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Effects of Various Levels of Dietary Potassium Bromate on Wistar Rats

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Abstract: The toxicity to male Wistar rats of potassium bromate ($KBrO_3$) was investigated. $KBrO_3$ was fed to rats at 75, 150, 600 and 1200 mg kg^{-1} diet for 4 weeks. The rats fed diets containing 600 and 1200 mg kg^{-1} of $KBrO_3$ had the lowest growth rate but none of the rats died during the 4 week period. Depression in growth, nephropathy, hepatopathy and lymphocytic infiltration in vital organs were accompanied by anemia, leukopenia and alterations in serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities with changes in concentration of urea, cholesterol and other serum constituents. Diet consisting of 150 mg kg^{-1} of $KBrO_3$ was less toxic to rats.

Key words: Potassium bromate, nephropathy, hepatopathy

INTRODUCTION

The concept of potassium bromate ($KBrO_3$) use as an oxidizer to mature flour, condition dough during baking and to improve the quality of paste products dates back to the turn of the past century (Mack, 1988; Chipman *et al*., 1998).

$KBrO_3$ has also been used as a constituent in cold wave hair solutions (Mack, 1988; Chipman *et al*., 1998; Ueno *et al*., 2000) and generated as a disinfecting byproduct from bromate in the process of ozonation and chlorination of raw water (Ueno *et al*., 2000; Parsons and Chipman, 2000).

In the Sudan, health problems have been suspected as a result of inadvertent use of potassium bromate following ingestion of prepared bread for varying periods. Indeed, physicians have placed emphasis on the misuse of potassium bromate and consequent development of renal failure.

Although the suggestion that potassium bromate leads to the development of embryotoxicity, teratogenicity and carcinogenicity in some experimental animals, information on the exact cytotoxic concentration range at which these effects occur as well as species susceptibility and other factors is scarce.

The present research was planned to investigate the effect of various levels of dietary potassium bromate in male Wistar rats. The criteria for assessment include effects on growth and pathological, biochemical and hematological alterations.

MATERIALS AND METHODS

Study Design

Forty 9-week-old male Wistar rats were housed within the premises of the Medicinal and Aromatic Plants Research Institute, National Center for Research, Khartoum, under illumination at night and early morning with feed and drinking water provided *ad libitum*. The rats were allotted at random to five groups, each of 8 rats. Group 1 continued to be fed the normal diet and served as

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control. Potassium bromate (BDH, England) was thoroughly mixed with normal diet and fed to rats at 75 mg kg^{-1} (Group 2), 150 mg kg^{-1} (Group 3), 600 mg kg^{-1} (Group 4) and 1200 mg kg^{-1} (Group 5) for 4 weeks.

Average body weight and body weight gain were measured weekly for each group. After 4 weeks of treatment, rats from each group were killed under diethyl ether anesthesia to identify gross lesions and specimens of the liver, intestines, kidneys, spleen and heart were immediately fixed in 10% neutral buffered formalin and processed for histopathology. Blood samples were collected from the cervical blood vessels of each rat for serum analysis and hematology.

Blood Analyses

Serum samples were analyzed for the activity of Aspartate aminotransferase (AST), alanine Aminotransferase (ALT) and Alkaline phosphatase (ALP) and for concentrations of total protein, albumin, globulin, bilirubin, cholesterol and urea.

Hemoglobin (Hb) concentration, Red Blood Cell (RBC) counts, Packed Cell Volume (PCV), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin (MCH), Mean Corpuscular Hemoglobin Concentration (MCHC) and White Blood Cell (WBC) counts were determined by standard methods (Schalm *et al*., 1975).

Statistical Analysis

The significance of differences between means was compared at each time point using Duncan's multiple range test after ANOVA for one-way classified data (Snedecor and Cochran, 1989).

RESULTS

Effect on Growth

The rats fed diets consisting of 600 (Group 4) and 1200 mg kg^{-1} of potassium bromate (Group 5) had the lowest ($p<0.05$) growth rate and consumed less feed but none of the animals died during the course of the experiment (Table 1).

Pathologic Changes

No significant macroscopic or microscopic changes were observed in the tissues of the rats on a diet containing 75 mg kg^{-1} of potassium bromate (Group 2) as compared with the rats on the control diet (Group 1). Small fatty vacuoles in the epithelial cells of the renal proximal convoluted tubules and the centrilobular hepatocytes and hemorrhage and congestion of the blood vessels of the heart (Fig. 1) and kidneys were seen in the rats fed a diet containing 150 mg kg^{-1} of potassium bromate (Group 3). In the rats fed a diet containing 600 mg kg^{-1} of potassium bromate (Group 4), there was congestion of the blood vessels of the heart, kidneys and liver, fatty cytoplasmic vacuolation or focal necrosis of the centrilobular hepatocytes and of the cells of renal proximal convoluted tubules (Fig. 2) with packing of the glomeruli and cardiac muscle fibers with lymphocytic infiltration and detachment of the bronchiolar epithelial cells into the lumen. Focal lymphocytic infiltration was also observed around the bronchioles. In the rats fed a diet containing potassium bromate at 1200 mg kg^{-1} (Group 5), fatty

Table 1: Body weight and body weight gain of potassium bromate-fed rats

Groups	Body weight (g)	Body weight gain (g)
1	107.6 ± 3.9^{a}	42.0 ± 1.3^{a}
2	107.6 ± 3.9^{a}	34.3 ± 1.1^{ab}
3	84.8 ± 2^{b}	28.0 ± 2.2^{b}
4	81.3 ± 2.1^{b}	20.0 ± 1.7^{c}
5	78.0 ± 1.2^{b}	18.0 ± 1.9^{c}

Values are means±SE. Means within columns with no common letter(s) are significantly different ($p<0.05$)

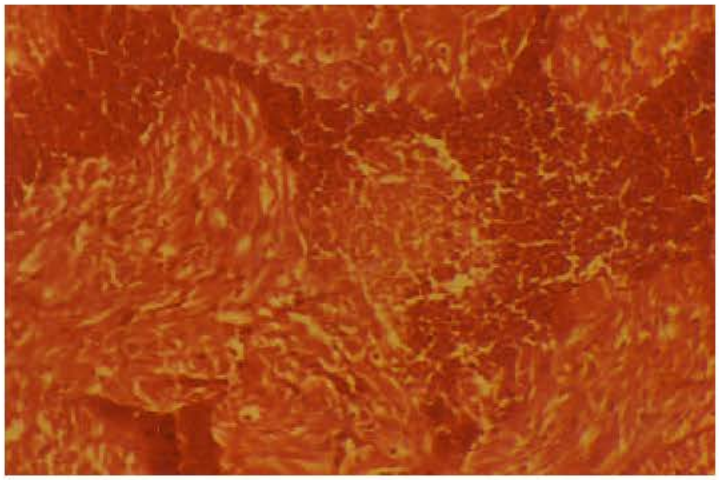

Fig. 1: Cardiac congestion and hemorrhage in a rat fed diet containing 150 mg kg^{-1} of potassium bromate for 30 days. H and E x 100

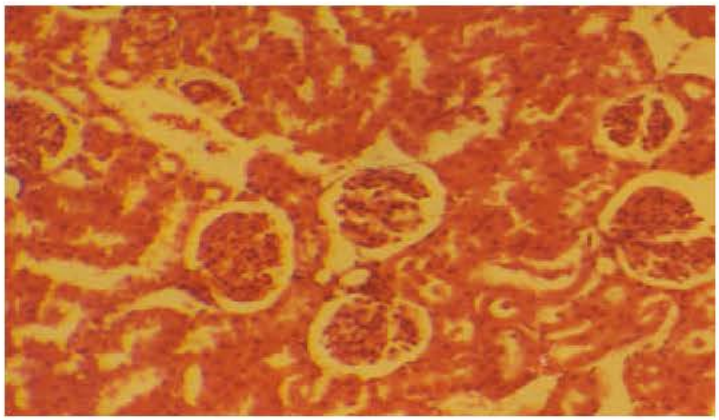

Fig. 2: Necrosis of the renal proximal convoluted tubules and segmentation or packing of the glomeruli in a rat fed diet containing 600 mg kg^{-1} of potassium bromate for 30 days. H and E x 100

cytoplasmic vacuolation or focal necrosis of the renal cortical and medullary tubules, centrilobular hepatocytes, packing of scattered glomeruli, catarrhal enteritis with minute erosions on the intestinal lamina propria and accumulation of lymphocytes in the renal cortex, intestinal lamina propria and between some of the cardiac muscle fibers were observed. No significant lesions were seen in the spleen of the rats in groups 2-5 or in the vital organs of the control rats (Group 1) throughout the feeding period.

Serobiochemical and Hematological Changes

The activities of serum AST and ALT were higher ($p<0.05$) in Groups 2-5 than control (Group 1). The concentration of total protein and albumin did not change but that of globulin was

Table 2: Serobiochemical and hematological changes in rats fed various levels of dietary potassium bromate

	Groups				
Parameters	1	2	3	4	5
AST (IU)	10.0±1.5^{b}	28±1.8^{a}	25±0.9^{a}	25±2.1^{a}	24±1.3^{a}
ALT (IU)	5.0±0.4^{c}	10±0.9^{b}	27±1.4^{a}	18±1.9^{ab}	28±2.1^{a}
ALP (IU)	393.8±6^{a}	217.9±4.1^{c}	238.3±4.5^{b}	277±3.3^{ab}	297±4.3^{ab}
Total protein (g dL^{-1})	9.3±0.7^{a}	7.9±0.6^{a}	8.5±0.5^{a}	9.3±0.8^{a}	9.3±0.8^{a}
Albumin (g dL^{-1})	3.4±0.2^{a}	3.5±0.3^{a}	3.4±0.3^{a}	3.4±0.3^{a}	3.4±0.3^{a}
Globulin (g dL^{-1})	5.9±0.4^{a}	4.4±0.2^{b}	5.1±0.5^{ab}	5.9±0.3^{ab}	5.9±0.3^{ab}
Cholesterol (mg dL^{-1})	78.4±3.1^{b}	56.7±2.9^{c}	90.1±3.1^{ab}	107.5±4.5^{a}	107.5±4.5^{a}
Urea (mg dL^{-1})	8.5±1.9^{b}	8.6±2^{b}	7.9±1.6^{b}	11.7±1.1^{a}	11.7±1.1^{a}
Hb (g dL^{-1})	9.2±0.9^{b}	12± 0.9^{a}	8.6±0.6^{b}	10.5±1^{a}	10±0.9^{a}
RBC (×10^{6} mm)	5.4±0.5^{a}	5.8±0.6^{a}	3.9±0.9^{b}	4.24±0.2^{b}	4.02±0.3^{b}
PCV (%)	29.0±0.3^{ab}	36.3±0.2^{a}	27±0.7^{b}	32±0.3^{ab}	30±0.3^{ab}
MCV (m^{3})	53.7±2.1^{c}	62.6±3.2^{b}	69.2±3.5^{ab}	75.5±2.5^{a}	74.6±2.5^{a}
MCH (pg)	17.03±1.3^{b}	20.7±1.2^{ab}	22.1±1.9^{a}	24.8±1.2^{a}	24.9±1.3^{a}
MCHC (%)	31.7±1.7^{a}	33.1±1.9^{a}	31.9±1.7^{a}	32.8±1.2^{a}	33.3±1.4^{a}
WBC (×10^{3} mm)	6.15±1.2^{ab}	7.5±1.4^{a}	5.3±0.7^{b}	7.3±1.3^{a}	6.4±0.9^{ab}

Values are means±SE; Means within rows with no common letter(s) are significantly different ($p<0.05$), 1: Control; 2: 75 mg kg^{-1} ($KBrO_3$); 3: 150 mg kg^{-1} ($KBrO_3$); 4: 600 mg kg^{-1} ($KBrO_3$) and 5: 1200 mg kg^{-1} ($KBrO_3$)

lower ($p<0.05$) in Groups 2 and 3 than control and other groups. The concentrations of cholesterol and urea were higher ($p<0.05$) in Groups 3-5 than other groups and control (Table 2).

The values of RBC were lower ($p<0.05$) in Groups 3-5 than other groups. The values of MCV and MCH were higher ($p<0.05$) in Groups 2-5 than control (Group 1). The MCHC values did not change but those of WBC were lower ($p<0.05$) in group3 than control and other groups.

DISCUSSION

Potassium bromate used to strengthen bread dough was found to cause cancer of the kidneys, thyroid gland and other organs of rats and mice and was consequently banned in many countries like the United Kingdom, Canada and California (Umemura *et al*., 1995), Sai *et al*. (1992) found that glutathione plays an essential protective role against renal oxidative DNA damage and nephrotoxicity caused by $KBrO_3$ in rats. Khan *et al*. (2003) suggested that *Nigella sativa*, *Black cumin*, is a strong chemoprotective agent and may suppress $KBrO_3$ -mediated renal oxidative stress, toxicity and tumor promotion response in rats.

In the present investigation, none of the dietary $KBrO_3$ concentrations (75-1200 mg kg^{-1}) has caused renal tumor, probably because of the short duration (4 weeks) of feeding. It has been previously shown that $KBrO_3$ induced methemoglobinemia in mice due to the reduction of glutathione peroxidase activity in the blood with increase in superoxide and nitrous oxide (Watanabe *et al*., 2002). In this study, methemoglobinemia was not observed in $KBrO_3$ -fed rats.

The results indicated that $KBrO_3$was toxic but not fatal to Wistar rats fed for 4 weeks. Depression in body weight gain and the occurrence of hepatonephropathy suggest that $KBrO_3$ is a toxicant that impairs growth and reduces the excretion rate through injury to kidneys and liver, The damage to vital organs could explain the loss in body weight. It is likely that injury to these organs probably contributed to the increased AST and ALT activities and cholesterol and urea concentrations. The mechanism by which $KBrO_3$ damaged body tissues has yet to be defined.

The anemia was macrocytic normochromic, a conclusion indicated by the high MCV and normal MCHC values, Leukopenia was also observed in the rats fed $KBrO_3$ at 150 mg kg^{-1}. The increased lymphocytes infiltrated into vital organs.

Evaluation of the interaction of $KBrO_3$ and plant constituents is in progress.

REFERENCES

Chipman, J.K., J.E. Davies, J.L. Parsons, J.O. Nair, G. Neill and J.K. Fawell, 1998. DNA Oxidation by potassium bromate a direct mechanism or linked to lipid peroxidation. Toxicology, 126: 93-102.

Khan, N., S. Sharma and S. Sultana, 2003. *Nigella sativa* (*Black cumin*) ameliorates potassium bromate-induced early events of carcinogenesis: Diminution of oxidative stress. Hum. Exp. Toxicol., 22: 198-203.

Mack, R.B., 1988. Round up the usual suspects. Potassium bromate poisoning. North Carolina Med. J., 49: 243-245.

Parsons, J.L. and J.K. Chipman, 2000. The role of glutathione in DNA damage by potassium bromate. Mutagenesis, 15: 311-316.

Sai, K., M. Hayashi, A. Takagi, R. Hasegaura, T. Sofuni and Y. Kurokawa, 1992. Effects of antioxidants on induction of micronuclei in rats peripheral blood reticulocytes by potassium bromate. Mutation Res., 269: 113-118.

Schalm, O.W., N.C. Jain and G.H. Carroll, 1975. Veterinary Hematology. 3rd Edn., Lea and Febiger, Philadelphia.

Snedecor, G.W. and W.C. Cochran, 1989. Statistical Methods. 8th Edn., Iowa State University Press, Ames, Iowa.

Ueno, H., K. Oishi, Y. Sayato and K. Nakamuro, 2000. Oxidative cell damage in Kat-sod assay of oxyhalides as inorganic disinfection by-products and their occurrence by ozonation. Arch. Environ. Contam. Toxicol., 38: 1-6.

Umemura, T., K. Sai, A. Takagi, R. Hasegawa and Y. Kurokawa, 1995. A possible rate for oxidative stress in potassium bromate ($KBrO_3$) carcinogenesis. Carcinogenesis, 16: 593-597.

Watanabe, S., S. Togashi and T. Fukui, 2002. Contribution of nitric oxide to potassium bromate-induced elevation of methemoglobin concentration in mouse blood. Biol. Pharmacol. Bull., 10: 1315-1319.