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PRINCIPAL INVESTIGATORS:
Joseph A. Cotruvo and Richard J. Bull

OBJECTIVES:
The project aim was to examine the relevant data base on bromate toxicology, including cancer, and develop a specific research strategy that would provide a scientifically credible basis for determining the risk of bromate at low environmentally relevant doses.

BACKGROUND:
Bromate is a dilemma to water suppliers and bottled water producers because it is formed during ozonation of bromide-containing source waters. It is also a contaminant in hypochlorite produced by electrolysis of salts containing bromide. Bromate is regulated at 0.010 mg/L as a probable or possible human carcinogen. There is the possibility that it could be reduced further due to the current projected upper bound lifetime cancer risks at the MCL projected at 2/10,000 (USEPA) or 5/100,000 (WHO), depending upon the risk assumptions and with recent improvements in analytical methods at low concentrations.

HIGHLIGHTS:
Although there may be more than one mode of action represented, it appears that bromate’s carcinogenic effects at low doses are most likely mediated through intracellular in vivo chemical interactions with thiols (e.g., glutathione). Those chemical interactions are likely to be responsible for bromate’s degradation prior to absorption from the GI tract and its distribution. The research needs to focus on the collection of quantitative data that relates dose at target tissues to ingested doses, with molecular interactions and pathology. Improvements in the risk estimates will depend on how well these dose-response relationships can be measured at low doses. It is likely that bromate doses at target sites will be non-linear at lower ingestion doses because of pre-systemic degradation, the potential role of anion carriers in its distribution, and potential for secondary factors that may be invoked if tissue thiol levels become depleted by high bromate doses.

Use of the potassium bromate salt in the animal tests does not affect the carcinogenicity and risk. This was one of the directed questions addressed in the strategy workshop.

APPROACH:
An international expert workshop examined bromate’s basic chemistry and toxicology and proposed a practical roadmap of research that would provide the data to lead to a better quantitative understanding of bromate’s metabolism, toxicology, and risk. Topics included assessments of the etiology of bromate-induced cancer, possible genotoxicity, risk assessment methods, regulatory risk assessment guidance, neurotoxicity and ototoxicity (auditory), oxidative stress, mechanisms of DNA damage induced by bromate, DNA damage biomarkers and repair, the chemistry of bromate decomposition and metabolism, pharmacokinetic modeling, statistical methods for risk modeling to reduce uncertainties, and critical elements of a biologically based
dose-response model. Subgroups recommended a series of studies to generate data that would contribute to more robust scientifically based risk assessments. The health research strategy includes development of a pharmacokinetic (PBPK) model for bromate’s metabolism and distribution and quantifies the pre-systemic and systemic decomposition of bromate. The PBPK model would be integrated with measures of adverse responses to provide a quantitative understanding of the dose-response at low environmentally relevant doses.

RESULTS/FINDINGS:
A four-part phased research strategy was developed consisting of the following elements:

• Phase I would test the hypothesis that the relationship between external dose of bromate at toxicologic responses is non-linear at low doses. Pre-systemic and systemic metabolic processes indicate the likelihood of non-linear kinetics being operative at low doses.

• Phase II would focus on the research course if the kinetics of bromate and/or biomarker responses are found to be linear relative to external dose. This would eliminate elaboration of the relatively unique toxicity in the male rat kidney that is not relevant to humans by utilizing female rats in future studies. Detailed chronic toxicity in the female rat and a lifetime bioassay beginning with in utero exposure would be carried out. Concurrent screening for ototoxicity would occur.

• Phase III would address the direction to be taken if neurologic and auditory toxicity do not occur at low chronic doses. This would also include the fetus as a compartment for pharmacokinetic modeling.

• Phase IV would be invoked in the event that a developmental toxicity study and additional neurotoxicity and ototoxicity studies would be indicated by the screening studies in the earlier phases.

Total cost was estimated at $2.2 to $3.1 million; however, the strategy is progressive. The predominant cost would be for a rat bioassay, if indicated by the earlier phases.

IMPACT:
It is likely that the proposed pharmacokinetic studies will show that at least a portion of the bromate ingested by rats at low levels never reaches the target organs due to pre-systemic metabolism occurring in the stomach, GI tract, liver, and blood. If they indicate a non-linear relationship between bromate consumed and cancer, for example, it would require development of a non-linear low dose cancer risk model that would likely reduce the projected risk for bromate concentrations at the MCL. Thus, the risk rationale for the Maximum Contaminant Level Goal (MCLG) would have to be reconsidered. Demonstrating that the mechanisms by which bromate causes cancer do not occur at the low drinking water doses to which humans are exposed would strongly support the development of a new cancer risk assessment model.