Final Report on the Safety Assessment of Sodium Metaphosphate, Sodium Trimetaphosphate, and Sodium Hexametaphosphate[1]

These inorganic polyphosphate salts all function as chelating agents in cosmetic formulations. In addition, Sodium Metaphosphate functions as an oral care agent, Sodium Trimetaphosphate as a buffering agent, and Sodium Hexametaphosphate as a corrosion inhibitor. Only Sodium Hexametaphosphate is currently reported to be used. Although the typical concentrations historically have been less than 1%, higher concentrations have been used in products such as bath oils, which are diluted during normal use. Sodium Metaphosphate is the general term for any polyphosphate salt with four or more phosphate units. The four-phosphate unit version is cyclic, others are straight chains. The hexametaphosphate is the specific six-chain length form. The trimetaphosphate structure is cyclic. Rats fed 10% Sodium Trimetaphosphate for a month exhibited transient tubular necrosis; rats given 10% Sodium Metaphosphate had retarded growth and those fed 10% Sodium Hexametaphosphate had pale and swollen kidneys. In chronic studies using animals, growth inhibition, increased kidney weights (with calcium deposition and desquamation), bone decalcification, parathyroid hypertrophy and hyperplasia, inorganic phosphaturia, hepatic focal necrosis, and muscle fiber size alterations. Sodium Hexametaphosphate was a severe skin irritant in rabbits, whereas a 0.2% solution was only mildly irritating. A similar pattern was seen with ocular toxicity. These ingredients were not genotoxic in bacterial systems nor were they carcinogenic in rats. No reproductive or developmental toxicity was seen in studies using rats exposed to Sodium Hexametaphosphate or Sodium Trimetaphosphate. In clinical testing, irritation is seen as a function of concentration; concentrations as high as 1% produced no irritation in contact allergy patients. Because of the corrosive nature of Sodium Hexametaphosphate, it was concluded that these ingredients could be used safely if each formulation was prepared to avoid skin irritation; for example, low concentration in a leave-on product or dilution of a higher concentration as part of product usage.

INTRODUCTION

Sodium Metaphosphate, Sodium Trimetaphosphate, and Sodium Hexametaphosphate are inorganic polyphosphate salts that serve as chelating agents in cosmetic formulations. In addition, Sodium Metaphosphate is an oral care agent, Sodium Trimetaphosphate functions as a buffering agent and chelating agent, and Sodium Hexametaphosphate is a corrosion inhibitor in cosmetics. Only Sodium Metaphosphate is in current use in cosmetic formulations.

CHEMISTRY

Definition and Structure

Sodium Metaphosphate

Sodium Metaphosphate (CAS No. 10361-03-2) is an inorganic salt that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

$$(NaPO_3)_n$$

Sodium Metaphosphate is the general term for various polyphosphates. The term describes both straight-chain phosphates that contain four or more phosphate units and two cyclic phosphate compounds, trimetaphosphate and tetrametaphosphate. A Food and Drug Administration (FDA) review of the safety of phosphates in foods stated that, commonly, Sodium Metaphosphate has an average chain length of 20 to 100 (FDA 1975). The term Sodium Metaphosphate is also used to describe short-chain vitreous compositions, molecules which have the polyphosphate formula $Na_{n+2}P_nO_{3n+1}$, with n as small as 4 to 5. However, these compounds are more correctly called sodium polyphosphates (Lewis 1997).

The *Food Chemical Codex* describes Sodium Metaphosphate as a high-molecular-weight sodium polyphosphate that is composed of two long metaphosphate chains that spiral in opposite directions about a common axis (National Academy of Sciences [NAS] 1996). Cosmetic grade Sodium Metaphosphate consists of dimers to high-molecular-weight straight chains and cyclic structures (Nikitakis and McEwen 1990a). Lewis (1997) described Sodium Metaphosphate, stating that "cyclic sodium metaphosphate, based on rings of alternating phosphorus and oxygen atoms, range[s] from the Trimetaphosphate to at least the decametaphosphate." Vitreous sodium phosphates having Na_2O/P_2O_5 mole ratios near unity are classified as Sodium Metaphosphates as well. The average number of

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Rebecca S. Lanigan, former Scientific Analyst and Writer, prepared this report. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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phosphorus atoms per molecule in these glasses ranges from 25 to infinity.

Synonyms for Sodium Metaphosphate are Insoluble metaphosphate; Insoluble sodium metaphosphate; Sodium metaphosphate, insoluble; Maddrell('s) Salt; IMP; Kurrol's Salt (also a name for a potassium salt); Graham('s) Salt; Metafos; Metaphosphoric acid [HPO_3], sodium salt, homopolymer; Polymeric sodium metaphosphate; Poly(sodium metaphosphate); Sodium phosphate; and Sodium polymetaphosphate (Chemline 1996; Hazardous Substances Data Base 1996; NAS 1996; Registry of Toxic Effects of Chemical Substances [RTECS] 1995; Wenninger, Canterbery, and McEwen 2000).

Sodium Trimetaphosphate

Sodium Trimetaphosphate (CAS No. 3398-33-2) is the inorganic salt that conforms to the formula (Wenninger, Canterbery, and McEwen 2000):

$$(NaPO_3)_3$$

It is a crystalline cyclic polyphosphate that is either anhydrous or contains six molecules of water of hydration (FDA 1975), and is composed of three metaphosphate units (NAS 1996).

The anion structure of Sodium Trimetaphosphate is shown in Figure 1 (Nelson, Melton, and Van Wazer 1975).

A synonym for Sodium Trimetaphosphate is Metaphosphoric acid, trisodium salt (Wenninger, Canterbery, and McEwen 2000).

Sodium Hexametaphosphate

Sodium Hexametaphosphate (CAS No. 10124-56-8) is an inorganic salt that conforms to the formula:

$$(NaPO_3)_6$$

The commercial product generally has an average chain length between 10 and 15, but the name Sodium Hexametaphosphate often applies to other soluble, glassy sodium polyphosphates (FDA 1975). Lewis (1993) stated that Sodium Hexametaphosphate is "probably" a polymer where n is between 10 and 20.

Sodium Hexametaphosphate is also known as Graham('s) Salt; Metaphosphoric acid, hexasodium salt (Wenninger, Canterbery, and McEwen 2000); Sodium hexa-*m*-phosphate (Lewis 2000); Hexasodium hexametaphosphate; Hexasodium metaphosphate; Phosphate, sodium hexameta; Sodium phosphate (Hazardous Substances Data Base 1996); and Hexametaphosphate, sodium salt (Lewis 1993; RTECS 1995). Sodium Hexametaphosphate is also known commonly as Calgon, which is a trade name (Grant 1972; Budavari 1989; RTECS 1995).

The United States Department of Agriculture (USDA) stated that the term "Sodium Hexametaphosphate" was an ambiguous chemical name, and instead used the names "Sodium Metaphosphate, insoluble" and "Sodium Polyphosphates, glassy" in its rule amending federal meat and poultry inspection regulations concerning the sodium metaphosphates (USDA 1982).

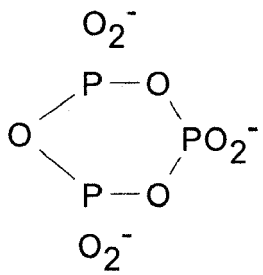

FIGURE 1
Anion structure of Sodium Trimetaphosphate.

Chemical and Physical Properties

In general, the glassy sodium polyphosphates are amorphous polyphosphates composed of metaphosphate units arranged in linear chains or cyclic forms. They are usually identified by their Na_2O/P_2O_5 ratio or their P_2O_5 content. The sodium polyphosphates are very soluble in water, and the pHs of polyphosphate solutions range from 3.0 to 9.0 (NAS 1996).

Sodium Metaphosphate

The Na_2O/P_2O_5 ratio of Sodium Metaphosphate is approximately 1.0. This ingredient occurs as an odorless and tasteless, fine, white, crystalline powder (Nikitakis and McEwen 1990a; NAS 1996). Sodium Metaphosphate is "practically insoluble" in water, but dissolves in mineral acids and in solutions of potassium and ammonium chlorides. It does not dissolve in sodium chloride solutions (NAS 1996). The cosmetic grade chemical is not soluble in most organic solvents (Nikitakis and McEwen 1990a).

For cosmetic grade Sodium Metaphosphate, the apparent density is 1.03 to 1.11. The pH of a 25% aqueous suspension (*w/v*) at 25°C is 5.0 to 6.0. Upon assay, Sodium Metaphosphate contains 67.5% to 70.5% P_2O_5 (Nikitakis and McEwen 1990a). For the food grade chemical, a 1-in-3 slurry in water has a pH of approximately 6.5. It contains 68.7% to 70.0% of P_2O_5 (NAS 1996).

Sodium Trimetaphosphate

Sodium Trimetaphosphate is a water-soluble, crystalline cyclic polyphosphate (FDA 1975). It is made of hexahydrate, efflorescent, triclinic-rhombohedral prisms. The molecular weight of Sodium Trimetaphosphate is 305.92 Da. It contains 22.55% sodium, 47.07% oxygen, and 30.38% phosphorus. The melting point is 53°C. Sodium Trimetaphosphate loses water on storage at 20°C, and is anhydrous at 100°C. One gram dissolves in 4.5 ml water, and Sodium Trimetaphosphate is insoluble in alcohol. The density of Sodium Trimetaphosphate is 1.789, and the density of the anhydrous form is 2.49 (Budavari 1989).

Sodium Hexametaphosphate

Technical grade Sodium Hexametaphosphate is a glassy, amorphous sodium polyphosphate with the appearance of white or clear, free-flowing, odorless granules. The Na_2O/P_2O_5 molar ratio is approximately 1:1. The pH of a 1% solution is 6.8 to 7.2, and the minimum P_2O_5 limit is 66.5%. The molecular weight is 972 to 1592 Da (Monsanto 1996). Other references listed the molecular weight of Sodium Hexametaphosphate as 611.76 Da (Lewis 1993).

Sodium Hexametaphosphate is available as powder flakes, agglomerated particles, or glassy plates. It is either pure or adjusted with mild alkalies. Sodium Hexametaphosphate is miscible in water and insoluble in organic solvents (Budavari 1989; Lewis 1993b, 1997). The maximum loss on ignition of Sodium Hexametaphosphate is 1.0% (Nikitakis and McEwen 1990b).

Reactivity

When heated to decomposition, phosphates can emit highly toxic fumes of PO_x and Na_2O (Lewis 1993, 2000); phosphates also react violently with magnesium (Lewis 2000) and are strong caustics (Lewis 1993). Sodium phosphates can melt with loss of steam when exposed to fire (Hazardous Substances Data Base 1996).

The polyphosphate anions found in Sodium Metaphosphate and related compounds can bind calcium more tightly than sodium and, therefore, exchange their sodium ions when calcium ions are present (Hazardous Substances Data Base 1996). Calcium sodium metaphosphate can form from the partial replacement of sodium by calcium.

Sodium Hexametaphosphate has dequestering, dispersing, and deflocculating properties, and precipitates proteins. At very low concentrations, Sodium Hexametaphosphate inhibits the corrosion of steel (Lewis 1997) and other metals by forming a thin passivating film on their surfaces (Water Quality Association 1995).

Sodium Hexametaphosphate increases the solubility of certain ions (Water Quality Association 1995). Sodium Hexametaphosphate can prevent the precipitation of slightly soluble, scale-forming compounds such as calcium carbonate and calcium sulfate (Lewis 1997) by forming soluble complexes with those compounds. Sodium Hexametaphosphate does not prevent the formation of nuclei of calcium carbonate and other compounds, but rather inhibits the growth of those nuclei, thus halting precipitation at the threshold (threshold treatment) of its occurrence (Grant 1972).

Sodium Hexametaphosphate slowly depolymerizes in aqueous solution to form Sodium Trimetaphosphate and sodium orthophosphate (Felts and Bucks 1981; Hazardous Substances Data Base 1996).

Method of Manufacture

Originally, Sodium Metaphosphate was prepared by heating two parts $NaNO_3$ and one part H_3PO_4. Sodium Metaphosphate can be manufactured by the dehydration of sodium phosphate (e.g., $Na_2H_2P_2O_7$ to $Na_2P_2O_6 + H_2O$ and NaH_2PO_4 to $NaPO_3 + H_2O$). Sodium Trimetaphosphate is prepared by tempering (hardening by heating and subsequent cooling) Sodium Hexametaphosphate at ~500°C for 8 to 12 hours, by heating Na_2HPO_4 and NH_4NO_3 to 320°C, or by heating NaH_2PO_4 at 530°C (Budavari 1989).

Sodium Hexametaphosphate is derived by a thermal process from food-grade phosphoric acid and commercial soda ash (Lewis 1997). Furnace grade phosphoric acid is reacted with sodium carbonate to form monosodium phosphate. This molten product is heated to 340°C to 400°C to form Sodium Metaphosphate or is fused at 760°C and rapidly cooled to produce Sodium Hexametaphosphate. In a similar process, NaH_2PO_4 or $NaNH_4HPO_4$ is heated to 250°C and then slowly heated to 350°C. First $Na_2H_2P_2O_7$ and then insoluble Sodium Metaphosphate are obtained. Sodium Metaphosphate is stable to ~500°C; at 505°C, it changes to Sodium Trimetaphosphate, and above 607°C to Sodium Hexametaphosphate (Hazardous Substances Data Base 1996).

It was noted that several commercial preparations of Sodium Hexametaphosphate labeled "Reagent Grade" actually consist of varying chain lengths, and cannot be truly designated as chemically pure or reagent grade (Hazardous Substances Data Base 1996).

Impurities

Sodium Metaphosphate contains maximum concentrations of 0.1% chloride, 4.0% "water soluble matter" (unit of measure not listed), 0.4% sodium sulfate, 3 ppm arsenic (as As), and 10 ppm lead (as Pb) (Nikitakis and McEwen 1990a). Food grade Sodium Metaphosphate contains ≤3 ppm arsenic (as As), ≤0.005% fluoride, and ≤10 ppm heavy metals (as Pb) (NAS 1996).

Sodium Hexametaphosphate can contain a small, unspecified amount of sodium pyrophosphate (Grant 1972). The maximum concentrations found in Sodium Hexametaphosphate of arsenic (as As), heavy metals (as Pb), and water insolubles are 3.0 ppm, 20 ppm, and 0.05%, respectively (Nikitakis and McEwen 1990b). The Stauffer Chemical Company (1971) reported that Sodium Hexametaphosphate had 66.2% unadjusted calgon fines, 2.0% coarse light soda ash, 25.8% drymet fines, and 6.0% crystamet fines (percentages by weight).

USE

Cosmetic

Sodium Metaphosphate serves as a chelating agent and oral care agent; Sodium Trimetaphosphate acts as a buffering agent, chelating agent, and pH adjuster; and Sodium Hexametaphosphate functions as a chelating agent and corrosion inhibitor in cosmetic formulations (Wenninger, Canterbery, and McEwen 2000). In 1998, Sodium Hexametaphosphate was reported used in 47 cosmetic product formulations (FDA 1998),

TABLE 1
Product formulation data (FDA 1998)

Product category	Total no. of formulations in category	Total no. of formulations containing Sodium Hexametaphosphate
Bath oils, tablets, and salts	124	4
Other bath preparations	159	3
Eyeliner	514	1
Eye makeup remover	84	1
Mascara	167	5
Other eye makeup preparations	120	1
Face powders	250	1
Foundations	287	12
Lipstick	790	1
Makeup bases	132	1
Body and hand (excluding shaving)	796	6
Foot powders and sprays	35	1
Moisturizing preparations	769	5
Skin fresheners	184	1
Other skin care preparations	692	4
1998 total uses of Sodium Hexametaphosphate		**47**

which are listed in Table 1. Sodium Metaphosphate and Sodium Trimetaphosphate were not reported used.

Current concentration of use data were not available; however, historical data from 1984 indicated that Sodium Metaphosphate was used at concentrations of 5% to 10% and Sodium Hexametaphosphate was used at concentrations greater than 50%. The most common concentrations were ≤0.1% (FDA 1984).

Noncosmetic

Sodium Metaphosphate

Sodium Metaphosphate was used at concentrations of 0.1% in baked goods and baking mixes; 0.2% in fats and oils; 0.1% in milk and milk products; 0.3% in cheese; 0.04% in meat and poultry products; 0.4% in processed vegetables and juices; 0.03% in soft candy; 0.01% in sugar and confections; 0.4% in jams, jellies, and sweet spreads; 0.2% in gelatins, puddings, and fillings; 0.1% in snack foods; <0.01% in nonalcoholic beverages; and 0.02% in baby formulas. These percentages represented the weighted means (FDA 1975).

In 1975, the calculated average daily intakes (by age group) of added phosphates were 17 mg/kg (0 to 5 months; average weight 5 kg), 31 mg/kg (6 to 11 months; average weight 8 kg), 29 mg/kg (11 to 23 months; average weight 11 kg), and 24 mg/kg (2 to 65+ years; average weight 60 kg) after consumption of Sodium Metaphosphate.

Sodium Trimetaphosphate

Sodium Trimetaphosphate functions as a starch-modifying agent in foods (FDA 1975; NAS 1996). It can also be used as a bone-imaging agent (Nelson, Melton, and Van Wazer 1975).

Sodium Hexametaphosphate

Sodium Hexametaphosphate is used as an emulsifier, sequestrant, and texturizer in foods (NAS 1996). Sodium Hexametaphosphate is generally recognized as safe (GRAS) as a substance migrating to food from paper and paperboard products, and is GRAS as a sequestrant. The safety of Sodium Hexametaphosphate in dietary supplements was recognized by the FDA. Sodium Hexametaphosphate is used in foods as a curing agent, dough strengthener, emulsifier, firming agent, flavor enhancer, flavoring agent, humectant, nutrient supplement, pH control agent, processing aid, sequestrant, stabilizer and thickener, surface-active agent, synergist, and texturizer at concentrations "not to exceed good manufacturing practice." The maximum concentrations in use are 0.17% in baked goods; 0.3% in nonalcoholic beverages; 0.2% in frozen dairy desserts; 0.52% in jams and jellies; 3.0% in cheeses and poultry products; 0.5% in gelatin, puddings, and meat products; 0.38% in processed vegetables; 0.16% in snack foods; 0.04% in infant formulas; and 0.05% or less in all other food categories (Rothschild 1990). The Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO) stated that the maximum tolerable daily intake (MTDI) of Sodium Hexametaphosphate and other sources of phosphorus is 70 mg/kg; the MTDI is an end point for contaminants with no cumulative properties, and represents the permissible human exposure as a result of the substance in food or drinking water (FAO/WHO 1996).

When Sodium Hexametaphosphate is diluted prior to application to raw agricultural commodities, and used as an adjuvant for pesticide chemicals (as a surfactant, emulsifier, wetting agent, suspending agent, dispersing agent, or buffer), the chemical is

exempt from tolerance requirements. Sodium Hexametaphosphate is used to decrease the cooked out juices in canned hams, pork shoulders and loins, chopped ham, poultry products, and bacon. The allowed limits for this use are 5.0% in pickling solutions, and 0.5% in the product itself; only a clear solution should be injected into the product. Sodium Hexametaphosphate is also used as a scald agent to remove hair from hog and feathers from poultry carcasses. When used as a scald agent, Sodium Hexametaphosphate is permitted in an amount sufficient for the purpose in scald water, but must be removed during subsequent cleaning operations. Sodium Hexametaphosphate is used in the potable water supply at a limit of 10 ppm to retard scale formation in pipes of feeders of poultry and other animals (Rothschild 1990).

Sodium Hexametaphosphate is used as a water softener and detergent, and is utilized in leather tanning, dyeing, laundry work, textile processing, and for threshold treatment (see Chemistry—Reactivity) of softening industrial water supplies (Budavari 1989). The polyphosphate controls scale formation in condensers, heat exchangers, pipelines, and boilers. It is commonly added to potable water to aid in corrosion control and antiscaling of distribution equipment and lines at concentrations up to 11.9 mg/l. In the textile industry, Sodium Hexametaphosphate chelates calcium and iron to keep their salts from redepositing on the fabric surface. Sodium Hexametaphosphate helps disperse dyes and pigments. It also chelates foreign metal ions to improve the efficiency of photographic film (Monsanto 1996). Sodium Hexametaphosphate is also used as a precipitation retarder for dental impression materials (Hazardous Substances Data Base 1996).

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, and Excretion

The rate of absorption of phosphorus from polyphosphates was dependent upon the hydrolysis of the sodium polyphosphates to sodium orthophosphate (Datta et al. 1962; FDA 1975). In young rats given 110 mg/kg sodium [^{32}P]orthophosphate (Na_2HPO_4) or 165 mg/kg sodium [^{32}P]pyrophosphate ($Na_4P_2O_7$) by gavage, no difference was detected in the uptake of [^{32}P] at 6 hours after administration. However, when rats were given 177 mg/kg Sodium [^{32}P]Hexametaphosphate, the rate of uptake of radioactivity was decreased and more of the radioactivity was excreted in the feces. Rats given 5% pyrophosphate in the diet excreted phosphate (80% in urine, 20% in feces) as sodium orthophosphate.

After oral administration, metaphosphates must be first hydrolyzed to Tripolyphosphate, and next to orthophosphate, which can be absorbed. Little, if any, cyclic metaphosphate is absorbed through the intestinal wall. Ten percent to 40% of phosphorus from orally administered Sodium Hexametaphosphate was absorbed in the intestinal tract. The balance of the phosphorus was eliminated in the feces. Urinary excretion of phosphorus was the chief mode of elimination, and the phosphorus was mainly excreted as organic and inorganic phosphate. Sodium Hexametaphosphate appeared to be hydrolyzed in the bowel to phosphoric acid (Hazardous Substances Data Base 1996).

Investigators determined that the cyclic polymers (e.g., Sodium Trimetaphosphate) were slowly hydrolyzed, and were recovered promptly from the urine as intact molecules (Gosselin et al. 1952, 1953). Linear polyphosphates such as Sodium Hexametaphosphate were extensively hydrolyzed to orthophosphate in rats and rabbits after intravenous (IV), intraperitoneal (IP), and subcutaneous administration. At pH 7.4, hydrolysis of Sodium Hexametaphosphate liberated 0.62 mole H^+ per mole P; the similar hydrolysis of Sodium Metaphosphate released 0.84 mole H^+ per mole P.

During an in vitro study by Gosselin et al. (1952), polyphosphates, including Sodium Trimetaphosphate and Sodium Hexametaphosphate, were added to heparinized rabbit blood. Aliquots of the treated blood samples were incubated at 38°C for 150 minutes at pH 7.2 to 7.5. This incubation did not cause a significant change in the plasma concentration of labile P in any blood sample containing the polyphosphates, but the amount of plasma orthophosphate was increased. The investigators concluded that significant hydrolysis of the polyphosphates did not occur during incubation, and that the blood cells exposed to the phosphates leaked orthophosphate more rapidly than control cells. Similar results for both Sodium Trimetaphosphate and Sodium Hexametaphosphate were reported.

After the in vitro study, two in vivo studies were performed. In the first, two adult rabbits per group were injected IV with Sodium Trimetaphosphate and sodium tetrametaphosphate. Serum phosphate concentrations were constant during the 1-hour preinjection periods, and both compounds were removed from the plasma at approximately exponential rates. The short-term distribution volume of Sodium Trimetaphosphate was calculated to be 12% of body weight. It caused a significant change in the serum concentration of orthophosphate late in the experiment, but the observed change was small. Urinary excretion of orthophosphate was relatively constant during water diuresis in any one rabbit, but varied from 30 to 100 μg P/min among the group of rabbits. Labile P was not generally detectable in the urine (control). After IV administration, Sodium Trimetaphosphate appeared promptly in the urine, but only small amounts were detectable after 3 hours. The rate of orthophosphate excretion was 83, 56, and 44 μg ortho-P/min in three consecutive 20-minute periods. The rate of orthophosphate excretion returned to preinjection concentrations within 2 hours.

For the second in vivo study, albino rats were given Sodium Hexametaphosphate by stomach tube. They had significant amounts of sodium orthophosphate and traces of "labile" phosphate recovered in the urine. The investigators also provided evidence for the hydrolysis of cyclic oligomers in the alimentary tract. When two fasted male rats were given 46 to 100 mg/kg Sodium Trimetaphosphate by the oral route, 40% of the dose was excreted in the urine (2% labile

phosphate, 38% sodium orthophosphate). In a similar study, 22% of an administered sodium tetraphosphate dose was detected in the urine as 4% labile phosphate and 18% sodium orthophosphate. Cyclic phosphates (parenteral route) were recovered largely intact in the urine, indicating that the alimentary tract was important in the hydrolysis of polyphosphates to orthophosphates.

When Sodium Hexametaphospate or calcium sodium hexametaphosphate was administered by stomach tube to rats or rabbits, only trace amounts of labile P were detected in the urine. Urinary excretion of orthophosphate was significant, but represented only a small fraction of the dose. After a single IV injection of the hexametaphosphate (calcium salt) in a fasting rabbit, the serum labile P concentration increased immediately, then rapidly decreased. Control concentrations were reached within 2 hours. The serum orthophosphate concentration increased and remained high for 24 hours, likely the result of in vivo hydrolysis of the polyphosphate. When five rabbits were injected (IV) with 20 to 30 mg P/kg calcium sodium hexametaphosphate, the serum concentration of labile P decreased exponentially (half-time = 10–15 minutes). The volume of distribution of calcium sodium hexametaphosphate was estimated at 10% to 13% of the body weight.

When Sodium Hexametaphosphate was given to rabbits by the IP route, the increases in plasma concentration were slower, less pronounced, and more prolonged. Prompt and sustained increases in orthophosphate excretion by fasted rabbits were observed, as well as relatively small amounts of labile P in the urine. Excretion of labile P ceased within a few hours, but the excretion of orthophosphate continued for longer than 24 hours. Sixty of 66 rats given Sodium Hexametaphosphate excreted more orthophosphate than rats of the high-dose control group. Fifteen percent to 20% of Sodium Hexametaphosphate was recovered in the urine within 24 hours. Subcutaneous Sodium Hexametaphosphate was "poorly tolerated by rats," and only small amounts of labile P were recovered in the urine. In this group, approximately 80% of the P given as Sodium Hexametaphosphate was represented in the first day's urine. Also, the concentration of excreted orthophosphate did not differ from the control concentration in the second 24 hours (Gosselin et al. 1952).

Similar findings were reported by Fingerhut, Ruf, and Lang (1965). After oral administration of sodium pyrophosphate, sodium tripolyphosphate, and sodium polyphosphate (P_2O_5 = 64%) to rats, only sodium orthophosphate was absorbed.

Dymsza, Reussner, and Thiessen (1959) investigated the effects on the calcium-phosphorus balance of the intake of metaphosphate (food-grade Sodium Hexametaphosphate) and orthophosphate in male Wistar rats. The control diet contained 4% of United States Pharmacopeia (USP) Salts XIV (0.5% calcium, 0.4% phosphorus from orthophosphate). The phosphorus in the four experimental diets was supplied entirely by either orthophosphate (from dibasic potassium phosphate, DPP) or Sodium Hexametaphosphate. The control and normal-orthophosphate diets contained 0.87% DPP. The high-orthophosphate diet contained 5.1% DPP. The normal and high-metaphosphate diets contained 0.93% and 3.5% Sodium Hexametaphosphate, respectively. The four experimental diets contained 0.43% (normal orthophosphate), 0.46% (normal metaphosphate), 1.3% (high orthophosphate), and 1.2% (high metaphosphate) phosphorus. Twelve animals were in each group.

At 50 days, ~10% more calcium was retained by rats fed the control diet or diets containing Sodium Hexametaphosphate than rats fed the two orthophosphate diets. Phosphorus retention did not differ among the five diets. Unretained calcium was excreted mainly in the feces (1% to 2% of total calcium intake was eliminated in the urine). Less fecal elimination of calcium occurred with the metaphosphate diet than with the orthophosphate diet. A large portion of unretained phosphorus was absorbed and subsequently excreted in the urine. The results suggested that high doses of dietary phosphate increase serum phosphorus (after absorption) temporarily, and the blood and kidneys readily dispose of large concentrations of absorbed phosphorus.

After 60 days of treatment, rats of the control group had more efficient feed and protein utilization, compared to rats fed Sodium Hexametaphosphate or orthophosphate, but utilization did not differ between the four experimental groups. Rats fed the high-orthophosphate diet consumed the most feed and gained the most weight. Rats fed the high-metaphosphate diet gained the least weight. Other clinical differences were not observed. No advantageous or deleterious effects of the phosphates were observed.

The rats were fasted for 18 hours, then killed for necropsy. Rats fed the experimental diets had larger hearts, kidneys, and testes per 100 g of body weight than rats of the control group. The kidneys in particular were affected, probably due to the increased "load" from the high salt intake. The renal weights did not differ among the four experimental groups. No abnormalities of the organs were observed. After necropsy, analysis for calcium and phosphorus were performed on the dried carcasses. Femur lengths did not differ between groups. Metaphosphate-fed rats had greater carcass calcium and phosphorus content than rats of the other groups, but carcass and femur ash values did not significantly differ among groups. Orthophosphate-fed rats had significantly less carcass calcium content than metaphosphate-fed rats. Carcass phosphorus content was greatest with the metaphosphate diets, intermediate with the orthophosphate diets, and least with the control diet. Rats fed metaphosphate had greater calcium storage than with orthophosphate. As the femur analysis had no changes in ash or calcium among the five groups, the investigators concluded that the increased amounts of calcium (metaphosphate) and phosphorus (orthophosphate) were not stored in the bones, but in other tissues (Dymsza, Reussner, and Thiessen 1959).

Cytotoxic Effects

The cytotoxicity of calcium sodium metaphosphate glass fiber (see Chemistry—Reactivity) was evaluated in in vitro tests

using Chinese Hamster Ovary cells (CHO), rat alveolar macrophages, and rat lung epithelial cells (Li and Myers 1988). The fiber was either fractionated by sedimentation into small and large fibers or was unfractionated. Release of lactate dehydrogenase was an end point for cytotoxicity in all three systems, and inhibition of colony formation was also used in CHO cells. Cytotoxicity of the calcium sodium metaphosphate fiber was compared to that of a variety of mineral dusts and fibers, including two types of asbestos, two glass fibers, calcium sulfate fiber, titanium dioxide, and calcium sodium metaphosphate glass. The metaphosphate fiber was less cytotoxic than asbestos, similar in cytotoxicity to the glass fibers, and more cytotoxic than calcium sulfate fiber and titanium dioxide. Small metaphosphate fiber was more cytotoxic, and the large fiber was less cytotoxic, than the unfractionated fiber.

Miscellaneous Effects

When beagles (six to nine per group) were given dry dog chow or plain biscuits that were coated with Sodium Hexametaphosphate for 4 weeks, the salt caused significant, dose-dependent reductions in dental calculus (tartar) formation. These reductions ranged from 60% to 80% compared to dogs given control chow and biscuits. The percentages of Sodium Hexametaphosphate added to the feed were 0.59% to 2.93%. In contrast, feed formulated with P_2O_7 caused 15% to 47% reductions in the formation of dental calculus (Stookey, Warrick, and Miller 1995).

Sodium Hexametaphosphate (1 mM) disrupted plaque in vitro by depleting its calcium content (Nordbø, Rølla, and Gjermo 1980). The controls were distilled water and sodium chloride (1 mM). During a clinical study by the same investigators, 12 volunteers rinsed with 15% sucrose every second hour for 3 days to enhance the formation of plaque, and rinsed with the salt solutions (20 mM) four times daily for 3 days. In another clinical study (Finn et al. 1978), 57 children chewed sugarless or sucrose-containing gum (3 g) containing 1.5% Sodium Trimetaphosphate three times daily for 3 years. In these studies, however, Sodium Hexametaphosphate and Sodium Trimetaphosphate did not have significant effects on the in vivo disruption of plaque.

Vaara (1992) reported that, in a growth inhibition assay, Sodium Hexametaphosphate sensitized strains of *Pseudomonas aeruginosa* to rifampin, fusidic acid, dactinomycin, sodium dodecyl sulfate (SDS), and octoxynol-9. Sodium Hexametaphosphate at a concentration of 0.3% decreased the minimum inhibitory concentration (MIC) by a factor of ~10, and 30-fold sensitization occurred when 1% Sodium Hexametaphosphate was used. When the investigators used a bactericidal assay, the addition of 0.3% Sodium Hexametaphosphate decreased the minimum bactericidal concentration (MBC) of rifampin by a factor of ~30. The bacteriolytic assay resulted in the sensitization of target bacteria to lysis by SDS and octoxynol-9 when 0.1% Sodium Hexametaphosphate was added. Sodium Hexametaphosphate enhanced drastically the binding of fluorescent *N*-phenylnaphthylamine to the membrane of target cells during a fluorescent-probe binding assay. Strains of *Pseudomonas* (except *P. cepacia*) and *Escherichia coli* were susceptible to the osmotic membrane permeabillity-increasing action of Sodium Hexametaphosphate.

Vaara (1992) also reported that the addition of chelators such as Sodium Hexametaphosphate sensitized the target cell to bacteriolytic detergents immediately, such that lysis occurred within a few minutes of application. In contrast, gram-negative enteric bacteria tolerated high concentrations of Sodium Hexametaphosphate alone without the loss of viability. In another study, the polyphosphates, including Sodium Trimetaphosphate and Sodium Hexametaphosphate, sensitized *Salmonella typhimurium* to heat in peptone diluent or complex laboratory media (Seward, Lin, and Melachouris 1986).

Sodium Hexametaphosphate (0.5%) had antimicrobial activity against *Staphylococcus aureus* 196E in brain heart infusion broth media, even after heat sterilization for 15 minutes at 121°C (Jen and Shelef 1986).

High concentrations of Sodium Hexametaphosphate in water interfered with trace mineral metabolism (Hazardous Substances Data Base 1996).

In a study by Irving, Schibler, and Fleisch (1966), the polyphosphates did not inhibit normal bone formation or the healing of rickets when a physiological dose of 50 IU vitamin D by gavage was given to 18 female Wistar rats. The rats were injected subcutaneously with 10 mg/kg of the polyphosphates daily for 28 days. Similar or greater concentrations of Graham's Salt injected subcutaneously did not inhibit the uptake of radiolabeled calcium when vitamin D was also administered.

Dietary phosphates (not specified) caused increased incidences of hypocalcemia, hyperparathyroidism, and bone resorption in male Sprague-Dawley rats and adult dogs as compared to animals of the control groups (Laflamme and Jowsey 1972; Sie, Draper, and Bell 1974). Bone resorption was also observed when B7D2F1 Bar Harbor mice were fed up to 1.2% phosphate for up to 25 months (Krishnarao and Draper 1972).

In humans (three females, two males), a single oral dose of 1 g phosphorus caused a 60% to 125% increase in parathyroid hormone (PTH) concentration, as determined using a serum immunoassay (Reiss et al. 1970). Peak PTH concentrations were attained within 1 hour, and PTH returned to base line concentrations in 2 hours. The increase of PTH was likely initiated by a small decrease of total and ionized calcium. No correlation was observed between serum phosphorus and PTH concentration.

Schibler, Russell, and Fleisch (1968) injected subcutaneously female Wistar rats with Graham's Salt (average chain length = 20 phosphate units; probably Sodium Hexametaphosphate) or tetrasodium pyrophosphate over a period of 5 days. The polyphosphates inhibited aortic calcification after the rats were treated with 75,000 U/kg vitamin D_3 by gavage (Table 2). Renal calcification induced by vitamin D_3 was not inhibited. Neither Graham's Salt nor the other salt affected the percentage of total plasma calcium that was in an ionized or ultrafiltrable form. The inhibitory action of the polyphosphates was not explained

TABLE 2
Inhibition of calcification by Graham's Salt (Schibler, Russell, and Fleisch 1968)

Treatment	No. of rats	% Mortality	% of rats with >10 mg Ca/g dry aorta
Rats weighing ~160 g			
Untreated	10	0	0
Vitamin D_3	49	6.1	78.3
Vitamin D_3 + 1 mg/kg Graham's Salt	10	0	90.0
Vitamin D_3 + 10 mg/kg Graham's Salt	48	8.3	13.6
Rats weighing ~270 g			
Untreated	10	0	0
Vitamin D_3	15	13.3	100
Vitamin D_3 + 1 mg/kg Graham's Salt	18	38.8	63.6
Vitamin D_3 + 10 mg/kg Graham's Salt	19	52.6	0

by the complexing of calcium. The investigators attributed the inhibitory action to the local inhibition of growth of calcium phosphate crystals, but could not exclude a direct action of the salts on cellular processes.

Felts and Bucks (1981) reported that extrahepatic lipoprotein lipase was released selectively into the circulation of Long Evans and Simonsen Albino rats by the injection of 0.2 to 5.0 mg/kg polymetaphosphate $[(KPO_3)_n]$ and other negatively charged compounds.

Horse heart cytochrome *c* aggregated to form stable protein complexes in the presence of the highly charged Hexametaphosphate anion (Whitford, Concar, and Williams 1991). The likely mechanism involved the binding of the anion to the surface of cytochrome *c*, thus "reducing intermolecular electrostatic repulsion and facilitating protein self-association." Protein association was elicited by stoichiometric amounts of Hexametaphosphate. The primary mode of association involved a single anion-binding site on the protein surface.

ANIMAL TOXICOLOGY

Acute Toxicity

In adult CD-1 outbred mice, the acute oral LD_{50} of Sodium Hexametaphosphate was 3.7 ± 0.17 g/kg. The LD_{50} for adult Wistar rats was 2.4 ± 0.23 g/kg. The rats and mice had stupor and prostration prior to death (Food and Drug Research Laboratories, Inc. [FDRL] 1974a).

The IP LD_{50} of Sodium Hexametaphosphate was 192 ± 46 mg P/kg in male rats (Gosselin and Megirian 1955).

Gosselin et al. (1953) reported IP LD_{50} values of the polyphosphates for Rochester (ex-Wistar) rats as follows: sodium pyrophosphate (243 mg/kg; 68 females), sodium tripolyphosphate (525 mg/kg; 74 females), Sodium Hexametaphosphate (690 mg/kg; 29 males), sodium orthophosphate (326 mg P/kg; 70 males), sodium tetrametaphosphate (3650 mg/kg; 57 females), and Sodium Trimetaphosphate (3650 mg/kg; 57 females). Sodium Hexametaphosphate caused immediate behavioral agitation even at sublethal doses (e.g., 100 mg/kg) with severe weight loss. Similar doses of calcium hexametaphosphate did not cause signs of pain or anorexia; the 24-hour LD_{50} was three times greater than that of the sodium salt. The in vivo hydrolysis of Sodium Hexametaphosphate in this study resulted in severe metabolic acidosis and hypocalcemia. Rats given IP or IV Sodium Hexametaphosphate excreted 41% more acid than rats of the control group during the first day, but by the second day, acid excretion decreased somewhat below that of the controls. Moderately severe systemic acidosis occurred within the first hour of treatment on the first day due to the rapid acid production. Hyperpnea was usually obvious within a few minutes of treatment, and a prompt and severe decrease of plasma CO_2 became apparent in treated rats. Mortality was high within the first 3 hours of treatment. Treatment with calcium sodium hexametaphosphate produced acidosis whatever the route and whatever the associated cation. Acidosis did not occur after treatment with Sodium Trimetaphosphate. Single IP doses (up to 250 mg P/kg in four rats) of Sodium Hexametaphosphate produced no electrocardiogram evidence of hypocalcemia, but the metaphosphate was more toxic by the IV route. The respiratory rate slowed, but the apical cardiac impulse stopped before or simultaneously with the cessation of breathing. Death occurred when the average cumulative IV dose of Sodium Hexametaphosphate was 48 mg P/kg; however, the lethal dose of the calcium salt was three to seven times greater at this rate of infusion. Calcium Sodium Hexametaphosphate caused accelerated respiration, pulmonary edema, and cyanosis, and the cardiac action outlasted breathing movements. The investigators concluded that the mode of death for rats given the two salts was different. The observed hypocalcemia was due to the in vivo formation of a chelate complex between Ca^{2+} and the hexametaphosphate anion. Treatment of rats with Sodium Trimetaphosphate did not result in hypocalcemia.

Sodium salts such as the metaphosphates were likely toxic due to their excess alkalinity rather than from simple sodium excess (Hazardous Substances Data Base 1996).

The British Industrial Biological Research Association (BIBRA) reported that the acute IP LD_{50} of Sodium Trimetaphosphate was 3650 ± 620 mg/kg for female rats (BIBRA Working Group 1964). Sodium Trimetaphosphate had an acute oral LD_{50} of >100 mg/kg in mice (Budavari 1989).

The acute oral LD_{50} of Sodium Hexametaphosphate in female rats was 2900 ± 258 mg/kg (BIBRA Working Group 1964). Mice given 4320 mg/kg, and rats given 6200 mg/kg Sodium Hexametaphosphate had peripheral nerve, sensation (flaccid paralysis without anesthesia), and behavior changes (somnolence and convulsions) after oral administration (RTECS 1995). Other details, including the number and strains of the experimental animals, were not available.

The Stauffer Chemical Company (1971) reported that the acute oral (gavage) LD_{50} of concentrated Sodium Hexametaphosphate was 2710 mg/kg, and the no-effect level of 0.2% aqueous Sodium Hexametaphosphate was 4640 mg/kg in the male Sprague-Dawley rat. Five rats per group were given single doses of the concentrated test material (as a 20% solution) and the 0.2% concentration in water. The dose concentrations were 1000 to 10000 mg/kg. The rats were fasted for 24 hours prior to treatment and were observed for 14 days after administration of Sodium Hexametaphosphate for mortalities and signs of toxicity. All dead animals and the 14-day survivors of the highest test concentrations were necropsied. For the concentrated material, doses greater than 1000 mg/kg caused severe depression and bloody nasal discharge. No signs of toxicity were observed among rats given 0.2% Sodium Hexametaphosphate at the 4640 mg/kg dose. Rats given 1000 mg/kg and survivors given 2150 mg/kg of the concentrated material were grossly normal; dead animals of the other dose groups had severe gastrointestinal hemorrhages.

The acute IP LD_{50} of Sodium Hexametaphosphate in mice was 870 mg/kg. The compound caused acute tubular necrosis and renal failure and alterations of the ureters and urinary bladder (Stauffer Chemical Company 1971).

No signs of toxicity were noted when rabbits were given IV 140 mg/kg of Sodium Hexametaphosphate. Mice given subcutaneous injections of 1300 mg/kg Sodium Hexametaphosphate had no signs of toxicity (RTECS 1995).

Short-Term Toxicity

The short-term effects of the polyphosphates have been well characterized in the published literature (BIBRA Working Group 1964; FDA 1975). Significant factors involved in the toxicities of the polyphosphates were total intake of phosphate, calcium, and vitamin D, as well as the acid-base balance of the feed mixture as a whole. In rats, phosphate overdose caused metastatic calcification in the kidneys, stomach, and aorta; resorption of bone; and necrosis of the renal tubular epithelium (FDA 1975).

In a feeding study, the no-observed-effect levels (NOELs) in rats of Sodium Hexametaphosphate, sodium tripolyphosphate, Sodium Trimetaphosphate, and sodium tetrametaphosphate were each <2% after a period of one month (BIBRA Working Group 1964). Male weanling rats (five per group) were given feed containing 0.2%, 2.0%, or 10% of the polyphosphates. Rats of the control groups were given basal diet alone, 10% sodium chloride, or 5% disodium orthophosphate. Calcium was added to each diet to ensure a balanced ratio of calcium to phosphorus. The rats were killed on days 3, 7, 15, and 28. Rats fed 10% Sodium Trimetaphosphate had tubular necrosis that was apparent by day 15, but this effect was transient and had cleared by day 28. Rats given orally 10% sodium chloride or 10% polyphosphates had retarded growth. Rats fed 10% Sodium Hexametaphosphate had pale and swollen kidneys, as well as increased renal weight relative to body weight. The growth inhibition observed in rats given the low concentration of Sodium Hexametaphosphate could not be explained. Rats of the high-dose group had increased renal weights and had tubular degeneration and necrosis ("phosphate nephritis"); rats given 10% Sodium Hexametaphosphate were particularly affected. To a lesser degree, these lesions were observed in rats fed 2.0% Sodium Hexametaphosphate, and none were observed in rats of the low-dose group.

Subchronic Toxicity

The BIBRA Working Group (1964) reported a study in which dogs (one per group) were fed 0.1 g/kg/day Sodium Hexametaphosphate, Sodium Trimetaphosphate, sodium tripolyphosphate, and sodium tetrametaphosphate for 1 month (low-dose test). Four other dogs were given feed containing the polyphosphates for five months; the initial dose was 1 g/kg/day and was increased to 4 g/kg/day by the end of the study (high-dose test). All dogs given 4 g/kg/day of the polyphosphates had weight losses ($\geq$1.4 kg), and three had increased eosinophil counts and decreased neutrophil proportions. Only traces of reducing substances and protein were detected in the urine. Dogs of the high-dose test had increased heart weights, and hypertrophy of the left ventricle. The kidneys of all dogs given 4 g/kg/day of the polyphosphates had tubular damage similar to the phosphate nephritis observed previously in rats. Dogs of the low-dose test had hematologic values in the normal ranges. Only traces of reducing substances and protein were detected in the urine. Heart and renal weights were normal, and no significant effect was observed in any organ. Dogs fed 0.1 g/kg/day Sodium Hexametaphosphate had a slight, but insignificant, loss of weight, but organ weights and urine and blood analyses were not affected by the treatment. No microscopic abnormalities were observed. No adverse effects were noted for dogs fed 0.1 g/kg/day Sodium Trimetaphosphate. In a 154-day study by the same investigators, a dog was fed a diet containing 1 g/kg/day Sodium Hexametaphosphate initially, and 4 g/kg/day for the final month of the study. The dog lost significant weight and had an increased heart weight. Left ventricular

hypertrophy and renal changes (phosphate nephritis) were observed.

Chronic Toxicity

Male and female weanling rats (50 per group) were fed basal diet plus 0.05%, 0.5%, or 5.0% Sodium Hexametaphosphate or 0.1%, 1.0%, or 10.0% Sodium Trimetaphosphate for a 2-year period. Rats of the control group were fed basal diet alone (BIBRA Working Group 1964). Rats of the control group had no observed effects on growth. Of rats given the low and median doses of Sodium Hexametaphosphate, no adverse effects were noted. Males of the high-dose group had reduced growth, but females of the same group were only slightly affected. Rats of the high-dose group had greater feed consumption at days 90 and 210, as compared to rats of the control group. The investigators attributed this to interference with absorption of nutrients. A dose-related increase in mortality was not observed during the test period; however, overall mortality was 64% to 78% (females surviving better than males). The median life span was greatest in males given the medium dose of Sodium Hexametaphosphate. The most common cause of death was respiratory infection. Rats fed 0.5% to 5.0% Sodium Hexametaphosphate had increased kidney to body weight ratios. Renal infections were observed more frequently in rats of groups given Sodium Hexametaphosphate than in rats of the control group. Female rats of the high-dose group had "possibly increased" lung weights and decreased splenic weights. The incidence of renal infection made difficult the interpretation of organ weights. One female rat fed 0.5% Sodium Hexametaphosphate, and 13 of 20 rats given 5.0% Sodium Hexametaphosphate had calcification of the renal tubules. Hematologic parameters did not differ from those of controls. Only traces of protein and reducing substances were found in the urine. The femur lengths were not significantly affected by treatment with Sodium Hexametaphosphate. The femurs of all rats had comparable water, ash, calcium, and phosphorus contents, and appeared normal in radiographs.

In this BIBRA Working Group report, rats given 0.1% and 1.0% Sodium Trimetaphosphate had no retardation of growth, with the exception of males of the median-dose (1.0%) group. The males had slight growth retardation up to the age of 6 months, after which the retardation became more pronounced; however, growth was normal by the second year. Rats of both sexes given 10.0% Sodium Trimetaphosphate had substantial reduction in growth, despite normal feed consumption at 1 and 4 months. The observed reduction in growth rate was in part attributed to a cathartic action by Sodium Trimetaphosphate. Hematologic indices did not differ from control values, except for lower red cell counts and hematocrits in female rats of the high-dose group. Only traces of reducing substances and protein were found in the urine. Eighty-eight percent of females of the high-dose group, 58% of females of the low-dose group, and 70% of males of the low-dose group died before termination of the study. The principal causes of death were respiratory infection and pericarditis-peritonitis; except for females of the high dose group, mortality did not appear to be influenced by lower doses of dietary Sodium Trimetaphosphate. Rats of the high-dose group generally had increased organ weight to body weight ratios (due to the retardation of growth), but the liver was considerably smaller than in rats of other groups. Males given 10.0% Sodium Trimetaphosphate had shorter femurs, but the ratio of femur length to body weight was comparable in all groups. Females fed 10.0% Sodium Trimetaphosphate had shorter femur lengths as well, but the ratio was greater than those observed in other groups (indicating true retardation of growth). The ratio of calcium to phosphorus was normal in all rats, but the calcium and phosphorus concentrations in rats of the high-dose group were increased. Males of this group had less water and more ash in the femurs, whereas females had more water and less ash. No microscopic changes were found that could be attributed to the administration of Sodium Trimetaphosphate. Concretions were observed in the kidneys of some rats, particularly females, of the control, low-dose, and median-dose groups. Calcification of the collecting tubules of the kidneys were observed in rats of the high-dose group. This lesion was considered due to infection by a nematode. The overall yield of neoplasms was low, and no correlation between the dietary concentration of Sodium Trimetaphosphate and tumor incidence was observed.

Rats fed 8% Sodium Metaphosphate or sodium orthophosphate for 7 months had gradual bone decalcification with metastatic calcium deposits, significant hypertrophy and hyperplasia of the parathyroid glands, inorganic phosphaturia, and renal calcium deposition (Saxton and Ellis 1941; FDA 1975).

Omoto et al. (1986) fed 1% and 5% Sodium Metaphosphate to 4-week-old male ICR mice for 1 year. Microscopic examinations of liver, kidneys, and muscles, and softex-photographic observations of the bones were performed at 6 and 12 months. The livers had nuclear size alteration, abnormal numbers of nuclei, and focal necrosis. Glomerular incrassate, atrophy, and tubule epithelium desquamation were observed in the kidneys. The bones had alterations of osteoporosis and calcium deposition, and muscle fiber size alteration was noted. These effects were observed for both dose groups, but mice of the 5% treatment group were more markedly affected.

The World Health Organization (1964) reported that the no-effect levels in rats of Sodium Hexametaphosphate and sodium tripolyphosphate ranged from 1.5 g/kg/day (short-term study) to 3.75 g/kg/day (long-term study).

Skin Irritation

Sodium Hexametaphosphate (concentration not specified) had the maximum primary irritation index (PII) score of 8.0 in the standard Draize dermal irritation assay using six rabbits, and was corrosive (Stauffer Chemical Company 1971). All rabbits of this group had erythema and edema scores of 4 (severe) for both intact and abraded skin sites at 24 and 72 hours. A 0.2% solution of Sodium Hexametaphosphate was also evaluated in the same study. At 24 hours, three rabbits had erythema scores

of 1 at abraded skin sites. No signs of primary irritation were observed at 72 hours postapplication. The overall PII rating of 0.2% Sodium Hexametaphosphate was 0.13, and the compound was classified as a mild irritant.

In a second study (Stauffer Chemical Company 1972), 26 compounds, including the metaphosphates and other polyphosphates, were evaluated for dermal irritancy potential using the Draize procedure. In this study, 0.5 g amounts of the test substances were dissolved in appropriate solvents (concentrations not stated) and applied under 1 × 1-inch gauze pads to the intact and abraded skin of six albino rabbits. The patches were attached to the skin with adhesive tape and the trunk of each rabbit was wrapped in a rubberized cloth sheath for 24 hours. After patch removal, Sodium Metaphosphate had a PII of 0.38 (mild irritant), Sodium Trimetaphosphate had a PII of 0 (nonirritant) and undiluted, powdered Sodium Hexametaphosphate had a PII of 1.62 (mild irritant).

Ocular Irritation

Six New Zealand White rabbits (1.6 to 2.1 kg) were used to determine the acute ocular irritation of Sodium Hexametaphosphate (Stauffer Chemical Company 1971). Ten milligram of concentrated Sodium Hexametaphosphate or 0.1 ml of a 0.2% solution in water was instilled into the conjunctival sac of the eye. The untreated eye of each rabbit served as its control. The eyes were then observed at 24, 48, and 72 hours. Ocular irritation was evaluated using the *Illustrated Guide for Grading Eye Irritation Caused by Hazardous Substances* (Daston and Freeberg 1991). Under the conditions of this study, concentrated Sodium Hexametaphosphate was corrosive and nonremissible. The 0.2% solution of Sodium Hexametaphosphate was nonirritating to the eyes of rabbits.

GENOTOXICITY

Sodium Metaphosphate (67.8% pure; in DMSO) was nonmutagenic in the *Salmonella*/microsome assay using *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537; the salt was tested at a maximum dose of 35.0 μg/plate, with and without S9 metabolic activation (Ishidate et al. 1984). Sodium Metaphosphate (67.8% pure; in saline) was nongenotoxic in Chinese hamster fibroblasts when tested using in vitro chromosomal aberration tests. For this assay, the maximum dose was 1.0 mg/ml, and the solvent was physiological saline. At 48 hours, the incidence of polyploid cells was 1.0% and the incidence of cells with structural chromosomal aberrations was 0.0%.

The genotoxic potential of Sodium Hexametaphosphate was investigated both with and without metabolic activation (Litton Bionetics, Inc. 1975). Tissue homogenates were prepared from the liver, lungs, and testes of ICR mice, Sprague-Dawley rats, and *Macaca mulatta* monkeys. The indicator organisms were *Saccharomyces cerevisiae* strain D4 and *S. typhimurium* strains TA1535, TA1537, and TA1538. The positive controls were ethylmethane sulfonate, 2-nitrosofluorene, quinacrine or quinacrine mustard, dimethylnitrosamine, and 2-acetylaminofluorene. Both plate tests and suspension tests were used. Sodium Hexametaphosphate was tested at 0.035% in the plate tests, and at 2.5% and 5.0% in the suspension tests.

Sodium Hexametaphosphate was not mutagenic for *S. typhimurium* strains TA1535, TA1537, or TA1538 in direct or activation plate tests. Test results were negative for the nonactivation suspension tests. Initially, test results from the activation suspension assays using rat tissues and strain TA1538 were unusually high, but repeat data indicated that "the original tests were aberrant and did not reflect true mutagenic activity." In addition, the suspension test using rat testes and strain TA1537 at the high-dose concentration (with activation) had unusually high results, but other data did not support the response; the difference was considered either a random test fluctuation or the result of contaminants. For suspension assays using *S. cerevisiae* as the test organism, the results were negative with and without activation. The investigators concluded that Sodium Hexametaphosphate was "not genetically active for bacterial and yeast indicator organisms under the conditions of this evaluation" (Litton Bionetics, Inc. 1975).

CARCINOGENICITY

During a 2-year feeding study using rats (see Chronic Toxicity) by the BIBRA Working Group (1964), no correlation existed between tumor incidence and the concentration of phosphate supplementation.

No benign or malignant neoplasms were observed when male and female Fischer 344 rats (80/sex/group) were treated with up to 25 mg/m^3 calcium sodium metaphosphate fibers during a chronic inhalation and oncogenicity study for up to 24 months (Nair et al. 1992).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Three generations of rats were reared and maintained on diets containing 0.5% Sodium Hexametaphosphate or 0.05% Sodium Trimetaphosphate (BIBRA Working Group 1964). Two litters per generation were examined. The rats (16 females and 8 males per group) were mated when the rats were each 100 days old. Sodium Hexametaphosphate and Sodium Trimetaphosphate had no effect on fertility, litter size, growth, or survival of offspring. Third generation rats had no evident abnormal organ weights or microscopic changes.

In other studies, pregnant Wistar rats and CD-1 mice were treated via oral intubation with up to 1600 mg/kg Sodium Hexametaphosphate on days 6 to 15 of gestation (Food and Drug Research Laboratories, Inc. 1974b). Body weights were recorded on days 6, 11, 15, and 20 (rats) or days 6, 11, 15, and 17 (mice) of gestation. All rats were observed daily for appearance and behavior. On day 20, the dams underwent caesarian section, and the weights of live pups, sex, numbers of corpora lutea, resorption sites, and live and dead fetuses were recorded. All fetuses were examined for gross abnormalities, and one

third of each litter were prepared for visceral examinations. The remaining two thirds were examined for skeletal defects. For pregnant rats and mice given up to 240 mg/kg/day and 370 mg/kg/day, respectively, no effects on nidation, maternal survival, or fetal survival were observed. The incidence of skeletal or visceral abnormalities of the fetuses did not differ from that of controls.

CLINICAL ASSESSMENT OF SAFETY

Acute Toxicity

Sodium Hexametaphosphate is listed by Lewis (2000) as having moderate to high toxic potential. Moderate toxicity means that a compound can cause reversible or irreversible changes to exposed tissue and considerable discomfort, but not permanent injury or death. High toxicity means that a compound is capable of causing death or permanent injury after normal use exposure, that it is incapacitating and poisonous, and that it requires special handling. Gosselin, Smith, and Hodge (1984) rated Sodium Hexametaphosphate as having a toxicity rating of 2: slightly toxic (probable lethal dose = 5–15 g/kg for a 70-kg person). When ingested in large amounts, nausea, vomiting, and diarrhea "are probable." Systemic acidosis could also occur, as Sodium Hexametaphosphate appears to be hydrolyzed to phosphoric acid within the intestines. A third publication (Lewis 1993) stated that Sodium Hexametaphosphate was poisonous by the IV route, moderately toxic by IP and subcutaneous routes, and mildly toxic by ingestion.

No health hazards were associated with Sodium Hexametaphosphate in foods or in natural waters. Sodium Hexametaphosphate, potassium hexametaphosphate, and other complex phosphate salts formed complexes with calcium and could seriously reduce the serum concentration of ionic calcium when ingested. They were less corrosive to mucous membranes than sodium or potassium hydroxide (Hazardous Substances Data Base 1996).

Concentrations of 0.1% and 5% Sodium Hexametaphosphate were found "much too injurious to use for the purpose of removing calcium from the cornea" (Hazardous Substances Data Base 1996).

The Joint FAO/WHO Committee on Food Additives noted "the necessity for tests for cyclic phosphate, which may occur in polyphosphates and create certain health hazards"; however, these hazards were not detailed. The Committee also estimated that the lowest concentration of phosphorus that might conceivably produce nephrocalcinosis in humans was 6600 mg/day, based upon 1% phosphorus in the diet causing nephrocalcinosis in rats (FDA 1975).

A Select Committee of the FDA concluded that no evidence suggested that Sodium Hexametaphosphate, Sodium Trimetaphosphate, or other polyphosphates would be hazardous to consumers at 1975 use concentrations or expected future concentrations (FDA 1975).

Short-Term Toxicity

Four physically active men fed 750 mg phosphorus (as phosphoric acid, an end metabolite of Sodium Hexametaphosphate) daily for 1 week had a slight decrease of calcium excretion in their urine (Malm 1953; FDA 1975). The basal diet contained approximately 450 mg calcium and 1400 mg phosphorus daily. When the men were fed greater amounts of phosphate for up to 12 weeks, a greater decrease in urinary calcium excretion was observed. No decrease in the utilization of calcium was observed. The results suggested that adults could ingest as much as 2000 mg phosphorus daily without adverse effect on calcium balance, as long as they also received 450 to 600 mg calcium daily.

In another study (Leichsenring et al. 1951; FDA 1975), six women on a basal diet (300 mg calcium, 800 mg phosphorus) had depressed calcium utilization after they were switched to a diet supplying 1500 mg calcium and 1400 mg phosphorus, as compared to six women shifted to a diet supplying 1500 mg calcium and 800 mg phosphorus.

Changes in the composition of the urine that were suggestive of a "disturbed metabolism" were not apparent after 15 young adults drank 2 to 4 g phosphoric acid in fruit juices daily for 10 days. In addition, the ingestion of 6 g sodium dihydrogen phosphate daily for 15 days by two adults did not cause apparent adverse effects (Lauersen 1953; FDA 1975).

Skin Irritation and Sensitization

Alkali metal phosphates in general are strong caustics and irritants (Lewis 1993). When 1% aqueous Sodium Hexametaphosphate was patch tested by the Dutch Contact Dermatitis Group using 1 to 20 patients with suspected or verified contact allergy reactions to cosmetic products, no signs of irritation were observed (de Groot 1994).

The dermal effects of an azo dye mixture (dye, Erionyl Black GD) containing 2.04% Sodium Hexametaphosphate were evaluated using a panel of 200 subjects (Food and Drug Research Laboratories, Inc. 1973). A 1-ml volume of a 4% aqueous solution of the dye mixture was used to saturate lintine discs (1.25 inches diameter). One disc was placed in contact with the test site of each subject and covered with a water-impermeable plastic sheet, which was affixed to the skin with adhesive tape. The individuals were exposed to the mixture for 2-day periods twice a week for 4 weeks (Monday through Wednesday; Wednesday through Friday). On Friday of each week, the covers were removed and the treatment sites were examined and graded. At week 6, each treatment site was challenged with the dye mixture for 48 hours, then was graded. "Visible skin changes signifying reactions" (marked erythema to marked erythema and edema, with or without vesicles) were noted in 2 of the 200 subjects. Upon rechallenge, the investigators concluded that the dye mixture had human sensitization potential but was not necessarily irritating.

SUMMARY

The Sodium Metaphosphates are straight-chain and cyclic polyphosphate salts. Sodium Metaphosphate is both a general term for these polyphosphates and a particular salt. Sodium Metaphosphate and Sodium Hexametaphosphate are GRAS food additives.

The Metaphosphates function in cosmetics as chelating agents; in addition, Sodium Metaphosphate is an oral care agent, Sodium Trimetaphosphate is a buffering agent and pH adjuster, and Sodium Hexametaphosphate is a corrosion inhibitor. In 1998, Sodium Hexametaphosphate was reportedly used in 47 cosmetic formulations, and Sodium Metaphosphate and Sodium Trimetaphosphate were not reportedly used. Current concentration of use data were not available; in 1984, the most common concentrations of use were $\leq$0.1%, but Sodium Metaphosphate and Sodium Hexametaphosphate were reportedly used at 5% to 10% and >50%, respectively.

After oral administration, Metaphosphates are hydrolyzed to tripolyphosphate and orthophosphate, the latter of which is absorbed. Little absorption occurs of cycllic Metaphosphates through the intestinal wall; investigators determined that cyclic Metaphosphates were hydrolyzed slowly and were recovered in the urine as intact molecules. Sodium Hexametaphosphate was hydrolyzed in the intestines to phosphoric acid. Urinary excretion of phosphorus was the chief mode of elimination.

The acute oral LD_{50} values in mice and rats of Sodium Hexametaphosphate were 3.7 g/kg and 2.4 to 2.9 g/kg, respectively. Aqueous Sodium Hexametaphosphate at a concentration of 0.2% had an acute oral LD_{50} of 4.6 g/kg in rats. The IP LD_{50} values in rats and mice of Sodium Hexametaphosphate were .19 to .69 g/kg and .87 g/kg, respectively. In the latter study, the IP LD_{50} of Sodium Trimetaphosphate was ~3.7 g/kg. In rats, in vivo hydrolysis of Sodium Hexametaphosphate caused severe metabolic acidosis and hypocalcemia. No signs of toxicity were observed after IV (rabbits, .14 g/kg) and subcutaneous (mice, 1.3 g/kg) injections of Sodium Hexametaphosphate.

In short-term toxicity studies using rats, the NOELs of Sodium Hexametaphosphate and Sodium Trimetaphosphate were <2% after 1 month of treatment. Rats fed 10% Sodium Trimetaphosphate had transient tubular necrosis at day 15 that cleared by day 28. Rats given 10% of the Metaphosphates or 10% sodium chloride had retarded growth, and those fed 10% Sodium Hexametaphosphate had pale and swollen kidneys that were increased in weight.

In a subchronic toxicity study, dogs were fed 0.1 to 4 g/kg/day polyphosphates, including Sodium Hexametaphosphate and Sodium Trimetaphosphate, for up to 5 months. The dogs of the high-dose group had weight loss, increased eosinophil counts, decreased neutrophil proportions, tubular nephritis, increased heart weights, and hypertrophy of the left ventricle.

Male and female rats were fed 0.05% to 5% Sodium Hexametaphosphate or 0.1% to 10% Sodium Trimetaphosphate in a 2-year chronic toxicity study. Rats of the high-dose groups had growth inhibtion and/or increased renal weights. Rats fed 8% Sodium Metaphosphate for 7 months had gradual bone decalcification with metastatic calcium deposits, significant hypertrophy and hyperplasia of the parathyroids, inorganic phosphaturia, and renal calcium deposition. In another study, mice fed 1% and 5% Sodium Metaphosphate had hepatic focal necrosis, desquamation of the kidneys and renal tubular epithelium, osteoporosis and calcium deposition, and muscle fiber size alterations.

In a Draize dermal irritation study using rabbits, an unspecified concentration of Sodium Hexametaphosphate had a maximum PII score. The rabbits had severe erythema and edema at both intact and abraded skin sites, and the test compound was corrosive. A 0.2% solution of the salt was mildly irritating. In another study, Sodium Metaphosphate and Sodium Hexametaphosphate were mildly irritating and Sodium Trimetaphosphate was nonirritating. In an ocular toxicity assay using rabbits, concentrated Sodium Hexametaphosphate was corrosive and a 0.2% solution was nonirritating.

Sodium Metaphosphate was nonmutagenic in the *Salmonella*/microsome assay using six strains of *S. typhimurium*, and was nongenotoxic in the chromosomal aberration tests using Chinese hamster fibroblasts. Sodium Hexametaphosphate was not mutagenic in three strains of *S. typhimurium*, rat tissues, and in *S. cerevisiae*, with or without metabolic activation. Feeding of the Metaphosphates did not increase tumor incidence in a 2-year study using rats, and calcium sodium metaphosphate was noncarcinogenic in another study.

Sodium Hexametaphosphate and Sodium Trimetaphosphate were not reproductive or developmental toxins in a multigeneration feeding study using rats and a study in which rats and mice were fed the salts during gestation.

In humans, Sodium Hexametaphosphate was classified as having slight to high toxic potential. It was reported as being poisonous by the IV route, moderately toxic by IP and subcutaneous routes, and mildly toxic by ingestion. No health hazards have been associated with the presence of Sodium Hexametaphosphate in foods or in potable water.

Sodium and potassium hexametaphosphates were less corrosive to mucous membranes than sodium and potassium hydroxides. Alkali metal phosphates in general were strong caustics and irritants. A 1% aqueous solution of Sodium Hexametaphosphate was nonirritating when 20 patients with suspected or verified contact allergy reactions were patch tested. A 4% aqueous solution of an azo dye mixture (containing 2.04% Sodium Hexametaphosphate) caused marked erythema to marked erythema and edema in 2 of 200 subjects.

DISCUSSION

The Metaphosphates can contain lead at concentrations up to 10 to 20 ppm. Sodium Hexametaphosphate contains up to 20 ppm lead and is used in lipstick formulations, which can be ingested. An analysis provided to the Cosmetic Ingredient Review (CIR) Expert Panel indicated that the average amount of lead a consumer would be exposed to from lipstick was 1000

times less than the amount from food, water, and air (Cosmetic, Toiletry, and Fragrance Association 1997). The Panel therefore concluded that the presence of lead in the Metaphosphates would not be of concern.

The CIR Expert Panel was concerned about the irritancy potential of Sodium Hexametaphosphate, which was severely irritating and corrosive to the skin and eyes of rabbits when tested in concentrated form. In 1984, the typical concentrations of use of Sodium Metaphosphate and Sodium Hexametaphosphate were ≥0.1%; the greater concentrations reported (>50%) were likely to be in bath oils, salts, and tablets, which are diluted during normal use. As lower concentrations the Metaphosphates were nonirritating to mildly irritating. The Expert Panel concluded that these ingredients are safe for use in cosmetics when care is taken in formulation to avoid skin irritation.

CONCLUSION

Based on the available data, the CIR Expert Panel concludes that Sodium Metaphosphate, Sodium Trimetaphosphate, and Sodium Hexametaphosphate are safe for use in cosmetics when formulated to avoid skin irritation.

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