Trihalomethane Comparative Toxicity: Acute Renal and Hepatic Toxicity of Chloroform and Bromodichloromethane Following Aqueous Gavage

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Bromodichloromethane (BDCM) and chloroform (CHCl₃) are by-products of drinking water chlorination and are the two most prevalent trihalomethanes (THMs) in finished drinking water. To date, no comprehensive comparison of the acute renal and hepatic effects of BDCM and CHCl₃ following oral gavage in an aqueous dosing vehicle has been conducted. To characterize BDCM- and CHCl₃-induced nephro- and hepatotoxicity following aqueous gavage and compare directly the responses between these THMs, 95-day-old male F-344 rats were given single oral doses of 0.0, 0.75, 1.0, 1.5, 2.0, or 3.0 mmol BDCM or CHCl₃/kg body wt in an aqueous 10% Emulphor solution. Compound-related hepatic and renal damage was evaluated by quantitating clinical toxicity markers in the serum and urine, respectively. Both THMs appear to be equally hepatotoxic after 24 h, but BDCM caused significantly greater elevations in serum hepatotoxicity markers than CHCl₃ at 48 h following exposure to 2.0 and 3.0 mmol/kg. In addition to more persistent liver toxicity than CHCl₃, BDCM also appears to be slightly more toxic to the kidney at lower doses. Potency differences between the two THMs may be due to pharmacokinetic dissimilarities such as greater metabolism of BDCM to reactive metabolites or more extensive partitioning of BDCM into kidneys and fat depots, resulting in prolonged target tissue exposure.

Bromodichloromethane (BDCM) and chloroform (CHCl₃) are disinfection by-products formed as a result of drinking water chlorination. BDCM and CHCl₃ have been reported to be the two most prevalent disinfection by-products and trihalomethanes (THMs) in chlorinated drinking water in the United States (Krasner et al., 1989). BDCM in finished waters typically occurs at concentrations ranging from 6 to 17 µg/L but levels exceeding 180 µg/L have been reported. Similarly, CHCl₃ concentrations range between 0.7 and 540 µg/L with an average concentration of 14 µg/L (EPA, 1990; Krasner et al., 1989). Weak, but significant epidemiological associations between consumption of chlorinated drinking water containing THMs and cases of human bladder and lower intestinal tract cancers have been reported (Cantor et al., 1978; Morris et al., 1992; Bull et al., 1995; King and Marrett, 1996). These reports are more compelling because similar target sites for cancer were found in chronic rodent studies with brominated THMs. In rodent bioassays, BDCM caused increased incidences of tumors in the large intestine and kidneys of both sexes of F-344 rats. In addition, chronic BDCM treatment increased liver neoplasms in female B6C3F₁ mice and kidney tumors in male mice (NTP, 1987; Dunnick et al., 1987). Similarly, chronic administration of CHCl₃ to rodents resulted in increased incidences of liver tumors in male and female B6C3F₁ mice and kidney tumors in Osborne-Mendel rats (NCI, 1976; Jorgenson et al., 1985).

Although both THMs have been shown to be carcinogenic in rodents, the NCI and NTP bioassays were conducted using corn oil as the dosing vehicle, a potentially confounding factor in toxicological evaluations of drinking water contaminants. Lifetime administration of CHCl₃ in drinking water to female mice did not increase the incidence of liver tumors (Jorgenson et al., 1985). These different outcomes suggest that the vehicle and/or the mode of administration can significantly influence the results of THM cancer bioassays. A number of recent reports support the hypothesis that chloroform acts to produce cancer in rodents through a nongenotoxic–cytotoxic mode of action with carcinogenesis resulting from events secondary to chloroform-induced cyto-
lethality and regenerative cell proliferation (Larson et al., 1994, 1995, 1996; Pereira, 1994; Butterworth et al., 1995; Templin et al., 1996a,b). These studies have established correlations between chloroform dosing regimens that produce cancer in a given animal model and those that induce cytotoxic responses. In oral exposure studies, cytotoxicity was noted after corn oil gavage of high chloroform doses, but not with drinking water administration of similar daily doses, suggesting that dose rate is an important determinant of toxicity (Larson et al., 1994, 1995). Unlike chloroform, the brominated THMs are clearly mutagenic and potentially genotoxic in mammals (U.S. EPA, 1995; Pegram et al., 1997), but it is important to examine and compare their cytotoxicity to that of chloroform, in part, because of the role that cytotoxicity may play in the genesis of THM-induced cancer in rodents.

Vehicle differences have been noted in the acute and subchronic toxicities of THMs. Corn oil gavage of high doses of BDCM and CHCl₃ was more acutely hepato- and nephrotoxic than aqueous gavage or drinking water administration, respectively (Lilly et al., 1994; Larson et al., 1994, 1995). Bull et al. (1986) reported greater hepatotoxicity in B₆C₃F₁ mice gavaged for 90 days with CHCl₃ dissolved in corn oil than that seen with delivery in 2% Emulphor solutions. The toxicity and pharmacokinetics of other volatile organic compounds (VOCs) have also been reported to depend upon the gavage vehicle (Munson et al., 1982; Condie et al., 1983; Kim et al., 1990a,b; Gallo et al., 1993).

The acute and subchronic toxicities of BDCM and CHCl₃ in rodents have been compared using a corn oil vehicle (Chu et al., 1982; Munson et al., 1982; Condie et al., 1983). However, as suggested above, the response of animals to acute or long-term exposure to these compounds in an aqueous solution could be significantly different than that resulting from corn oil administration. To evaluate more accurately the relative acute oral toxicity caused by these chemicals and collect relevant data for use in human risk assessment, the compounds should be administered in a vehicle which more closely simulates human exposure, i.e., an aqueous vehicle. Therefore, the purpose of this study was to compare directly the acute renal and hepatic toxicity of CHCl₃ and BDCM in an aqueous gavage vehicle and to characterize further any differences between THM-induced responses in experimental animals. Oral gavage rather than drinking water dosing was chosen as the method of administration so that direct comparisons based on equivalent molar doses could be readily made between the THMs. Clinical chemistries were determined as indicators of toxicity, because these parameters have been shown to correlate well with histopathology findings at higher THM doses, to reflect accurately time-dependent toxicity, and to be more sensitive than standard microscopic examination in detecting effects at lower doses (Lilly et al., 1994, 1996; Thornton-Manning et al., 1994).

### MATERIALS AND METHODS

**Animals and husbandry.** This study was conducted under federal guidelines for the use and care of laboratory animals (National Institutes of Health, 1985). Male Fischer-344 rats were obtained from Charles River Breeding Laboratories (Raleigh, NC) at 90 days of age, housed two per cage, and acclimated for 3 days to a 12-h light/12-h dark cycle with light from 0600 to 1800 h. The animal room was maintained at 20–22°C with 40 to 60% relative humidity in facilities accredited by the American Association for Accreditation of Laboratory Animal Care. Rats were provided Purina Rodent Chow 5001 (Ralston Purina Co., St. Louis, MO) and tap water ad libitum. Animals were assigned to groups based on body weight and housed individually in either plastic metabolism cages with stainless steel-grid flooring (Nalgene Corp., Rochester, NY) or in polyethylene shoe-box cages with heat-treated pine shavings as bedding. Rats were acclimated to the metabolism cages for 3 days prior to dosing and were provided Bioserv 45 mg pelleted Rodent Chow (Bio-Serv, Frenchtown, NJ) and tap water ad libitum.

**Study design and chemicals.** BDCM was obtained from Aldrich Chemical Co. (Milwaukee, WI; purity = 98.09%) and CHCl₃ from Fisher Scientific Corp. (Fair Lawn, NJ; purity = 99.9%). The rats housed in metabolism cages were given (n = 5) a single, oral dose by gavage of 0.0, 0.75, 1.0, 1.5, 2.0, or 3.0 mmol BDCM or CHCl₃/kg body wt dissolved in 10% Emulphor EL-620 solution (GAF Chemical Corp., Wayne, NJ). Equivalent doses in mg/kg are shown in Table 1.

All BDCM and CHCl₃ doses were administered in a constant volume of 5 ml/kg by oral intubation. Control animals received 5 ml of 10% Emulphor/kg. These rats were used for urine collections from 12 h prior to gavage to 48 h postdosing and killed after 48 h to collect samples for serum chemistry. The rats in shoe box cages were given identical doses in 10% Emulphor and were used for 24-h serum chemistry. All rats were dosed between 0900 and 1100 h.

**Clinical chemistry.** Urine samples were collected over the 12-h period prior to dosing, then from 0 to 12, 12 to 24, 24 to 36, and 36 to 48 h after dosing. Collected urine was maintained at 4 ± 1°C by a system of insulated copper tubing surrounding urine collection vessels with cold coolant pumped through the copper coils. Following collection, urine volume was measured and samples were centrifuged at 800g for 10 min. Rats were euthanized by induction of anesthesia with carbon dioxide followed by exsanguination via cardiac puncture. Blood samples were held on ice in serum separation tubes for 30 min and allowed to clot. Samples were then centrifuged at 1400g for 30 min at 4°C. Aliquots of serum were stored at −80°C until analyzed, and urine was stored at 4°C for a maximum of 12 hr prior to clinical chemistry analysis. Analyses conducted on sera and urine included alanine aminotransferase (ALT), aspartate aminotransferase (AST), urea nitrogen (BUN), creatinine (CRE), lactate dehydrogenase (LDH), and total protein (TFR). Serum sorbitol dehydrogenase (SDH) and urine N-acetylglucosaminidase (NAG) activities were also determined. Urine and serum analyses were conducted with a COBAS Fara II analyzer (Hoffman-LaRoche Co., Branchburg, NJ) and appropriate reagent kits.
**RESULTS**

**Organ and body weights.** No significant decreases in body or liver weight were observed at any dose of BDCM or CHCl$_3$ at 24 h postexposure compared to control values (Table 2). However, significant body weight losses were noted 48 h following administration of 1.5, 2.0, and 3.0 mmol BDCM/kg and at CHCl$_3$ doses of 2.0 and 3.0 mmol/kg. Doses of 1.5, 2.0, and 3.0 mmol BDCM/kg resulted in decreased absolute liver weights after 48 h but only the highest CHCl$_3$ dose (3.0 mmol/kg) caused these decrements in liver weight. The highest dose of both THMs resulted in decreased relative liver weights after 48 h. Rats gavaged with the two highest BDCM doses exhibited significantly greater absolute kidney weights 24 h postexposure compared to controls, and doses of 1.5, 2.0, and 3.0 mmol BDCM/kg resulted in increased relative kidney weights. Significant CHCl$_3$-induced elevations in kidney weights at 24 h occurred in the same dose–response pattern noted with BDCM. Although no increases in absolute kidney weights were observed 48 h after BDCM or CHCl$_3$ gavage, 3.0 mmol BDCM/kg caused elevations in relative kidney weight. In addition, relative kidney weights were significantly greater 48 h postgavage with 3.0 mmol BDCM/kg compared to an equimolar dose of CHCl$_3$. No CHCl$_3$ dose produced an increase in relative kidney weights at 48 h postexposure.

**Hepatotoxicity.** The serum hepatotoxicity indicators AST and ALT (Fig. 1) were elevated over controls 24 h following dosing with 1.5, 2.0, and 3.0 mmol BDCM or CHCl$_3$/kg. Levels of serum SDH were significantly increased at all doses of both THMs at 24 h. Activities of serum ALT were greater than controls at 0.75 and 1.0 mmol BDCM/kg and 1.0 mmol CHCl$_3$/kg as indicated by a one-way ANOVA. In addition, AST was significantly elevated following 1.0 mmol BDCM/kg at 24 h using this analysis technique. After 48 h, the serum levels of AST, ALT, and SDH in the THM-treated groups were lower than at 24 h. This same trend of a decrease in toxicity from 24 to 48 h after aqueous administration of BDCM was evidenced by liver histopathology findings from a previous study (Lilly et al., 1994). In that investigation, hepatocellular necrosis was observed in 100% of rats dosed with 400 mg BDCM/kg at 24 h, but in only 33% of the rats at 48 h. In the present study, doses of 1.5, 2.0, and 3.0 mmol BDCM/kg continued to cause greater release of all three marker enzymes than in controls at 48 h, and SDH was also elevated at 1.0 mmol BDCM/kg. In CHCl$_3$-dosed rats, the only increases observed at 48 h were AST at 3.0 mmol/kg, ALT at 2.0 mmol/kg, and SDH at 2.0 and 3.0 mmol/kg. Interestingly, BDCM administered at 2.0 and 3.0 mmol/kg caused significantly greater elevations of AST, ALT, and SDH at 48 h than equal doses of CHCl$_3$, suggesting that BDCM-induced hepatotoxicity is more persistent than that of CHCl$_3$ following administration in an aqueous vehicle.

**Nephrotoxicity.** Activities of the urinary indicators of renal damage, LDH, NAG, and AST, following oral administration of 1.5, 2.0, or 3.0 mmol BDCM or CHCl$_3$/kg are presented in Fig. 2. Since there were no significant increases over controls and/or no compound-related differences noted after treatment with 0.75 or 1.0 mmol THM/kg, levels of marker enzymes for only the highest three doses are reported for ease of presentation. Following gavage with 1.5, 2.0, and 3.0 mmol BDCM/kg, significant increases in urinary LDH were observed at 24, 36, and 48 h with only two exceptions: 3.0 mmol/kg at 24 h and 2.0 mmol/kg at 48 h. Increases in NAG were produced by 1.5, 2.0, and 3.0 mmol BDCM/kg at 24 h, 3.0 mmol BDCM/kg at 36 h, and 2.0 and 3.0 mmol/kg at 48 h.
following delivery of 1.5 mmol BDCM/kg, and at 3.0 mmol/kg.

3 mmol BDCM/kg resulted in significantly greater levels of
BUN were noted 24 h postgavage with the 3.0 mmol/kg
dose. Elevated only by the 2.0 and 3.0 mmol/kg doses of CHCl,
3 h after gavage; but at 48 h, AST levels were
incrased compared to controls at 24 and 36 h with the 1.5,
3 doses caused increases in urinary AST
molecules levels 24, 36, and 48 h postexposure.
All three BDCM doses caused increases in urinary AST
activities 24, 36, and 48 h postexposure.

After CHCl treatment, levels of urinary LDH were also
increased compared to controls at 24 and 36 h with the 1.5,
2.0, and 3.0 mmol CHCl/kg doses and remained elevated
at 48 h in the highest dose group. At 36 and 48 h, animals
were also treated with 3.0 mmol/kg exhibited higher urinary NAG
activities than controls. As with BDCM, treatment with the
three highest CHCl doses caused increases in urinary AST
24 and 36 h after gavage; but at 48 h, AST levels were
incrased only by the 2.0 and 3.0 mmol/kg doses of CHCl.
Significant elevations in the serum nephrotoxicity marker
BUN were noted 24 h postgavage with the 3.0 mmol/kg
dose of both BDCM and CHCl, but only BDCM caused
an increase in BUN at 48 h (Fig. 3).

Significant differences between BDCM and CHCl in the
severity of renal toxicity were also observed. At 24 h, 2.0
mmol BDCM/kg resulted in significantly greater levels of
urinary LDH and AST than an equal dose of CHCl. In
addition, higher LDH activity was noted at 36 and 48 h
following delivery of 1.5 mmol BDCM/kg, and at 3.0 mmol/
kg, the BDCM-induced NAG increase at 36 h was greater
than the concomitant increase with CHCl. Similarly, elevations
of BUN at 24 and 48 h were greater following challenge
with 3.0 mmol BDCM/kg than with the same CHCl dose. Responses to CHCl significantly exceeded those of BDCM
only at the highest dose of CHCl at the 24-h time point:
increases in urinary LDH, NAG, and AST were greater than
the elevations induced by an equimolar dose of BDCM.

Blood concentration results. Blood concentration–time
profiles following oral gavage of 1.5 mmol BDCM or CHCl/
kg are presented in Fig. 4. Both THMs appear to be rapidly
absorbed from the GI tract following aqueous gavage. Peak
blood levels were observed 2 to 6 min postexposure to either
THM. Levels of BDCM and CHCl in venous blood were
similar except at the latest time point (6 h) when the concen-
tration of BDCM was significantly greater than that of
CHCl.

DISCUSSION

To date, this comparative work represents the most com-
prehensive characterization of the acute toxicity of BDCM.
and CHCl₃ following oral gavage in an aqueous vehicle. The study was conducted at five different dose levels and provides data on temporal changes in hepatic and renal toxicity by examining clinical chemistry endpoints which have been shown to correlate well with histopathological results in other studies (Plaa and Charbonneau, 1994; Davis and Berndt, 1994) and in experiments with BDCM-challenged rats (Lilly et al., 1994, 1996; Thornton-Manning et al., 1994). This investigation provides a data base from which toxicity extrapolation, necessary for human noncancer risk assessments, may be conducted by supplying response data from low, nearly nontoxic doses to exposure levels which caused marked organ damage. In addition, this work characterizes and compares THM acute toxicity using an aqueous dosing vehicle, which is more closely related to the primary vehicle of human exposure, drinking water.

One of the most important aspects of investigating target-organ toxicity in animals exposed to a structurally similar
FIG. 2. Urinary activities of renal damage indicators over time following administration of BDCM or CHCl₃ in an aqueous dosing vehicle. Each data point represents the mean ± SE of five animals. *, Mean is significantly greater than control (p ≤ 0.05). †, Significant difference between BDCM and CHCl₃ at that dose level and time point (p ≤ 0.05).

class of compounds (in this case, THMs) is to provide relative potencies of the individual components of the group. Additionally, it has been recognized that assessment of toxicity of a series of compounds on a mole-per-kilogram basis has "considerable merit" and should be more rigorously pursued in the toxicology community as a viable alternative to weight-per-kilogram dose considerations in comparative toxicity studies (Klaassen, 1986). Therefore, in the present study, the acute toxicities of BDCM and CHCl₃ were evaluated using equimolar doses rather than mg/kg doses, permitting a direct comparison of BDCM and CHCl₃ on a molecular basis, and thus facilitating more accurate assignment of relative potencies.

The results of the current toxicity assessment indicate that, at low doses, BDCM is a slightly more potent nephrotoxicant than CHCl₃. Significantly greater elevations of urinary markers of renal toxicity were noted following administration of 1.5 and 2.0 mmol BDCM/kg compared to CHCl₃ and these doses of BDCM, but not CHCl₃, also induced increases in NAG (Fig. 2). These observations suggest that, at low doses
in an aqueous vehicle, BDCM is more acutely nephrotoxic than CHCl₃.

Both THMs appear to be equally hepatotoxic after 24 h over the entire range of doses examined in this study. However, at 48 h, elevations of liver damage indicators were significantly greater with BDCM than with CHCl₃ (Fig. 1).

FIG. 3. Levels of the serum nephrotoxicity indicator, blood urea nitrogen (BUN), 24 and 48 h postexposure to various doses of BDCM or CHCl₃ in an aqueous dosing vehicle. Each bar represents the mean ± SE of five animals. *, Mean is significantly greater than control (p ≤ 0.05). †, Significant difference between BDCM and CHCl₃ at that dose level (p ≤ 0.05).

FIG. 4. Blood concentration–time profiles following administration of 1.5 mmol BDCM or CHCl₃/kg in an aqueous dosing vehicle. Each data point represents the mean ± SD of three animals. *, Significant difference between blood concentrations of BDCM and CHCl₃ at that time point (p ≤ 0.05).
These data suggest that the hepatotoxicity induced by aqueously administered BDCM is more persistent than that of CHCl₃. Elevations of hepatotoxicity indicators remained evident at 48 h postexposure to BDCM (although decreased from 24-h levels), while CHCl₃-induced damage was markedly decreased or no longer observable. The abatement of liver toxicity from 24 to 48 h indicated in this study by the changes in clinical chemistry indicators was also observed previously using histopathological methods (Lilly et al., 1994), demonstrating that these clinical parameters can accurately reflect time-dependent changes in THM-induced toxicity. The same comparison and conclusion is valid for the urinary renal toxicity markers employed here. Comparison of the present data to the previous histopathology results (Lilly et al., 1994) and similar comparisons using other prior reports (Thornton-Manning et al., 1994; Lilly et al., 1996) demonstrate that significant increases in clinical indicators occurred at doses that produced no observable histopathology, indicating that these clinical markers can detect BDCM-induced organ damage with greater sensitivity than light microscopic evaluation of tissue sections. The more thorough examination of dose- and time-dependent toxicity in the present study compared to previous results (Lilly et al., 1994) provides a better basis for determination of relative target tissue sensitivity to BDCM. Although we had previously concluded that the kidney was the more sensitive organ to BDCM, the present data indicate that the liver is, in fact, affected at lower oral doses of both THMs than the kidney. These results establish an acute, oral NOAEL and LOAEL for BDCM-induced nephrotoxicity of 1.0 and 1.5 mmol/kg, respectively. However, the possibility remains that BDCM is more toxic to the kidney than the liver when inhaled or when dose is expressed on a mmol/g tissue basis.

Taken collectively, the results of this study suggest that BDCM is a more potent acute toxicant than CHCl₃. Similar results have been reported by other investigators examining THM toxicity. Bowman (1978) reported LD50 values for male mice following acute oral doses of BDCM and CHCl₃ delivered in an emulphor:alcohol:saline solution. BDCM was more acutely toxic than CHCl₃, with LD50 values of 450 mg/kg (2.7 mmol/kg) versus 1120 mg/kg (9.4 mmol/kg) for CHCl₃. LD50 values for rats were similar between the two THMs in a later investigation in which the compounds were administered in corn oil (Chu et al., 1982). Examination of nonlethal endpoints of acute THM toxicity (p-aminohippuric acid accumulation in renal cortical slices and urinary glucose excretion) following injection of equimolar doses of THMs resulted in more pronounced renal damage, particularly in the proximal tubule section of the nephron, following BDCM exposure compared to CHCl₃ (Kroll et al., 1994a,b). Hewitt et al. (1983) examined the effects of 0.25 ml BDCM/kg (3.0 mmol/kg) and 0.2 ml CHCl₃/kg (2.5 mmol/kg) in male Sprague–Dawley rats. After 24 h, the increase in serum AST was greater following BDCM treatment than with CHCl₃.

Differences in toxicity responses between BDCM and CHCl₃ may be due to a number of pharmacokinetic (PK) dissimilarities. These may include differences between: (1) deposition of the chemicals into tissues, which can be estimated by tissue/air partition coefficients (PCs), and (2) metabolic transformation. The BDCM tissue/air PCs for blood, fat, and kidney are 31.4, 526, and 32.9, respectively (Lilly et al., 1997). Corley et al. (1990) reported CHCl₃ blood, fat, and kidney PCs of 20.8, 203, 11.0, respectively. The smaller blood/air PC of CHCl₃ could result in a greater amount of CHCl₃ being eliminated via exhalation than BDCM, leading to lower availability of CHCl₃ for bioactivation to toxic intermediates and therefore less overt toxicity. Studies examining the relative rates of exhalation of BDCM and CHCl₃ will be necessary to test this hypothesis. In addition to potentially greater amounts of CHCl₃ being exhaled, greater fat and kidney PCs of BDCM should result in more extensive partitioning of BDCM into fat and kidney and, with slower subsequent release from these depots, a more prolonged target tissue exposure is likely. The latter hypothesis is consistent with the greater persistence of BDCM-induced toxicity that was especially apparent in the liver. The differences in blood concentrations at 6 hr following gavage demonstrate the greater systemic longevity of BDCM compared to CHCl₃ (Fig. 4). Similarities in the initial phase of the THM blood concentration curves may be due to a balance between more rapid absorption and greater tissue loading of BDCM than CHCl₃.

The cytotoxicity of BDCM and CHCl₃ is mediated via their metabolism to reactive intermediates, most notably phosgene and/or a dichloromethyl free radical. BDCM has been shown to have a greater potential for formation of free radicals (Tomasi et al., 1985; Waller and McKinney, 1993) and for binding to macromolecules than CHCl₃ (Gao and Pegram, 1992). If BDCM undergoes more rapid metabolism to reactive intermediates in the kidney compared to CHCl₃, more renal damage would be observed. This contention is evident in greater renal toxicity following low dose BDCM exposure (Fig. 2). It should be noted that the differences in hepatic and renal toxicity may be explained by a combination of the PK differences described above.

In summary, these results suggest that BDCM is a more potent acute renal toxicant, especially at low doses, and a more persistent hepatotoxicant than CHCl₃ following administration in an aqueous vehicle. Differences between THMs in biological responses to acute aqueous exposure may be due to PK dissimilarities, including differences in chemical tissue deposition and/or metabolism to reactive intermediates. These findings support other evidence (Lilly et al., 1994; Pegram et al., 1997), indicating that risk assessments for THMs in drinking water should not rely primarily on...
the CHCl₃ data base. As evidenced by the results of this study, the potential risks posed by brominated THMs deserve serious consideration. In addition, this work illustrates the utility of comparing the toxicity of similar compounds on a molar basis to aid in the assignment of relative potencies.

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