EPA Information Quality Guidelines Processing Staff
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To Whom It May Concern:

I am writing in reference to:

> Response to Request for Correction (RFC) of documents that present bromate in all forms as carcinogenic pursuant to United States Environmental Protection Agency (U.S. EPA) and Office of Management and Budget (OMB) Information Quality Guidelines (RFC #12385)

The response was dated 2004apr28 and post-marked 2004may12. The author was Paul Gilman, Ph.D, Assistant Administrator.

My RFC was directed against all US EPA web pages and revisable documents that present bromate as a carcinogen, not just the few originally referenced. This should have been clear in my original RFC.

There were gross overgeneralizations in the response: *"There is no evidence to suggest that any of the soluble forms of this chemical would behave differently."* I will abbreviate this as: **A. All salts are the same.**

There was unsubstantiated content in the response: *"The bromate assessment represents the Agency's consensus opinion on health effects associated with exposure to this chemical."* I will abbreviate this as: **B. US EPA et. al. decided that bromate ion is a carcinogen.**

There was a blatant appeal to authority (or popular opinion) in the response: *"EPA's assessment of the carcinogenic potential of bromate is supported by the International Programme on Chemical Safety, which determined that bromate causes an increase of tumors in experimental animal models (WHO, 2000), and Health Canada which classified bromate as probably carcinogenic to humans (1999)."* I will abbreviate this as: **C. Other regulatory bodies have also assessed that bromate ion is a carcingoen.**

There was information that was not pertinent in the response: *"The results from these studies can be generalized to the bromate ion and its soluble salt forms because the water solubility of potassium bromate at room temperature (25°C) is approximately 75000 mg/L (WHO, 1999), and the highest concentration of potassium bromate used in the cancer bioassays was 800 mg/L. Thus, the potassium bromate in these solutions would have completely disassociated into potassium and bromate ions".* I will abbreviate this as: **D. Because a salt is soluble, it should be similar to other salts.**

There was yet another gross overgeneralization in the response: *"Moreover, potassium is an essential element and the recommended daily requirement for rodents is substantially greater than what the animals were exposed to in the cancer bioassays (NRC, 1995). Consumption of an essential element within the range of recommended dietary concentrations would not be expected to produce toxic effects."* I will abbreviate this as: **E. Essential elements taken in "recommended dietary concentrations" are non-toxic.**

There was another gross overgeneralization in the response: *"Considering the solubility of potassium bromate and that potassium is an essential element, the increased incidence of cancer observed in the rodent bioassays is, therefore, presumed to be due to free bromate ions."* I will abbreviate this as: **F. Since potassium ion cannot be bad, it must be bromate ion.**

There was reference to a particular study in the response, that was not performed to the necessary standards to be meaningful. *"Furthermore, the mutagenic potential of both potassium and sodium bromate has recently been demonstrated in vitro."* I will abbreviate this as: **G. The US EPA/US FDA did their own mutagenicity study and found bromate ion to be a mutagen.**

OK, lets review them in order:

A. All salts are the same.

1. 1990, in a paper "Toxicity and Carcinogenicity of Potassium Bromate - A New Renal Carcinogen" by Vuji Kurokawa, Akihiko Maekawa, Michihito Takahashi, and Vuzo Hayashi, potassium bromate was found to be a mutagen in Salmonella, and sodium bromate was negative for mutagenicity at similar doses on four different strains of Salmonella. (The pertinent section was labeled 'Mutagenicity'.)
2. Eckhardt performed a mutagenicity test with sodium bromate in 1982, with negative results on Salmonella (the standard for this purpose).
3. The ratios of the LD_{50} values for equivalent sodium and potassium salts are:
    - IRP-MUS 147/177 = 0.83 ($NaBrO_3$/$KBrO_3$ LD_{50} mg/kg bw)
    - IRP-MUS 5000/1013 = 4.9 (NaBr/KBr LD_{50} mg/kg bw)
    - ORL-RAT 301/157 = 1.8 ($NaBrO_3$/$KBrO_3$ LD_{50} mg/kg bw)
    - ORL-MUS 7000/3120 = 2.2 (NaBr/KBr LD_{50} mg/kg bw)

Current data shows that potassium bromate salt behaves differently from sodium bromate salt as relates to mutagenicity in the Ames test (testing with Salmonella). The LD_{50} ratios listed above show that bromine compounds containing sodium are one to five times more toxic than bromine compounds containing potassium. All this information is in the public domain, and has been since about 1990. An assumption that testing with potassium bromate is

equivalent to testing with bromate alone is in error. Potassium is not just some sort of “amplifier”, and has an effect separate from the halogen (and its oxidation state) it is attached to. Sodium bromate has not been shown to be a carcinogen. Only potassium bromate has been. And the two salts are biologically different based on published experiment.

B. US EPA et. al. decided that bromate ion is a carcinogen.

4. I have had discussions with one of the US EPA scientists that did the initial research on this topic. Neither the assessment, nor the MCL, was based on any information his group provided, and was unwarranted based on the information available at the time, even up to 1 year ago.
5. Presumably, relevant review of the MCLs for bromate will include members of the global scientific community, and include US EPA’s own research staff.
6. Bromate ion is reduced to bromide ion (eventually) by time and natural systems. These systems include common containers, simple thermal decay (even at refrigerator temperatures), mixing in water, lowered pH (such as stomach acid). All present in US EPA and US NIH/NIEHS test protocols.

The decision to assess bromate ion as a carcinogen was based on the documented carcinogenicity of potassium bromate, the bread additive. It is public knowledge that no experimental finding of carcinogenicity has been made against sodium bromate. Potassium bromate has been well researched (although hypobromite ion and/or bromide ion controls were also largely missing). Sodium bromate has not been well researched, and has been shown to behave differently. The US EPA has used the “light” of information regarding potassium bromate to assess into the “dark” of all bromate ion.

C. Other regulatory bodies have also assessed that bromate ion is a carcinogen.

7. Note that both agencies made their assessments after the US EPA made its assessment. The citations made are the same citations made by the US EPA.
8. Note also, that the US EPA made request of US NIH/NIEHS (National Institutes of Health/National Institute of Environmental Health Sciences), to test sodium bromate in a drinking water model. No evidence of carcinogenicity has been found to date. There have been positive results in the mouse micronucleus testing, however this is not indication of either carcinogenicity or mutagenicity of bromate ion over bromide ion.

Everyone is following the US EPA’s lead on this topic. They cite identical papers, and their citations end essentially where the US EPA makes its assessment. US EPA assumed that testing with potassium bromate was identical to testing with bromate alone. This fundamental mistake in biology was made at the US EPA, by not consulting its research staff, and has been propagating ever since.

D. Because a salt is soluble, it should be similar to other salts.

9. In this case, solubility is not the issue. When a mammal gets an "overdose" of potassium, it has systems in place to deliver the excesses to the large intestine and the kidneys. If one were to review where the tumors were cited, they were found in/near these organs. Sodium is eliminated in the same organs, but carcinogenicity has not been found with sodium bromate.
10. Oxidative damage (the investigated mechanism for carcinogenicity) can be produced by either an oxidant (bromate ion, hypobromite ion, bromide ion), or ionizing radiation.
11. The potassium pump in all mammalian cells differentiates quite well between salts, preferentially concentrating potassium ions, and expelling sodium ions. Biologically, the two salts are different. It is also a system that is regulated, taking some time to compensate for sudden changes in sodium and potassium levels outside the cell.

"All salts are the similar" is clearly not a true statement, based on the comparison of sodium and potassium salts. No biochemist would make such a fundamental error.

E. Essential elements taken in 'recommended dietary concentrations' are non-toxic.

12. I don't find in the studies I have researched that the animals were fed diets that were depleted in potassium and bromine, to eliminate the effects of increased potassium and bromine uptake.
13. US NIH/NIEHS found that the concentration in sodium bromate solutions stored in the refrigerator for a one week period decayed by 9%. At room temperature, in non-sterile "glassware", the decay rate will be higher. The concentration of bromate in any liquid solution is entirely unknown, unless such concentration is directly measured.
14. Note that the dose of potassium (in potassium chloride) given by some states for lethal injection (160mEq and 50cc) is less than one day's intake for a human (3.5 gm). And yes this is not "consumed", but it is a sudden dose. Lavage is also a sudden dose, only limited to mass transfer rate across the small intestine. Toxic effect differences are indeed witnessed between the two ions, Na^+ and K^+, and in more than just acute exposure.

Bromine does not have a "recommended dietary concentration", and takes days to get out of typical animal's systems being studied. Normal potassium (or bromine) content in the animal feed was not reduced to compensate for what was added to their water. The same error occurred with sodium bromate testing. So the animals were fed increased levels of both potassium and bromine. None of the key carcinogenicity-positive or mutagenicity-positive studies have baseline bromide ion-equivalent studies been run in similar animal systems, to discount effects of the presence of a biologically active halogen. A halogen which one US state has limited in their water, and OSHA has restricted exposure to employees. But not the EPA.

F. Since potassium ion cannot be bad, it must be bromate ion.

15. Excesses of potassium ion are also eliminated in the same organs as bromate ion (but not bromide ion). Potassium has at least one common isotope that is radioactive. Sodium does not. The produced radiation can be measured and used in a general way to determine overall physical health (or age) of a person. One mode of decay produces 10-12 gamma photons, of sufficient energy (a few thousand to a few tens of eV) to ionize many other molecules, and be readily absorbed by nearby organs. Providing excesses of potassium, in addition to normal dietary uptake, delivers additional radiation dose to the kidneys, and surrounding organs. Certainly less than what is accomplished by delivering an alpha emitter to the thyroid, but the same sort of mechanism.
16. Lethal injection uses a potassium salt to halt normal cellular processes.
17. Bromate ion reduces in normal containers, the stomach (assuming lavage is not employed), the bloodstream, and the kidneys. Bromide ion goes to different organs, and is eliminated in other ways. By "reduced" I mean "becomes less oxidized, approaching the bromide ion state."
18. Bromate ion reduces, in different stages to hypobromite ion, and finally to bromide ion. This occurs in water, over time, with or without "contaminants".
19. The US EPA/US FDA study you cited referenced an increase in the number of micronucleated polychromatic erythrocytes (immature blood cells with multiple nucleii, where only one should be found) using potassium bromate. The study by the US NIH/NIEHS found no such increase with sodium bromate.

There has been no clear line drawn in differentiating the effects of bromate ion from hypobromite ion, or (more importantly) bromide ion, on similar animal systems, in simultaneous testing. There is clear evidence that potassium **in excess** is harmful, and behaves differently than sodium. We are discussing excesses of these ions being applied to animal systems, in the naïve belief that the response is linear. Linearity has not been shown. A dose response study using the Ames test would be one way to establish linearity. Dose response studies on even potassium bromate in an Ames test doesn't seem to have been run. No point in doing this with sodium bromate, since sodium bromate did not show mutagenicity in Salmonella.

G. The US EPA/US FDA did their own mutagenicity study and found bromate ion to be a mutagen.

20. The cells tested were lymphoma cells, already cancerous. This described behavior has not been noted in normal cells. Therefore neither "carcinogenicity" nor "suspected carcinogenicity" has been demonstrated. All that can be shown is mutagenicity, and that for an already damaged cell, incapable of repairing the damage that made it a lymphoma.
21. The study did not dose control cultures with equivalent amounts of

potassium and sodium bromide. This would establish a baseline behavior to eliminate the significant presence of a known (partially) radioactive (and biologically critical) material and a known organic molecule-attacking halogen.

22. Horse serum was used, and bromide content is undocumented and uncontrolled in this substance.
23. The study did not attempt to determine how much bromate ion existed in the medium prior to adding and after removing the cell culture, nor its pH. The medium, the choice of "glassware", and the storage and processing temperatures will take their toll on bromate ion concentration. The results are therefore applicable only to bromate ion, hypobromite ion, and bromide ion. And very similar to the results using table salt.
24. The study appears to have reported fatal equivalent doses to an animal, or is "expected" in their bloodstreams (or lymphatic systems, since this is indicative of cells that could be found there), and far in excess of other bromate ion studies.
25. The bromate salts (and methylmethanesulfonate, a known non-clastogenic mutagen) were dissolved in saline solution, which were then added to cultures. Controls were apparently not similarly dosed with an equivalent amount of saline, containing sodium ion, potassium ion, and phosphate buffer (capable of altering pH).
26. According to the FDA website: <URL: http://www.cfsan.fda.gov/~redbook/redivc1c.html>, titled "IV.C.1.c. Mouse Lymphoma Thymidine Kinase Gene Mutation Assay", the following procedures were not documented as having been observed in the US EPA/US FDA study:
    - "assure that there are two normal looking chromosome 11s and to identify any other irregularities";
    - "Each lot of horse serum should be tested for its ability to support optimal cell growth in suspension culture (low and high cell densities), high plating efficiency and small colony mutant recovery";
    - "Prior to use, the culture needs to be cleansed of pre-existing mutant cells";
    - "This [cleansing] is accomplished using methotrexate to select against TK-deficient cells";
    - "Thymidine, hypoxanthine and guanine are added to the culture to ensure optimal growth of the TK-competent cells (Turner et al., 1984).";
    - "Cells should be exposed to the test substance both in the presence and absence of an appropriate metabolic activation system.";
    - "When testing water-unstable substances, the organic solvents used should be free of water";
    - "Negative controls, consisting of solvent or vehicle alone in the treatment medium, and treated in the same manner as the treatment groups should be included";

- “In addition, untreated controls should also be used unless there are historical data demonstrating that no deleterious or mutagenic effects are induced by the chosen solvent.”;
- “stability of the test substance-including both the "neat" sample and the sample in the solvent/vehicle/medium”;
- “This should be done both prior to and at the end of the treatment period”;
- “justification for choice of vehicle/solvent”;
- “solubility and stability of the test substance in solvent/vehicle, if known”;
- “[Cells] absence of mycoplasma”;

27. Bromine/bromide has been found to be responsible for a number of mutagenic behaviours through the compound 5-bromouracil (5BU). A substance produced by normal cellular systems, only requiring the presence of bromine. 5BU has been noted to emulate T to C transitions. The production of 5BU does not require bromate ion, only bromine.
28. The cited study found “There were two G:C to A:T transitions, one T:A to A:T transversion and one G:C to C:G transversion. No G:C to T:A transversion was found (unpublished data).” Note that 50% of the “mutations” are consistent with a change of C to T (perhaps activated 5BU to inactivated 5BU).
29. All detailed or special analysis was performed using only potassium bromate dosed samples, not sodium bromate. Potassium is not a “response amplifier”.
30. As a check, “High-dose-level effects of mutagenicity assays utilizing mammalian cells in culture”, A.H. Seeberg, P. Mosesso, and R. Forster; Mutagenesis, V3n3:pp213-218, 1998. Found that sodium and potassium chloride were found to be mutagens, in a similar type of assay to what was done by the EPA. The chromosome damage included deletions (not found with bromate/bromide) and exchanges (which was found with bromate/bromide
31. As yet another check, “Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds”, J. Wangenheim, and G. Bolcsfoldi; Mutagenesis, V3n3:pp193-205,1998. Found that sodium chloride (and even ethanol, aka alcohol suitable for human consumption) to be a mutagen.
32. Even a change in pH has been shown to show clastogenic mutagenicity in mammalian cells. The saline solution used in the testing contained a phosphate buffer… easily capable of altering the pH of the growth medium.

I would expect that peer review of the procedures and analysis could find more discrepancies. I find its “findings” suspect, since the published procedures were not followed. I further find that the behaviors of potassium and sodium bromate are similar in mutagenic capacity to sodium and potassium chloride. Rather than *“further supports the conclusion that bromate and the soluble salt forms of this ion are likely to be carcinogenic to humans”*, **you have simply chosen a test**

that seems to fail all salts.

As for definitions:
Bromate ion – BrO_3^-
Bromide ion – Br^-
Carcinogen - A cancer-causing substance or agent.
Clastogenic - any substance or process which causes breaks in chromosomes.
Erythrocyte – red blood cell
Hypobromite ion – BrO^-
Lymphoma - Any of various usually malignant tumors that arise in the lymph nodes or in other lymphoid tissue.
Mutagen - An agent, such as a chemical, ultraviolet light, or a radioactive element, that can induce or increase the frequency of mutation in an organism.

- Potassium bromate has been shown to be a mutagen, and a carcinogen.
- Sodium bromate has not been shown to be a carcinogen, by any testing.
- Sodium bromate and sodium bromide have been shown to express mutagenic behaviour in already cancerous cells. **As has potassium and sodium chloride and even pH change.**
- Bromate decay through municipal water works, water delivery systems, and in animal or human digestive systems has not been documented that I could find, to assist in establishing reasonable municipal-drinking-water-supply bromate ion levels.

Based upon the response I received, it is evident that the US EPA cannot assert that bromate ion is a possible human carcinogen. Based on publicly available information, the behavior of potassium bromate is significantly different in important respects than sodium bromate. Sodium bromate does not result in transgenic behaviors significantly differently than the behavior of other non-regulated salts. Potassium bromate has been found to cause cancer and to be a mutagen, while sodium bromate when similarly tested has found to be neither. Findings against bromate ion that did not measure the average or effective amount of bromate to which test organisms were exposed, were findings against bromate, hypobromite, and bromide ions. Testing commissioned by the EPA that does not conform to published procedures, that yields results similar to common salt, but is considered to be supporting evidence for "possible human carcinogenicity" simply highlights that competent peer review is not being sought.

The US EPA assessment against bromate appears to not have been a well informed "consensus opinion". It appears that US EPA is in substantial non-compliance with the "*EPA Information Quality Guidelines.*" Furthermore, this error has cost the municipal drinking water industry millions of dollars in testing, capital expenditure, operational expense, maintenance cost, increased levels of mercury entering our solid waste disposal streams (spent UV bulbs which must

be periodically replaced), and increased levels of chlorine and chlorinated byproducts entering our water and waste streams. Bromide is perfectly capable of keeping biogrowth down in municipal delivery systems, no need to have to buy yet another halogen to do it.

The Guidelines will require that any inference of “possible human carcinogen” be removed from all revisable US EPA documentation. Until such time that sodium bromate testing shows mutagenicity/carcinogenicity in mammalian cells, that uses equivalent sodium bromide dosing controls, otherwise follows the established procedures, reasonably estimates dose-response behavior, and estimates bromate ion decay in delivery systems, any such assessment:

- does not improve public safety,
- decreases the safety of future populations, and
- needlessly increases the cost of water.

When will these errors on EPA documentation be repaired?

Thank you for your attention.

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