Original article

Association Between Sub-lethal Doses of Potassium Bromate and Blood Dyscrasia

Running Title: Potassium bromate and blood dyscrasia

ABSTRACT

Bromate is a commonly used additive in baked food products. However, it was later implicated as a causative agent of cancer and other related health problems like induction of oxidative or mutagenic DNA damage; yet some bakers still, secretly, indulge in its usage. This study was taken to investigate possible association between blood dyscracia and consumption of low levels of this compound. Toxicity study of bromate was carried out on 20 albino rats using standard method. Then, haemogram and organometrics of another 20 albino rats (divided into four groups) administered with different concentrations of the bromate were determined before and after 60 days of administration for possible blood dyscracias, also using standard methods. Toxicity test revealed an oral LD_{50} of 18.8 ± 6.2 mg/kg bodyweight. Significant increases ($p < 0.05$) were observed in haemoglobin concentration and mean cell haemoglobin concentration after 60 days of administration, while total white blood cells and absolute differentials of white blood cells did not show any statistical differences ($p > 0.05$) when pre-administration values were compared to post-administration values. Spleen weight revealed no significant difference ($p > 0.05$) in pre compared to post administration while liver and kidney weights revealed significant increases ($p < 0.05$) in the experimental groups compared to controls. The study revealed no association between blood dyscracias and bromate at the doses and duration of exposures, though significant changes in organometrics indicated possible long term effects.

Keywords: Potassium bromate; Sub-lethal doses; Blood dyscracia

INTRODUCTION

A bromate is a chemical compound (a salt or ester) containing the reactive group BrO_3, which is bromine base – oxo-anion, implicated in different health problems (APA, 2017; ECHA, 2019). Potassium bromate is used as a flour improver in bakery industries, acting as a maturing agent, principally in the late dough stage, giving strength to the dough during late proofing and early baking process (Abdulmumeen, 2012). It is also used in permanent hair wave neutralizing solutions, in brewery industries, in explosives, dying of textiles and as a laboratory reagent (Kathleen, 2006; Ahmad and Mahmood, 2012). Exposure to bromate can be either through residual bromate in finished bakery products or bakery equipment (occupational exposure), ingestion (when present in water or food such as bread) or by inhalation (Ojo-Rotimi et al, 2013; Okafor et al, 2013; Achukwu et al, 2018).

Evaluations have shown that potassium bromate is a genotoxic carcinogen, classifying it as a possible carcinogen to humans (IARC, 1999; USEPA, 2001). These findings and classification led to the ban on use of $KBrO_3$ as a food additive in many countries, including Nigeria. However, studies in Nigeria have shown that many Bakers are not complying with the ban which implies that individuals are in constant exposure to sub-lethal doses of it (Ojeka et al, 2006). In 2012, WHO and FAO formally withdrew specifications of potassium bromate as food additive. This was followed by full evaluation under the WHO Guidelines for Drinking-water Quality which concluded that all evidence indicated that bromate has potential to be a human carcinogen (WHO, 2017; EU, 2020). Unfortunately, this has not stopped, in its entirety, the use of this additive in food industries, particularly in Nigeria (Achukwu et al, 2018; Naze et al, 2018).

Studies have reported significant changes in all cellular elements and many biochemical parameters in rats exposed to potassium bromate (Achukwu et al, 2009; Shehab and Ghadhban, 2021). Toxico-kinetic studies strongly suggest that sulphydryl-containing compounds such as glutathione (GSH), a potent antioxidant, contribute to the reduction of bromate to bromide in body tissues of mammals (Joseph and Richard, 2010). This reduction process generally results

in low net accumulation of bromate and bromide ion in animal tissues; thus reducing their adverse effects on the tissue. The relationship between DNA damage and $KBrO_3$ shows positive correlation between extent of DNA damage and amount of $KBrO_3$ ingested (Spassova et al, 2013). After absorption into the bloodstream, $KBrO_3$ is converted into oxides and radicals that may affect DNA, playing role in developing cancer (Mack et al, 2021) and this has earlier been noted in human liver and intestinal cells (Geter et al, 2006; Zhang et al, 2011). Likewise, administration of low doses of potassium bromate (50 – 200mg/kg bodyweight) to male albino mice resulted to neurotoxic symptoms, reduced brain levels of GSH, extensive damage to the medulla and cerebral cortex as well as significant alterations in cell morphology (Scholpa et al, 2014; Ajarem et al, 2016).

The induction of oxidative stress, resulting from depletion of glutathione and vitamin E levels, and increased level of methaemoglobin associated with bromate from many literatures might likely impact negatively on the physiology of blood cells, especially red blood cells. Furthermore, the sites of biodegradation of bromate (like the red blood cells) are also a huge concern for the physiology of blood and as such there is possibility of bromate causing blood dyscracias. This study evaluated the possible effects of sub-lethal doses of bromate on blood cells that may lead to dyscrasias, given that the present insistent uses of the substance in food industries, especially in developing countries like Nigeria, is mostly sub-lethal. This will increase the awareness on the harmful effects, or otherwise, of potassium bromate to encourage or discourage the quest for bromate substitutes as food additive, especially in bread industry.

MATERIALS AND METHODS

Animal preparation: Forty healthy female albino rats aged 2-3 months, weighing 150 – 180g were obtained from the Animal House of the Faculty of Veterinary Medicine, University of Nigeria Nsukka, Nigeria for the study. The rats were kept at University of Nigeria Teaching Hospital Enugu in stainless steel wire mesh cages (perforated beneath for the exit of the rats' wastes to prevent coprophagy), at a temperature of 28^{o}C – 32^{o}C and 13: 11 light: dark cycle.

They were fed with standard commercially prepared pelleted feed product of Top-feed (Nsukka, Nigeria), and pyrogen free water *ad libitum*.

Study design: Twenty (20) of the albino rats were divided into 5 groups (A to E), 4 rats in a group. The bodyweights of the rats were measured before commencement of potassium bromate administration and also periodically (days 0, 15, 30, 45, and 60) within the experimental period and the concentration of bromate administered adjusted accordingly based on the measured weights. Groups A, B, C, D, and E, were given oral graded-doses of 0, 10, 15, 20, 25 mg/kg bodyweight of potassium bromate respectively daily for 60 days. Group A served as the control. The $KBrO_3$ was administered orally through drinking water after depriving the rats normal drinking water overnight. The rectal temperatures of the rats were taken 24 hours prior to each sample collection and rats with temperature above normal (36 – 38ºC) excluded.

Acute toxicity test: Acute toxicity test was done with the remaining 20 female albino rats to determine the LD_{50} using standard method (Raj et al, 2013). The rats were divided into five groups and administered different doses of $KBrO_3$ ranging from 10 to 50mg/kg bodyweight and observed within 24hrs period for signs of cytotoxic effects such as dullness, depression, restlessness, diarrhea, lacrimation, pilo erection, lying in a prone position and death in extreme cases. After 24hrs the number of rats that showed signs of toxicity was counted in each group and the percentage calculated. The percentage was then transformed to probit using Finney's table (Finney, 1971). The percentage dead for 0 and 100 were corrected before determining their probits using the formulae;

$$\text{For } 0\% \quad \text{dead} = 100\,(0.25/n) \qquad \text{and}$$

$$\text{For } 100\% \quad \text{dead} = 100\,(n - 0.25/n),$$

Where n represent number of rats per group.

The probit values thus obtained were plotted against log-dose and then the dose corresponding to probit 5, i.e., 50%, was determined. The approximate standard deviation at 95% confidence limit was calculated using a standard formula (Ghosh, 1984). The probits of 84 and 16 from Finney's table were determined, approximately 6 and 4, respectively. Their log-dose values were then obtained from the probit against log-dose graph and substituted accordingly.

Blood sample collection: Blood samples were collected from each of the experimental rat through the retro-bulbo plexus of the media cantus into ethylene diamine tetracetic acid container on day 0 and day 60. The samples were used for haemogram and blood film using methods of Dacie and Lewis (2006). Photomicrographs of blood films with striking features were taken.

Harvest of organs for Histology: After sample collection on day 60, the rats were euthanatized by intra-peritoneal injection of 250mg/kg bodyweight of Thiopentone Sodium and the kidney, liver and spleen were excised and weighed. The organosometrics were determined using the formula;

$$\text{Percentage organ weight} = \text{organ weight} \times 100/\text{bodyweight}.$$

Statistical analysis: Data were analyzed using statistical package for social sciences (SPSS 16.0) and presented as mean with standard deviation and subjected to inferential statistics using one-way analysis of variance. Probability value less than 0.05 was considered statistically significant.

RESULTS

From the toxicity test, the oral LD_{50} of $KBrO_3$ for albino rats was 18.8 ± 6.2mg/kg bodyweight at 95% confidence interval. The haematocrit, red blood cell and platelet counts showed no significant differences ($p > 0.05$) among the values of all the groups. However, these values obtained in day 60 samples were relatively higher than the values obtained on the first day. On the other hand, the haemoglobin concentrations, though showed no significant differences among the groups on the first day, were significantly increased on the day 60 in all the groups. On day 60 also,

haemoglobin obtained from group B was significantly lower ($p < 0.05$) than those from groups C and E while the control group did not differ significantly ($p > 0.05$) from any of the experimental groups (Table 1).

Table 1: Haemogram of albino rats administered with graded-doses of potassium bromate and controls

Parameter	Experimental period	Means, with standard deviation in brackets				
		Group A	Group B	Group C	Group D	Group E
Haematocrit (%)	Before administration (Day 0)	44.00 (1.83)	45.75 (1.76)	45.38 (0.48)	44.38 (2.87)	45.13 (2.84)
	After administration (Day 60)	44.63 (3.45)	44.50 (2.12)	47.38 (1.25)	46.63 (1.80)	47.38 (1.31)
Haemoglobin (g/dl)	Before administration (Day 0)	15.25 (0.62)	15.14 (1.29)	15.45 (0.31)	15.54 (1.48)	15.27 (0.52)
	After administration (Day 60)	16.25 [ab] (1.50)	15.39 [a] (0.87)	17.21 [b] (0.28)	16.09[ab] (1.19)	17.11 [b] (0.25)
Red blood cell counts (10^6/µl)	Before administration (Day 0)	11.17 (0.89)	11.96 (1.05)	11.13 (1.23)	11.21 (1.55)	11.76 (1.41)
	After administration (Day 60)	11.67 (1.58)	11.86 (1.23)	13.00 (0.32)	12.40 (1.12)	12.72 (0.81)
Platelet counts (10^3/µl)	Before administration (Day 0)	537.50 (89.58)	537.50 (50.58)	572.50 (114.71)	540.00 (50.99)	537.50 (113.25)
	After administration (Day 60)	577.50 (149.30)	640.00 (173.01)	555.00 (134.78)	710.00 (167.93)	565.00 (134.78)

[a b] indicates level of significance between the means of the groups, $p < 0.05$

The mean MCV and MCH for all the groups did not differ significantly ($p > 0.05$). Though MCV values in day 60 were relatively lower than day 0 values, the changes were not statistically significant. For MCH, the values showed no specific trend in the variation between day 0 and day 60. However, mean MCHC values at day 60 were significantly higher ($p < 0.05$) than those from day 0 in all the groups but there was no statistical difference between groups (Table 2).

Table 2: The absolute indices of rat groups given graded-doses of potassium bromate and the controls

Parameter	Experimental period	Means, with standard deviation in brackets				
		Group A	Group B	Group C	Group D	Group E
MCV (fl)	Before administration (Day 0)	39.49 (1.65)	38.41 (2.15)	41.11 (3.84)	39.91 (3.06)	38.57 (2.34)
	After administration (Day 60)	38.28 (2.79)	37.70 (2.18)	36.46 (0.37)	37.76 (2.19)	37.32 (1.47)
MCH (pg)	Before administration (Day 0)	13.70 (1.03)	12.68 (0.44)	14.01 (1.44)	13.94 (0.72)	13.09 (1.24)
	After administration (Day 60)	13.94 (1.21)	13.04 (0.73)	13.25 (0.33)	13.00 (0.60)	13.49 (0.87)
MCHC (g/dl)	Before administration (Day 0)	34.68 (1.28)	33.07 (2.06)	34.06 (0.77)	34.98 (1.30)	33.88 (1.12)
	After administration (Day 60)	36.42 [a] (1.77)	34.58[ab] (0.71)	36.34[ab] (0.78)	34.48 [b] (1.75)	36.12[ab] (0.97)

[a b] indicates significance levels between the means of the groups at $p < 0.05$. [MCV – Mean corpuscular volume; MCH – Mean corpuscular haemoglobin; MCHC – Mean corpuscular haemoglobin concentration].

The mean total white cell counts, absolute lymphocyte, neutrophil, monocyte, eosinophil, and basophil counts did not show any significant difference ($p > 0.05$) between day 0 and day 60 and between groups. Neutrophil and monocyte had decreasing trend from day 0 to day 60 while others did not show any trend in their differences (Table 3).

Table 3: The total and differential leucocytes counts of rat groups given graded-doses of potassium bromate and the controls

Parameters	Experimental period	Means, with standard deviation in brackets				
		Group A	Group B	Group C	Group D	Group E
Total White Blood Cell counts (10^3/µl)	Before administration (Day 0)	12.14 (1.69)	12.98 (2.54)	12.05 (1.86)	12.24 (2.09)	12.24 (2.06)
	After administration (Day 60)	12.98 (0.91)	11.93 (2.51)	12.78 (1.63)	12.34 (2.66)	12.50 (2.01)
Lymphocyte counts (10^3/µl)	Before administration (Day 0)	7.66 (1.76)	9.49 (1.58)	8.09 (0.84)	7.88 (1.72)	8.28 (2.25)
	After administration (Day 60)	9.68 (0.41)	8.22 (1.90)	8.59 (1.21)	8.37 (2.64)	7.88 (1.81)
Neutrophil counts (10^3/µl)	Before administration (Day 0)	3.45 (1.08)	2.45 (0.82)	2.99 (1.30)	3.64 (0.49)	2.62 (0.64)
	After administration (Day 60)	2.87 (0.64)	3.09 (0.57)	3.04 (0.61)	3.23 (1.11)	3.82 (0.49)
Monocyte counts (10^3/µl)	Before administration (Day 0)	0.47 (0.34)	0.36 (0.15)	0.37 (0.24)	0.38 (0.16)	0.44 (0.17)
	After administration (Day 60)	0.16 (0.07)	0.20 (0.18)	0.31 (0.11)	0.29 (0.20)	0.19 (0.13)
Eosinophil counts (10^3/µl)	Before administration (Day 0)	0.38 (0.28)	0.64 (0.52)	0.52 (0.40)	0.47 (0.35)	0.49 (0.25)
	After administration (Day 60)	0.27 (0.31)	0.37 (0.18)	0.54 (0.18)	0.31 (0.10)	0.57 (0.24)
Basophil counts (10^3/µl)	Before administration (Day 0)	0.09 (0.06)	0.04 (0.07)	0.08 (0.10)	0.04 (0.00)	0.08 (0.07)
	After administration (Day 60)	0.05 (0.06)	0.06 (0.06)	0.09 (0.11)	0.05 (0.05)	0.06 (0.07)

No significant differences between the means of the groups at $p > 0.05$

Generally, the experimental groups had a higher mean percentage organ weight than the control group. The mean percentage organ weight for the liver from group A was significantly lower ($p < 0.05$) than that of group D but not with other groups. The mean percentage organ weight for the kidney from group A was significantly lower ($p < 0.05$) than those from other experimental groups (groups B, C, D and E). However, the experimental groups did not differ significantly ($p > 0.05$) among themselves. For spleen, there were no significant differences in their mean percentage weights ($p > 0.05$) between the control group and any of the experimental group or even between the experimental groups (Table 4).

Table 4: The liver, kidney and spleen percentage weight of rat groups given graded-doses of potassium of bromate and the controls

Parameter	**Means, with standard deviation in brackets**				
	Group A	**Group B**	**Group C**	**Group D**	**Group E**
Liver weight %	3.22 [a] (0.19)	3.41[ab] (0.19)	3.44[ab] (0.19)	3.58 [b] (0.23)	3.47[ab] (0.24)
Kidney weight %	0.56 [a] (0.03)	0.65 [b] (0.04)	0.62 [b] (0.02)	0.64 [b] (0.02)	0.62 [b] (0.01)
Spleen weight %	0.34 (0.02)	0.33 (0.04)	0.36 (0.04)	0.39 (0.07)	0.37 (0.05)

[a b] indicates level of significance between the means of the groups at $p < 0.05$

1 **2**

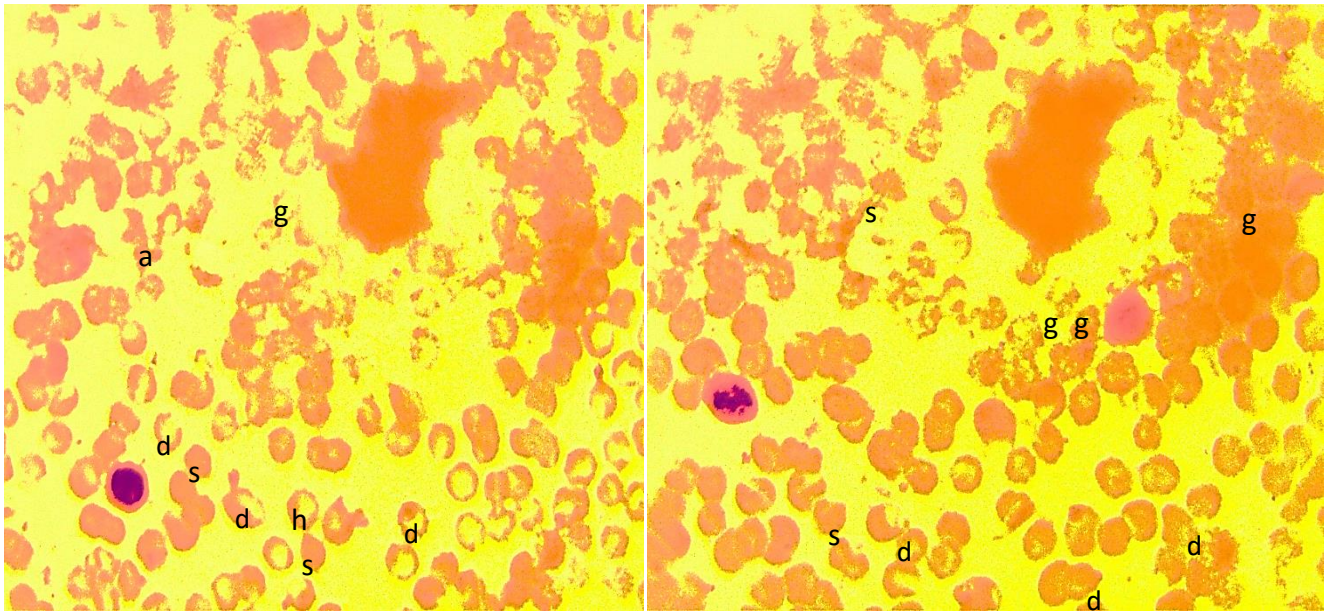

Figure 1: Photomicrograph of blood film of group A, pre-administration (1) and post-administration (2).

3 **4**

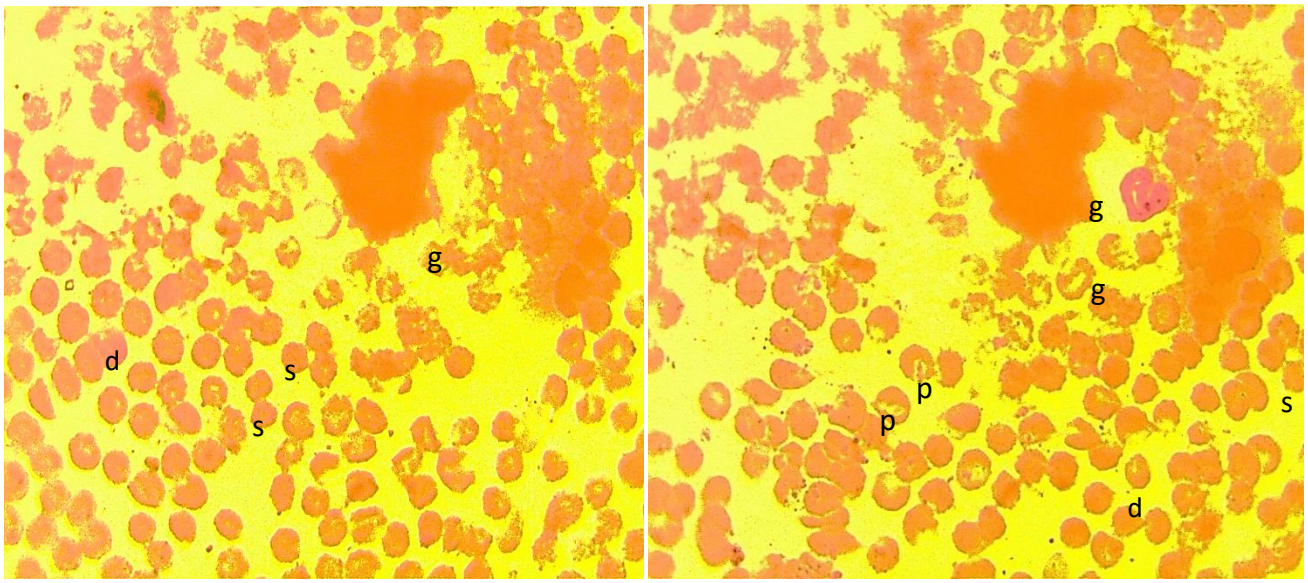

Figure 2: Photomicrograph of blood film of group E, pre-administration (3) and post-administration (4).

Key: 1 Hypochromic cells (h), piokilocytes (p), schistocytes (a), spherocytes (s), ghost cells (g), different degree of haemoglobinisation (d).

DISCUSSION

This study observed the effects of bromate on blood cell counts, as earlier reported (Achukwu et al, 2009), only on the haemoglobin and MCHC values while absolute neutrophil, monocyte and platelet counts showed no trend. However, the values of these parameters – haemoglobin and MCHC at day 0 were significantly higher than the day 60 values. Thus, the findings disagree with some other previous studies that reported anaemia and leucopenia (Abdel-Gadir et al, 2007), decreased cellular elements and impaired renal and hepatic histology (Altoom et al, 2018) following higher dose-dependent (75 – 1200mg of $KBrO_3$/kg bodyweight) administration of bromate on different types of rats. The disagreement between the present and the previous studies may be dependent on the dose of the bromate used in each study, implying that higher doses of bromate may cause blood dyscrasias, among other adverse effects. This is plausible because the present study agrees with another previous study (Omer et al, 2008) that reported no effects on haematological parameters after the administration of relatively higher doses of bromate (50 – 100mg of $KBrO_3$/kg bodyweight) than the present study, but noticed adverse effects when the dose was increased to 200mg. Likewise, other studies (Guo et al, 2001; Campbell, 2006; Crofton, 2006; Abdel-Gadir et al, 2007) have shown that rats treated with low doses of bromate over a periods of time (ranging from 12 weeks to 10 months) developed no adverse effects or accumulation of bromide in their tissues, implying that bromate toxicity is only dose but not duration dependent. This may explain some of the deviations of this study from the said previous studies.

On the organosometric, this study recorded significantly higher mean percentage liver weight in experimental groups than the control group. This is partly in agreement with earlier study (Guo et al, 2001) which also recorded significantly increased absolute and relative spleen weights with significant changes in some liver function parameters for group of rats that received 100 and 200mg bromate/kg bodyweight. However, the group that received 50mg/kg bodyweight in the said study did not show any significant variation from the control group, also implying dose dependence. This study is also in agreement with other studies that have reported increased kidney weight and extensive toxic effects, and severe damage of liver tissues, again with a dose of 100mg bromate/kg bodyweight (Dodd

et al, 2013; Hassan et al, 2019). The significant changes in the organs observed in the present study may be a prelude to possible organ damage which has earlier been associated with bromate (Ben-Saad et al, 2016). It is worthy to note that doses used in the present study (10 – 25mg/kg body weight) were less than those used in the earlier studies (Guo etal,2001; Dodd et al, 2013; Hassan et al, 2019), yet the results were similar. This indicates that bromate toxicity is not only dose dependent but also duration dependent. Therefore, though the allowable dose in bread of 0.02mg/kg of bread (Akunyili, 2005) may be seen as non-toxic level, and many bread industries in Nigeria have been found to add more than this dose (Naze etal, 2018), this may inadvertently accumulate to toxic level with time.

The blood films for both day 0 and day 60 samples from the entire albino rats showed no significant variations pre- and post- administration of potassium bromate. These blood films showed mixed population of both normal and abnormal red cell morphology. The consistency of ghost cell and schistocytic cell in almost all the blood films may not be enough to justify association with the potassium bromate administered; this may have been caused by technical errors. Though some scholars reported haemolysis following $KBrO_3$ administration (Robert and William, 1999), this study is of the opinion that haemolysis is more likely to be linked to pre-analytical procedures that may include route of administration and method of sample collection.

Conclusion

The results showed that bromate did not have significant effects on many haematological parameters, as well as the blood films of the rats. It is the opinion of this study that some of the observed changes in peripheral blood parameters may not really be due to potassium bromate. However, with the observed significant effects on both liver and kidney, it is possible that prolonged exposure at these doses will likely impact negatively on many of the haematological parameters, especially when various roles of the organs in haemopoeisis are affected. Therefore, while the study revealed no association between blood dyscracias and bromate at the administered doses and duration of exposure, organosometric showed that long consumption of bromate will likely affect erythropoeisis.

Recommendation

Though the present study did not find any association between low doses of bromate and blood dyscrasias, it gave a pointer that prolonged use of it will lead to other adverse effects, especially organ toxicity, that can culminate into blood dyscrasias, making bromate an unnecessary and potentially harmful food additive that should be avoided. It is recommended that studies should be undertaken to verify the possibility of Genetically Modified Organism (GMO) ingredients or components of the confectionary, contributing to the observed adverse effects in some previous studies.

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REFERENCES

Abdel-Gadir EH, Abdel-Gadir WS, Adam SE. (2007). Effects of various levels of dietary potassium bromate on Wistar rats. J Pharmacol Toxicol. 2(7):672-676

Abdulmumeen HA, Ahmed NR, Agboola RS. (2012). Food preservatives, additives and applications. Intern J Chem Biochem Sci. 1:36-47

Achukwu PU, Eze RI, Omorodion NT. (2018). Formulation of rapid method for detection and estimation of bromate in serum and confectionaries consumed in Enugu Nigeria. Res J Food Nutr. 2(2):62-70

Achukwu PU, Ufelle SA, Ukaejiofo EO, Ejezie FE, Nwachukwu DN, Nwagha UI. et al. (2009). The effect of potassium bromate on some haematological parameters of Wistar Rats. Niger J Physiol Sci. 24(1):59-61

Ahmad MK, Mahmood R. (2012). Oral administration of potassium bromate, a major water disinfection by-product, induces oxidative stress and impairs the antioxidant power of rat blood. Chemosphere. 87:750-756

Ajarem J, AltoomNG, Allam AA, Maodaa SN, Abdel-Maksoud MA, Chow BK. (2016). Oral administration of potassium bromate induces neurobehavioral changes, alters cerebral neurotransmitters level and impairs brain tissue of swiss mice. Behavioral and Brain Functions. 12(1):14

Akunyili ND. (2005). Eradication of potassium bromated from Nigerian bakery industry. NAFDAC. 5:1-6

Altoom NG, Ajarem J, Allam AA, Maodaa SN, Abdel-Maksoud MA. (2018). Deleterious effects of potassium bromate administration on renal and hepatic tissues of Swiss mice. Saudi J Biol Sci. 25:278–284

APA. (2017). Bromate. The American Heritage Science Dictionary. American Psychological Association. http://www.dictionary.com/browse/bromate. (accessed 28/1/2022)

Ben Saad H, Driss D, Ben Amara I, Boudawara O, Boudawara T, EllouzChaabouni S. et al. (2016). Altered hepatic mRNA expression of immune response-associated DNA damage in mice liver induced by potassium bromate: Protective role of vanillin. Environ Toxicol. 31:1796–1807

Campbell KC. (2006). Bromate-induced ototoxicity. Toxicology. 221:205–211

Crofton KM. (2006). Bromate: concern for developmental neurotoxicity? Toxicology. 221:212–216

Dacie J, Lewis SM. (2006). Practical Haematology. 10th ed. Churchil Livingstone, Edinburgh. pp, 21-57.

Dodd DE, Layko DK, Cantwell KE, Willson GA, Thomas RS. (2013). Subchronic toxicity evaluation of potassium bromate in Fischer 344 rats. Environ Toxicol Pharmacol. 36(3):1227–1234

ECHA. (2019). Sodium bromated-registration dossier. European Chemical Agency. https://echa.europa.eu/de/registration-dossier/-/registered-dossier/14239/7/7/2. (accessed 28/1/2022)

EU. (2020). Directive 2020/2184 of the European Parliament and of the Council of 16 December 2020 on the quality of water intended f-or human consumption. European Union.

Finney DJ. (1971). Probit Analysis.3rd ed. Cambridge, Cambridge University Press, 1971

Geter DR, Ward WO, Knapp GW, DeAngelo AB, Rubis JA, Owen RD. et al. (2006). Kidney toxicogenomics of chronic potassium bromate exposure in F344 male rats. Transl Oncogenomics. 1:33

Ghosh MN. (1984). Statistical analysis: In: Fundamentals of Experimental Pharmacology. 2nd edition Scientific book agency Calcutta pp 187-189.

Guo TL, McCay JA, Karrow NA, Brown RD, Musgrove DL, Luebke RW. et al. (2001). Immunotoxicity of sodium bromate in female B6C3F1 mice: a 28-day drinking water study. Drug Chem Toxicol. 24:129–149

Hassan I, Husain F, Khan R, Ebaid H, Al-Tamimi J, Alhazza I. et al. (2019). Ameliorative effect of zinc oxide nanoparticles against potassium bromate-mediated toxicity in Swiss albino rats. Environ Sci Pollut Res. 26:9966–9980

IARC. (1999). International Agency for Research on Cancer, Working group on the evaluation of carcinogenic risks to humans: Potassium bromate. IARC Monograph on the Evalulation of Carcinogenic Risks to Humans. 73:481– 496

Joseph C, Richard B. (2010). Bromate toxicity including mechanisms of cancer induction: State-of-the-science report and health research strategy. Project #3025 Subject Area: High-Quality Water Awwa Research Foundation 6666 West Quincy Avenue, Denver, CO 80235-3098.

Kathleen CM. (2006). Bromate induced ototoxicity. Toxicology. 221:205-211

Mack M, Schweinlin K, Mirsberger N, Zubel T, Bürkle A. (2021). Automated screening for oxidative or methylation induced DNA damage in human cells. Altex. 38:63–72

Naze AU, Epete OA, Owhoeke E. (2018). Bromate Content in Thirty Different Brands of Bread Baked in Port Harcourt Metropolis Rivers State, Nigeria. J. Appl. Sci. Environ. Managt. 22(8): 1321-1324

Ojeka EO, Obidiaku ML, Enukorah C. (2006). Spectrophotometric determination of bromate in bread by oxidation of dyes. J Appl Sci Environ Management. 10(3):43-46

Ojo-Rotimi J, Kajang-Duniya D, Adebayo-Gege GI, Akintayo CO. (2013). Analysis of potassium bromate and hydrocyanic acid contents of commonly consumed loaves of bread and wheat flour samples in Karu, Nasarawa State, Nigeria. J Environ Sci Toxicol Food Technol. 6(1):42-46

Okafor CS, Okeke D, Okoli CC. (2013). Determination of the levels and hepatic effects of potassium bromate in bread samples sold in Awka metropolis, Nigeria. Res J Sci IT Management. 2(3):17-20

Omer R, Abuelgasim AI, Elmahdi B. (2008). Effects of potassium bromate on liver and blood constituents of Wistar albino rats. Am J Food Technol. 3(5):310- 314

Raj J, Chandra M, DograTD, Pahuja M, Raina A. (2013). Determination ofmMedian lethal dose of combination of Endosulfan and Cypermethrin in Wistar Rat. Toxicol Intern. 20(1):1-5

Robert IA, William BC. (1999). Carcinogenicity of potassium bromate in rabbit. Biology Education. 34:114–120

Scholpa NE, Zhang X, Kolli RT, Cummings BS. (2014). Epigenetic changes in p21 expression in renal cells after exposure to bromate. Toxicol Sci. 141(2):432–440

Shehab ZA, Ghadhban RF. (2021). Effect of potassium bromate on some hematological and biochemical parameters and protective role of vitamin C on laboratory rats (Rattus_Rattus). Ann Rom Soc Cell Biol. 25(2):669–674

Spassova MA, Miller DJ, Eastmond DA, Nikolova NS, Vulimiri SV, Caldwell J. et al. (2013). Dose-response analysis of bromate-induced DNA damage and mutagenicity is consistent with low-dose linear, non-threshold processes. Environ Mol Mutag. 54(1):19– 35

USEPA. (2001). Toxicological review of bromate in support of summary information on the Integrated Risk Information System (IRIS). Washington (DC): US Environmental Protection Agency. Report No.: EPA/635/R- 01/002.

WHO. (2017). Guidelines for Drinking-Water Quality: Fourth Edition Incorporating the First Addendum. World Health Organization, Geneva: ISBN: 9789241549950.

Zhang Y, Jiang L, Geng C, Li L, Shao J, Zhong L. (2011). Possible involvement of oxidative stress in potassium bromate-induced genotoxicity in human HepG2 cells. Chemico-biological Interactions. 189(3):186–191