
Safety Assessment of Simple Carbonate Salts as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

INTRODUCTION

The safety of the following 6 simple carbonate salts as used in cosmetics is reviewed in this safety assessment:

Magnesium Carbonate
Ammonium Bicarbonate
Ammonium Carbonate
Calcium Carbonate
Potassium Bicarbonate
Potassium Carbonate

According to the *International Cosmetic Ingredient Dictionary and Handbook*, the functions of these ingredients in cosmetic products include: absorbents, bulking agents, opacifying agents, pH adjusters, buffering agents, abrasives, and oral care agents (Table 1).¹

CHEMISTRY

Definition and General Characterization

The simple carbonate salts are alkaline salts formed by treating carbonic acid with an appropriate base (e.g., adding carbonic acid to sodium hydroxide will produce sodium carbonate). However, most of these salts are also naturally occurring as minerals. All of the ingredients in this report are related as either alkaline earth metal (column I or II) or ammonium salts of carbonic acid. This group is comprised of simple carbonate salts, wherein any property differences due to the variable cation(s) can be contrasted. Contrasting these differences in one report is more informative and more efficient than assessing the safety of each salt in separate reports.

Chemical and Physical Properties

These ingredients are typically colorless or white solids with low formula weights. While the carbonate salts may be fairly alkaline in concentrated solution, in formulation an acceptable pH can be easily obtained. Data on the chemical and physical properties of simple carbonate salts are presented in Table 2.

Method of Manufacture

Ammonium Carbonate

Ammonium Carbonate may be prepared from gaseous ammonia, carbon dioxide, and steam.²

Calcium Carbonate

The byproduct process, the carbonation process, and the calcium chloride process of manufacture from limestone are methods of production of Calcium Carbonate.²

Composition/Impurities

Magnesium Carbonate

The following specifications for Magnesium Carbonate are referenced in the “Evaluation of the Health Aspects of Magnesium Salts as Food Ingredients” by the Select Committee on Generally Recognized as Safe (GRAS) Substances: not less than 40% and not greater than 43.5% magnesium oxide, not greater than 3 ppm arsenic, not greater than 30 ppm heavy metals, not greater than 10 ppm lead, and not greater than 0.6% calcium oxide.³

Potassium Bicarbonate

Potassium Bicarbonate contains no less than 99% Potassium Bicarbonate.²

USE

Cosmetic

The safety of the simple carbonate salts included in this safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data (See Table 3) indicate that 5 of the 6 ingredients in this safety assessment are currently being used in cosmetic products; Potassium Bicarbonate is not being used in cosmetic products.

According to the 2016 VCRP data, the greatest reported use frequency is for Magnesium Carbonate (317 product formulations, mostly leave-on products), followed by Calcium Carbonate (174 product formulations, mostly leave-on products) (Table 3).⁴ The results of a concentration of use survey provided in 2015 indicate that Ammonium Bicarbonate has the highest maximum concentration of use; it is used at concentrations up to 93.4% in rinse-off products (hair bleaches) (Table 3).⁵

Cosmetic products containing simple carbonate salts may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., Calcium Carbonate at maximum use concentrations up to 35% in eye area cosmetics) and mucous membranes (e.g., Calcium Carbonate at maximum use concentrations up to 10% in dentifrices). Additionally, some of these ingredients are being used in products that may result in incidental ingestion. For example, Calcium Carbonate is being used in dentifrices at maximum use concentrations up to 10%, and in lipstick at maximum use concentrations up to 8%. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Magnesium Carbonate is used in aerosol color hair sprays at maximum use concentrations up to 0.18%, and in face powders at maximum use concentrations up to 4%. Calcium Carbonate is used in powders (dusting and talcum, excluding aftershave talc) at maximum use concentrations up to 5%, and in face powders at maximum use concentrations up to 15%. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters $>10\text{ }\mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles below $10\text{ }\mu\text{m}$, compared with pump sprays.^{6,7,8,9} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{6,7} Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are no more than about $1\text{ }\mu\text{g/kg/day}$.^{10,11,12}

Calcium Carbonate and Magnesium Carbonate appear on the list of colorants allowed in cosmetic products that are marketed within the European Union.¹³

Noncosmetic

The following carbonate salts are direct food additives that are classified as GRAS in the United States: Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, Potassium Bicarbonate, and Potassium Carbonate.¹⁴

The Joint FAO/WHO Expert Committee on Food Additives has determined that Magnesium Carbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Carbonate are not limited in terms of overall daily intake (mg/kg body weight).¹⁵ The Committee noted that these bases are required for pH adjustment in food technology, and that the amounts and concentrations used are not likely to have any toxicological significance. Furthermore, the Committee placed no restriction on the food-additive use of these bases, provided that the contribution made to the dietary load of potassium, calcium, and magnesium is assessed and considered to be acceptable.

Combinations of viscous xylocaine, aluminum hydroxide-Magnesium Carbonate, and diphenhydramine hydrochloride have been used to treat mucosal toxicity resulting from chemotherapy and radiotherapy in the treatment of esophageal cancer.¹⁶

TOXICOKINETICS

Calcium Carbonate

Calcium Carbonate (0.40 mCi of calcium ^{14}C -carbonate pellet) was implanted intraperitoneally into a male rat.¹⁷ Approximately 72% of the radioactivity was excreted as respiratory carbon dioxide between 2 h and 142 h after implantation (most after 69 h). Approximately 30% of the dose was recovered in unabsorbed pellet. Urinary radioactivity accounted for 0.27% of the dose and fecal radioactivity accounted for approximately 0.07% of the dose; 1% of the absorbed dose was retained by the tissues.

Potassium Carbonate

Following ingestion, Potassium Carbonate rapidly dissociates in the gastric juice to yield carbonate ions (CO_3^{2-}) and potassium ions (K^+).¹⁸

TOXICOLOGY

Acute Toxicity

Dermal

Potassium Carbonate

In a Registration, Evaluation, and Authorization (REACH) dossier on Potassium Carbonate, data on “Biocide #5654” (composition not stated) were used in an acute dermal toxicity evaluation of this chemical that was performed according to the U.S. Environmental Protection Agency (EPA) pesticide assessment guidelines.¹⁸ The test substance, moistened with distilled water, was applied to the skin of young adult, New Zealand white rabbits (5 males, 5 females [fasted]) for 24 h. The area of application, dose per cm^2 , and whether or not the site was covered were not stated. Application of the test substance was followed by a 14-day observation period. None of the animals died. Dermal irritation was observed at the test site; however, irritation scores were not provided. There were no gross findings at necropsy, and neither adverse pharmacologic effects nor abnormal behavior were observed. The dermal LD_{50} was > 2 g/kg body weight.

Oral

Ammonium Bicarbonate

An LD_{50} of 1.576 g/kg was reported for rats (number and strain not stated) in an acute oral toxicity study on Ammonium Bicarbonate.¹⁹ Additional study details were not included.

Potassium Carbonate

In an acute oral toxicity study using rats (number and strain not stated), a mean LD_{50} of 1.87 (1.34 – 2.60) g/kg was reported after intubation with Potassium Carbonate (0.20 g/ml).²⁰ Additional study details were not included.

In a REACH dossier on Potassium Carbonate, data on “potash calc.” (composition not stated) were used in an acute oral toxicity evaluation of this chemical using a procedure that was equivalent to the now discontinued OECD Guideline 401.¹⁸ Fasted Sprague-Dawley rats (5 males, 5 females) were dosed with the test substance; dosing was followed by a 14-day observation period. None of the animals died, and there were no treatment-related clinical signs, necropsy findings, or changes in body weight. The LD_{50} was > 2 g/kg body weight.

Inhalation

In a REACH dossier on Potassium Carbonate, an acute inhalation toxicity evaluation using the data on “Biocide #5654” (composition not stated) was performed according to the U.S. EPA pesticide assessment guidelines.¹⁸ Sprague-Dawley rats (5 males, 5 females) were exposed to the aerosolized test substance (mass mean aerodynamic diameter ≈ 3.6 μ) for 4.5 h. The gravimetric chamber concentration was 4.96 ± 1.14 mg/L, with approximately 3% of the particles below 1 μ , and 38% below 3 μ . Exposure was followed by a 14-day observation period. None of the animals died. Dermal necrosis and corneal opacity were observed in all animals, and damage was most severe around the mouth and on the forelimbs. There were no test substance-related gross necropsy findings. The LC_{50} was $> 4.96 \pm 1.14$ mg/L air.

Intravenous

Ammonium Bicarbonate

The acute intravenous (i.v.) toxicity of Ammonium Bicarbonate (in 0.03 M sodium hydroxide) was evaluated using groups of 10 young albino mice, and a mean LD₅₀ value of 3.10 ± 0.28 mM/kg body weight was reported.²¹ Additional study details were not included.

Ammonium Bicarbonate and Ammonium Carbonate

The acute i.v. toxicity of an Ammonium Carbonate/Ammonium Bicarbonate mixture (in 0.03 M sodium hydroxide) was evaluated using groups of 10 young albino mice.²¹ The test substance was defined as commercial reagent grade Ammonium Carbonate, and was described as a mixture of approximately equal parts Ammonium Bicarbonate and Ammonium Carbonate. A mean LD₅₀ value of 1.02 ± 0.11 mM/kg body weight was reported. Additional study details were not included.

Repeated Dose Toxicity

Oral

Calcium Carbonate

Five rats were fed [⁴⁵Ca] Calcium Carbonate (dose = 0.3 g/kg body weight) in feed for 3 days.¹⁷ The strain of rats tested was not stated. All of the animals remained healthy.

Potassium Bicarbonate

In a 4-week toxicity study, groups of 10 male and 10 female SPF-bred Wistar rats (CpB:WU;Wistar random) were fed unsupplemented rodent diet (control) or this diet containing 2% or 4% Potassium Bicarbonate.²² The animals were killed at the end of the study. None of the animals died during the study, and no treatment-related abnormalities were reported. There were no consistent or treatment-related effects on red blood cell variables, clotting potential or total and differential white blood cell counts in any of the groups. The relative kidney weight (relative to body weight) was increased, however, this finding was not consistent or considered to be dose-related. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most histopathological changes observed were considered equally distributed among the treatment groups and the controls, and represented normal background pathology for rats of this strain and age.

In a 13-week toxicity study, groups of 10 male and 10 female SPF-bred Wistar rats (CpB:WU;Wistar random) were also fed unsupplemented rodent diet or a diet containing 2% or 4% Potassium Bicarbonate.²² The results reported in this study were identical to those stated in the 4-week study above, except for the following results: Zona glomerulosa hypertrophy (classified as non-neoplastic histopathological change) was observed at a concentration of 4%, and this finding was statistically significant ($p < 0.01$) when compared to the control. The finding of oncocytic kidney tubules (classified as non-neoplastic histopathological change) was statistically significant when compared to the control at a concentration of 4% ($p < 0.01$).

In an 18-month toxicity study, groups of 15 male and 15 female SPF-bred Wistar rats (CpB:WU;Wistar random) were fed unsupplemented rodent diet or this diet containing 2% or 4% Potassium Bicarbonate.²² The animals were killed at the end of the study. There were no consistent or treatment-related effects on red blood cell variables, clotting potential or total and differential white blood cell counts in any of the groups. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most histopathological changes observed were considered equally distributed among the treatment groups and the controls, and represented normal background pathology for rats of this strain and age. Zona glomerulosa hypertrophy (classified as non-neoplastic histopathological change) was observed at a concentration of 4%, and this finding was statistically significant ($p < 0.01$) when compared to the control. The finding of oncocytic kidney tubules (classified as non-neoplastic histopathological change) was statistically significant when compared to the control at a concentration of 2% ($p < 0.05$) and 4% ($p < 0.01$). The finding of simple urothelial hyperplasia of the urinary bladder (classified as non-neoplastic histopathological change) was statistically significant ($p < 0.05$) when compared to the control at concentrations of 2% and

4%. Additionally, the finding of papillary/nodular hyperplasia of the urinary bladder (classified as non-neoplastic histopathological change) was statistically significant when compared to the control at a concentration of 2% ($p < 0.05$).

Inhalation

Potassium Carbonate

The potential for subacute toxicity and neurotoxicity of a Potassium Carbonate-based scrubbing solution used in petroleum refineries was evaluated in Sprague-Dawley Crl:CD BR rats.²³ Exposures were to aerosols of a “used” scrubbing solution by whole-body inhalation, 6 h/day, for 21 consecutive days at target concentrations of 0 (filtered air – control), 0.1, 0.2, or 0.4 mg/L (30 animals/sex/group). A functional observation battery (FOB) and locomotor activity tests were conducted and monitored. No apparent adverse effects were noted at any exposure level, as determined by clinical observations, food consumption, hematology, serum chemistry, ophthalmologic observations, and gross pathology. Statistically significant increases in lung weights were noted at all concentrations, but returned to control values at the end of exposure, except for the 0.4 mg/L group (females). There were no significant changes in other organ weights. Histopathologic findings were restricted to the respiratory tract and were characterized by minimal to moderate epithelial hyperplasia, epithelial necrosis, and cytoplasmic vacuolation at levels I and II of the nasal cavities. Lung bronchiolization and alveolar macrophage infiltration were also observed. The respiratory tract findings were considered a local response to the high alkalinity of the test material, as substantiated by the return to normal upon cessation of exposure. Exposure to the scrubbing solution had no adverse effect on FOB endpoints and locomotor activity evaluations, brain weight and size, and neuropathologic evaluations. The authors concluded that inhalation exposure to a Potassium Carbonate-based, scrubbing solution aerosol for 21 days did not result in any persistent systemic toxicity or neurotoxicity in either male or female rats.

Nephrotoxicity

A study investigated the possible toxic effects of Potassium Carbonate emulsion on some biomarkers of tissue damage in rabbits.²⁴ The oral exposure (drinking) of rabbits to Potassium Carbonate (K_2CO_3) emulsion at 50mg/L and 100mg/L for 14 consecutive days caused a significant increase in creatinine and uric acid at 100mg/L by 48.6% and 126.3% respectively. Also, Potassium Carbonate (K_2CO_3) emulsion significantly increased serum blood urea nitrogen (BUN) at 50 mg/L and 100mg/L. The results, however, suggested that oral exposure (drinking) to Potassium Carbonate emulsion could precipitate kidney damage.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Calcium Carbonate

Female Swiss mice were bred after feeding (number of animals/feeding duration not stated) with a diet supplemented with 0.5%, 1%, or 2% Calcium Carbonate.¹⁷ First and second litters were studied. The highest concentration of Calcium Carbonate yielded an intake of approximately 3 g/kg body weight. When compared to the control diet, this diet significantly decreased the number and total weight of the weanling mice, and increased the proportion of deaths. Calcium Carbonate (2%) in the diet also caused hypertrophy of the heart and a tendency toward decreased thymus weight in weanling rats.

Potassium Carbonate

The teratogenicity of Potassium Carbonate was evaluated using groups of 22 to 25 CD-1 mice, according to a protocol similar to OECD Technical Guideline 414.^{18,25} The test substance was administered, by gavage, at doses of 0, 2.9, 13.5, 62.5, or 290 mg/kg body weight/day, on gestation days 6 through 15. On day 17, Caesarean section was performed on all of the dams, and the following information was recorded: sex, numbers of corpora lutea, implantation sites, resorption sites, live and dead fetuses, and body weights of live pups. The urogenital tract of each dam was examined in detail for anatomical normality. All of the fetuses were examined grossly for the presence of external congenital abnormalities. One-third of the fetuses in each litter were subjected to detailed visceral examinations, and the remaining two-thirds were examined for skeletal defects. There were no effects on mortality, body weight gain, or the urogenital tracts of dams. The no-effect-level (NOEL) for maternal toxicity was 290 mg/kg body weight/day. There were no effects on any of the following: numbers of corpora lutea, live litters, implantations, resorptions, live and dead fetuses, the sex ratio of the fetuses, or the average fetal weight. The incidence of soft tissue and skeletal abnormalities within groups treated with Potassium

Carbonate did not differ from that of sham-treated controls. The NOEL for developmental toxicity/teratogenicity was 290 mg/kg body weight/day.

The teratogenicity of Potassium Carbonate was also evaluated using groups of 22 to 25 albino rats (Wistar-derived stock).²⁵ The test substance was administered, by oral intubation, at doses of 0, 1.8, 8.4, 38.8, or 180 mg/kg body weight/day according to the procedure in the preceding experiment, except that Caesarean section was performed on day 20. There was no discernible effect on nidation or on maternal or fetal survival. Furthermore, the number of abnormalities observed in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in the sham-treated controls.

Inhalation

Potassium Carbonate

The developmental toxicity potential of a Potassium Carbonate scrubbing solution, used extensively in petroleum refineries to remove CO₂ from hydrogen gas streams, was evaluated.²⁶ Pregnant female CD (Sprague-Dawley) rats (number not stated) were exposed to aerosols of a "used" scrubbing solution at 0.05, 0.1, 0.2, or 0.3 mg/l for 6 h/day on days 6-19 of pregnancy. Control animals were exposed to filtered air under the same exposure conditions. Dams were killed on day 20 of pregnancy and a laparohysterectomy was performed. The mass median aerodynamic diameter of the aerosol revealed that all particles ranged from 1.6 to 2.8 µ, with geometric standard deviations between 2.0 and 2.3 µ. The overall pregnancy rate was high (> 95%) and equivalent across all groups. All pregnant dams had live litters, and 22-24 litters were examined in each group. Treatment-related clinical signs consisted of rales, observed at all exposure levels, and gasping was noted only at the 0.3 mg/l exposure level. The occurrence of rales was presumably a localized effect on the respiratory tract, and was likely due to the irritating properties of the scrubbing solution. Maternal toxicity was exhibited in the 0.3 mg/l group, including reduced body weight, weight gain, and food consumption, and one possible treatment-related death on gestation day 17. At the scheduled necropsy, there were no treatment-related, gross pathological observations and no statistically significant reproductive and developmental effects. The incidences of fetuses with skeletal variations involving the sternum were clustered in two litters at the highest exposure level, with atypically low-term fetal body weights. Under the conditions of this investigation, Potassium Carbonate scrubbing solution was not a developmental toxicant.

GENOTOXICITY

In Vitro

Potassium Bicarbonate

The genotoxicity of Potassium Bicarbonate was evaluated in the Ames test using *Salmonella typhimurium* and *Saccharomyces cerevisiae* strains.²⁷ Neither the test concentration nor assay results were included in this abstract.

Potassium Carbonate

In the Ames test, Potassium Carbonate was not genotoxic in *Saccharomyces cerevisiae* strain D4 (yeast) or in the following bacterial strains with or without metabolic activation: *S. typhimurium* strains: TA1535, TA1537, and TA1538. Details relating to the test procedure were not included.¹⁷

In a summary of data in a REACH dossier on Potassium Carbonate, data on potassium chloride were used to evaluate the genotoxicity of this chemical in the L5178Y mouse lymphoma cell mutagenesis assay, at concentrations up to 5000 µg/ml with and without metabolic activation.^{18,28} Ethyl methanesulfonate and 3-methylcholanthrene served as positive controls. Results were negative with and without metabolic activation. The positive controls were genotoxic.

ANTI-GENOTOXICITY

in vitro

Magnesium Carbonate

The anti-genotoxicity of Magnesium Carbonate in the presence of hydrogen peroxide was evaluated in the Ames test using *Salmonella typhimurium* strain 102.²⁹ Magnesium Carbonate was tested at a concentration of 25 mM or 50 mM, and

each concentration was tested in the presence of 82 mM or 164 mM hydrogen peroxide. Magnesium Carbonate did not cause a decrease in the number of revertants induced by hydrogen peroxide. The number of revertants induced by hydrogen peroxide (164 mM) alone was 695.50 ± 62.7 . The combination of Magnesium Carbonate (50 mM) + hydrogen peroxide (164 mM) yielded 746 ± 202 revertants. A control value of 334.20 ± 47.98 revertants was reported.

Magnesium Carbonate was also evaluated for anti-genotoxicity at concentrations of 50 mM and 100 mM (in the presence of hydrogen peroxide) in the suspension test using strain D7 of *Saccharomyces cerevisiae*.²⁹ Both stationary and logarithmic phase cells were used. The high concentration of Magnesium Carbonate (100 mM) was found to be cytotoxic only in cells from the logarithmic growth phase. Magnesium Carbonate significantly decreased the gene conversion frequency that was induced by 200 mM hydrogen peroxide. Also, the point reverse mutations induced by 200 mM and 400 mM hydrogen peroxide decreased significantly in the presence of Magnesium Carbonate. In the logarithmic growth phase, Magnesium Carbonate caused a significant decrease in the gene conversion frequency that was induced by 50 mM and 100 mM hydrogen peroxide. The anti-genotoxic effect of Magnesium Carbonate was not found to be dose-dependent.

The effects of magnesium carbonate on the genotoxicity induced by nickel subsulfide were examined using Chinese hamster ovary cells and Balb 3T3 fibroblast cells. The cells were incubated, with and without nickel subsulfide (at 1 µg/ml), in the presence of various concentrations of Magnesium Carbonate (0.6, 1.2, 2.4 µg/ml) to give final molar ratios of 0.25, 0.5, and 1.0. The suppression of up to 64% of the proliferation of BALB/3T3 fibroblasts by nickel subsulfide (1 µg/ml) was reversed by Magnesium Carbonate, having recovered slowly in a dose-dependent manner. The nickel compound increased not only the number of micronuclei, but also the amount of DNA-protein cross-links examined with CHO and BALB/3T3 cells, respectively. These genotoxic effects of nickel were again lessened by Magnesium Carbonate. The nickel subsulfide at 1 µg/ml increased the number of micronuclei from 12 to 54 in controls, out of 500 binucleated cells. This number was reduced to 34 upon Magnesium Carbonate co-treatment at 2.4 µg/ml. The DNA-protein cross-links coefficient of 1.63 obtained in the presence of nickel was decreased to 1.39 with Magnesium Carbonate co-treatment at 2.4 µg/ml.

CARCINOGENICITY

Oral

Potassium Bicarbonate

The effect of Potassium Bicarbonate on rat urinary bladder epithelium, without prior exposure to a bladder tumor initiator, was studied.³⁰ In 4 studies, ranging in duration from 4 to 130 weeks, equimolar amounts of K⁺ were administered in the diet to male and female weanling, SPF-bred Wistar rats (Cpb:WU; Wistar random) (85 rats/sex/ group) as Potassium Bicarbonate. Increased urinary volume and potassium levels were observed, and urinary pH was increased. The feeding of Potassium Bicarbonate resulted in simple epithelial hyperplasia and, after prolonged administration, in papillary/nodular hyperplasia, papillomas, and transitional cell carcinomas of the urinary bladder. Based on these results, the authors concluded that Potassium Bicarbonate is capable of inducing urinary bladder cancer in rats without prior application of an initiator.

Groups of 10 weanling male SPF-bred albino rats (Cpb: WU; Wistar random) were fed a basal diet or diet supplemented with Potassium Bicarbonate (2.5% in the diet) for up to 13 weeks.³¹ A group of 10 rats was also fed 6% monosodium glutamate (MSG) in the diet. Feeding with MSG induced slight growth retardation, decreased food intake (mainly with the purified diet), and increased kidney-to-body weight ratios. The addition to stock diet of 2.5% Potassium Bicarbonate, instead of MSG, induced changes in growth rate, food intake, and kidney weight that were similar to those observed with 6% MSG. The rats that received 6% MSG in the diet showed an increased incidence and degree of focal and diffuse hyperplasia of the bladder epithelium. The group that received Potassium Bicarbonate in the diet also had epithelial hyperplasia in the urinary bladder. Hyperplasia of the epithelium lining the renal pelvis and of the epithelium lining the renal pelvis and papilla was not observed in these animals.

Another 13-week study was performed using groups of 10 weanling male SPF-bred albino rats (Cpb: WU; Wistar random) to compare the effects of 5% Potassium Bicarbonate in a stock diet and in a purified diet.³¹ Unsupplemented stock and purified diets served as controls. The rats were gradually accustomed to the high level of Potassium Bicarbonate (5%) by feeding 1% in the diet during week 1, 2% in the diet during week 2, 3% in the diet during week 3, 4% in the diet during weeks 4 and 5, and 5% in the diet from week 6 on. Growth was retarded by 5% Potassium Bicarbonate in the groups on either basal diet, though the difference was not statistically significant with the stock diet but was statistically significant with the purified diet. None of the rats showed any abnormalities in condition or behavior. The microscopic examinations of the urinary bladder, ureters, kidneys, liver, testes, thyroid with parathyroids, adrenals and bone revealed changes considered to be related to treatment only in the bladder epithelium. These changes comprised various forms and degrees of epithelial

hyperplasia and very small intra-epithelial cysts. An increased incidence and severity of hyperplasia occurred in each of the two groups that received Potassium Bicarbonate. Generally, the hyperplastic changes were diffuse, and their degree varied from minimal to moderate. More severe hyperplasia (papillomatous) was present in one rat fed Potassium Bicarbonate in the stock diet. Both the incidence and the degree of the epithelial changes indicated a more marked effect of Potassium Bicarbonate in the stock diet than in the purified diet.

In a 30-month carcinogenicity study, groups of 50 SPF-bred weanling Wistar rats (CpB:WU;Wistar random) per sex were fed a natural ingredient diet (controls) or diet supplemented with 2% or 4% Potassium Bicarbonate.²² There were no treatment-related mortalities. At necropsy, macroscopic examination did not reveal any significant differences among test and control groups, except for macroscopic lesions in the urinary bladder of some rats. Most histopathological changes observed were considered equally distributed among the treatment groups and the controls and represented normal background pathology for rats of this strain and age.

Dose-related increases in the incidence of zona glomerulosa hypertrophy (classified as non-neoplastic histopathological change) occurred in all treatment groups (both sexes) and was statistically significant ($p < 0.01$) when compared to the control. At week 13, oncocytic tubules were noted in males and females fed 2 or 4% Potassium Bicarbonate; after 30 months, the incidence of this lesion was much higher in the treated rats when compared to the background incidence in controls. No progression to oncocytomas was noted. The incidences of simple epithelial hyperplasia and of papillary/nodular hyperplasia of the urinary bladder were increased in the 2% and 4% Potassium Bicarbonate groups. Urothelial hyperplasia (classified as non-neoplastic histopathological change) and papillary/nodular hyperplasia of the urinary bladder were statistically significant ($p < 0.01$) when compared to the control. There was an increased incidence of papillomas, and one female of this group had a transitional cell carcinoma. These changes indicate an association between prolonged treatment with Potassium Bicarbonate and urinary bladder cancer. Except for the preneoplastic and neoplastic lesions in the urinary bladder, there were no treatment-related changes in any specific tumor type among the groups. In females, relatively high incidences of adenocarcinomas were found in the uterus with 4% Potassium Bicarbonate, but because these changes were not accompanied by preneoplastic alterations in the 18- and 30-month studies (See section on Repeated Dose Toxicity) and because their incidences were within the range of historical control data, they were not deemed treatment-related.

Additionally, the total number of rats with tumors or the total incidence of tumors was not affected by treatment. Although the number of Potassium Bicarbonate-fed males with malignant tumors reached the level of statistical significance, when the number of urinary bladder lesions were excluded from evaluation, the difference when compared to the controls was not significant. In summary, apart from the effects on the urinary bladder, treatment with Potassium Bicarbonate did not affect type, incidence, or multiplicity of tumors, nor the time of tumor appearance and the ratio of benign-malignant tumors.²²

IRRITATION AND SENSITIZATION

Skin Irritation and Sensitization

in vitro

Calcium Carbonate

The dermal corrosivity potential of undiluted Calcium Carbonate was evaluated using Corrositex®, an *in vitro* test method for assessing the dermal corrosivity potential of chemicals and chemical mixtures.³² This methodology is based on the ability of a corrosive chemical or chemical mixture to pass through, by diffusion and/or destruction/erosion, a biobarrier and to elicit a color change in the underlying liquid Chemical Detection System (CDS). The biobarrier is composed of a hydrated collagen matrix in a supporting filter membrane, while the CDS is composed of water and pH indicator dyes. Calcium Carbonate was not a corrosive agent.

Non-human

Calcium Carbonate

Undiluted Calcium Carbonate was applied to intact skin of rabbits (number and strain not stated).³² The skin was evaluated for corrosion within 3 minutes, and at 1 h or 4 h post-application. Calcium Carbonate was not a corrosive agent.

Potassium Carbonate

Data on “potash hydrate” (composition not stated) were used to evaluate the skin irritation potential of Potassium Carbonate in 6 New Zealand white rabbits.¹⁸ The test substance (500 mg, moistened with saline) was applied, under a 2.5 cm x 2.5 cm occlusive dressing, to abraded and intact dorsal skin for 24 h. Reactions were scored at 24 h and 72 h post-application according to the Draize scoring system (0 to > 5 [severe irritant]). Skin irritation was not observed (Scores = 0) at intact sites at 24 h or 72 h post-application. For abraded sites, an erythema score of 4 and an edema score of 2 were observed in all 6 rabbits at 24 h. At 72 h, an erythema score of 4 was observed in all rabbits; the edema score was 0. A primary irritation index of 2.5 (abraded and intact scores included; 8 = maximum index value) was reported, classifying the test substance as a moderate skin irritant.

The skin sensitization potential of a Potassium Carbonate tradename material was evaluated in the Buehler test (repeated insult patch test) using 10 guinea pigs.¹⁸ The test substance (moistened with distilled water) was applied, under an occlusive patch, to the skin at a concentration of 95% w/w (minimum irritating concentration) during the 3-week induction period and challenge phase. The induction and challenge phases were separated by a 14-day non-treatment period. Challenge test sites were evaluated for erythema at 24 h and 48 h after patch application. Negative and positive (dinitrochlorobenzene) control groups consisted of 5 and 10 guinea pigs, respectively. Skin irritation was not observed in test or negative control animals during the induction phase. Additionally, skin sensitization was not observed during the challenge phase. Faint to moderate erythema was observed at positive control sites. It was concluded that the Potassium Carbonate tradename material was not a skin sensitizer in guinea pigs.

Case Reports

Potassium Carbonate

A male crystal factory worker with a 1-month history of eczema on the hands, arms, and legs was patch-tested with a 1% aqueous solution of Potassium Carbonate.¹⁸ The patch test procedure was not stated. Skin sensitization was not observed.

Ocular Irritation

in vitro

Magnesium Carbonate

The ocular irritation potential of Magnesium Carbonate was evaluated in the *in vitro* bovine corneal opacity and permeability test (BCOP).³³ In the BCOP test method, changes in corneal opacity caused by chemical damage are determined by measuring decreases in light transmission through the cornea. Changes in permeability of the cornea resulting from chemical damage are determined by measuring increases in the quantity of sodium fluorescein dye that passes through all corneal cell layers. Both measurements are used to calculate an *in vitro* irritancy score (IVIS), which is used to predict the *in vivo* ocular irritation/corrosion potential of a test substance. The following scores are considered positive: corneal opacity (CO) or iris (IR) score ≥ 1 or conjunctival chemosis (CC) or conjunctival redness (CR) ≥ 2 . There was no evidence of CC or CR or lesions of the iris. A CO score of 1 was reported, and the reaction had cleared by day 3. Therefore, Magnesium Carbonate caused only corneal opacity.

Potassium Carbonate

Data on sodium carbonate monohydrate were used to evaluate the skin irritation potential of Potassium Carbonate in 9 New Zealand white rabbits.¹⁸ The test substance (0.1 ml) was instilled into the conjunctival sac, after which the eye was either rinsed (3 rabbits) or not rinsed (6 rabbits). Untreated eyes served as controls. Reactions were scored according to the Draize scale for up to 14 days post-instillation. Conjunctival redness was observed in all 6 rabbits that were not subjected to ocular rinsing, and in 1 rabbit after ocular rinsing. Conjunctival chemosis was observed in all 6 rabbits (no ocular rinsing) and in 2 rabbits after ocular rinsing. Corneal opacity, ulceration, and pannus were also observed in rinsed eyes. Necrosis/ulceration, alopecia, and bleeding were observed in eyes that were not rinsed. Signs of ocular irritation persisted to the end of the study in rabbits (unrinsed eyes) and in one rabbit (no ocular rinsing). It was concluded that sodium carbonate monohydrate was irritating to the eye.

SUMMARY

The simple carbonate salts have the following functions in cosmetic products: absorbents, bulking agents, opacifying agents, pH adjusters, buffering agents, abrasives, and oral care agents.

Collectively, information supplied to FDA by industry as part of the VCRP and a survey of ingredient use concentrations conducted by the Council indicate that the following simple carbonate salts are being used in cosmetic products: Magnesium Carbonate, Ammonium Bicarbonate, Ammonium Carbonate, Calcium Carbonate, and Potassium Carbonate. The highest use frequency is reported for Magnesium Carbonate (317 uses). The Council survey data also indicate that the simple carbonate salts are being used in cosmetics at maximum ingredient use concentrations up to 93.4% (i.e., Ammonium Bicarbonate in in rinse-off products [hair bleaches]).

Calcium Carbonate (0.40 mCi of calcium ^{14}C -carbonate pellet) was implanted intraperitoneally into a male rat.¹⁷ Approximately 72% of the radiolabeled carbonate was excreted as respiratory carbon dioxide between 2 h and 142 h after implantation. Following ingestion, Potassium Carbonate rapidly dissociates in the gastric juice to yield carbonate ions (CO_3^{2-}) and potassium ions (K^+).

In an acute dermal toxicity study on a tradename material that was considered similar to Potassium Carbonate, the LD_{50} in rabbits was > 2 g/kg body weight. An acute oral $\text{LD}_{50} \approx 2$ g/kg was reported for Ammonium Bicarbonate and Potassium Carbonate in studies involving rats.

In an acute inhalation toxicity study on a tradename material that was considered similar to Potassium Carbonate, a mean LD_{50} of > 4.96 mg/L air (rats) was reported. Mean acute i.v. toxicity values of 3.10 and 1.02 mM/kg were reported for Ammonium Bicarbonate and Ammonium Carbonate, respectively, in studies involving albino rats.

Rats fed Calcium Carbonate at 0.3 g/kg for 3 days had no indication of toxicity. In repeated dose oral toxicity studies (4-week, 13-week, and 18-month studies) of Potassium Bicarbonate (2% or 4% in diet), most of the histopathological changes observed were considered equally distributed among treatment groups, and represented normal background pathology for SPF-bred Wistar rats.

Inhalation exposure to an aerosolized Potassium Carbonate-based scrubbing solution for 21 days did not result in any persistent systemic toxicity or neurotoxicity in either male or female rats.

The results of a study in which rabbits were dosed orally (drinking) with Potassium Carbonate emulsion (50mg/L and 100mg/L) for 14 consecutive days, suggested that Potassium Carbonate emulsion exposure could precipitate kidney damage.

Female Swiss mice were bred after feeding with a diet supplemented with 0.5%, 1%, or 2% Calcium Carbonate. Calcium Carbonate (2%) in the diet caused hypertrophy of the heart and decreased thymus weight in weanling rats. In teratogenicity studies involving rats and mice, NOELs of 290 mg/kg and 180 mg/kg (highest dose in each study), respectively, were reported for Potassium Carbonate. The results of an inhalation developmental toxicity study on a Potassium Carbonate scrubbing solution (up to 3 mg/l) were negative.

Ames test results for Potassium Bicarbonate and Potassium Carbonate were negative for genotoxicity. Additionally, anti-genotoxic effects of Magnesium Carbonate have been reported in *in vitro* tests involving *Saccharomyces cerevisiae* strain D4, Balb 3T3 fibroblast cells, or Chinese hamster ovary cells, but not in the Ames test using *S. typhimurium* strain 102. Potassium Bicarbonate in the diet has been associated with bladder cancer in rats.

Undiluted Calcium Carbonate was not a corrosive agent when applied to the skin of rabbits. In a repeated insult patch test, a Potassium Carbonate tradename material (tested at 95% w/w) was not a skin sensitizer in guinea pigs.

Magnesium Carbonate caused only corneal opacity in the *in vitro* bovine corneal opacity and permeability test. Sodium carbonate monohydrate was irritating to the eyes of rabbits, and these data were also used to predict the ocular irritation potential of Potassium Carbonate.

Table 1. Definitions, Structures, and functions of the ingredients in this safety assessment (INCI Dictionary¹; CIR Staff)

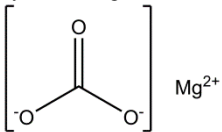
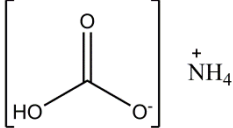
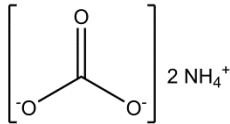
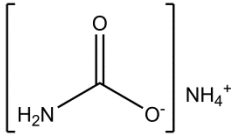
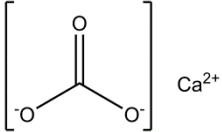
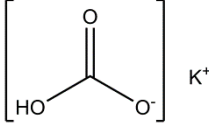
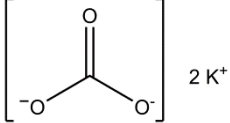
Ingredient/CAS No.	Definition & Structure	Function
Magnesium Carbonate 546-93-0 7757-69-9	Magnesium Carbonate is a basic dehydrated Magnesium Carbonate or a normal hydrated Magnesium Carbonate. 	Absorbents; Bulking Agents; Opacifying Agents; pH Adjusters
Ammonium Bicarbonate 1066-33-7	Ammonium Bicarbonate is an inorganic salt that conforms to the formula: 	pH Adjusters
Ammonium Carbonate 10361-29-2 506-87-6 8000-73-5	Ammonium Carbonate is a mixture of Ammonium Bicarbonate and ammonium carbamate.  	Buffering Agents; pH Adjusters
	Ammonium Carbonate Ammonium Carbamate	
Calcium Carbonate 471-34-1	Calcium Carbonate is the inorganic salt that conforms to the formula: 	Abrasives; Buffering Agents; Bulking Agents; Opacifying Agents; Oral Care Agents
Potassium Bicarbonate 298-14-6	Potassium Bicarbonate is the inorganic salt that conforms to the formula: 	Buffering Agents; pH Adjusters
Potassium Carbonate 584-08-7	Potassium Carbonate is the inorganic salt that conforms to the formula: 	pH Adjusters

Table 2. Properties of Simple Carbonate Salts.^{2]}

Property	Value	Background Information
Ammonium Bicarbonate		
Form/Odor	Shiny, hard, colorless or white prisms or crystalline mass. Faint odor of ammonia.	Comparatively stable at room temperature. Volatile with decomposition at ~ 60°. Decomposes in hot water.
Formula Weight	79.06	
Solubility	Soluble in water: 14% (10°); 17.4% (20°); 21.3% (30°). Insoluble in alcohol and acetone.	
Ammonium Carbonate		
Form	Flat, columnar, prismatic crystals or elongated flakes.	Commercial preps are usually a mixture with ammonium carbamate and Ammonium Bicarbonate.
Formula Weight	96.09	
Melting Point	43°C	
Calcium Carbonate		
Form	Odorless, tasteless powder or crystals.	Two crystal forms are of commercial importance: Aragonite (orthorhombic; melting point: 825°C (decomposes); density: 2.83; formed at temperatures above 30°; Calcite (hexagonal-rhombohedral; melting point 1339°C; density: 2.52; formed at temperatures below 30°.
Formula Weight	100.09	
Solubility	Soluble in 1N acetic acid, 3N hydrochloric acid, 2N nitric acid. Practically insoluble in water. Insoluble in ethanol.	
Potassium Bicarbonate		
Form	Colorless, transparent crystals, white granules or powder.	Contains not less than 99% KHCO ₃ .
Formula Weight	100.11	
Solubility	Soluble in 2.8 parts water, 2 parts water at 50°. Almost insoluble in ethanol.	
Potassium Carbonate		
Form	Hygroscopic, odorless granules or granular powder.	
Formula Weight	138.20	
Solubility	Soluble in 1 part cold water and in 0.7 part boiling water. Practically insoluble in alcohol.	
Density	2.29	
Melting Point	891°C	

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.^{4,5}

	Magnesium Carbonate		Ammonium Bicarbonate		Ammonium Carbonate	
	# of Uses	Conc. (%)	# of Uses	Conc. (%)	# of Uses	Conc. (%)
Totals/Conc. Range	317	0.1-14.4	70	3-93.4	27	0.6-6.5
Duration of Use						
<i>Leave-On</i>	225	0.1-7	2	NR	3	0.6-3
<i>Rinse off</i>	90	0.12-14.4	68	3-93.4	24	2-6.5
<i>Diluted for (bath) Use</i>	2	NR	NR	NR	NR	NR
Exposure Type						
<i>Eye Area</i>	70	0.2-2	NR	NR	NR	NR
<i>Incidental Ingestion</i>	2	NR	NR	NR	NR	NR
<i>Incidental Inhalation- Sprays</i>	9*	0.18**	1**	NR	3*	NR
<i>Incidental Inhalation- Powders</i>	109	0.5-4**	1**	NR	NR	NR
<i>Dermal Contact</i>	283	0.1-7	1	NR	1	NR
<i>Deodorant (underarm)</i>	NR	NR	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	3	NR	9	3-6.1	2	0.6-3
<i>Hair-Coloring</i>	27	0.12-14.4	60	1.5-93.4	24	2-6.5
<i>Nail</i>	NR	NR	NR	NR	NR	NR
<i>Mucous Membrane</i>	5	NR	NR	NR	NR	NR
<i>Baby Products</i>	3	NR	NR	NR	NR	NR
	Calcium Carbonate		Potassium Carbonate			
	# of Uses	Conc. (%)	# of Uses	Conc. (%)		
Totals/Conc. Range	174	0.0036-35	4	0.0019-2.5		
Duration of Use						
<i>Leave-On</i>	113	0.001-35	1	0.002-0.0068		
<i>Rinse off</i>	59	0.0036-25	3	0.0019-2.5		
<i>Diluted for (bath) Use</i>	2	NR	NR	NR		
Exposure Type						
<i>Eye Area</i>	16	2-35	NR	0.002-0.005		
<i>Incidental Ingestion</i>	41	0.045-10	NR	NR		
<i>Incidental Inhalation- Sprays</i>	17*	0.07-25**	1*	0.006-0.0068*		
<i>Incidental Inhalation- Powders</i>	42	0.047-25**	NR	NR		
<i>Dermal Contact</i>	129	0.001-35	4	0.0019-0.0068		
<i>Deodorant (underarm)</i>	NR	NR	NR	NR		
<i>Hair - Non-Coloring</i>	1	0.01-6	NR	NR		
<i>Hair-Coloring</i>	NR	< 0.01-8	NR	2-2.5		
<i>Nail</i>	1	10-15	NR	NR		
<i>Mucous Membrane</i>	54	0.0036-10	NR	NR		
<i>Baby Products</i>	NR	NR	NR	NR		

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses.

*It is possible that these products may be sprays, but it is not specified whether the reported uses are sprays.

**Not specified whether a powder or spray, so this information is captured for both categories of incidental inhalation.

Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.

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