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Review

Potential carcinogenic hazards of non-regulated disinfection by-products: Haloquinones, halo-cyclopentene and cyclohexene derivatives, *N*-halamines, halonitriles, and heterocyclic amines

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ABSTRACT

Drinking water disinfectants react with natural organic material (NOM) present in source waters used for drinking water to produce a wide variety of by-products. Several hundred disinfections by-products (DBPs) have been identified, but none have been identified with sufficient carcinogenic potency to account for the cancer risks projected from epidemiological studies. In a search for DBPs that might fill this risk gap, the present study projected reactions of chlorine and chloramine that could occur with substructures present in NOM to produce novel by-products. A review of toxicological data on related compounds, supplemented by use of a quantitative structure toxicity relationship (QSTR) program TOPKAT® identified chemicals with a high probability of being chronically toxic and/or carcinogenic among 489 established and novel DBPs. Classes of DBPs that were specifically examined were haloquinones (HQs), related halocyclopentene and cyclohexene (HCP&H) derivatives, halonitriles (HNs), organic *N*-chloramines (NCls), haloacetamides (HAMs), and nitrosamines (NAs). A review of toxicological data available for quinones suggested that HQs and HCP&H derivatives appeared likely to be of health concern and were predicted to have chronic lowest observed adverse effect levels (LOAELs) in the low μg/kg day range. Several HQs were predicted to be carcinogenic. Some have now been identified in drinking water. The broader class of HNs was explored by considering current toxicological data on haloacetonitriles and extending this to halopropionitriles. 2,2-dichloropropionitrile has been identified in drinking water at low concentrations, as well as the more widely recognized haloacetonitriles. The occurrence of HAMs has been previously documented. The very limited toxicological data on HAMs suggests that this class would have toxicological potencies similar to the dihaloacetic acids. Organic *N*-halamines are also known to be produced in drinking water treatment and have biological properties of concern, but no member has ever been characterized toxicologically beyond bacterial or *in vitro* studies of genotoxicity. The documented formation of several nitrosamines from secondary amines from both natural and industrial sources prompted exploration of the formation of additional nitrosamines. *N*-diphenylnitrosamine was identified in drinking waters. Of more interest, however, was the formation of phenazine (and subsequently *N*-chorophenazine) in a competing reaction. These are the first heterocyclic amines that have been identified as chlorination by-products. Consideration of the amounts detected of members of these by-product classes and their probable toxicological potency suggest a prioritization for obtaining more detailed toxicological data of HQs > HCP&H derivatives > NCls > HNs. Based upon a ubiquitous occurrence and virtual lack of *in vivo* toxicological data, NCls are the most difficult group to assign a priority as potential carcinogenic risks. This analysis indicates that research on the general problem of DBPs requires a more systematic approach than has been pursued in the past. Utilization of predictive chemical tools to guide further research can help bring resolution to the DBP issue by identifying likely DBPs with high toxicological potency.

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Contents

1. Introduction

Chlorination of drinking water has been consistently linked with an increased risk of bladder cancer in different geographic areas around the world (IARC, 2004) and less consistent associations were found with cancers of other organs. The odds ratios obtained in epidemiological studies are small, but the numbers of cases that would be attributable to chlorination could be relatively large compared to other chemical exposures from the environment (Morris et al., 1992; Poole, 1997; Villanueva et al., 2003, 2004). The USEPA's background document for the Stage II Disinfection By-product Rule (U.S. EPA, 2003a,b) implies a lifetime cancer risk from chlorinated drinking water of approximately one additional cancer per thousand population per lifetime (Bull and Reckhow, 2008).

Regulation of disinfectant by-products (DBPs) from the chlorination of drinking water has focused upon trihalomethanes (THMs) and haloacetic acids (HAAs). The members of these classes that have been studied in experimental animals are weak carcinogens (Bull et al., 2006). Therefore, they would appear as improbable causes of risks of the magnitude that have been suggested by epidemiological data. At the concentrations that are found in drinking water and assuming an equivalent potency of THMs and HAAs for humans as found in experimental animals, the potencies of these chemicals are at least two orders of magnitude too weak as carcinogens to significantly contribute to the risk associated with chlorination of drinking water (more fully documented in Section 4). This simple comparison raises the question of whether much more potent carcinogens are produced in the chlorination of drinking water than those routinely measured in response to regulation.

Water from surface sources contains organic and inorganic chemicals that are largely of natural origin. Natural organic matter (NOM) in water is a complex mixture comprised of small amounts of nutrients (e.g. simple amino acids and sugars) to relatively large conglomerates of biological products (Leenheer et al., 2000). Within this amorphous material, a substantial portion of the total organic carbon (TOC) is comprised of complex polymeric structures known as humic and fulvic acids. The structures of these organic acids include a large variety of moieties comprised of substituted phenols, furans, and heterocycles connected by aliphatic carbon chains. There are numerous carbonyl and hydroxyl substitutions. Substructures within fulvic and humic acids have been described by degradation studies, including the use of pyrolysis (e.g. Martin et al., 1994) and functional groups detected using a variety of direct and indirect methods (e.g. Ritchie and Perdue, 2003). From these studies numerous substructures have been identified (Schulten and Schnitzer, 1998). Utilizing these substructures to predict the types of reactions that will occur with chlorine or chloramine allows prediction of both halogenated and non-halogenated organic by-products to be tractable. A key question is whether by-products formed with alternate forms of disinfection (e.g. chloramine, chlorine dioxide, or ozone) differ significantly from those formed with free chlorine. Epidemiological data suggest that risk from bladder cancer is reduced when chloramine is introduced in place of free chlorine (Zierler et al., 1988; McGeehin et al., 1993). Similar findings have been reported when ozone was used in advance of treating water with chlorine (Chevrier et al., 2004). However, these case control studies of alternative disinfectants have focused exclusively on bladder cancer. Therefore, they do not indicate absence of carcinogenic risk at other sites (e.g. GI tract, kidney), which may be produced by products that differ from those derived from simple chlorination.

In the present study, chemicals that were probable products of reactions of the disinfectants with substructures within NOM, as well as selected members of established DBP classes have been