Bromate decomposition kinetics with simulated stomach/gastric juice was studied to contribute to more accurate determination of the risk of environmentally relevant exposures to bromate. Any presystemic reduction in the stomach would yield lower risks.

Bromate is rapidly reduced by hydrogen sulfide (H₂S); half-lives were 153 min at zero H₂S and 2, 24, and 32 min at 10⁻⁴, 10⁻⁵, and 10⁻⁶ M H₂S, respectively. Half-lives at 10⁻⁴ and 10⁻⁵ M are biologically relevant for the retention time for water in an empty stomach. Common dietary inorganic reducing agents (ferrous, iodide, and nitrite) generally enhanced bromate reduction with H₂S. Oxidizing agents (hypochlorous acid/chlorine, chloramine, and ferric ion) usually modestly reduced decomposition rates with H₂S. Consumption of chlorinated or chloraminated drinking water containing bromate would not materially affect the extent of presystemic bromate reduction. Current studies by the authors are quantifying bromate reduction from the greater systemic liver and blood metabolism, where rapid reactions with glutathione and other reducing agents occur.

Bromate decomposition chemistry in simulated gastric juice that could occur during the residence time of water in the stomach is described in this article. It is intended to demonstrate that presystemic chemistry in the stomach can reduce the systemic dosage—and thus the toxic effects of certain chemicals—and that a risk assessment that does not take this into consideration will overestimate the apparent toxicity. Given that risk assessments are fundamental to setting drinking water maximum contaminant level goals (MCLGs) and maximum contaminant levels (MCLs), it is imperative that they be as realistic as possible and reflect mechanisms of toxicity at typical low environmental doses when they become known, rather than rely primarily on high-dose/low-dose extrapolation assumptions. Regulations should be periodically revised to reflect significant new scientific knowledge.

BACKGROUND

Bromate ion (BrO₃⁻) is a potential contaminant in treated drinking water. Although other oxidative processes can also produce bromate in water, the two principal sources are oxidation of bromide ion during ozonation and introduction of bromate as a constituent of hypochlorous acid (HOCl) produced by electrolysis of salt containing some bromide. Bromate is an animal carcinogen at high doses (e.g., ~6.1 mg/kg/d in male rats; DeAngelo et al, 1998). The susceptibility of animals to bromate carcinogenicity in the kidney is highly variable, ranging from the most susceptible male rat to the female rat (~1/2), mouse (~1/5), and hamster (~1/50) (Gold, 2005). Bromate has been regulated by the US Environmental Protection Agency (USEPA) as a probable human carcinogen.
with a MCLG of zero and an enforceable MCL of 0.010 mg/L (USEPA, 1998). The World Health Organization (WHO) guideline is also 0.010 mg/L (WHO, 2004). The hypothetical upper-bound human lifetime exposure risks have been calculated at 0.010 mg/L (10 µg/L) of 2/10,000 (2 × 10–4) by USEPA and 5/100,000 (0.5 × 10–4) by WHO. The calculation models assume that effects observed at high animal test doses can be extrapolated to human exposures at much lower environmentally relevant doses and that some finite (although small) risk will occur at any nonzero dose for a genotoxic carcinogen. The USEPA policy is to consider an MCL for a carcinogen within the nominal risk range of 1/1,000,000 to 1/10,000 as safe and protective of public health. WHO guidelines for genotoxic carcinogens are usually set at the nominal upper-bound risk value of 1/100,000, and WHO then describes how the value can be adjusted by a factor of 10 above or below the guideline (i.e., 1/10,000 to 1/1,000,000).

The concern from high-dose bromate studies in male test rats pertains to cancers in the kidney, thyroid, and testes; the liver is not a target organ. However, a substantial body of evidence indicates that effects observed at high doses may not be likely to occur at much lower doses (Bull & Cotruvo, 2006; Cotruvo & Bull, 2006). There is even the possibility that a “practical threshold” of exposure exists, below which there is essentially no bromate-related cancer risk. Animals, including humans, have redundant processes for detoxifying oxidants such as bromate as well as mechanisms to repair deoxyribonucleic acid damage caused by low levels of oxidative stressors. Risk assessments have not considered either of those processes and therefore must be overestimating the actual risks, if any, that may occur at low doses.

Bromate ion can engage in a series of oxidation–reduction reactions where it can be re-formed and is in equilibrium with several oxybromine and bromine species unless sufficient reactive-reducing agents are present to irreversibly consume all of the oxidized bromide species. Bromate is a strong oxidizing agent, especially at low pH, with a redox potential of 1.44 V (Singh et al, 1989). Under strongly acidic conditions, such as human gastric juice, bromate is capable of slowly oxidizing chloride and bromide ions to chlorine (Cl2), bromine (Br2), and bromine chloride (BrCl; Keith et al, 2006; Schulek et al, 1960), which would rapidly undergo further reactions with constituents present in gastric juice. Bromate is rapidly reduced in the presence of better reducing agents such as sulfide ion (Keith et al, 2006) and sulfite ion (Gordon et al, 2002). Studies with chromium(VI) in gastric juice have demonstrated that the stomach has the capacity for reduction of certain oxidizing agents (Paustenbach et al, 2003; Kerger et al, 1997).

Bromate oxidation–reduction processes in acidic solution. Eq 1 shows the stoichiometric reaction of bromate with chloride (Cl–) in acidic conditions:

\[
BrO_3^- + 5Cl^- + 6H^+ = 2Cl_2 + BrCl + 3H_2O
\]

(1)

The preliminary one-term experimental rate law (Keith et al, 2006) is

\[
-d[BrO_3^-]/dt = 2.2[BrO_3^-] [H^+]^2 [Cl^-]^{1.75}
\]

(2)

The one-term rate law in the presence of hydrochloric acid (HCl) can be rewritten as two terms that represent parallel pathways:

\[
-d[BrO_3^-]/dt = k_1[BrO_3^-] [H^+]^2 [Cl^-] + k_2[BrO_3^-] [H^+]^2 [Cl^-]^2
\]

(3)

The two-term rate law constants, \(k_1\) and \(k_2\), were determined by plotting the (experimental rate/[BrO_3^-] [H+]^2 [Cl–] versus [Cl–]); the equation of the line is \(y = 3.83x + 0.283\) and the correlation coefficient is 0.917. Rate constants \(k_1\) and \(k_2\) are 0.28 L^3 mol^-3 min^-1 and 3.8 L^4 mol^-4 min^-1, respectively. The preliminary two-term experimental rate law becomes

\[
-d[BrO_3^-]/dt = 0.28[BrO_3^-] [H^+]^2 [Cl^-] + 3.8[BrO_3^-] [H^+]^2 [Cl^-]^2
\]

(4)

Bromate will also oxidize organothiols. For example, under acidic conditions, bromate oxidizes cysteamine (NH2CH2CH2SH) first to taurine (NH2CH2CH2SO3H); then the taurine is brominated to the N-Br compound (Morakinyo et al, 2008). The reaction is reversible back to taurine with reducing agents such as iodide ion.

The reaction scheme shown in the sidebar on page 79 illustrates some opportunities for re-formation of bromate during oxidation–reduction processes in the presence of excess oxidizing species. This phenomenon is important when considering the kinetics of bromate disappearance under reducing conditions with varying amounts of reducing agents. Bromate can be re-formed to some degree if it is not removed by sufficient reducing agent to convert all of the oxidizing species to inactive forms. Under incomplete reduction conditions, regeneration of bromate would result in a net lessening of the apparent rate of conversion.

A comprehensive research plan was developed to examine in vivo metabolism and detoxification chemistry of bromate for a physiologically based pharmacokinetic (PBPK) model and to generate a revised risk assessment with a more scientifically credible methodology. Earlier publications (Keith et al, 2006; 2005) described the kinetics of bromate reduction with chloride and initial studies of hydrogen sulfide (H2S) in simulated gastric juice. PBPK models address the kinetic processes that function in a living animal as they affect the transport and metabolism of a chemical and dosages to organs where the chemical may be transported. This simulated stomach kinetics information is basic to other studies of the overall decomposition of bromate in the liver and bloodstream of...
animals (AwwaRF, 2007). Additional sulfide ion kinetics and the mitigating or enhancing effects of several common oxidizing and reducing agents present in drinking water or in the stomach are reported in this article.

MATERIALS AND METHODS

Reagents. Solutions and standards were prepared from reagent-grade chemicals. Triple-distilled water (TDW) was prepared using a purification system.1

The chemicals required for ion chromatography (IC) operation were carbonate eluent, postcolumn reagent, and sulfuric acid (H2SO4). A 9.00 × 10⁻³ M carbonate eluent was used. An ammonium molybdate stock solution of 0.247 g in 100.0 mL of TDW was prepared. The postcolumn reagent was prepared fresh daily from 8.620 g of potassium iodide (KI) in 100 mL of TDW, addition of 43.0 µL of ammonium molybdate stock solution, followed by dilution to 200.0 mL with TDW. The carbonate eluent and polymer chain reaction were degassed with nitrogen before IC operation.

Bromate ion standards were prepared by dilution from a bromate stock solution of 0.131 g of potassium bromate (purity 99.88%) in 100.0 mL of TDW. A second stock solution was prepared by diluting 1.00 mL of the 1.00-g/L bromate stock solution in 100.0 mL of TDW to a final concentration of 1.00 × 10⁻² g/L. Both solutions were stored at 4°C for a maximum of 21 days. HCl solutions of 0.170, 0.100, 5.00 × 10⁻², and 1.00 × 10⁻² M were prepared by adding 10.45, 6.15, 3.07, and 6.10 × 10⁻¹ mL, respectively, of 4.07 M HCl and diluting to 250.0 mL with TDW.

Preparation and measurement of stock HOCl/Cl₂ and NH₂Cl solutions. A 750-mL HOCl/Cl₂ solution was prepared by adjusting the pH of TDW with 50% sodium hydroxide (NaOH) to 11.4±0.1 and bubbling high-purity chlorine gas to a pH of 2.0. The solution was stored in an inert plastic bottle and refrigerated at 4°C for a maximum of seven days.

A 165-mL NH₂Cl solution was prepared by mixing 0.803 g of ammonium chloride (Standard Methods, 1985) with 160 mL of HOCl/Cl₂ solution; following adjustment of the pH to 8.20±0.05 with carbonate-free NaOH, the solution was stored in an inert plastic bottle and refrigerated at 4°C for a maximum of seven days. Concentrations of HOCl/Cl₂ or NH₂Cl stock solutions were determined by iodometric titration with standardized sodium thiosulfate.

Measurement of ferrous ion and ferric ion in solution. Solutions required for the measurement of ferrous ion and ferric ion...
and ferric ion included hydroxylamine, 0.170 M HCl, sodium acetate, ammonium acetate buffer, potassium permanganate, and phenanthroline (Standard Methods, 1985). Concentrations of ferric ion in solution were calculated by subtracting ferrous ion from the total iron concentrations.

Bromate-reduction experimental procedure. Before the bromate-reduction experiments, the pH of the matrix and of a 200-µg/L bromate standard in the matrix was measured to confirm that the pH was in the specified range. Check standards measured before and after calibration standards confirmed IC performance.

After the calibration and check standards measurements, the temperature of the solution was raised to 37°C±1°C in a water bath to mimic human body temperature. An initial concentration of 200 µg/L bromate was chosen for all bromate-reduction experiments to minimize experimental error because the minimum reporting level for bromate in the IC was ~3 µg/L, and chloride interferences in IC separations necessitated higher initial concentrations. The solution and sample were mixed, start time was recorded, and an aliquot was measured immediately by IC and at 30-min intervals until at least 50% reduction of bromate had occurred.

Measurement of H2S in gastric juice. A method was developed to measure H2S in human gastric juice (Orion Research Inc., 1980; Shanthi & Balasubramanian, 1996). A sulfide antioxidant buffer (SAOB) was prepared by mixing 110 mL of concentrated NaOH, 67 g of disodium EDTA, and 35 g of ascorbic acid and diluting to 1 L with deaerated TDW. A sulfide ion/SAOB stock solution was prepared by adding 5.00 mL of stock sulfide solution and 250.0 mL of SAOB and diluting to 500 mL with deaerated TDW. An iodine solution was prepared by adding 1.000 g KI, 10.00 mL of 7.946 × 10⁻³ M potassium iodate, and 1.00 mL of concentrated H2SO4 and diluting to 100.0 mL with deaerated TDW. A total of 1.00 mL of gastric juice was mixed with 25.0 mL of SAOB and diluted to 50.0 mL with deaerated TDW. The standard potential of the solution and the calibration curve line equation were used to calculate the sulfide ion concentration in the gastric juice, which is proportional to the H2S concentration. The H2S concentration in the human gastric juice sample was 7.7 × 10⁻⁵ M.

The H2S concentration was also measured by the method of standard additions. Nine additions for a total of 590 µL of 1.13 × 10⁻¹ M standard were added to a 50.0-mL solution containing 1.00 mL of gastric juice, 25.0 mL of SAOB, and 24.0 mL of TDW. The standard addition method gave the concentration of 9.2 × 10⁻⁵ M. The average of the results of the two methods was 8.5 × 10⁻⁵ M H2S. The ±10% difference in the two methods could be partly attributable to the volatility of H2S in the low-pH gastric juice samples.

DISCUSSION

Bromate reduction with H2S. The current research measured H2S concentrations in a human gastric juice sample provided by Bernard Bouscarel of the George Washington University School of Medicine in Washington, D.C. The composition of gastric juice will vary throughout the human population, and some people are known to be achlorhydric (Best & Taylor, 1961). For this reason, the effect of varying H2S and hydrogen ion with constant 0.170 M Cl⁻ was studied (Keith et al, 2006). Table 1 shows that under these conditions, the bromate half-life decreased from 153 min in 0.170 M HCl and no H2S to ~2 min in 0.170 M HCl and 10⁻⁴ M H2S; thus, 0.170 M HCl and 10⁻⁴ M H2S can effectively reduce bromate ion by more than 95% in <10 min. Reaction rates with these reducing agents are slower as acidity is decreased. Studies have shown that after ingestion of water on an empty stomach, approximately 30 min is required for 90% of the water to leave the stomach; about 50% is retained for 10 min (Cooke, 1970). Therefore, the decomposition half-life should be considerably <30 min to be biologically relevant.

The stoichiometric reaction of H2S and bromate is shown in the subsequent equations. For simplicity, the major reactants (BrO₃⁻ + S²⁻) are shown, but typically not all of the products are shown, and hydrogen ions, hydroxide ions, and water molecules are omitted because they are rapidly used in subsequent reactions.

\[4\text{BrO}_3^- + 3\text{S}^2^- \rightarrow 4\text{Br}^- + 3\text{SO}_4^{2-}\]  \hspace{1cm} (5)

Indications are that H2S reacts in stepwise reduction processes to form the bromine-containing intermediate BrO₂, which reacts with additional H₂S to form bromite ion (BrO₂⁻), which is further reduced to bromide if sufficient H₂S is available. If there is insufficient reducing agent present—as in some of the test matrices in the current research but unlikely in vivo partly because of continuous swallowing of saliva—disproportionation is a possible reaction for the regeneration of bromate ion:

\[2\text{BrO}_2 \rightarrow \text{BrO}_2^- + \text{BrO}_3^-\]  \hspace{1cm} (6)

At 10⁻⁴ M H₂S, there is a large molar excess of H₂S relative to bromate, resulting in the rapid and probably
complete reduction of bromate and its intermediate oxy-
bromine species to bromide; at 10⁻⁵ M H₂S, the bromate 
reduction rate decreases. The bromate half-life in 0.170 
M HCl and 10⁻⁴ M H₂S is ~2 min; the half-life with 10⁻⁵ 
M H₂S is 14 min. At 10⁻⁶ M H₂S, bromate is now in 
excess, compared with H₂S, and that increases the 
apparent bromate half-life to 32 min. Even 10⁻⁶ M H₂S has a 
significant effect on the bromate-reduction rate, 
compared with HCl alone.

The expanded preliminary rate law becomes

\[-d[BrO_3^-]/dt = k_1[BrO_3^-] [H^+]^2 [Cl^-] + k_2[BrO_3^-] [H^+]^2 [Cl^-]^2 + k_3[BrO_3^-] [H_2S]^m [H^+]^n\] (7)

The reaction order with respect to H₂S is 0.55±0.05. 
Thus, an increase of the H₂S concentration will have a 
less than first-order effect on bromate reduction. The 
order with respect to hydrogen ion is 1.10±0.04; increasing 
concentrations of hydrogen ion may have a slightly 
greater than first-order effect on bromate reduction.

In summary, the addition of 10⁻⁴ to 10⁻⁶ M H₂S 
greatly increases the rate of bromate reduction in simu-
lated gastric juice. After ingestion of a glass of water in 
an empty stomach, the 20–40 cc (Best & Taylor, 1961) 
or 50–100 cc of gastric juice (Kotiaho et al, 1992) would 
initially be diluted, followed by rebound as more gastric 
juice is secreted. Approximately 1.14 meq (approximately 
3.4 meq/L) of acid is secreted in each 5-min period after 
-ingestion of 350 cc of water (Cooke, 1970). The presence 
of 8.5 × 10⁻⁵ M H₂S (approximately 10⁻⁴ M) measured in 
human gastric juice could therefore have a significant 
effect on the bromate reduction rate in the stomach.

COMMONLY INGESTED AND AVAILABLE OXIDIZING 
AGENTS AND THEIR EFFECT ON BROMATE REDUCTION 
in simulated gastric juice

Free available chlorine. Studies were designed to mea-
sure the bromate reduction rate in the presence of reduc-
ing and oxidizing agents, with and without varying 
concentrations of H₂S. Free available chlorine (Cl₂, 
HOCI, OCl⁻) is a disinfectant and strong oxidizing agent 
commonly present in drinking water at residual concen-
trations of ~0.1 to 2 mg/L. For beyond worst-case simu-
lations, concentrations of 2, 4, and 10 mg/L free avail-
able chlorine were added to 200 µg/L bromate ion at 
37°C in simulated gastric juice (0.170 M HCl, with and 
without H₂S). Half-lives for each bromate experiment 
are shown in Table 1.

The data in Table 1 show that at 10⁻⁴ M H₂S, the rate 
of bromate reduction was significantly greater than with-
out H₂S and was not significantly changed in the presence 
of 2 mg/L HOCl. At 4 mg/L HOCl, the rate was slower 
but still biologically relevant with respect to retention time 
in the stomach. At 10⁻⁵ M H₂S, the decomposition rate 
was slowed but still biologically relevant at both 2 and 4 
mg/L HOCl. At 10⁻⁶ M H₂S and HOCl, the rate was 
slower and no longer biologically relevant.

As expected, the presence of a sufficient quantity of 
competing oxidizing agent decreased the rate of bromate 
reduction (the half-life increased), but it was a function of 
the relative concentrations of H₂S and HOCl. With water 
consumption, it would also be a function of the rate of 
reaction of the HOCl with other components (including 
saliva), which should be rapid (seconds or less). At 10⁻⁴ 
M H₂S, the rate reduction was small, if any, at common 
levels of residual chlorine in drinking water. The rate 
reduction would also be affected by direct competitive 
reactions between H₂S and the remaining HOCl to pro-
duce sulfur, sulfite ion, or sulfate ion and possibly other, 
more-reactive, sulfur-containing intermediates. In the pH 
range of 6–12, re-formation of bromate ion in the presence 
of an excess oxidizing agent has been described by the 
following set of reactions (Bousher et al, 1990). However, 
with excess reducing agents present, as in the human gas-
trointestinal tract, this would not be expected to occur.

\[2HOBr → HBrO_2 + HBr\] (8)

\[HBrO + HBrO_2 → HBrO_3 + HBr\] (9)

The net reaction is

\[3HBrO = HBrO_3 + 2HBr\] (10)

With free available chlorine in the range of 6–12 pH, 
a possible set of mechanistic reactions that would result 
in the re-formation of bromate ion is as follows (Furman 
& Margerum, 1998):

\[HBrO + HOCl⁻ → HBrO_2 + HCl\] (11)

\[HBrO_2 + HOCl → HBrO_3 + HCl\] (12)

The net reaction is

\[HBrO + 2HOCl = HBrO_3 + 2HCl\] (13)

| TABLE 1 | Bromate half-life in 0.170 M HCl with HOCl/Cl₂ and H₂S |
| HOCI mg/L | Bromate Half-life—min |
| 0 H₂S | 10⁻⁴ M H₂S | 10⁻⁵ M H₂S | 10⁻⁶ M H₂S |
| 0 | 153 | -2 | 14 | 32 |
| 2 | 200 | -2 | 19 | 43 |
| 4 | 211 | 5 | 21 | 273 |

HCl—hydrochloric acid, HOCl—hypochlorous acid, H₂S—hydrogen sulfide.
**NH₂Cl.** The mild oxidizing agent and disinfectant, NH₂Cl, is commonly found in distributed drinking water at median residual concentrations of ~1.5 to 2.7 mg/L (McGuire & Meadow, 1988). NH₂Cl is not as strong of an oxidizing agent as HOCl/Cl₂; however, under strong acidic conditions, protonation could alter its normal chemistry because of a shift of the equilibrium between NH₂Cl and the hydrolysis products ammonia (NH₃) and HOCl. At pH 4, NH₂Cl is entirely converted to dichloramine (NRC, 1980). NH₂Cl at levels up to 15 mg/L has been shown to decompose in human gastric juice in 30 s or less (Kotiaho et al, 1992), whereas saliva at much higher pH values requires more than 2 h.

Concentrations of 4 and 10 mg/L NH₂Cl (to simulate extremes) were added to 200-µg/L bromate samples at 37°C in simulated gastric juice (0.170 M HCl, with and without H₂S). The calculated half-lives are shown in Table 2. With 10⁻⁴ and 10⁻⁵ M H₂S, which is excess reducing agent compared with bromate, the decomposition rate was slowed with 4 and 10 mg/L NH₂Cl but was still somewhat faster than HOCl at 4 mg/L (Table 1) and was biologically relevant with respect to retention time in the stomach. At 10⁻⁶ M H₂S and 10 mg/L NH₂Cl, bromate was in excess, compared with H₂S, and the rate was slower and no longer biologically relevant. At 4 and 10 mg/L and 10⁻⁴ M H₂S, NH₂Cl decreased the rate of bromate ion reduction in about the same range as HOCl at 4 mg/L; half-lives for 10⁻⁴ M H₂S were 9 and 7 min with 4 and 10 mg/L NH₂Cl, respectively (Table 2), versus half-life of 5 min with 4 mg/L HOCl (Table 1). At 10⁻⁵ H₂S, the rate was somewhat faster than HOCl at 4 mg/L.

Chloramine exists in equilibrium with NH₃ and HOCl (NH₄⁺ and OCl⁻); HOCl and HCl are in equilibrium with Cl₂ and H₂O.

\[
2 \text{NH}_2\text{Cl} + \text{H}^+ = \text{NHCl}_2 + \text{NH}_4^+ \quad (14)
\]

\[
\text{NH}_2\text{Cl} + \text{H}_2\text{O} = \text{HOCl} + \text{NH}_3 \quad (15)
\]

\[
\text{HOCl} + \text{HCl} = \text{Cl}_2 + \text{H}_2\text{O} \quad (16)
\]

However, a decreased rate of bromate ion reduction may also be attributable to the initial reaction of bromate to form bromine-containing intermediates, such as BrO₂⁻, which might possibly be reoxidized by excess NH₂Cl (or more likely HOCl) to re-form bromate:

\[
\text{BrO}_2^- + \text{NH}_2\text{Cl} + \text{H}_2\text{O} = \text{BrO}_3^- + \text{NH}_4^+ + \text{Cl}^- \quad (17)
\]

These results indicated that ingestion of NH₂Cl at concentrations typically found in drinking water would have little effect on bromate reduction in the stomach.

**Ferric ion.** Ferric ion is commonly consumed in foods such as dairy products and vegetables. The average intake of ferrous ion plus ferric ion is between 6 and 12 mg per day. Chlorine would readily oxidize ferrous ion to ferric ion. Highly excessive concentrations of 1, 2, 5, and 10 mg/L iron(III) were added to 200 µg/L bromate ion at 37°C in simulated gastric juice (0.170 M HCl, with and without H₂S); half-lives for bromate decomposition are shown in Table 3.

In the presence of ferric ion, 0.170 M HCl, and 10⁻⁴, 10⁻⁵, or 10⁻⁶ M H₂S, the rate of bromate reduction decreased by factors of 2 to 3, compared with the absence of ferric ion. Additional ferric ion gave a fairly constant slowing effect on the bromate reduction rate at each H₂S concentration. The half-lives at 10⁻⁴ M H₂S were biologically relevant, whereas the 10⁻⁵ M H₂S and 10⁻⁶ M H₂S half-lives were not.

\[
\text{BrO}_3^- + \text{H}_2\text{S} \rightarrow \text{BrO}_2^- \quad (18)
\]

\[
\text{BrO}_3^- + \text{Fe}^{3+} \rightarrow \text{BrO}_2^- + \text{Fe}^{2+} \quad (19)
\]

\[
\text{H}_2\text{S} + 2\text{Fe}^{3+} = 2\text{Fe}^{2+} + 2\text{H}^+ + \text{S(s)} \quad (20)
\]

Any of these reactions would result in less H₂S being available to react with bromate and thus slow the reduction rate.

---

**TABLE 2** Bromate half-life in 0.170 M HCl with NH₂Cl and H₂S

<table>
<thead>
<tr>
<th>NH₂Cl mg/L</th>
<th>0 H₂S</th>
<th>10⁻⁴ M H₂S</th>
<th>10⁻⁵ M H₂S</th>
<th>10⁻⁶ M H₂S</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>153</td>
<td>2</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>4</td>
<td>276</td>
<td>9</td>
<td>9</td>
<td>231</td>
</tr>
<tr>
<td>10</td>
<td>278</td>
<td>7</td>
<td>10</td>
<td>185</td>
</tr>
</tbody>
</table>

NH₂Cl—monochloramine, HCl—hydrochloric acid, H₂S—hydrogen sulfide

**TABLE 3** Bromate half-life in 0.170 M HCl with ferric ion and H₂S

<table>
<thead>
<tr>
<th>Ferric Ion mg/L</th>
<th>0 H₂S</th>
<th>10⁻⁴ M H₂S</th>
<th>10⁻⁵ M H₂S</th>
<th>10⁻⁶ M H₂S</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>153</td>
<td>2</td>
<td>14</td>
<td>32</td>
</tr>
<tr>
<td>1</td>
<td>182</td>
<td>4</td>
<td>35</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>181</td>
<td>5</td>
<td>39</td>
<td>85</td>
</tr>
<tr>
<td>5</td>
<td>154</td>
<td>5</td>
<td>42</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>164</td>
<td>6</td>
<td>42</td>
<td>85</td>
</tr>
</tbody>
</table>

HCl—hydrochloric acid, H₂S—hydrogen sulfide
The source and oxidation state of ferrous ion and ferric ion in the stomach is not likely to be Fe(OH₂)₆²⁺ and/or Fe(OH₂)₆³⁺. The iron will probably be complexed species (such as FeCl₂⁺) and/or other more complicated ferric ion–ligand complexes or complexes with organic materials. The oxidation potential of Fe(CN)₅(NH₃)³⁻ is Eₒ = –0.374 V, that of Fe(CN)₅(H₂O)⁻³ is Eₒ = –0.491 V, and that of Fe(CN)₅(NO₂)⁻³ is Eₒ = –0.516 V.

Summary of oxidizing agents’ effects on bromate-reduction half-lives with H₂S. A comparison of the oxidizing agents ferric ion, Cl₂, and NH₂Cl in the presence of H₂S showed that each has a concentration-dependent, greater or lesser slowing effect on the net bromate-reduction rate. With 10⁻⁴ M H₂S and ferric ion, at all tested concentrations, the bromate reduction rate was more rapid than with NH₂Cl but slower than with Cl₂ at 4 mg/L. The reduction rates at 10⁻⁵ M H₂S and ferric ion were slower than those of Cl₂ and NH₂Cl at all doses tested. With 10⁻⁶ M H₂S and ferric ion, the reduction rate was significantly faster than that of Cl₂ at 4 mg/L and NH₂Cl at all doses tested.

As expected, all of the oxidizing agents tested can compete with bromate in the oxidation of sulfide, and they often reduced the net rates of bromate reduction. However, the decreases of the reduction rates were usually small with 10⁻⁴ M H₂S and 10⁻⁵ M H₂S. Rates of bromate reduction were sensitive to pH and were slower as pH rose. With water consumption on an empty stomach, the pH would be initially in the range of 1–3 before rebound, and the retention time would be in the range of ~10–30 min. In the presence of ingested food, the pH would initially be in the range of 3–4 before rebounding to lower pH values, but the retention times could also extend to several hours.

COMMONLY INGESTED AND AVAILABLE REDUCING AGENTS AND THEIR EFFECT ON BROMATE ION REDUCTION IN SIMULATED GASTRIC JUICE

Additional reducing agents should contribute to the reduction of bromate under simulated stomach conditions, an assumption that was verified by the current studies. Iodide, nitrite, and ferrous ion were individually studied by adding them to 200 µg/L bromate at 37°C in 0.170 M HCl, with and without H₂S, and the half-lives of bromate reduction were calculated.

Iodide ion (I⁻). The reducing agent, I⁻, is an essential nutrient consumed daily from seafood, milk, and table salt (WHO, 1996). Typical consumption of iodine is approximately 100–200 µg/d, and iodide is recirculated by the sodium iodide symporter (NIS). The effect of bromate reduction with iodide was measured by adding excess concentrations of 1, 2, 5, and 10 mg/L I⁻ to 200 µg/L bromate at 37°C in simulated gastric juice (0.170 M HCl, with and without H₂S). The calculated half-life for each bromate experiment is shown in Table 4. The data demonstrated that iodide was an effective reducing agent for bromate under these conditions and that there was a consistent trend of shorter half-lives with increased iodide concentration at all H₂S concentrations, after an initial slowing at 1 or 2 mg/L iodide.

A plot of log bromate half-life (min) versus log iodide concentration (milligrams per litre) in the absence of H₂S is linear, and the equation of the line is y = –0.85x + 2.06. The reaction order of 0.85 for iodide, which is < 1, indicated that iodide was competing with other reducing agents to reduce bromate. The reduction of bromate in the presence of acid and iodide can be represented by the balanced stoichiometric equation

\[
\text{BrO}_3^- + 9I^- + 6H^+ = 3I_3^- + Br^- + 3H_2O
\]  

(21)

The initial steps in the reaction are probably

\[
\text{BrO}_3^- + I^- \rightarrow \text{BrO}_2^- + \text{I}^-
\]  

(22)

With 10⁻⁴ M H₂S and 1 or 2 mg/L iodide, the rate of bromate reduction was slightly decreased. The effect was minimal, perhaps because the reaction was already fast in the presence of 10⁻⁴ M H₂S and HCl. Therefore, addition of iodide had little overall effect on the rate.

The plot of log of bromate half-life versus log of iodide with 10⁻⁶ M H₂S concentration is linear, and the equation of the line is y = –0.61x + 1.69. The reaction order with respect to iodide ion was 0.6. The order of < 1 indicated that iodide was competing with H₂S to reduce bromate. A comparison of the 0.6 order with 10⁻⁶ M H₂S and the 0.85 order without H₂S indicated that iodide had a small but positive effect on the rate of bromate reduction with 10⁻⁶ M H₂S. Both iodide and H₂S reacted with bromate, resulting in a small net increase in the rate of bromate reduction, compared with H₂S alone.

The ingestion of foods containing typical concentrations of iodide would have a small effect on the rate of bromate reduction in the stomach. All of the rates of reduction with

<table>
<thead>
<tr>
<th>Iodide Ion mg/L</th>
<th>Bromate Half-life—min</th>
</tr>
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<tbody>
<tr>
<td>0 H₂S</td>
<td>10⁻⁴ M H₂S</td>
</tr>
<tr>
<td>0 153</td>
<td>2</td>
</tr>
<tr>
<td>1 111</td>
<td>5</td>
</tr>
<tr>
<td>2 66</td>
<td>4</td>
</tr>
<tr>
<td>5 28</td>
<td>1-1.5</td>
</tr>
<tr>
<td>10 16</td>
<td>1-1.5</td>
</tr>
</tbody>
</table>

HCl—hydrochloric acid, H₂S—hydrogen sulfide
iodide in these studies at 10⁻⁴ M H₂S would be biologically relevant; they are marginal at 10⁻⁵ M H₂S.

Nitrite ion. Nitrite is consumed daily in processed meats and vegetables (Epley et al, 2005), and it is produced by reduction of nitrate and recycled into the stomach through saliva. The estimated dietary intake of nitrite in the United Kingdom in 1985 was 2.4–4.2 mg/d (Meah et al, 1994) and that of nitrate was 54 mg/d. Nitrate is commonly found in drinking water, and nitrite can be found in non-disinfected water under reducing conditions. The MCLs for nitrite and nitrate are 1 and 10 mg/L, respectively, as N. Nitrite is recirculated to the stomach via saliva. In the current study, concentrations of 1, 2, 5, and 10 mg/L nitrite were added to 200 µg/L bromate at 37°C in simulated gastric juice (0.170 M HCl, with and without H₂S). Calculated half-lives are shown in Table 5.

Nitrite under these conditions was a very effective reducing agent for bromate. All of the half-lives increased the rate of reduction, compared with H₂S alone. Half-lives listed as 1–1.5 min in Table 5 are all at the lower limits of the experimental sampling and analysis procedure. At 10⁻⁵ M H₂S, there was a molar excess of H₂S and nitrite compared with bromate, whereas at 10⁻⁶ M H₂S, bromate was in excess. A plot of log bromate half-life (min) versus log nitrite (milligrams per litre) in the absence of H₂S gives a linear equation of

\[ y = 1.07x + 1.33 \]

and a slope of –0.94 V, –0.54 V, –0.14 V, respectively. Thermodynamically, it might be expected that the initial step of bromate reduction would be most favored with H₂S and least favored with nitrite. Table 4 shows that overall bromate reduction was slower with iodide and faster with H₂S. Bromate reduction is most probably kinetically controlled, indicating that BrO₂⁻ and BrO₂⁻ intermediates markedly affect the rate at which each of the reducing agents removes and/or allows reformation of bromate ion. Thus small amounts of nitrite should result in an increase in the rate of bromate ion reduction in the stomach and compensate for gastric juices with lower H₂S concentrations.

Ferrous ion. Ferrous ion is commonly consumed in foods such as meats, poultry, and fish. Ferrous ion will be readily oxidized to ferric ion in chlorinated drinking water. Concentrations of 1, 2, 5, and 10 mg/L ferrous ion were added to 200 µg/L bromate ion at 37°C in simulated gastric juice (0.170 M HCl, with and without H₂S). Half-lives were calculated as shown in Table 6. The addition of ferrous ion generally reduced the half-life of bromate because the rate was increased by reduction of bromate ion.

Each step in the reduction mechanism occurs by means of a two-electron transfer process. With 10⁻⁴ M H₂S, the addition of nitrite had little apparent effect on the rate of bromate reduction because the rate was already very rapid with 10⁻⁴ M H₂S and HCl. The absence of an oxidizing agent or one-electron reduction process resulted in no regeneration of bromate with 10⁻⁴ M H₂S, HCl, and nitrite. The bromate reduction rate appeared to remain constant for all nitrite concentrations and is indicative of a two-term rate law for the loss of bromate ion.

With 10⁻⁶ M H₂S and nitrite, effects on the bromate-reduction rate were mixed. A plot of log bromate half-life (min) versus log nitrite (milligrams per litre) with 10⁻⁶ M H₂S gives a linear equation of

\[ y = -1.23x + 1.52 \]

and a slope of –1.23, and reaction order with respect to nitrite is approximately 1.2; increasing concentration of nitrite will have a greater than first-order effect on bromate reduction.

The effect of nitrite concentration on the rate of bromate reduction can be described by the following two-term rate law:

\[ \text{Rate} = k_1 [\text{BrO}_3^-][\text{NO}_2^-] + k_2 [\text{BrO}_3^-][\text{NO}_2^-]^2 \]

The oxidation potentials of nitrite ion, iodide ion, and H₂S are –0.94 V, –0.54 V, –0.14 V, respectively. Thermodynamically, it might be expected that the initial step of bromate reduction would be most favored with H₂S and least favored with nitrite. Table 4 shows that overall bromate reduction was slower with iodide and faster with H₂S. Bromate reduction is most probably kinetically controlled, indicating that BrO₂⁻ and BrO₂⁻ intermediates markedly affect the rate at which each of the reducing agents removes and/or allows reformation of bromate ion. Thus small amounts of nitrite should result in an increase in the rate of bromate ion reduction in the stomach and compensate for gastric juices with lower H₂S concentrations.

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\[ y = -0.58x + 1.97 \]

TABLE 5 Bromate half-life in 0.170 M HCl with nitrite ion and H₂S

<table>
<thead>
<tr>
<th>Nitrite Ion mg/L</th>
<th>Bromate Half-life—min</th>
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<tbody>
<tr>
<td>0 H₂S</td>
<td>0.170 M H₂S</td>
</tr>
<tr>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>20</td>
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<tr>
<td>2</td>
<td>10</td>
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<td>5</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>1–1.5</td>
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</tbody>
</table>

HCl—hydrochloric acid, H₂S—hydrogen sulfide
respect to ferrous ion. The stoichiometric reaction of ferrous ion and bromate in acid is

\[ \text{BrO}_3^- + 6 \text{Fe}^{2+} + 6 \text{H}^+ = 6 \text{Fe}^{3+} + \text{Br}^- + 3 \text{H}_2\text{O} \] (29)

Initial steps in the reaction of bromate ion with ferrous ion in acid likely are

\[ \text{BrO}_3^- + \text{Fe}^{2+} \rightarrow \text{Fe}^{3+} + \text{BrO}_2 \](30)

\[ \text{BrO}_2 + \text{Fe}^{2+} \rightarrow \text{BrO}_2^- + \text{Fe}^{3+} \] (31)

Ferrous ion can react with bromate, \(\text{BrO}_2\), and \(\text{BrO}_2^-\) and minimize regeneration of bromate; however, the generated ferric ion can possibly react with those species to re-form some bromate ion. Ferric ion can also react with and remove \(\text{H}_2\text{S}\), but the ferrous ion that is formed can reduce additional bromate and \(\text{BrO}_2\). This cycle can result in a steady-state bromate reduction rate with ferrous ion and \(10^{-4}\) to \(10^{-5}\) M \(\text{H}_2\text{S}\).

\[ \text{H}_2\text{S} + 2 \text{Fe}^{3+} = 2 \text{Fe}^{2+} + 2 \text{H}^+ + \text{S}(s) \] (32)

Results suggested that the consumption of foods containing even small amounts of ferrous ion would have a positive effect on the rate of reduction of bromate ion in the stomach.

**CONCLUSIONS**

The kinetics of bromate ion decomposition under simulated stomach/gastric juice conditions was investigated as the first part of a series of studies aimed at more accurately determining the risk of environmentally relevant exposures to bromate in drinking water. Depending on dose, presystemic decomposition may not reduce all of the ingested bromate, and \(\text{pH}\) and gastric juice composition will vary by individual and stomach contents. These kinetics studies showed that bromate decomposition begins in the stomach after ingestion, as a prelude to further metabolism in the liver and blood. Human gastric juice is secreted at \(~0.150–0.170\) M, commonly in the \(\text{pH}\) range of 1–2; however, there are individuals with higher \(\text{pH}\) values, including some who are achlorhydric. The bromate reduction rate with inorganic ions is \(\text{pH}\)-dependent and much more rapid at low \(\text{pH}\).

Presystemic decomposition can begin in the stomach because of the acidity and the presence of inorganic reducing agents, and it should contribute to a lower dose to target organs. Bromate ion will slowly oxidize chloride ion to chlorine and \(\text{BrCl}\) under highly acidic conditions, and the decomposition rate is significantly increased with \(\text{H}_2\text{S}\). Analysis of a human gastric juice sample quantified \(\text{H}_2\text{S}\) at a mean concentration of \(8.5 \times 10^{-5}\) M, which could be a somewhat low measurement because of the volatility of \(\text{H}_2\text{S}\) under the acidic conditions of gastric juice and probable losses from its volatility during gastric juice sample collection from the donor and analysis. Kinetic studies of bromate reduction were carried out with 200 \(\mu\)g/L bromate at 37°C in simulated gastric juice at 0.170 M HCl, with and without \(\text{H}_2\text{S}\) additions of \(10^{-4}\), \(10^{-5}\), and \(10^{-6}\) M to produce baseline rates of the effect of \(\text{H}_2\text{S}\). Half-lives of the reactions ranged from 153 min at zero \(\text{H}_2\text{S}\) to 2, 24, and 32 min at \(10^{-4}\), \(10^{-5}\), and \(10^{-6}\) M \(\text{H}_2\text{S}\), respectively. Half-lives at \(10^{-5}\) M \(\text{H}_2\text{S}\) and in particular \(10^{-4}\) M \(\text{H}_2\text{S}\) are biologically relevant for retention time of water in an empty stomach of \(~10–30\) min.

The current research also studied the mitigating effects of several oxidizing agents (\(\text{HOCl/Cl}_2\), chloramine, and ferric ion) and rate-enhancing effects of reducing agents (ferrous ion, iodide ion, and nitrite ion) that may be present in drinking water or in the stomach. Reducing agents generally enhanced the removal rates of bromate ion in the presence of \(\text{H}_2\text{S}\). Oxidizing agents usually reduced the rates of bromate decomposition in the presence of \(\text{H}_2\text{S}\); however, the rate reductions were modest at concentrations found in drinking water. This indicated that consumption of chlorinated or chloraminated water containing bromate would not materially affect the presystemic bromate reduction that could occur in the stomach. Studies to quantify rates of bromate reduction occurring from the greater liver and blood metabolism processes with glutathione and other reducing systems are nearing completion.

**ACKNOWLEDGMENT**

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**TABLE 6**

<table>
<thead>
<tr>
<th>Ferrous Ion mg/L</th>
<th>Bromate Half-life—min</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0 (\text{H}_2\text{S})</td>
</tr>
<tr>
<td>0</td>
<td>153</td>
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<tr>
<td>1</td>
<td>91</td>
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<td>2</td>
<td>62</td>
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<tr>
<td>5</td>
<td>39</td>
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<tr>
<td>10</td>
<td>23</td>
</tr>
</tbody>
</table>

\(\text{HCl}\)—hydrochloric acid, \(\text{H}_2\text{S}\)—hydrogen sulfide
Divisions and a vice-president of environmental health sciences for NSF International. Jason D. Keith is a technical sales representative for ion chromatography equipment. Richard J. Bull is a principal in MoBull Consulting in Richland, Wash. Gilbert E. Pacey is a professor and Gilbert Gordon is a professor emeritus , both at Miami University in Oxford, Ohio.

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Date of acceptance: 03/31/10

FOOTNOTES
1Barnstead NanoPure, Barnstead International, Dubuque, Iowa
2API 4000, Applied Biosystems/MDS Sciex, Foster City, Calif.
3Varian ICP/MS with SPS-3 autosampler, Varian Inc., Palo Alto, Calif.
4Nalgene Labware, Thermo Fisher Scientific, Rochester, N.Y.