Halofuranones, haloquinones, and related compounds

JA Cotruvo, RJ Bull, M Whittaker, J Crook
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Background

3-Chloro-4-(dichloromethyl)5-hydroxy-2(5H)furanone (MX) is well known as a disinfection by-product. There are a large number of analogs of MX that have been identified.

A study was commissioned by the AwwaRF to predict likely reaction products with substructures in natural organic matter. A series of haloquinone derivatives and some related cyclohexene and cyclopentene derivatives were identified as likely DBPs (Bull et al., 2006). The later compounds have at least a superficial resemblance to MX. Quinones are known as reactive intermediates of well known carcinogens as benzene and PAHs. The further activation of quinones to toxic forms are known to be accelerated with halogen substitution in the ring. It is anticipated that these compounds will be preferentially formed in chloraminated water vs. chlorinated water (Bull et al., 2006). In fact, haloquinones are likely major intermediates in the formation of THMs and HAAs, which are currently regulated in drinking water. Excess chlorine destroys the ring structure to give rise to these more commonly recognized DBPs. Heasley et al., (2004) have demonstrated the formation of the haloquinones from phenol and cresol precursors in laboratory studies.

Occurrence

A recent study documented the occurrence of several chlorinated and brominated analogs of MX (Krasner et al. 2006). These data are provided in DBP-1. Concentrations of MX were found to occur at mean concentrations of 0.020 and with the highest concentration being 0.18 µg/L. The concentrations found in this survey exceeded those previously reported. MX has apparently been rarely measured in wastewater intended for potable reuse. Only one survey of MX concentrations in chlorinated sewage was located, where a range of concentrations from 2-142 ng/L was reported (Fukui et al., 1992). In our industry data base a concentration of 5 ng/L was reported by one system following reverse osmosis treatment. The molecular weight of MX is over 200, so it seems improbable that it would penetrate reverse osmosis membranes. Other related compounds, such as mucochloric acid, have molecular weights as low as 168. There appears to be no data indicating whether MX is removed by soil aquifer treatment or GAC.

Analogs of MX occurred at concentrations of up to 0.81 µg/L (3-chloro-4-(bromochloromethyl-5-hydroxy-2(5H)-furanone) (Krasner et al., 2006). While MX was detected in all waters, the median concentrations of the other forms were below detection. This variation undoubtedly reflects the variation in the bromide concentration of the treated water.

The occurrence of the halogenated quinones, cyclohexene, and cyclopentene derivatives is being investigated in a new AwwaRF project. Preliminary data should be available on selected members of these classes within a year. Considering that much of the mass of the haloquinones are converted to THMs and HAAs with excess chlorine, the collective concentration of chemicals in this class in excess of a µg/L could be possible in chloraminated water. The likely concentrations of other cyclohexene and cyclopentane concentrations are more difficult to

estimate. The smallest haloquinone, 2-chloro-1,4-dibenzoquinone has a molecular weight of 148 and is non-polar. These two properties might allow it to penetrate reverse osmosis membranes. We were unable to identify chemicals of comparable polarity and molecular weight that have been studied.

TTC Analysis

MX and several of its congeners are mutagenic. MX has been shown to be carcinogenic in rats with a TD_{50} of approximately 1 mg/kg per day. These compounds were subjected to QSTR analysis and predicted to be non-carcinogenic. However, MX was also predicted to be non-carcinogenic. Thus, chemicals related to MX were identified as important DBPs that required toxicological characterization (Woo et al., 2002; Bull et al., 2006)

A QSTR analysis predicted chronic LOAELs for these the haloquinones in the µg/kg per day range (approximating the potency of NDMA). The program also predicted that several of the haloquinone structures would be carcinogenic and mutagenic and these predictions are consistent with what is known of quinone toxicity, more generally (Bolton et al. 2000). Examples of haloquinones that were predicted to be carcinogenic include 2,6-dichloro-1,4-dibenzoquinone, 2,3,6-trichloro-1,4-dibenzoquinone, 2,3,6-dichloro-1,4-benzoquinone-4-(N-chloro)amine.

The predicted cyclohexene and cyclopentene DBPs had varied structures. Examples of the type of compounds that were identified were predicted to be of likely toxicological importance included 3,5-dichloro-1-hydroxy-4-keto-cyclopent-2-enoic acid and 2,3,6-trichloro-4,5-diketophenylprop-2-enol (Bull et al., 2006). Several were predicted to be probable carcinogens, but these compounds, like MX, fell largely outside the predicitve space of the QSTR models.

Given the above information a TTC analysis is not appropriate for these compounds. Chemical-specific data are necessary to assess the risk they might pose to the public health.

Research Recommendations

We propose to nominate chemicals in these three groups for study by the U.S. Environmental Protection Agency if the AwwaRF study suggests they occur in drinking water at substantive concentrations (based on their predicted toxic effects, substantive amounts would be as little as 10 ng/L as the predicted potency is in the same range as the dialkylnitrosamines). We believe the key group of DBPs will be the haloquinones as the prediction of carcinogenic activity by the QSTR program could be supported by a systematic literature search of the mechanisms of toxic effects produced by quinones.

Based upon QSTR analyses, the endpoint of primary concern for these chemicals will be potential carcinogenic effects. However, because of the potentially large number of chemicals within this group that could be produced, we would suggest that preliminary short-term in vivo testing be conducted to determine which members of the class are most likely to be a carcinogenic hazard at the concentrations that are identified in drinking water. The QSTR predictions of carcinogenicity are qualitative, although there was an attempt to estimate potency using a predicted chronic LOAEL. These predictions could well be in error for individual

chemicals. Considerations of the basic mechanisms that are involved in the toxicology of quinones, some confidence can be expressed in the likelihood that the kidney will be a important, but not necessarily the only, target organ for the haloquinones. The likelihood that multiple mechanisms are likely to be involved in cancer induced by these compounds indicate that other target organs cannot be ignored.

There is less pressure to do novel research with MX as one can use the MX cancer data can at least allow a ballpark prediction of the likely potency of the more closely related analogs of MX (i.e. the brominated analogs). It is probable that the other analogs will be less potent. To establish that, however, would require a broader set of toxicological data on these related compounds than is presently available (largely limited to mutagenic activity). The problem of assessing the carcinogenic potency of compounds related to MX would be the second priority for this proposed project, if haloquinones are seen not too occur in appreciable concentrations in chloraminated water. Toxicological evaluation of selected cyclohexene and cyclopentene derivatives would be proposed within the group of MX-like compounds.

Agencies to be Approached

Developing a toxicological database for chemicals in these classes will be a major undertaking. Some of these chemicals are not commercially available, requiring synthesis to conduct studies. These structures were predicted based upon substructures that occur in NOM, but there is a high probability that compounds will be substituted with substituents not anticipated in the predictive chemistry effort (Bull et al., 2008). Therefore, pursuing the toxicology of these compounds will be a program, not a single project.

We will suggest that if the haloquinones, in particular, are detected in substantive concentrations in chloraminated water, that a coordinated research effort be mounted involving both the U.S. EPA and the National Toxicology Program. This would allow for a coordination of the synthesis and purification of any test materials and an interagency planning and coordination effort to minimize the costs of the studies. It is anticipated that NHEERL might be in a better position to perform some of the screening studies and NTP would be called upon to conduct chronic bioassays using their usual contractual mechanisms.

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