



**DRINKING WATER RESEARCH FOUNDATION**

August 2004

## STUDY SUMMARY

### ***THE RATE OF BROMATE DECOMPOSITION IN THE HUMAN STOMACH: PHASE I***

*Investigators:* Joseph A. Cotruvo Ph.D. Joseph Cotruvo & Associates LLC, Washington, DC, Jason Keith, B.S., Miami University, Gilbert Gordon PhD, Miami University, Gilbert Pacey PhD, Miami University, Richard Bull PhD, MoBull Associates, Richland, Washington

#### THE ISSUE

The research program was undertaken to develop a comprehensive quantitative understanding of the fate of bromate (and other reactive substances) in the stomach under relevant typical human physical characteristics and exposure conditions, so that the actual systemic uptake of bromate will be predictable under those conditions. Bromate is produced in drinking water and bottled water by ozonation of bromide, and it is introduced to drinking water during chlorination as a contaminant generated during chlorine production by electrolysis of salt containing bromide. The MCL in drinking water is 10 ppb and the projected upperbound lifetime cancer risk at that value is greater than 1 in 10,000. If it can be shown that bromate is at least partially decomposed in the stomach prior to uptake, or in the blood, then the actual dose under drinking water conditions would be less than is currently assumed, and the calculation based on high dose exposures in test animals would be overestimating the actual risk at low doses.

#### RESEARCH STRATEGY

The oxidation/reduction chemistry of bromate was studied under conditions to simulating human gastric pH, chloride content, hydrogen sulfide and thiol-containing proteins. The rates of reaction were determined under a range of conditions and concentrations and kinetic rate laws were developed. The rates and half-lives were compared to retention time in the stomach under conditions of water consumption absent food.

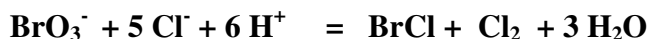
#### MAJOR FINDINGS AND SIGNIFICANCE

Phase I studied reactions of bromate with hydrogen chloride, hydrogen sulfide, and organothiols (RSH) under acidic pH conditions as could be found in the stomach. The analytical technique utilized was Ion Chromatography which was capable of quantifying bromate in acid solutions in the range of 1 ug/L. However, after extensive laboratory studies in HCl solution at gastric juice concentrations wherein the chloride concentrations would be more than  $10^6$  times the bromate challenge levels of interest, interferences between chloride and bromate made it more difficult to conduct studies in the 10 ug/L range. After major experimental modifications, a procedure was

developed that allowed studies of bromate reactions at 200 ug/L in the HCl medium with excellent accuracy and precision. It was concluded that 200 ug/L of bromate was a sufficiently low concentration to challenge the hypothesis that bromate could be reactive at low concentrations under gastric conditions, and it was therefore used as the screening level for the subsequent experimental studies in Phase I. (ICP/Mass spectrometric techniques are available that would be able to detect and quantify levels of bromate (and bromide) in the presence of very high chloride. Such an instrument has been purchased and it will be used in subsequent studies allowing measurement at low ppb levels.)

Phase I of this research demonstrated that chloride can react with bromate by acid sensitive processes and that chloride is oxidized and bromate is chemically reduced.

The net chemical reaction is essentially as follows:



This reaction would be in equilibrium that would be shifted far to the left, and the slow step is likely the process leading to formation of the halogen species that should react instantaneously as formed in the presence of oxidizable material.

The experimental rate law was determined to be:

$$-d[\text{BrO}_3^-]/dt = k [\text{BrO}_3^-] [\text{H}^+]^2 [\text{Cl}^-]^{1.5}$$

This representation indicates that it is a complex probably multistep reaction that is highly sensitive to the acidity, since the rate of decomposition is proportional to the square of the hydrogen ion concentration. Since there is approximately  $10^6$  molar excess of chloride versus bromate and the reaction is greatly affected by hydrogen ion, the reaction may involve the formation of a transient small amount of a protonated  $\text{HBrO}_3$  specie perhaps in an activated complex that includes hydrogen ion, bromate, and chloride. This is indicated because the rate of reaction usually drops rapidly below approximately 0.1 moles/liter.

pH	H <sup>+</sup>	Cl <sup>-</sup>	BrO <sub>3</sub> <sup>-</sup> % Reduction	t <sub>1/2</sub> minutes
0.8	0.17	0.17	12	153
1	0.10	0.17	5	454

*Above conditions: Initial bromate concentration was 200 ug/L, at 37 degrees C. This was a static simulation that did not take into consideration that gastric juice would be continually secreted into the stomach during the contact time period, and that protein amine groups probably buffer the acidity in actual gastric juice.*

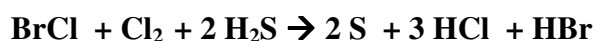
Under biologically relevant conditions the rate of this reaction is slow given that the likely retention time half-life in the stomach of water that was ingested in the absence of food might be in the range of 15-30 minutes; only a small amount of bromate would react in that time frame by this simulation.

However, actual gastric juice is in a chemically reduced state and in addition to HCl and water it contains numerous proteins and potentially other reducing agents such as hydrogen sulfide and ascorbic acid. It is also constantly being replenished during digestive processes. A single sample of human gastric juice was obtained, with some difficulty, and analyzed for hydrogen sulfide. Hydrogen sulfide was demonstrated to be present at a concentration of  $\sim 8.5 \times 10^{-5}$  molar (more than 340 ug/L) in the single sample. No indication was found that this quantitative analysis of

gastric juice had been conducted prior to this study. When sulfide was added to the simulated gastric juice under similar conditions we demonstrated a significantly increased rate of bromate reduction, as below, except that these bromate reductions occurred in only 15 minutes rather than 30 minutes of contact at 37 degrees C.

pH	H <sup>+</sup>	Cl <sup>-</sup>	% Reduction BrO <sub>3</sub> <sup>-</sup>		t <sub>1/2</sub> minutes	
			H <sub>2</sub> S @ 10 <sup>-4</sup> M	10 <sup>-5</sup> M	H <sub>2</sub> S @ 10 <sup>-4</sup> M	10 <sup>-5</sup> M
0.8	0.17	0.17	97	57	2	14
1	0.10	0.17	93	21	15	43

Thus, because it is a much stronger reducing agent than chloride, but still acid sensitive, the hydrogen sulfide could be reacting directly with bromic acid or possibly with the bromine chloride or chlorine that are generated as follows. The former mechanism is suspected.



Combining the reactions of bromate with HCl and H<sub>2</sub>S the rate law can be rewritten in more specific mechanistic terms and expanded to:

$$-d[\text{BrO}_3^-]/dt = k_1[\text{BrO}_3^-][\text{H}^+]^2[\text{Cl}^-] + k_2[\text{BrO}_3^-][\text{H}^+]^2[\text{Cl}^-]^2 + k_3[\text{BrO}_3^-][\text{H}_2\text{S}][\text{H}^+]^n$$

Experiments were also conducted simulating gastric juice supplemented with cysteine, an amino acid and/or glutathione (glutamylcysteineglycine) as protein surrogates, both of which contain organic thiol (SH), as well as amine groups that would buffer the acidity. Increased rates were found of the conversion of bromate relative to HCl alone, but less than the hydrogen sulfide effect.

## CONCLUSIONS

The research demonstrated that bromate and chloride react slowly under strongly acid conditions in simulated gastric juice. Hydrogen sulfide in actual gastric juice was measured and it was found that small amounts of hydrogen sulfide react rapidly with bromate in simulated gastric juice at physiologically relevant rates under acidic conditions. It was also demonstrated that organic thiol amino acid type compounds will reduce bromate under acidic conditions, although at a slower rate than hydrogen sulfide. Future research plans will extend these results with a more authentic simulated gastric juice and actual gastric juice, and also under typical human conditions of concurrent consumption of food and chlorinated water.

*This Study Summary was created by the Drinking Water Research Foundation (DWRf) and is intended as general information about the project. The project was funded by the National Water Research Institute, Southern Nevada Water Authority and the DWRf and parts of it are being prepared for publication in several technical journals.*