Journal of the American College of Toxicology
13(5):400–414, Raven Press, Ltd., New York

Final Report on the Safety Assessment of Sodium Bromate and Potassium Bromate[1]

Abstract: Sodium Bromate and Potassium Bromate are inorganic salts that act as oxidizing agents. Whereas there are currently no reported uses of Potassium Bromate, Sodium Bromate is used in permanent waves and related hair care products. No current data were available to indicate the concentrations at which this ingredient is used. Bromate was poorly absorbed, if at all, through the skin in several in vivo and in vitro studies. The oral median lethal dose of Potassium Bromate in rats was 200–400 mg/kg. A guinea pig sensitization study suggested at most a mild sensitizing potential for Sodium Bromate. Potassium Bromate was found to be mutagenic in a mammalian cell assay and in one of three bacterial strains tested. Potassium Bromate produced a dose-dependent increase in renal neoplasms in an oral feeding study in rats. A two-stage, 26-week carcinogenesis study in rats suggested that Potassium Bromate was both a tumor promoter and a tumor initiator. Renal cell tumors, of a type not seen in controls, were seen in male golden hamsters administered Potassium Bromate in drinking water. Potassium Bromate applied to the skin of mice or injected subcutaneously into newborn mice or rats, however, was noncarcinogenic. The high reactivity/poor skin absorption of these oxidizing agents was considered a likely explanation for the difference between the results seen with different routes of exposure. Based on the test concentrations reported, it is concluded that Sodium Bromate and Potassium Bromate are safe in cosmetic permanent wave formulations at concentrations not to exceed 10.17%, measured as Sodium Bromate. **Key Words:** Sodium Bromate—Potassium Bromate—Safety—Cosmetic use—Hair permanent wave—Rat—Hamster—Mouse—Guinea pig—Chemistry—Toxicity—Sensitization—Mutagenicity—Carcinogenicity.

Sodium Bromate, but not Potassium Bromate, is reported to be used in permanent wave cosmetic formulations. Most of the available safety test data in this report are for studies using Potassium Bromate.

CHEMICAL AND PHYSICAL PROPERTIES

Definition and Chemical Structure

Sodium Bromate and Potassium Bromate are the inorganic salts that conform to the following formula (Estrin et al., 1982; Weast, 1982): $NaBrO_3$ and $KBrO_3$.

[1] Reviewed by the Cosmetic Ingredient Review Expert Panel.

Address correspondence and reprint requests to Dr. F. A. Andersen at Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, U.S.A.

The chemical and physical characteristics of Sodium and Potassium Bromate are outlined in Table 1.

Analytical Methods

One method of analytical determination of soluble Bromates is the application of the Vandermullen procedure for bromide (Patty, 1962). The amount of Bromate in bread and fish-paste products can be determined by aqueous extraction, separation of Bromate from interfering ionic species by ion chromatography, and quantification by chromatography with electrochemical detection. This procedure has a reported detection limit of 1–2 mg/kg (Watanabe et al., 1982). Infrared spectral data for Sodium and Potassium Bromate have been published (Sadtler Research Laboratories, 1967). A minimum detection limit of 0.5 ppm Bromide in human body fluids by x-ray fluorescence was reported by Bromine Compounds, Ltd. (July 1992), Cosmetic, Toiletry and Fragrance Association [(CTFA), 1991], Rappaport et al. (1981), and Shenberg et al. (1987). The use of this procedure allows one to detect and quantify Bromide in guinea pig blood serum at 0.5 ppm ± 9%.

A suppressed ion chromatography method to quantify Bromate in guinea pig serum with a lower detection limit of 76 ppb has also been reported (Bromine Compounds, Ltd., July, 1992).

Reactivity

Potassium Bromate is a strong oxidizing agent that reacts vigorously with organic matter and is reduced to bromide. Potassium Bromate also oxidizes some metals, such as aluminum and copper, and some nonmetals, such as arsenic, phosphorus, selenium, and sulfur (Lewis, 1993; Sax, 1979).

In permanent hair wave chemistry, an oxidizing agent is added to establish new disulfide bonds between pairs of cysteine residues of adjacent polypeptide chains. After washing and cooling the treated hair, the polypeptide chains revert to an alpha-helical configuration, and the hair fibers curl because of disulfide cross-linkages formed where some torsion is exerted on the bundles of alpha-helical coils in the hair fibers. The oxidizing agent, which is referred to as a neutralizer, is then washed away. The neutralizers are usually Sodium Bromate or hydrogen peroxide solutions in mildly acidic formulations (Mack, 1988).

TABLE 1. *Chemical and physical characteristics of Sodium Bromate and Potassium Bromate*

Parameter	Sodium Bromate	Potassium Bromate	References
Physical characteristics	White crystal or crystalline powder, odorless	White crystal or crystalline powder, odorless, tasteless	Windholz, 1983
Molecular weight	150.91	167.01	Windholz, 1983
Specific gravity (g/ml)	3.4	3.27	Hawley, 1981
Index of refraction	1.594		Windholz, 1983
Melting point (°C)	381	434	Windholz, 1983

Method of Manufacture

Sodium Bromate is formed by passing bromine through a solution of sodium carbonate (Hawley, 1981). Potassium Bromate may be produced by passing bromine through a solution of potassium hydroxide (Lewis, 1993). These compounds are usually manufactured by large-scale industrial electrolytic processes.

Impurities

The following are the allowable limits of impurities present in the food-grade Potassium Bromate: not >3 ppm arsenic, and/or 10 ppm heavy metals such as lead (National Research Council, 1981). Commercial Potassium Bromate may contain up to 0.02–0.05% bromides, 0.001–0.01% sulfates, and 20 mg/kg iron. Potassium Bromate is commercially available in mixtures with 5% magnesium carbonate or 50% calcium carbonate (AmeriBrom, undated; American International Chemical, undated).

USE

Cosmetic Use

Sodium Bromate was present in 61 cosmetic formulations voluntarily reported in 1991 to the Food and Drug Administration (FDA) by the cosmetic industry. There were no reported uses of Potassium Bromate (FDA, 1991). Concentration of use values are no longer reported to the FDA by the cosmetic industry (Federal Register, 1992). However, product formulation data submitted to the FDA in 1984 stated that Sodium Bromate was used in permanent wave formulations within the concentration range of 10–25% (FDA, 1984). A cosmetic formulation was analyzed and found to contain 10.17% $NaBrO_3$, (8.59% BrO_3^-) (Bromine Compounds, Ltd., July 1992).

Non-Cosmetic Use

Sodium Bromate is used as an analytic reagent. When mixed with sodium bromide, it can dissolve gold from its ores (Lewis, 1993; Windholz, 1983). Potassium Bromate is used industrially as a laboratory reagent, a component of fusing material for explosives, and as a powerful oxidizing agent (Lewis, 1993). In food production, Potassium Bromate is used as a bread and flour improving agent, in the malting of barley, and in the manufacture of cheese (Windholz, 1983; Kurokawa et al., 1983a; Kulp and Hepburn, 1978; Sfat and Doncheck, 1981; World Health Organization, 1983; AmeriBrom, undated).

When Potassium Bromate is used as an improving agent in bread, reaction with oxygen creates a sponge-like quality which inhibits the generation of large bubbles (Ito, 1982). No detectable Potassium Bromate was found in baked bread made from flour containing 80 ppm; the studies reconfirmed the existing maximum level of Potassium Bromate in flour of 50 ppm (Thewlis, 1974). The FDA limits bromide in flour to concentrations up to 30 ppm as the result of adding 50 ppm Potassium Bromate [Code of Federal Regulations (CFR), 1984].

Occupational exposure to Potassium Bromate occurs mainly in production

plants during packaging processes. Areas in which exposure to Sodium or Potassium Bromate is in excess of 100 mg/m^3 require the use of a dust respirator (American Industrial Hygiene Association, 1981).

The Consumer Product Safety Commission requires that all home permanent wave neutralizing solutions containing >600 mg of Sodium Bromate or 50 mg of Potassium Bromate be enclosed in child-resistant packages (CFR, 1989).

International Use

Sodium Bromate and Potassium Bromate are included in the list of cosmetic ingredients approved for use in cosmetic formulations marketed in Japan (CTFA, 1984).

GENERAL BIOLOGY

Absorption and Excretion

Theiller strain mice were fed diets containing 79% bread crumbs made from flour treated with either 50 or 75 mg/kg Potassium Bromate. Concentrations of Bromide ranging from 1 mg/kg to 2 mg/kg Bromide were detected in the adipose tissue (Ginocchio et al., 1979).

The absorption of Sodium Bromate by excised guinea pig skin was determined for a cosmetic hair neutralizer (CTFA, 1991; Bromine Compounds, Ltd., January 1992). A 1.77-cm^2 piece of skin was exposed to 0.2 ml hair neutralizer containing 16.5 mg Bromate for 15 and/or 30 min, in glass diffusion cells, allowing transdermal diffusion into 5 ml buffered solution. The buffers were collected at 30, 60, 120, or 240 min after each exposure period. An X-ray fluorescence technique, based on neutron excitation by X-rays was used to detect bromine. The method detects bromine atoms in any form. The limit of detection was 0.5 ppm. The detection of total Bromide is given in Table 2. The total Bromide absorbed as a percentage of the exposure dose is given in Table 3.

The investigators calculated that the exposure dose of "Br" was 0.0165 g × 79.9/127.9 = 0.0103 g = 10.3 mg . . . [Calculation error: 0.0165 g × 79.9/149.9 = 0.00873 g = 8.73 mg] . . . . The maximum amount of Bromine that might be absorbed, as measured by Bromide, was 2.4 ppm in 5 ml receiving solutions, and/or 12 × 10^{-3} mg "Br" of the 10.3 mg exposure dose. The study indicated that the maximum amount of Bromine absorbed by the skin after a 30-min exposure

TABLE 2. *Total amount of Bromine detected (ppm, as Bromide)*

Collection time (min)	After 15-min exposure			After 30-min exposure		
	Sample 1	Sample 2	Mean	Sample 1	Sample 2	Mean
30	0.9	0.5	0.7	0.9	0.8	0.85
60	1.5	1.2	1.35	0.6	1.2	0.9
120	2.3	2.0	2.15	2.2	2.0	2.1
240	1.7	1.6	1.65	2.4	2.3	2.35

TABLE 3. *Total amount of bromine absorbed through excised skin*

Collection time (min)	Concentration bromide detected (ppm)		Total amount absorbed (mg × 10^{-3})		% Absorbed	
	15 min	30 min	15 min	30 min	15 min	30 min
30	0.7	0.85	3.50	4.25	0.034	0.041
60	1.35	0.9	6.75	4.50	0.066	0.044
120	2.15	2.1	10.75	10.50	0.104	0.102
240	1.65	2.35	8.25	11.75	0.080	0.114

Data are based upon the detection of Bromide.

was 0.12% (measured as bromide). The bromine was absorbed by the skin and then released. The amount released continued after cessation of exposure but reached a plateau after ~2 h.

A study to evaluate the potential in vivo transdermal absorption of Bromate from a hair neutralizer formulation containing 10.17% Sodium Bromate (BrO_3^-) has also been reported (Bromine Compounds, Ltd., July 1992). In this study 0.5 ml of the hair neutralizer was spread over a 5-cm^2 shaved area of 24 albino guinea pigs and allowed to remain for 15 min (3× the normal 5-min exposure used during actual hair treatment). At the end of the treatment, the exposed areas were rinsed with water several times and dried. Twenty-four control animals were exposed to a physiological saline solution. Two separate studies, each using the same procedures, were reported. The study used a hair neutralizer containing 10.17% Sodium Bromate (8.59% BrO_3^-). Blood samples were collected from both the test and control animals from the retro-orbital sinus at 1, 2, 3 and 4 h. Urine samples were also collected. Prior to analysis by suppressed ion chromatography, the blood components that would interfere with the Bromate chromatographic peak were removed. The method used gave a linear response in spiked samples within the investigated range of 100–1,000 ppb. The recovery of Bromate by the method used was estimated to be 87%, with a detection limit of 76 ppb BrO_3^-. The investigators reported that no Bromate was found in the blood samples of the controls or the animals treated with hair neutralizers containing 10.17% Sodium Bromate (8.59% BrO_3^-).

A separate parallel study using the same exposure method was conducted to measure the amount of Bromide in the blood of treated and untreated guinea pigs. The Bromide was measured by X-ray fluorescence with a limit of detectability of 0.5 ppm. Twenty-four animals were used in the controls and in each of the assays of the hair neutralizers. Elevated serum concentrations of Bromide were observed in some of the treated animals in one of the assays of one hair neutralizer, but not in the other. The investigators concluded that Bromate does not penetrate through guinea pig skin above the minimal limit of detection (76 ppb), and that the Bromide that was detected in serum is the nonoxidative form of Bromine.

Groups of four male Wistar rats were given oral doses of 50 mg/ml Potassium Bromate in a study of the excretion of the compound. Bromate (50 mg/kg) was rapidly absorbed from the digestive tract. The test compound was partly excreted in the urine (~35%) and feces (~1%) as Bromate, and similar amounts as bromide

(~40%) within 2 h of administration. Bromate was not detected in the blood nor in body organs 24 h after dosing (Fujii et al., 1984).

In order to determine the disappearance of $KBrO_3$ from digestive organs and plasma and its excretion in urine, a dose of 100 mg $KBrO_3$/kg was given to rats per os. The animals were killed at various time intervals. BrO_3^- disappeared gradually from the stomach and had the greatest concentrations in the small intestine after 30 min, reaching undetectable concentrations within 4 h. Maximal concentrations in the plasma were recorded after 15 min, returning to undetectable amounts after 2 h. Bromate in urine taken from the urinary bladder reached a peak after 1 h, then decreased rapidly with no further excretion into the urine of the urinary bladder after 4 h. Fujii et al. (1984) concluded that BrO_3^- given per os "is rapidly absorbed and degrades within a short period."

A solution of Potassium Bromate was administered orally to 11 groups of four rats each at doses of 0.625, 1.25, 2.5, 5.0, 10.0, 20.0, 40.0, 60.0, 80.0, or 100 mg/kg to determine the dose–response relationship of the excretion of BrO_3^- and Br^-. At doses of $\leq$2.5 mg/kg, no excretion of Bromate was observed 24 h following administration of the compound. At greater doses, the Bromate excretion observed was in increasing amounts proportional to the dose (Fujii et al., 1984).

TOXICOLOGY

Acute Oral Toxicity

In the rat, the oral LD_{50} of Potassium Bromate was 200–400 mg/kg, and the oral lethal dose that resulted in 100% mortality (LD_{100}) was 700 mg/kg. In the mouse, the oral LD_{50} was 400 mg/kg (Anonymous, 1981). Kurokawa et al. (1990) reported that the LD_{50} for rats, mice, and golden hamsters was exceeded following a single intragastric administration of $\geq$700 mg/kg $KBrO_3$. The LD_{50} values for these species were in the range of 300–500 mg/kg. The authors concluded that $KBrO_3$ should be classified as a very toxic chemical.

Acute Intraperitoneal Toxicity

After intraperitoneal administration to rats, the LD_{50} of Potassium Bromate was 50–200 mg/kg (Anonymous, 1981).

Chronic Oral Toxicity

Five groups of Wistar rats (60 male and 60 female in each group) were fed for 104 weeks bread-based diets using flour containing (a) 0 ppm $KBrO_3$, (b) 50 ppm $KBrO_3$, (c) 75 ppm $KBrO_3$, (d) 50 ppm $KBrO_3$ plus 30 ppm ascorbic acid plus 50 ppm benzoyl peroxide, and (e) 50 ppm $KBrO_3$ plus 30 ppm ascorbic acid plus 50 ppm benzoyl peroxide plus 15 ppm chlorine dioxide. The cumulative mortality of the treatment groups (b–e), as well as the mean body weights of the rats, did not differ significantly from the control group (a), except between weeks 12 and 72 when male rats in Group b had significantly higher weights (Fisher et al., 1979).

Sensitization

The Buehler method was used to evaluate the sensitization potential of a full strength (10.17% $NaBrO_3$) hair neutralizer product (SafePharm Laboratories, Ltd., June 1992). The test procedure followed was No. 406, Skin Sensitization—Buehler Test, Method B6 issued by the European Economic Commission (EEC, 1991). This test procedure stipulates that the material be applied to the shaved left flank of guinea pigs and covered for the 6-h induction exposure period and repeated at Days 7 and 14. After a 28-day nontreatment period, the test site is challenged with the test material covered with an occlusive cover for 6 h and the sites scored at 24 and 48 h on a 0–3 scale. Ten control animals are also to be included in the testing program. To determine the test concentrations to be used in the main study, four guinea pigs were exposed to 0.5 ml of the undiluted test material covered with an occlusive patch for 6 h. One guinea pig had an irritant reaction of 2 at 24 h, but no observable effect at 48 h. Two animals received a score of 1 at 24 h; the fourth animal had no observable effect. The 75% dilution used in the challenge phase produced a mild irritant reaction (score = 1) in 48 h. On the basis of the preliminary data, a 0.5-ml aliquot of the undiluted hair neutralizer was used for the three induction exposures and a 75% and 50% solution of the test material for the challenge.

With use of the sensitization assay as described, five of 19 guinea pigs that received the three induction doses of undiluted test material and challenged with the 75% diluted material had a reported sensitization reaction of 1 at 24 h; only two of the five animals had an observable effect at 48 h. There were no reactions in the controls that received only blank occlusive patches. Under the testing protocol used, the undiluted test formulation was judged to be a mild sensitizer. The SafePharm Laboratories, Ltd. report (June, 1992) also included an evaluation of the test procedure that was conducted February 8 to March 21, 1991, as required by EEC regulatory authorities. The laboratory reported that 17 of 19 guinea pigs gave a positive sensitization reaction to 0.5% 2,4-dinitrochlorobenzene (DNCB), a known sensitizer. Four of 10 control animals had a sensitization reaction score of 1 when the alcohol diluent without DNCB was assayed.

MUTAGENICITY

Potassium Bromate induced chromosomal aberrations in Chinese hamster fibroblast cells without metabolic activation in a dose-dependent manner (Ishidate, 1981, 1984).

Potassium Bromate was not mutagenic in the Ames assay, with activation using *Salmonella typhimurium* strains TA92, TA1535, TA1537, TA94, and TA98. It was weakly mutagenic in strain TA100 and mutagenic in strains TA102 and 104 (Ishidate, 1984; Kurokawa, 1990). Potassium Bromate was not mutagenic when assayed with *Escherichia coli* strains WP2try$^-$ and WP2try$^-$ his$^-$, with or without metabolic activation. In the *Rec* mutagenic assay using *Bacillus subtilis* with and without activation, Potassium Bromate was negative [International Agency for Research on Cancer, (IARC), 1980; Ishidate, 1981; Kurokawa, 1990].

CARCINOGENICITY

Diets containing 250 or 500 ppm Potassium Bromate were fed to 53 male and 53 female F-344 rats each for 111 weeks. Because of an inhibition of body weight gain in the male rats, the 500 ppm concentration was reduced to 400 ppm at week 60. The first renal cell neoplasm was found in a male rat fed the 500-ppm diet at Week 14. All animals that survived the 111-week treatment period were anesthetized with ether for the collection of blood for hematological study and then killed for necropsy. Neoplasms were present in the kidneys, testis, peritoneum, thyroid, pituitary, and mammary glands, and spleen in both the treated and control rats. Renal cell neoplasms developed in 0% (control), 56% (250 ppm), and 80% (500 ppm) of the female rats, and 6% (control), 60% (250 ppm), and 88% (500 ppm) of the male rats. The male rats that survived beyond Week 14 and female rats that survived beyond Week 58 were included in the effective number of rats.

In the treated rats, other neoplasms found in the kidneys included two transitional cell carcinomas and one angiosarcoma. One liposarcoma was found in a control rat. More than 80% of the renal cell neoplasms were diagnosed as carcinomas. The mean survival time was the shortest in male rats fed 500 ppm Potassium Bromate diet (88.1 ± 18.1 weeks). The mean survival times for the other treated groups were 101–104 weeks. The survival of the controls at Week 104 for the female rats was 66% compared with 77.4% for the male rats. Under the conditions of this bioassay, Potassium Bromate was carcinogenic and induced renal cell carcinomas in high incidences in a dose–response relationship in both male and female F344 rats (Kurokawa et al., 1982, 1983a).

The carcinogenic enhancement effect of dietary concentrations of 500 or 1,000 ppm Potassium Bromate in 128 male F344 rats was examined, based on a two-stage, 26-week carcinogenesis study in which *N*-ethyl-*N*-hydroxyethylnitrosamine (EHEN) was used as an initiator. At the 500 ppm EHEN dose followed for 24 weeks with 500 ppm Potassium Bromate in the drinking water, 10 of 20 rats at risk developed renal cell tumors. Of the rats that received EHEN for only 2 weeks, 4 of 23 developed renal cell tumors. Although $KBrO_3$ causes cancer at 2 years, none developed in the rats that received $KBrO_3$ for 24 weeks. The authors concluded that Potassium Bromate can be classified as a carcinogen having both initiating and enhancing activities in the kidneys of rats (Kurokawa et al., 1983b). The initiating activity was not observed in a 104-week study, in which F344 rats at 6 weeks of age were given a single intragastrical dose of 300 mg/kg $KBrO_3$ followed by being maintained on a diet containing 4,000 ppm sodium barbital as a promoting agent (Kurata et al., 1992).

An experiment was designed to test the promoting and complete carcinogenic activities of Potassium Bromate when dermally applied to a group of 20 Sencar mice. To initiate carcinogenesis, 20 nmol of 7,12-dimethylbenz[a]anthracene in 0.2 ml of acetone was applied to the dorsal skin once only. Twice weekly applications of the tumor-promoting phorbol ester in 0.2 ml acetone to the same area of the dorsal skin provided a positive control; all of these mice developed squamous carcinoma at the site within 39 weeks. To test for skin tumor-promoting activity of Potassium Bromate, 8 mg in 0.2 ml of acetone was applied to initiated

skin twice weekly for 51 weeks; no neoplasms developed in this group. In the test for complete carcinogenicity for mouse skin, twice weekly applications of benzoylperoxide, 20 mg in 0.2 ml of acetone, resulted in a 25% incidence of squamous cell carcinoma in addition to three mice with benign skin tumors at 51 weeks. In contrast, no neoplasms appeared in the group of 20 mice treated with only Potassium Bromate. The author concluded that Potassium Bromate is neither a skin carcinogen nor a promoter of skin cancer in Sencar mice (Kurokawa et al., 1984).

In the preceding studies, along with the skin, the lungs, liver, kidneys, spleen, and uterus were collected from the mice in these experiments and were subsequently evaluated histologically for cancer. None was found in any of the organs. Hence, Kurokawa concluded that Potassium Bromate applied to the skin was neither a promoter nor a complete carcinogen for the internal organs. Kurokawa stated that "This may be because ionic compounds such as Potassium Bromate are poorly absorbed through the skin, as commented in the IARC monograph" (Y. Kurokawa, personal communication, 1992).

The carcinogenicity of Potassium Bromate was tested in newborn ICR mice and F344 rats of both sexes (Matsushima et al., 1986). The doses of 400–800 mg/kg selected for subcutaneous injection in the newborn were based on the maximum tolerated doses established in range finding studies. The test material was injected as either a single or four weekly injections; the animals were sacrificed between 78 and 82 weeks. There were no significant differences in survival time between the test and control groups. Potassium Bromate had no carcinogenic action at the injection site or in the major organs that were collected at necropsy and examined microscopically.

Fifty female $B6C3F_1$ mice were given $KBrO_3$ at doses of 1,000 or 500 ppm $KBrO_3$ in drinking water for 78 weeks, and regular tap water for the last 26 weeks (Kurokawa, 1987). Body weight gain was markedly inhibited in the 1,000-ppm group; the survival rates were similar between test and control groups. There was no significant difference between the test and the control groups in the number of tumors produced. In a subsequent study, 750 ppm $KBrO_3$ was administered orally for 88 weeks to groups of 27 male mice of $B6C3F_1$, BDF_1, and CDF_1 strains. There were no differences in growth rate or survival time between the treated and control animals. A significant increase in the number of adenomas of the small intestine in CDF_1 mice and of adenomas of the liver in $B6C3F_1$ mice were observed (Kurokawa, 1986b).

In another study, 180 male F344 rats were divided into 12 groups, then given 500 ppm of EHEN in their drinking water or distilled water for 2 weeks followed by Potassium Bromate, potassium bromide, or distilled water for the next 24 weeks. Groups 1–9 were given EHEN at 500 ppm three times per week for 2 weeks at the initiation stage. Groups 1–6 were given $KBrO_3$ in their drinking water at concentrations of 15, 30, 60, 125, 250, or 500 ppm for 24 weeks. Groups 7 and 8 were given KBr for 24 weeks at concentrations of 350 and 1,750 ppm. Group 9 was given distilled water after initiation with EHEN. Groups 10–12 were given distilled water for the first 2 weeks and then given $KBrO_3$ (500 ppm), KBr (1,750 ppm), or distilled water for 24 weeks. The numbers of dysplastic hepatic foci per cm^2 were significantly increased in a dose-related fashion from 15 ppm to 500 ppm

of $KBrO_3$ in the drinking water. The numbers of renal cell neoplasms per cm^2 were significantly greater in the 500-ppm group. The incidences of dysplastic hepatic foci and renal cell neoplasms did not significantly increase with increasing levels of $KBrO_3$ in the drinking water. The threshold concentration of Potassium Bromate in drinking water of the rats for the enhancement of renal carcinogenesis was between 15 and 30 ppm. No enhancement of renal carcinogenesis was observed with KBr (Kurokawa et al., 1985).

The carcinogenic potential of Potassium Bromate was studied in Syrian golden hamsters, a species that rarely develops spontaneous renal neoplasms. Groups of 20 male animals received 125, 250, 500, or 2,000 ppm Potassium Bromate in their drinking water for 89 weeks. There were no apparent differences in survival time between the nontreated group and the four test groups. A significant difference in the weight gain between the controls and the high-dose groups was reported. The authors concluded that although the incidence of renal cell tumors in the test groups was not statistically significant, the presence of these tumors that were not seen in the controls suggests that the Potassium Bromate has the potential to produce tumors in the Syrian golden hamster (Takamura et al., 1985).

Dose–response studies on the carcinogenicity of Potassium Bromate were performed using 148 male F344 rats. The animals were given $KBrO_3$ in their drinking water at concentrations of 15, 30, 60, 125, 250, or 500 ppm for a period of 104 weeks. The compound was dissolved in distilled water at a concentration of 1% as a stock solution, refrigerated at 4°C, and diluted twice weekly before use. Renal cell carcinomas were found in three of the 20 rats given 500 ppm Potassium Bromate. The combined incidences of renal cell adenocarcinomas and adenomas were significantly increased in rats treated with doses of 125, 250, or 500 ppm Potassium Bromate in a dose-related manner. Follicular adenomas and adenocarcinomas of the thyroid gland were found in rats treated with 60, 250, or 500 ppm Potassium Bromate. Mesotheliomas of the peritoneum were observed in rats fed doses >30 ppm Potassium Bromate. The rate at a dose of 500 ppm $KBrO_3$ was significantly increased. The incidence of interstitial cell adenomas of the testis was very high in both $KBrO_3$-treated and control rats. Papillomas of the urinary bladder were found in rats given water containing 15 or 250 ppm Potassium Bromate. In this study, renal carcinomas were observed in three of 20 (15%) rats given 500 ppm $KBrO_3$ (Kurokawa et al., 1986a).

Male and female Theiller strain mice were fed for 80 weeks diets containing 79% bread crumbs made from flour treated with 75 (Group I), 50 (Group II), and 0 mg (Group III) Potassium Bromate per kilogram. Of Groups I, II and III, 53, 46, and 35 male mice and 52, 54, and 53 female mice, respectively, underwent necropsy for detailed histopathological examination. No carcinogenic effects were produced in the mice that were fed bread made from flour that had been treated with Potassium Bromate before baking (Ginocchio et al., 1979). A similar feeding study using 60 male and 60 female Wistar rats was conducted (Fisher et al., 1979). No carcinogenic effects or other untoward effects were produced in either the male or female rats when maintained on the treated-bread diet for 104 weeks.

On the basis of the animal feeding studies, the IARC regards Potassium Bromate as an animal carcinogen and in the absence of adequate human data as

"possibly carcinogenic to humans" (IARC, 1987). The IARC (1986) report, in noting the negative data from the skin application study by Kurokawa (1984), stated: "The working group noted that ionic compounds such as Potassium Bromate are poorly absorbed through the skin and that 12-O-tetradecanoylphorbol 13-acetate and benzyl peroxide showed promoting activity when 7,12-dimethylbenz[a]anthracene was used as the initiator."

RISK ASSESSMENT

A risk assessment using the data from the carcinogenic bioassay by Kurokawa et al. (1983a) was prepared by Bromine Compounds, Ltd. (January 1992). In the Kurokawa et al. (1983a) study, male and female Fischer 344 rats were given Potassium Bromate in their drinking water at concentrations of 250 and 500 ppm for 111 weeks. The renal cell tumor data reported in this study were used for the low-dose extrapolation. Applying the Gaylor-Kodell model to data on the incidence of renal cell tumors and adjusting for the relative molecular weights of Sodium Bromate and Potassium Bromate yielded a cancer potency factor, or upper limit on lifetime risk per unit dose, of 0.06 mg/kg/day. Using this upper limit and the lifetime average daily doses for a range of users of hair-wave neutralizing solutions, the upper bound estimate of risk was calculated. To determine the absorbed dose per application, it was assumed that a normal 10% Sodium Bromate solution was used, of which 2% came into contact with the skin, and 0.12% was absorbed. The risk estimate ranged from 2.4×10^{-7} for a frequency of use of three times per year for 10 years to 1.2×10^{-6} for a frequency of use of five times per year for 30 years.

Hayashi et al. (1986) used the dose–response study by Kurokawa et al. (1986a) to calculate a virtually safe dose for Potassium Bromate of 0.95 ppm (3.8×10^{-3} mg/kg/day).

SUMMARY

Sodium and Potassium Bromate are inorganic salts; both are white, odorless crystals. Potassium Bromate in particular is a strong oxidizing agent that is highly reactive with organic matter. In cosmetics, Sodium and Potassium Bromate are used as neutralizers for permanent wave formulations. Both have the possibility of being in contact with various surfaces, including the hands, face, or eyes.

Rats given graded oral doses of Potassium Bromate excreted the compound in a dose-related manner. The remainder of the compound that was not excreted was partially reduced to the bromide ion. In an excised guinea pig skin absorption study, 0.12% of the Bromine was absorbed in 30 min. Bromides, but not Bromates, were detected in the serum of guinea pigs that received skin exposures to hair neutralizers containing 10.17% Sodium Bromate.

The oral LD_{50} of Potassium Bromate in the rat was 200–400 mg/kg, and the oral LD_{100} was 700 mg/kg. In mice, the oral LD_{50} was 400 mg/kg. When administered intraperitoneally, the LD_{50} in rats was 50–200 mg/kg.

Sodium Bromate was judged to be a mild sensitizer to guinea pigs when assayed and evaluated by the Buehler method. Preliminary range-finding studies, and the

negative controls included in a positive control study, indicated that the results observed may have been due to irritation and not sensitization.

In vitro chromosomal aberration tests of Potassium Bromate were weakly mutagenic when assayed in *S. typhimurium* strain TA100 and positive in TA102 and TA104, but not in TA92, TA1535, TA100, TA1537, TA94, and TA98, and when assayed in *E. coli* WP2try$^-$ his$^-$ with and without activation. Potassium Bromate caused chromosomal aberrations in Chinese hamster cells.

Potassium Bromate was carcinogenic in an oral feeding study in rats. The number of renal neoplasms developed in a dose-related manner. The data from this study were used to prepare a risk estimate for users of hair wave neutralizing solutions. The upper bound estimates of risk ranged from 2.4×10^{-7} to 1.2×10^{-6}. The results of a two-stage, 26-week carcinogenesis study in rats confirmed that Potassium Bromate was a carcinogen, with both tumor-initiating and tumor-promoting activities. In a dose–response study of the carcinogenic potential of Potassium Bromate conducted using rats, a greater incidence of renal neoplasms was observed in rats fed large doses. Based upon the 104-week dose–response feeding study with Potassium Bromate, a virtually safe dose of 0.95 ppm (38 μg/kg/day) Potassium Bromate was calculated in respect to renal tumors.

Drinking water containing 125, 250, 500, and 2,000 ppm Potassium Bromate was given to male golden hamsters, a species that rarely develops spontaneous renal neoplasms. Renal cell tumors, of a type not seen in the controls, developed in the three highest dose groups, but none in the control or low-dose group. Although the results were not statistically significant, the authors concluded that because of the low spontaneous development of renal cell tumors in this species, Potassium Bromate appears to have the potential to induce renal tumors in the golden hamster.

Potassium Bromate, when applied to the skin of mice or injected subcutaneously into newborn mice or rats, was noncarcinogenic to the skin, kidneys, liver, lungs, spleen, uterus, and other major internal organs.

DISCUSSION

The Cosmetic Ingredient Review (CIR) Expert Panel reviewed the available safety test data on the toxicity of Potassium and Sodium Bromate. Potassium Bromate, when ingested by experimental animals, had both tumor-initiating and tumor-promoting activities. However, when Potassium Bromate was applied to the skin of mice or was subcutaneously injected into newborn mice and rats, it was neither a skin or systemic carcinogen, nor tumor promoter.

Both Sodium and Potassium Bromate are highly reactive. Excised animal skin-penetration studies indicated that if absorption did occur, it would be minimal. In these animal studies, Sodium Bromate was applied to excised guinea pig skin, but the measurement of the amount of Bromate absorbed was determined by measuring total bromide, not Bromate. If Bromate absorption occurs, the rate of absorption is slow (0.12% in 30 min). Any chemical reaction that changed the chemical nature of Bromate to bromide would not be detected by the methods used. In a subsequent study, the investigators used a different assay method, one that detected only Bromates. Using this new method they found that when Sodium Bro-

mate was applied to the skin of guinea pigs no Bromates were detected in the blood. Parallel studies show that there was an elevation of bromide in the serum of some animals. Kurokawa (1992, personal communication), commented that the difference in his reported results for the negative carcinogenic response observed in the skin studies as compared with the positive carcinogenic response he reported when Potassium Bromate was ingested could be attributed to the poor absorption of Potassium Bromate through the skin. A similar comment was made by the IARC Working Group that reviewed the data from the skin carcinogenicity study (IARC, 1986).

The Expert Panel reviewed the estimates of carcinogenic risks to humans (2.4×10^{-7} to 1.2×10^{-6}) when the carcinogenic data from animal feeding studies and maximized absorption data were used. These lifetime human risk estimates were in the range considered to be acceptable by the FDA in its constituent food additive policy, which uses an upper level of risk of 1×10^{-6}. However, the Expert Panel believes that the data, which indicated that Bromates are either not absorbed or, at most, poorly absorbed, combined with the negative carcinogenic response in the animal skin painting studies, are sufficient to question the applicability of extrapolating the positive carcinogenic response reported in animal feeding studies to humans that receive skin exposure from a cosmetic formulation. This is further supported by the infrequent use and the short exposure times of ~5 min that users of permanent wave products have under actual use conditions.

The Expert Panel also requested and received a guinea pig sensitization study. A study utilizing the Buehler method was conducted and Sodium Bromate was classified as a mild sensitizer. However, the Panel noted that in the range-finding studies that were conducted to determine the concentration to be tested for sensitization, irritant scores of the same magnitude as that subsequently reported for the sensitization study were observed. In addition, in the laboratory's in-house quality control program the alcohol controls used in evaluating a known sensitizer had irritant scores similar to that reported for Sodium Bromate. The Expert Panel believes that the study data indicate that the hair formulation may be a mild irritant, and probably not a mild sensitizer.

The CIR Expert Panel recognizes that concentration of use data are no longer submitted to the FDA by the cosmetics industry. Because of this fact, the Expert Panel can no longer make the conclusion "safe as used," as was previously done, but must now make a conclusion based on the product and test concentrations used in the report.

CONCLUSION

On the basis of the data included in this report, the CIR Expert Panel concludes that Sodium Bromate and Potassium Bromate may be used in cosmetic permanent wave formulations at concentrations not to exceed 10.17%, measured as Sodium Bromate.

REFERENCES

AmeriBrom, Inc. (undated) *Potassium Bromate Technical Bulletin*. Lyon, France: International Agency for Research on Cancer, 209. (IARC Monograph).*

American Industrial Hygiene Association. (1981) Workplace environmental exposure level guide. Potassium Bromate. *Am Ind Hyg Assoc J* 42:A53–A55.

American International Chemical, Inc. (undated) *Potassium Bromate Specification Sheet.* Lyon, France: International Agency for Research on Cancer, 208. (IARC Monograph).

Anonymous. (1981) *Hazardous Materials Section. Dangerous Properties of Industrial Materials Report.* Vol 1(7):22–96.

Bromine Compounds, Ltd. (BCL). (January 1992) Assessment of the safety of Sodium Bromate for use in hair care products. Unpublished report.*

Bromine Compounds, Ltd. (BCL). (July 1992) Determination of Br and BrO_3^- (Bromate) in guinea pig serum following in vivo exposure to commercial hair neutralizer. Unpublished report.*

Code of Federal Regulations (CFR). (1984) Title 21, Part 15.20. Washington, DC.

Code of Federal Regulations (CFR). (1989) December 16, Part 1700.00 Washington, DC.

Cosmetic, Toiletry, and Fragrance Association (CTFA). (1984) CTFA list of Japanese cosmetic ingredients, 1st Ed. Washington, DC: CTFA, 80, 89.

Cosmetic, Toiletry, and Fragrance Association (CTFA). (1991) Submission of unpublished data. Skin penetration of sodium Bromate. (April 19, 1991).

Estrin NF, Crosley PA, Haynes CR, eds. (1982) *CTFA Cosmetic Ingredient Dictionary.* 3rd ed. Washington, DC: The Cosmetic, Toiletry, and Fragrance Association.

European Economic Commission (EEC). (1991) Guidelines for testing of chemicals (1991). No. 406. Skin sensitization—Buehler test. Method B6. Annex V of Council Directive 91/325/EEC.

Federal Register. (January 28, 1992) Modification in voluntary filing of cosmetic product ingredient and cosmetic raw material composition statements. Final Rule. 57:3128–30.

Fisher N, Hutchinson JB, Berry R, Hardy J, Ginocchio AV, Waite V. (1979) Long term toxicity and carcinogenicity studies of the bread improver Potassium Bromate. 1. Studies in rats. *Food Cosmet Toxicol* 17:33–9.

Food and Drug Administration (FDA). (1984) Cosmetic product formulation data. Ingredients and concentrations used in each product category. Computer Printout. Washington, DC: FDA.

FDA. (1991) Cosmetic product formulation data: Ingredients used in each product category. Computer printout. Washington, DC: FDA.

Fujii MO, Kawa K, Saito H, Fukuhura C, Onodaka S, Tanaka K. (1984) Metabolism of Potassium Bromate in rats. I. In-vivo studies. *Chemosphere* 13:1207–12.

Ginocchio AV, Warte V, Hardy J, Fisher N Hutchinson J, Berry R. (1979) Long-term toxicity and carcinogenicity studies of the bread improver Potassium Bromate. 2. Studies in mice. *Food Chem Toxicol* 17:41–7.

Hayashi Y, Kurokawa Y, Maekawa A, Takahaski M. (1986) Strategy of long-term animal testing for quantitative evaluation of chemical carcinogenicity. *Dev Toxicol Environ Sci* 12:383–91.

International Agency for Research on Cancer (IARC). (1980) *Molecular and Cellular Aspects of Carcinogenicity Screening Test.* IARC Publication no. 27, 330–3.

International Agency for Research on Cancer (IARC). (1986) *IARC Monograph Eval. Carcinog. Risk Chem. Hum.* 40:207–20.

International Agency for Research on Cancer (IARC). (1987) Overall evaluations of carcinogenicity: in: *Updating of IARC Monographs.* Vol 1 to 42 (suppl 7):70.

Ishidate M, Sofuni T, Yoshikawa K, et al. (1981) Chromosomal aberration tests in-vitro as a primary screening tool for environmental mutagens and/or carcinogens. *Gann Monogr Cancer Res* 27:95–108.

Ishidate M, Sofuni T, Yoshikawa K, et al. (1984) Primary mutagenicity screening of food additives currently used in Japan. *Food Chem Toxicol* 22:623–36.

Ito R. (1982) New considerations on hydrogen peroxide and related substances as food additives in view of carcinogenicity. *Pediatrician* 2:222–4.

Kulp K, Hepburn FN. (1978) Bakery processes and leavening agents. In: Mark HF, Othmer DF, Overburger CG, Seaborg GT, eds. *Kirk Othmer Encyclopedia of Chemical Technology,* Vol 3. New York: John Wiley and Sons, 438–49.

Kurata Y, Diwah BA, Ward JM. (1992) Lack of renal tumor-initiating activity of a single dose of Potassium Bromate, a genotoxic renal carcinogen in male F344/NCr Rats. *Food Chem Toxicol* 30:251–9.

Kurokawa Y, Hayashi Y, Maekawa A, Takahashi M, Kokubo T. (1982) Induction of renal cell tumors in F344 rats by oral administration of Potassium Bromate, a food additive. *Gann* 73:335–8.

Kurokawa Y, Hayashi Y, Maekawa A, Takahashi M, Kokubo T, Odashima S. (1983a) Carcinogenicity of Potassium Bromate administered orally to F-344 rats. *J Natl Cancer Inst* 71:965–72.

Kurokawa Y, Takashi M, Kokubo T, Ohno Y, Hayashi Y. (1983b) Enhancement by Potassium Bro-

mate of renal tumorigenesis initiated by *N*-Ethyl-*N*-Hydroxyethylnitrosamine in F-344 rats. *Gann* 74:607–10.

Kurokawa Y, Takamuri H, Matsushima Y, Imazawa T, Hayashi Y. (1984) Studies on the promoting and complete carcinogenic activities of some oxidizing chemicals in skin carcinogenesis. *Cancer Lett* 24:299–304.

Kurokawa Y, Aoki S, Hayashi Y, Matsoshima Y, Takamura N. (1985) Dose-related enhancing effect of Potassium Bromate on renal tumorigenesis in rats initiated with *N*-ethyl-*N*-hydroxyethyl-Nitrosamine. *Jpn J Cancer Res* 76:583–9.

Kurokawa Y, Aoki S, Matsushima Y, Imazawa T, Hayashi Y. (1986a) Dose–response studies on the carcinogenicity of Potassium Bromate in F-344 rats after long-term oral administration. *J Natl Cancer Inst* 77:977–82.

Kurokawa Y, Takayama S, Konishi Y, et al. (1986b) Long-term in-vivo carcinogenicity test of Potassium Bromate, Sodium Hypochlorite and Sodium Chlorite conducted in Japan. *Environ Health Perspect* 69:221–35.

Kurokawa Y, Matsushima Y, Hayashi Y. (1987) Long-term oral administration of Potassium Bromate to mice. In: *Proceedings of the 46th Annual Meeting of the Japanese Cancer Association, Tokyo.*

Kurokawa Y, Maekawa A, Takahashi M, Hayashi Y. (1990) Toxicity and carcinogenicity of Potassium Bromate—a new renal carcinogen. *Environ Health Perspect* 87:309–35.

Kurokawa Y. (1992) Personal communication to R. Elder from Kurokawa Y. (March 12, 1992).*

Lewis RJ Sr. (1993) Hawley's condensed chemical dictionary, 12th ed. New York: Van Nostrand Reinhold Co.

Mack RB. (1988) Round up the usual suspects—Potassium Bromate poisoning. *N C Med J* 49:243–5.

Matsushima Y, Takamura N, Imazawa T, Kurokawa Y, Hayashi Y. (1986) Lack of carcinogenicity of Potassium Bromate after subcutaneous injection to newborn mice and newborn rats. *Sci Rep Res Inst Tohoku Univ [Med]* 33:22–6.

National Research Council. (1981) Potassium Bromate. *Food chemicals* codex, 3rd ed. Washington, DC: National Academy of Sciences, 240.

Patty FA. (1962) *Industrial Hygiene and Toxicology*. Vol II. New York: Interscience Publishers, 2970–2.

Rappaport MS, Mantel M, Shenberg C. (1981) Determination of bromine in blood serum by ^{125}I excited x-ray fluorescence. *Med Phys* 9:194–8.

Sadtler Research Laboratories. (1967) Inorganics and related compounds-IR grating spectra. Vol 1:207.

Safepharm Laboratories, LTD. (June 1992) Sodium Bromate formulation: Buehler delayed contact hypersensitivity study in the guinea pig. Unpublished report to Bromine Compounds Ltd. Project No. 466/2, 26p.

Sax NI. (1979) *Dangerous Properties of Industrial Materials*. 6th ed. New York: Van Nostrand Reinhold.

Sfat MR, Doncheck JA. (1981) Malts and malting. In: Mark HF, Othmer DF, Overburger CG, Seaborg GT, eds. *Kirk Othmer Encyclopedia of Chemical Technology*. Vol 14. New York: John Wiley and Sons, 810–23.

Shenberg C, Mentel M. Izak-Brian T, Rachmiel B. (1987) Rapid and simple determination of selenium and other trace elements in very small blood samples by XRF. *Biol Trace Elem Res* 16:87–94.

Takamura N, Kurokawa Y, Matsushima Y, Imazawa T, Onodera H, Hayashi Y. (1985) Long-term oral administration of Potassium Bromate in male syrian golden hamsters. *Sci Rep Res Inst Tohoku Univ [Med]* 32:1–4, 43–6.

Thewlis B. (1974) The fate of Potassium Bromate when used as a breadmaking improver. *J Sci Food Agric* 25:12, 1471–5.

Watanabe I, Tanaka R, Kashimoto T. (1982) Determination of Potassium Bromate by ion chromatography (Jpn), p. 135–41 [Chem. abstr., 97, 180268c].

Weast RC. (1982) *CRC Handbook of Chemistry and Physics*. 63rd ed. Boca Raton, FL: CRC Press, B-131, B-146.

Windholz M, ed. (1983) *The Merck Index*. 10th ed., Rahway, NJ: Merck & Co., p. 1099.

World Health Organization (WHO). (1983) Evaluation of certain food additives and contaminants. Twenty-seventh Report of the Joint FAO/WHO Expert Committee on Food Additives (Tech Rep Series No 696). Geneva: World Health Organization, 27–8.

---

* Available for review: Director, CIR, 1101 17th Street NW, Suite 310, Washington, DC 20036.