbial pathogens and DBP. The Stage 1 Disinfectants and Disinfection By-products Rule was proposed in 1998 and the Stage 2 Rule in 2003. Among the most prevalent DBP in chlorinated water are the four trihalomethanes (THM), chloroform, bromoform, chlorodibromomethane (CDBM), and bromodichloromethane (BDCM). Together, these four compounds comprise total THM (TTHM). Other DBP include haloacetic acids (HAA) and haloacetonitriles (HAN). Altogether, EPA has identified nearly 600 DBP (U.S. EPA, 2002).

In 2001, Graves et al. published a critical review of the toxicological and epidemiological evidence to date. This paper is an extension of that effort and updates the weight of evidence analysis. The goal of this paper is to view the totality of the toxicological and epidemiological evidence to judge the overall weight of evidence concerning DBP exposure and reproductive and developmental effects.

Like outcomes are grouped and include the following effects: low birth weight, very low birth weight, preterm delivery, intrauterine growth retardation/small for gestational age, term low birth weight, small body length, and head circumference, congenital anomalies/birth defects (total and by type) including central nervous system anomalies, spontaneous abortion/miscarriage (i.e., early pregnancy loss), stillbirth/fetal death (i.e., late pregnancy loss), and neonatal death.

The tables include all statistical tests concerning an outcome in studies published since Graves et al. (2001). In this paper, "significance" refers to statistical significance at the standard level (i.e., significance at the $P = 0.05$ level). In the case of odds ratios[1] (OR) or relative risks[2] (RR) presented with confidence intervals, "statistical significance" means the lower limit of the 95th percentile confidence interval is $\geqslant 1.0$. OR and RR are followed by 95th percentile confidence intervals (CI) in parentheses unless otherwise noted. In addition, OR and RR are adjusted values unless otherwise noted. Of particular relevance was our frequent observation of attempt in individual studies to express the belief in the presence of a genuine association between exposure and reproductive outcomes by portraying numerical differences that were not statistically significant as if they were demonstrated associations. We have concluded that such statements do not constitute "positive" findings.

Table 1 lists recent toxicology literature (since Graves et al., 2001) by type of effect from those occurring before or early in pregnancy, through gestation, to after delivery. The toxicological effects are discussed as introductions to similar effects observed in humans. Findings are placed into perspective by considering the doses and circumstances at which effects are manifest, by examining the degree of concordance among the findings, and by considering differences with known or anticipated human exposures.

Table 2 lists all of the epidemiological studies of reproductive and developmental effects and DBP exposure. Study details are presented only for those investigations published since Graves et al. (2001). In addition, this paper summarizes several review articles.

Tables 1 and 2 together with the first tables in Graves et al. (2001) presents the totality of toxicological and epidemiological evidence concerning DBP exposure and reproductive and developmental effects.

As pointed out in Graves et al. (2001), the primary difficulty with the epidemiologic studies has been and continues to be the assessment of exposure. In all epidemiological studies but two, exposure assessment consists of indirect measures of exposure, based on water type (e.g., surface water versus ground water), method of water treatment (e.g., chlorination versus no chlorination), or on routine monitoring of municipal water supplies matched to maternal residence. In a recent article, Dodds et al. (2004) analyzed TTHM, BDCM, and chloroform concentrations in tap water from individual cases and controls. This individual ascertainment of exposure by integration of THM levels from inhalation, ingestion and from absorption exposures at home and at work is a welcome advance in the epidemiological study of DBP and fertility.

Weight of evidence consists of a critical examination of all scientific observations (positive as well as negative). Weight of evidence was judged by applying various characteristics to data bases. The principal elements include the quality of studies, reproducibility and replication of findings, consistency of findings across studies, and concordance among diverse findings (Tardiff and Rodricks, 1987). This paradigm is not the simple counting of studies with either positive or negative findings.

2. Recent reviews

The appearance of review articles is indicative of interest in the topic, and comprehensive review articles dealing with reproductive and developmental effects and DBP exposure are briefly described in the following paragraphs.

Reif et al. (2000) is a short report on work done for Health Canada that includes an extensive list of citations. In each of three areas—fetal growth, fetal viability, and fetal malformations—the authors explicitly state that the epidemiological evidence is inconsistent. In each of these areas, they grouped outcomes, some of which might have shown stronger results had they been considered separately.

Reif et al. found that (1) the epidemiological data did not suggest a dose–response pattern of increasing risk, (2) clear evidence of a threshold was lacking, and (3) no firm conclusions concerning population attributable risks could be drawn. The authors stated that discrepancies in the

[1] The odds ratio is an estimate of the relative risk used in case-control studies. It is the odds of an effect occurring in the exposed group compared to that in the unexposed group.

[2] Relative risk is the ratio of the incidence rate of those exposed to a factor (in this case, DBP) to the incidence rate among the unexposed.