Final Report on the Safety Assessment of Sodium Sulfate[1]

Sodium Sulfate is used as a viscosity increasing agent in cosmetic formulations, at concentrations that are reportedly as high as 97%. No evidence of systemic toxicity was seen in oral exposure studies in animals, although there was moderate ocular irritation in rabbits when a granular sodium carbonate–Sodium Sulfate mixture was instilled. No developmental or reproductive toxicity was reported in rats or mice; there was an increase in birth weight in the mice. Sodium Sulfate was negative in mutagenesis assays. In several studies in which Sodium Sulfate was given with other agents, the results depended on the carcinogenicity of the other agents. Clinical data indicated no significant adverse effects following dermal, oral, or inhalation exposure. Because some irritation was seen under patch test conditions, it was concluded that the concentration should be limited to a level known to produce only a very small frequency of irritation if used in a leave-on application. Accordingly, Sodium Sulfate was found to be safe for use in rinse-off formulations, and *safe at concentrations up to 1% in leave-on formulations.*

INTRODUCTION

The following is a compilation of studies concerning the testing of Sodium Sulfate (CAS No. 7727-73-3 for the decahydrate form and 7757-82-6 for the anhydrous form).

A comprehensive review of literature published from 1920 to 1972 concerning sulfates (Franklin Institute Research Laboratories 1973) is available through the National Technical Information Service (NTIS). The review had been used by the Select Committee on Generally Recognized as Safe (GRAS) Substances in affirming the status of Sodium Sulfate (as well as other sulfates) as a GRAS compound (FDA 1978).

CHEMISTRY

Definition and Structure

Sodium Sulfate (anhydrous) is the inorganic salt with the chemical formula Na_2SO_4 (USP 1995). The empirical formula for Sodium Sulfate in the *International Cosmetic Ingredient Dictionary* and *Handbook* is $H_2SO_4 \cdot 2Na$ (Wenninger, Canterbery, and McEwen 2000). The decahydrate form has the chemical formula $Na_2SO_4 \cdot 10H_2O$.

Received 3 February 2000; accepted 3 May 2000.

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International Journal of Toxicology, 19(Suppl. 1):77–87, 2000

1071-7544/00 $12.00 + .00

Synonyms include: disodium sulfate; sulfuric acid, disodium salt (Wenninger, Canterbery, and McEwen 2000); Glauber's salt (Taylor 1988); natriumsulfat; salt cake; sodium sulphate; thenardite; trona (RTECS 1995; Lewis 1993); bisodium sulfate; Caswell No. 793; and disodium monosulfate (Chemline 1995).

Physical and Chemical Properties

Some of the physical properties and chemical properties are listed in Table 1.

The decahydrate solution of Sodium Sulfate has a neutral pH (Budavari 1989). Sodium Sulfate reacts with aluminum, and emits toxic fumes of SO_x and Na_2O when heated to decomposition (Sax 1979; Lewis 1993).

CTFA lists the following specifications for cosmetic grade Sodium Sulfate (anhydrous): 3 ppm maximum Arsenic (as As) 20 ppm maximum Lead (as Pb), and 30 ppm maximum Selenium (as Se) (Nikitakis and McEwen 1990). The Sodium Sulfate sample must closely match the Cosmetic, Toiletry, and Fragrance Association (CTFA) Spectrum—IR with no indication of foreign materials (Nikitakis and McEwen 1990). These specifications are similar to those listed in the *Food Chemicals Codex (FCC)*, except that the FCC restricts lead to a maximum of 10 ppm (National Academy of Sciences 1981).

Method of Manufacture

Sodium Sulfate occurs naturally as the minerals mirabilite and thenardite (Budavari 1989). It can also be prepared by the neutralization of sulfuric acid with sodium hydroxide (Rothschild 1990).

USE

Purpose in Cosmetics

Sodium Sulfate is used in cosmetic formulations as a viscosity increasing agent—aqueous (Wenninger, Canterbery, and McEwen 2000).

Scope and Extent of Use in Cosmetics

United States

As of January 1997, there were 28 reported uses of Sodium Sulfate in cosmetic formulations (FDA 1997). See Table 2. Concentrations of use are no longer reported to the FDA (1992). Data submitted to Cosmetic Ingredient Review (CIR) indicated that one company uses Sodium Sulfate at 0.5% in facial toner and lotion, 3.5% in liquid bubble bath, 82.0% in powder bubble bath, and 96.3% in bath powder (CTFA 1996a). Another company

TABLE 1
Properties of Sodium Sulfate

Property	Characteristic	Reference
Molecular weight	142.04 Da (anhydrous) 322.20 Da (decahydrate)	Budavari 1989; Sax 1979; Lewis 1993a
Appearance	White crystals or powder, odorless (anhydrous)	Sax 1979
Melting point	888°C (anhydrous) 33°C (decahydrate)	Sax 1979; Lewis 1993b
Density	2.671 (anhydrous) 1.46 (decahydrate)	Sax 1979; Lewis 1993a Budavari 1989
Solubility	Soluble: water, glycerin Insoluble: alcohol	Sax 1979; Lewis 1993a

reported use at 1% to 5% in liquid hand soap and body wash soap, and 0.1% to 1% in shampoos (CTFA 1996b).

International

Sodium Sulfate is listed in the *Comprehensive Licensing Standards of Cosmetics by Category (CLS)*. Sodium Sulfate, which conforms to the specifications of the *Japanese Standards of Food Additives* and/or the *Japanese Standards of Cosmetic Ingredients*, has precedent for unrestricted use in all CLS cosmetic categories except eyeliners for which there has been no use precedence. Sodium Sulfate, anhydrous, which conforms to the standards of the *Japanese Cosmetic Ingredient Codex* has precedent for unrestricted use in all CLS categories except eyeliners and lip and oral preparations (Rempe and Santucci 1997).

Noncosmetic

Sodium Sulfate is recognized as a GRAS ingredient (FDA 1980; Rothschild 1990). Its use as a food additive is not restricted by the World Health Organization's (WHO) Joint Expert Committee on Food Additives (JECFA), except that intake is limited by its laxative action (FAO/WHO 1994).

TABLE 2
Frequency of use of Sodium Sulfate (FDA 1997)

Product category	No. formulations in category	No. containing Sodium Sulfate
Bath oil, tablets, and salts	117	1
Bubble baths	186	11
Bath soaps and detergents	341	1
Cleansing	630	2
Body and hand (excluding shaving)	776	3
Moisturizing	743	5
Night	185	1
Skin fresheners	181	1
Other skin care preparations	683	3
1997 total		**28**

GENERAL BIOLOGY

Absorption, Distribution, Metabolism, Excretion

Human absorption, distribution, metabolism and excretion studies are reported in the Clinical Assessment of Safety section of this report.

Oral

Krijgsheld et al. (1979) used male Wistar rats (300–330 g body weight [bw]) to investigate the absorption of inorganic sulfate following oral administration of $Na_2{}^{35}SO_4$. One set of animals had a permanent catheter placed in the right atrium to collect blood samples. The samples were analyzed by liquid scintillation to determine plasma ^{35}S concentrations. Groups of six animals were dosed under light anesthesia by gastric tube with 600 μCi/kg bw $Na_2{}^{35}SO_4$ in 2 ml water. One group received only the tracer dose. Another two groups received, in addition to the tracer, either 1.0 or 5.0 mmol nonradioactive Na_2SO_4. Feed and water were provided ad libitum.

Radioactivity was detected in the plasma 15 minutes after administration of the tracer dose. A peak activity of >4000 cpm was reached 1.5 to 2 hours following administration. By 10 hours, 50% of the maximum plasma concentration remained; by 19 hours only 10% of the maximum plasma radioactivity remained. In animals that also received nonradioactive Sodium Sulfate, the peak radioactivity was again reached at 1.5 to 2 hours post administration. However, the amount of radioactivity in the plasma decreased as the dose of nonradioactive Sodium Sulfate increased, indicating that the "fractional absorption of (labeled) Sodium Sulfate decrease(d) as the administered dose increase(d)."

The urinary excretion of sodium sulfate was studied in a different group of rats (Krijgsheld et al. 1979). Animals were treated via a gastric tube with 50 μCi/kg bw $Na_2{}^{35}SO_4$ in 2 ml water to which was added either varying amounts of sodium

chloride or between 0.25 to 5.0 mmol nonradioactive Na_2SO_4. Control rats received water with sodium chloride added. The rats were placed in metabolic cages and urine was collected for as long as 7 days following oral sulfate administration. Rats that received the two high sulfate doses (2.5 and 5.0 mmol) developed diarrhea that started 4 hours after administration and lasted for 4 hours; removal of the feces thus resulted in some loss of urine. Blood samples from the aorta were obtained 2 hours after oral administration from rats dosed with 0.5, 2.5, or 5.0 mmol Na_2SO_4 and were analyzed for sulfate concentration.

When the radioactive Sodium Sulfate was administered with either saline or the two lowest doses of nonradioactive Sodium Sulfate (0.25 or 0.5 mmol), about 90% of the administered dose was recovered in the urine within 24 hours. (The researchers attributed the remaining 10% to incorporation into unidentified macromolecules in the body.) When the amount of nonradioactive Sodium Sulfate was increased to 1.0, 2.5, and 5.0 mmol/rat, the percentage of radioactivity recovered in the 24-hour urine decreased to 73%, 67%, and 56%, respectively. Serum sulfate concentrations of 1.34, 1.95 and 2.13 mmol/L were found in blood samples from animals dosed with 0.5, 2.5, or 5.0 mmol nonradioactive Sodium Sulfate, respectively. Corresponding untreated controls had serum sulfate concentrations of 0.77 mmol/L, whereas those animals treated with varying amounts of sodium chloride and water (vehicle control) had concentrations between 0.57 and 0.66 mmol/L.

Its detection in the plasma soon after administration and the urinary excretion of 90% of the administered radioactivity within 24 hours (when low doses of nonradioactive sulfate were also added), indicating almost complete absorption of the dose from the gut. The researchers considered that orally administered Sodium Sulfate was rapidly absorbed in rats.

The results of Krijgsheld et al. (1979) corroborated those reported by Hwang (1966) in which 57% to 74% of an orally administered dose of 2800 mg/kg $Na_2{}^{35}SO_4$ was recovered in the 24-hour urine of four rats.

Parenteral

Dziewiatkowski (1949) conducted a study in which 1 mg $Na_2{}^{35}SO_4$ was administered intraperitoneally (IP) to 14 male and 13 female adult rats (180–330 g). Animals were killed at various times postdosing and tissue samples were collected. Approximately 67% of the administered ^{35}S was excreted in the urine within 24 hours. By 120 hours, 85% was recovered in the urine; when fecal excretion was included, 95% of the administered dose had been recovered. Rapid elimination was noted in the blood, liver, and brain with almost complete elimination by 48 hours. However, a notable rise in the ^{35}S concentration was noted at 8 hours in bone and at 24 hours in bone marrow. Elimination was slow in these two tissue samples with significant concentrations noted 120 hours after administration.

Odeblad and Boström (1952) used autoradiography to measure the incorporation of ^{35}S Sodium Sulfate into different organs of rats and rabbits. Five adult rats (200 g) received subcutaneous (SC) injections of 100 μCi ^{35}S as "carrier free" Na_2SO_4 diluted with 0.1 mg nonradioactive Na_2SO_4 in 0.2 ml distilled water/100 g bw. One adult rabbit was injected with 2.0 mCi ^{35}S as Na_2SO_4 in 4 ml of distilled water, containing 0.2 mg carrier. All animals were killed 48 hours after dosing and various organs were removed. In rats, "very large amounts" of radioactivity were detected in the epithelium of the esophagus and ileum, in the cornea, and in the cartilage of the trachea. In the rabbit, "large amounts" of radioactivity were detected in the tunica intima and tunica media of the aorta, and in the respiratory epithelium and cartilage plates of the lungs. The researchers considered ^{35}S to be taken up by tissues where sulfomucopolysaccharides are present.

Boström and Aqvist (1952) reported that $Na_2{}^{35}SO_4$ administered IP to rats was incorporated in small amounts into the chondroitin sulfuric acid of the costal cartilage within 24 hours, and in trace amounts into taurine isolated from the liver within 8 hours. The researchers reported that the exogenous sulfate was not incorporated into methionine or cysteine. Exogenous sulfate was taken up primarily into mucopolysaccharides.

In a study by Dohlman (1957), $Na_2{}^{35}SO_4$ was administered intravenously (IV) to rabbits which were then killed at various times postdosing; eyeballs were enucleated and analyzed for radioactive sulfur content. The radioactive sulfur was rapidly taken up by the eyeball with high concentrations being detected in the uvea. Turnover rates were also high in the uvea but slow in the cornea and lens. By day 3 after dosing, concentrations remained high in the inner layers of the cornea and sclera but were low in the uvea, retina, and the pia and dura of the optic nerve head. No radioactivity was detected within the aqueous humor or vitreous body.

$Na_2{}^{35}SO_4$ was injected into the femoral artery of a dog (Balchum, Dybicki, and Meneely 1960). After 100 minutes, 0.6% was retained in the trachea, 0.2% in the lungs, 4.6% in the liver, 0.26% in the spleen, 0.3% in the kidneys, and 0.6% in the brain.

Effects on Enzymes and Serum Parameters

Intravenous injection of Sodium Sulfate at <400 mg/L of blood into a 15-kg dog increased biliary volume and biliary salt excretion twofold (Chabrol and Maximin 1929).

Sodium Sulfate injected intravenously at 175 mg/kg into a rabbit produced a 22% drop in serum calcium concentrations in 4 hours. Inorganic phosphorus concentrations were decreased by 34% at 1.75 hours, but returned to normal at 4 hours. No changes were noted in the serum magnesium concentration (Brookfield 1934).

Fasted and fed female Golden labradors were infused with 3 parts of 5% creatinine and 2 parts of Sodium Sulfate (50 mM) at rates of 0.75 and 1.0 ml/min. The glomerular filtration rate was increased by 30% to 50% over initial values in fasted dogs. Sodium Sulfate administration increased the phosphate-filtered

load as measured from heparinized plasma; this effect was not noted when 5% creatinine alone was administered (Foulks 1955).

Kowarski, Kowarski, and Berman (1961) demonstrated that the addition of 1% Sodium Sulfate to milk fed to rats decreased calcium ionization and reduced calcium absorption from the gut. Calcium retention was reduced by 50%.

Duhm, Deuticke, and Gerlach (1969) reported that the addition of Sulfate to cultures of human erythrocytes in plasma inhibited, by almost 80%, the spontaneous degradation of 2,3-diphosphoglycerate. This effect of Sulfate was also noted in erythrocytes incubated in glucose-free media and in hemolysates under conditions in which no synthesis of 2,3-diphosphoglycerate occurred. High 2,3-diphosphoglycerate concentrations in vivo reduced the affinity of hemoglobin for oxygen and thus favored the release of oxygen in tissues.

Drug Interaction

Acetaminophen

Slattery and Levy (1977) reported that Sodium Sulfate increased the LD_{50} of IP acetaminophen in Swiss mice from 425 to 575 mg/kg. Groups of 10 mice (25–30 g) had received single IP injections of 300 to 800 mg/kg acetaminophen together with an equimolar amount of Sodium Sulfate. (Control groups received acetaminophen with varying amounts of sodium chloride.)

In a follow-up study using Sprague-Dawley rats, Galinsky, Slattery, and Levy (1979) demonstrated that plasma acetaminophen concentrations decreased and plasma acetaminophen sulfate concentrations increased more rapidly in Sodium Sulfate–treated rats as compared to controls that were given an identical amount of sodium in the form of sodium chloride. The researchers considered that the decreased acetaminophen toxicity caused by Sodium Sulfate dosing was due to accelerated elimination of acetaminophen. Similarly, Lin and Levy (1986) reported that concomitant administration of inorganic sulfate (delivered as Sodium Sulfate) to Sprague-Dawley rats increased by 1.5-fold the total clearance of large doses of acetaminophen (300 mg/kg), and increased by twofold the fraction of that dose eliminated as acetaminophen sulfate, when compared to rats that had not received supplemental sulfate. Clearance was limited by the activity of sulfotransferase enzymes that are responsible for acetaminophen sulfate formation.

Subsequent studies by Hjelle, Brzeznicka, and Klaassen (1986) using adult male CF-1 mice found that administration of either Sodium Sulfate (4 mmol/kg) or *N*-acetylcysteine (NAC) increased serum sulfate and hepatic adenosine 3′-phosphate 5′-phosphosulfate concentrations. The mice (23–32 g) received IP doses of 400 or 600 mg/kg acetaminophen (2.5 and 4 mmol/kg) dissolved in either Sodium Sulfate or NAC vehicle. No significant change in acetaminophen sulfation or elimination was noted with administration of NAC or Sodium Sulfate. However, unlike NAC, Sodium Sulfate did not attenuate the marked decrease in glutathione in the liver observed after acetaminophen administration. Also, NAC decreased covalent binding of tritium derived from [3H]-acetaminophen to liver protein. Sodium Sulfate did not. Sodium Sulfate did not protect against acetaminophen-induced hepatotoxicity whereas lethality was reduced in NAC-treated animals.

Selenium

Groups of five weanling Sprague-Dawley rats were fed diets containing 500 and 1000 mg Sodium Sulfate/kg feed in conjunction with 5, 10, and 20 mg Se/kg feed. Mortality was 60% and 100% in mice treated with 10 and 20 mg selenium, respectively, regardless of the Sodium Sulfate dosage; no deaths were found in the 0 and 5 mg selenium groups. The concurrent treatment with Sodium Sulfate did not significantly alter the course of selenite toxicity (i.e., feed intake, daily weight gain, testis weight, hepatic hemorrhage and necrosis, renal necrosis, arrested spermatogenesis). The main effect of the SO_4 was increased liver copper concentrations (Kezhou et al. 1987).

Effect on DDT Absorption

A group of six male Sprague-Dawley rats (230–330 g) was treated via feeding tube with 80 mg/kg ^{14}C-DDT in a volume of 10 ml/kg of cathartic (15% Sodium Sulfate containing 20% acacia). One hour later each rat received a second dose of the Sodium Sulfate cathartic without DDT at the rate of 10 ml/kg. A second dose of DDT with cathartic was given after 24 hours. A control group of rats was treated with distilled water containing 20% acacia. Feces and urine were collected during the experiment and analyzed for radioactivity by liquid scintillation. Rats were killed 24 hours after the second dose of DDT. Perirenal and peritesticular adipose tissue samples were collected and analyzed by gas chromatography. Although the difference was not of statistical significance, all Sodium Sulfate–treated rats had adipose DDT concentrations (95 ppm) below the control group (137 ppm). Once the values were corrected for contamination of urine with loose feces (resulting from Sodium Sulfate treatment), the liquid scintillation values corresponded with the adipose tissue measurements. It was estimated that 60.8% of the administered DDT was recovered in the feces of the Sodium Sulfate group rats versus 57.5% for the control rats (Keller and Yeary 1980).

ANIMAL TOXICOLOGY

Short-Term Oral Toxicity

A group of six weanling male Sprague-Dawley rats fed either 0.88, 8.64, or 138 mmol Sodium Sulfate/kg basal diet for up to 4 weeks had no significant differences in weight gain, feed intake, feed-gain ratio, or water intake as compared to control rats. Hemoglobin, red blood cell count, white blood cell count, serum protein, alkaline phosphatase, and inorganic phosphate concentrations were also comparable to values for the control group. No changes were observed in gastrointestinal organ weights or

in the length or color of the small intestine (Moinuddin and Lee 1960).

Acute Inhalation Toxicity

Amdur et al. (1978) found no adverse pulmonary effects in 10 guinea pigs exposed for 1 hour to 0.90 mg/m^3 Sodium Sulfate (particle size 0.1 μm). No change in resistance was noted. A slight decrease in compliance was observed; it was not statistically significant. Sodium Sulfate was the least irritating of the sulfate aerosols tested (ranked in decreasing order: ammonium sulfate > ammonium bisulfate > copper sulfate > sodium sulfate).

Sackner et al. (1981) performed a variety of studies to investigate the effects of sulfate aerosols on cardiopulmonary function in dogs and tracheal mucous velocity of sheep. In the studies described below, statistical analysis compared the response to sulfates against the response to sodium chloride (control).

In a brief exposure study, five intubated anesthetized dogs breathed aerosol generated from a 0.1% Sodium Sulfate solution (particle size 0.1–0.2 μm) for 7.5 minutes. The aerosol generated had a mass concentration of 1.0 mg/m^3. Measurements of lung volume and mechanics were made before exposure and at 5, 15, 30, 60, 120, and 180 minutes after exposure termination. After completion of the final measurements, the animals were exposed for 7.5 minutes to aerosol generated from a 1.0% Sodium Sulfate solution (particle size 0.1–0.2 μm). This aerosol had a mass concentration of 8.0 mg/m^3. Lung mechanics measurements were made at 5, 15, and 30 minutes following termination of the second exposure. No significant alterations in total respiratory resistance, static lung compliance, functional residual capacity, specific total respiratory conductance, and specific lung compliance were noted in the animals exposed to Sodium Sulfate.

In an intermediate exposure study, five intubated anesthetized dogs breathed aerosols generated from 0.5% Sodium Sulfate solution for 4 hours. The aerosol had a mass concentration of 5.0 mg/m^3. Measurements of lung volume, breathing mechanics, and hemodynamics were made before, hourly during, and for 2 hours after exposure. "No significant alterations" were noted (Sackner et al. 1981).

In studies of tracheal mucous velocity, Sackner et al. (1981) exposed six sheep for 20 minutes to aerosol generated from a 0.1% Sodium Sulfate solution. (The solutions used in the sheep study had the same particle size and mass concentration as described in the dog studies.) No significant change was noted in tracheal mucous velocity measurements taken at 30, 60, 120, and 180 minutes after exposure termination when compared to baseline values. The exposure did not significantly alter tracheal mucous velocity. In a second study, five sheep were exposed for 4 hours to an aerosol generated from a 0.5% solution of Sodium Sulfate. Measurements made before, at the end of, and 2 hours after termination of exposure produced tracheal mucous velocity values of 14.3, 11.9, and 12.0 mm/min, respectively. The differences in the values were not statistically significant.

In a study by Schlesinger (1984) comparing the irritancy potential of inhaled sulfate aerosols, the following ranking was determined: sulfuric acid > ammonium bisulfate > ammonium sulfate, (equivocal to) Sodium Sulfate. Five rabbits had been exposed for 1 hour to a maximum concentration of almost 2000 μg/m^3 Sodium Sulfate aerosol and measurements were made of bronchial mucociliary clearance. No significant adverse effects were reported.

Acute Parenteral Toxicity

In addition to the inhalation studies described in the earlier section, Sackner et al. (1981) also performed intravenous studies in which anesthetized dogs were injected with 1 mg of Sodium Sulfate in 10 ml sterile water. Measurements of breathing mechanics, functional residual capacity, pulmonary and carotid arterial pressures, cardiac output and arterial blood gases were done at 15, 30, 45, and 60 minutes following the IV injection. After the final measurement was taken, 10 mg Sodium Sulfate in 10 ml water was injected and the same parameters were again measured. Finally, 100 mg Sodium Sulfate in 10 ml water was injected and the same parameters at the same time intervals were measured again. A nondose dependent alteration in pulmonary function was noted. Specifically, 10 mg Sodium Sulfate, "produced a maximal fall in specific lung compliance of 11% 15 minutes after injection ($p < .05$)". This effect was not noted with either the 1 or 100 mg dose. The 10 mg dose of Sodium Sulfate also produced a, "rise in cardiac output of 11% at 60 minutes and a maximum increase of stroke volume of 22% at 45 minutes after injection ($p < .05$)." No significant hemodynamic changes resulted from the 1 or 100 mg dose.

Ocular Irritation/Toxicity

Griffith et al. (1980) classified a sodium carbonate–Sodium Sulfate granular mixture (1:1 *w/w*) as causing moderate ocular irritation. The test material was applied directly to one cornea of three albino rabbits at volumes of 0.01, 0.03, and 0.1 ml. Irritation was graded on days 1, 2, 3, 4, 7, and 14 following treatment. The reactions were scored using the Draize scale that allows a maximum score of 110. The average maximum scores noted were 11, 17, and 36 for the 0.01, 0.03, and 0.1 ml doses, respectively. These reactions took between 4 and 21 days to return to normal.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

In validation of an in vivo developmental toxicity screen, Seidenberg, Anderson, and Becker (1986) administered various chemicals to pregnant ICR/SIM mice (32–36 g) by oral intubation on days 8 through 12 of gestation. Sodium Sulfate, 2,800 mg/kg/day, was administered in a water vehicle to 28 mice. Animals were housed individually; feed and water were available ad libitum. Mice were weighed on days 7 and 13 to

determine maternal weight gain. The dams were allowed to deliver and neonates were examined, counted, and weighed on the day of birth and day 3. No maternal toxicity was observed in the Sodium Sulfate dose group; average weight gain was 8.6 g (compared to 8.5 g for nontreated controls that had received water via intubation). The Sodium Sulfate group had 24 litters with no resorptions (control had 25 with no resorptions). Survival of neonates was 100% between days 1and 3 in the Sodium Sulfate group. The average neonatal weight at birth for the Sodium Sulfate group (1.80 g) was significantly greater than that for control neonates (1.72 g; $p < .05$, assessed by a two-tailed analysis for variance). By day 3, neonates of the Sodium Sulfate group had an average weight of 2.58 g compared to 2.42 g for control neonates.

In a subsequent publication discussing the validity of the above described developmental screen, Seidenberg and Becker (1987) considered the slight but significant increase in neonatal body weight on day 1 to be a positive result for Sodium Sulfate. However, in outlining the protocol for the screen, it was stressed that "overt maternal toxicity is required"; such a dose was not reached in the Sodium Sulfate group. The researchers admitted, "a teratogen may produce a positive response in the developmental toxicity screen without inducing overt toxicity in dams." However, noting the lack of published teratogenic data via the oral route for Sodium Sulfate, the researchers were unable to interpret whether the results were valid or a false positive.

Parenteral

Sodium Sulfate induced a low incidence (6%) of skeletal anomalies in mice when injected subcutaneously on a single day of gestation (Arcuri and Gautieri, 1973).

Knight, Van Wart, and Roe (1978) studied the effects of salicylamide on the sequential uptake and loss of radiosulfate by maternal and fetal rat tissue. On day 17 of gestation, a control group of 24 pregnant Holtzman rats (230–250 g), maintained since gestation day 6 on a 25% casein diet, was injected intramuscularly with $Na_2{}^{35}SO_4$ at a dose of 25 μCi/100 g bw ($Na_2{}^{35}SO_4$ in water, 100 μCi/ml). (The experimental groups, which had been maintained on casein diets supplemented with varying amounts of salicylamide, also received an injection of Sodium Sulfate on day 17.) Dams were killed sequentially at intervals up to 24 hours postinjection. A blood sample was obtained at the time of killing, the maternal liver was extracted, and fetuses were grossly examined. Homogenates of each fetus and placenta, as well as maternal liver and serum, were analyzed by a scintillation counter. No malformations were noted in any of the 108 fetuses of the control group; there were six (5.55%) resorptions. In control rats, the uptake and retention of radiosulfate per unit weight of placenta or per placenta varied inversely with the number of placentas per dam or the placental weight. Uptake by the fetus was maximal after 2 hours, followed by a rapid decline in the following hour; the loss rate was slow. Uptake by the fetus was significantly correlated with maternal serum concentrations.

GENOTOXICITY

Sodium Sulfate at concentrations up to 275 μg/well was negative in the microscreen assay (Rossman et al. 1991). The assay measures prophage induction into *Escherichia coli* as an indicator of DNA damage to the bacteria.

Sodium Sulfate was among several salts tested for enhanced transformation of Syrian hamster embryo cells (HEC) by a simian adenovirus, SA7. A concentration of 7.0 mM Sodium Sulfate produced an enhancement 1.2 times that of the untreated control. (The enhancement was expressed as the ratio between the transforming frequency of treated, surviving cells and the transforming frequency of control cells.) The results for Sodium Sulfate were considered negative as a concentration >0.9 mM was necessary to produce the effect (Casto, Meyers, and Dipaolo 1979).

COCARCINOGENICITY

Yamamoto et al. (1973) explored whether supplemental administration of Sodium Sulfate would restore the carcinogenicity of *N*-hydroxy-*N*-2-fluorenylacetamide (*N*-OH-FAA) despite the presence of the inhibitor *p*-hydroxyacetanilide. Groups of rats were maintained for 16 weeks on feed containing: (1) 0.0213% (0.89 mmole/kg) *N*-OH-FAA; (2) carcinogen plus 0.89% (59 mmoles/kg) *p*-hydroxyacetanilide (a 66 molar excess); or (3) carcinogen plus inhibitor plus 2.52% (178 mmoles/kg, 3 molar equivalents) Sodium Sulfate. Following dosing, animals were maintained on untreated feed for an additional 10 weeks. Animals were killed at the end of the experiment and necropsy performed. Three animals from each group were housed in metabolism cages; urine was collected separately over a 24-hour period and analyzed for inorganic sulfate. Hepatomas were observed in all 10 animals of group 1, in four of the 20 rats of group 2, and in none of the 20 animals of group 3. Further, hyperplastic nodules were neither observed in four animals from group 2 nor in 11 animals from group 3. Sodium Sulfate appeared to inhibit the carcinogenicity of *N*-OH-FAA or increase the inhibitory affect of *p*-hydroxyacetanilide.

A second experiment was conducted by Yamamoto et al. (1973) using a higher dose (0.032%, 1.34 mmoles/kg) of *N*-OH-FAA as well as one-third the Sodium Sulfate amount of the above described study (0.84%, 59 mmoles/kg, 1 molar equivalent). Again rats were maintained for 16 weeks on treated feed followed, this time, by an additional 16 weeks on control feed. Hepatomas were noted in all 5 animals that received the carcinogen alone, in 6 of 12 animals that received the carcinogen plus inhibitor, in 5 of 6 animals that received the carcinogen, inhibitor, and 1 equivalent of dietary Sodium Sulfate, and in 4 of 12 animals that received the carcinogen, inhibitor plus 3 equivalents of Sodium Sulfate. With the greater amount of carcinogen used in this second study, Sodium Sulfate had no additional effect on the actions of *p*-hydroxyacetanilide.

Animals that received the carcinogen alone excreted free sulfate in the urine, whereas in animals that also received *p*-hydroxyacetanilide the sulfate was mostly conjugated. Groups

that also received 1 or 3 equivalents of Sodium Sulfate had greater concentrations of total and free urinary sulfate (Yamamoto et al. 1973).

Blunck and Crowther (1975) studied the Sodium Sulfate activation of the carcinogen (and azo dye) 3′-methyl-4-dimethylaminoazobenzine (MeDAB). Groups of 15 male Sprague-Dawley rats were fed for 16 weeks diets containing either 0.06% MeDAB or 0.06% MeDAB plus 0.84% Sodium Sulfate. Another group of five rats received feed containing only 0.84% Sodium Sulfate. The amount of feed available was restricted to that of the cage of rats consuming the least (approximately 10 g/rat/day for the first 2 weeks, then gradually increased to 17 g/rat/day by week 27). Rats had free access to tap water. After the treatment, the animals were fed a basal diet for 8 weeks. At this time, two rats from the MeDAB-dosed groups and one from the Sodium Sulfate–alone group were killed and the livers examined. The remaining rats were returned to their respective treatment diets for several 4-week periods, with a week between each period, during which they were fed basal diet. The study was terminated after 41 weeks. In a delayed-start second experiment, groups of five rats were maintained on the same dosing protocol as described for a total of 27 weeks. Pooling the results of the two experiments, 16 of the 20 rats given MeDAB, 18 of the 20 given MeDAB and Sodium Sulfate, and all 10 rats given Sodium Sulfate survived the initial 16-week dosing. At the end of the study, rats were killed and the livers examined. It was noted that Sodium Sulfate shortened the latent period (from 27 to 17 weeks), but did not affect the rate of neoplasm development. In addition, the relative risks of developing multiple neoplasms and metastatic neoplasms were increased with Sodium Sulfate supplementation. No liver abnormalities were noted in rats of the Sodium Sulfate alone or basal diet (control) groups.

Cohen and Bryan (1978) reported coadministration of Sodium Sulfate with the inhibitor *p*-hydroxyacetanilide (at an equimolar ratio with Sodium Sulfate) partially restored the leukemogenicity of *N*-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA) in mice. Female Swiss mice were maintained for 14 weeks on the following diets: (1) 0.05% NFTA alone; (2) NFTA plus *p*-hydroxyacetanilide; (3) NFTA, *p*-hydroxyacetanilide and Sodium Sulfate; (4) NFTA plus Sodium Sulfate; or (5) *p*-hydroxyacetanilide plus Sodium Sulfate. Treatment was followed by 16 weeks of control diet. A control group of 30 mice was fed a diet containing 1.88% Sodium Sulfate for 1.5 weeks and then the concentration was reduced to 0.94% Sodium Sulfate for the remaining 12.5 weeks. (The Sodium Sulfate dose was reduced so as to remain equimolar with the dose of *p*-hydroxyacetanilide that had to be halved due to toxicity.) An identical amount/protocol for Sodium Sulfate administration was used for mice of the respective treatment groups.

Leukemia was noted in 19 of 25 surviving animals of the NFTA group, in 3 of 23 animals of the NFTA plus *p*-hydroxyacetanilide group, in 20 of 24 animals of the NFTA plus Sodium Sulfate group, and in 12 of 25 of animals of the NFTA, *p*-hydroxy-acetanilide, plus Sodium Sulfate group. Mean cumulative chemical consumption for the Sodium Sulfate control group was 6.5 g/mouse. Twenty-five mice of this group survived to week 10. After a 30-week latent period, one animal of the control group developed leukemia. Papillomas of the stomach were not observed in the Sodium Sulfate control group (two were noted in the group receiving NFTA alone, and four in the group receiving NFTA plus Sodium Sulfate). Similar observations were noted in animals that received *p*-hydroxyacetanilide plus Sodium Sulfate; the only exception was that leukemia (in 1 of 19 animals) was noted after an 18-week latent period (Cohen and Bryan 1978).

Samelson, Nelson, and Nyhus (1985) reported that Sprague-Dawley rats with acid stool pH, produced by consumption of Sodium Sulfate had significantly ($p < .05$) fewer colon tumors was injections of dimethylhydrazine (DMH) than rats treated with DMH alone. A group of 23 rats was fed a diet supplemented with 50 mg Sodium Sulfate/20 g pellet. After 4 weeks of this diet, weekly SC injections of DMH base (15 mg/kg) were given to all rats for 16 weeks. Animals were killed 8 weeks after the last injection. The final number of colon tumors was as follows: no tumors in the untreated control group; 77 tumors in the group receiving DMH alone; and, 53 tumors in the group receiving Sodium Sulfate and DMH. A mean score of 3.5 tumors/rat was observed for the DMH-alone group and a mean of 2.3 tumors/rat was found for the Sodium Sulfate plus DMH group.

CLINICAL ASSESSMENT OF SAFETY

Absorption, Distribution, Metabolism, Excretion

Oral

Cocchetto and Levy (1981) investigated absorption of Sodium Sulfate in humans as measured by recovery of free sulfate in the urine. Five healthy males (66–79 kg bw) were orally dosed with 18.1 g of decahydrate Sodium Sulfate (56.3 mmol, equivalent to 8.0 g of the anhydrous salt), in either a single dose or four equally divided hourly doses. (The Sodium Sulfate was dissolved in 50 ml of warm water and ingested following a low-fat breakfast.) With a minimum of 1 week between treatments, the dosing protocol was repeated but reversed and those who had previously received a single dose now received the divided doses and vice versa. Urine was collected over 0 to 24, 24 to 48, and 48 to 72 hour periods. All subjects experienced severe diarrhea following the single dose of Sodium Sulfate, starting 2 hours following ingestion and lasting up to 24 hours. Panelists who received divided dosings experienced mild to no diarrhea.

The baseline individual average excretion rate of inorganic sulfate (determined by collection of three 24-hour urine samples prior to sulfate treatment) ranged from 13 to 25 mmol/24 h with the two individuals with the lowest body weights having the lowest baseline values. Although the baseline excretion of free sulfate was unaffected by changes in urine flow rate, the baseline excretion rate of total sulfate (including organically bound sulfate) increased almost linearly with increasing flow rate. This effect was also observed following sulfate administration.

Following Sodium Sulfate administration, the cumulative amounts of free sulfate excreted in the 24-, 48-, and 72-hour urine were significantly greater than the amount of free sulfate excreted in the same time periods in control experiments ($p < .01$). On average, 24 hours postdosing, 36.4% of the sulfate administered in a single dose (standard deviation [*SD*] 15.4%) and 43.5% of the divided dose (*SD* 12.0%) had been recovered. By 48 hours, an average of 49.5% of the single (*SD* 15.6%) and 53.1% of the divided dose (*SD* 7.5%) had been recovered. And by 72 hours, 53.4% of the sulfate administered in the single dose (*SD* 15.8%) and 61.8% administered in the divided dose (*SD* 7.8%) was recovered. The researchers noted "considerably less inter-individual variation" in urinary recovery of free sulfate following the divided dose.

A subsequent study by Morris and Levy (1983) in which eight panelists (six males, two females) ingested 9 g Sodium Sulfate (decahydrate) within a 1-hour period resulted in increased serum inorganic sulfate concentrations. The mean values were 0.410 mM prior to Sodium Sulfate intake, and 0.513 mM following ingestion of the test material ($p < .001$). Urinary excretion of inorganic sulfate also increased after ingestion of Sodium Sulfate. The renal clearance of endogenous creatinine was not affected.

Intravenous

Six normal human panelists received a 1-L infusion of 4% Sodium Sulfate, resulting in a decrease of urinary pH from 6.05 to 4.32 with a doubling of ammonia and titratable acid excretion. In 10 patients with renal disease and normal serum bicarbonate concentrations (>25.1 meq/L), the infusion resulted in a rise of urine pH without a change in ammonia or titratable acid excretion. Therefore, net acid excretion fell. In the same 10 patients with renal disease but with serum bicarbonate concentrations below 20 meq/L, the Sodium Sulfate infusion produced results similar to those in the six normal patients (Seldin et al. 1967).

Six males (aged 55–70 years) with normal renal function received an IV dose of 1.1 Mbq (30 μCi) radioactive Sodium Sulfate and collected urine for 72 hours. By 24 hours, 88% of the $Na_2{}^{35}SO_4$ dose was excreted in the urine; 87% was excreted by 72 hours. Heparinized blood samples were collected from another two panelists (one of each sex) every minute for the first 15 minutes after injection, and then every 15 minutes until 3 hours following injection. By extrapolating the early phase of the plasma disappearance curve, the researchers predicted that 1% to 2% of the administered Sodium Sulfate remained in the plasma 24 hours after injection (Burke and Staddon 1983).

Effect on Drug Absorption

Acetaminophen

Eight healthy adults received on separate occasions, 1 g acetaminophen; 1 g acetaminophen and 18 g Sodium Sulfate (decahydrate); 1 g acetaminophen and 10 g activated charcoal; and 1 g acetaminophen and 10 g activated charcoal and 18 g Sodium Sulfate, in random order. The Sodium Sulfate was administered such that at zero time, 4.5 g Sodium Sulfate USP was ingested in 50 ml water, followed by 4.5 g in 100 ml water at 2, 4, and 6 hours. Urine was collected for 48 hours and analyzed for acetaminophen, its metabolites, and inorganic sulfate. The panelists tolerated the various treatments well, except for instances of loose stools following Sodium Sulfate ingestion. Sodium Sulfate did not interfere with the absorption of acetaminophen by charcoal and, likewise, charcoal did not affect the absorption of Sodium Sulfate. Sodium Sulfate did not increase the formation of acetaminophen sulfate. This finding was consistent with expectations as the researchers noted administration of inorganic sulfate increases acetaminophen sulfation only when endogenous sulfate supplies are markedly depleted (i.e., very large doses of acetaminophen would be needed). The researchers considered that a combination of activated charcoal and Sodium Sulfate can be useful in the treatment of acetaminophen overdose (Galinsky and Levy 1984).

Other Drugs

Mattila, Takki, and Jussila (1974) reported that ingestion of 20 g Sodium Sulfate as two 10-g doses, 30 minutes apart resulted in diarrhea in 11 healthy panelists. Isoniazid (INH) was given with the first dose and sulfafurazole and acetylsalicylic acid were given with the second dose. Blood samples were taken at 30 minutes after the first dose (just prior to ingestion of the second dose) and at 30, 60, 120, and 240 minutes following the second dose. A control study had been conducted 3 days prior in which the drugs were administered following the same protocol but without Sodium Sulfate. Sodium Sulfate reduced serum concentrations and urinary excretion of INH and reduced the absorption rate and urinary excretion of sulfafurazole. The absorption of acetylsalicylic acid from a slow-release tablet was unaffected. The absorption of acetylsalicylic acid was slightly reduced in seven panelists when a single dose of Sodium Sulfate was administered.

Campbell et al. (1985) studied the effect(s) of Sodium Sulfate ingestion on methyldopa metabolism. Twenty-four panelists were randomized to ingest either 13.24 mg/kg Sodium Sulfate with 3.5 mg/kg methyldopa powder or methyldopa alone. One week later, the subjects were given the alternate treatment. Urine was collected for 24 hours following dosing. Sodium Sulfate ingestion increased the concentration of methyldopa sulfate (from 50.1% to 66.0%) and decreased the concentration of free methyldopa (from 27.3% to 17.1%) in the urine. A positive correlation ($r = .545$, $p < .01$) between platelet phenol sulfotransferase (PST) activity and the percentage of drug excreted as methyldopa sulfate was noted with concurrent intake of methyldopa and Sodium Sulfate. This relationship was not noted when methyldopa was taken alone ($r = -.340$, $p > .10$). PST catalyzes the metabolism of methyldopa sulfation; 3′-phosphoadenosine-5′-phosphosulfate (PAPS) serves as the sulfate donor for the PST reaction. No gastrointestinal problems associated with Sodium Sulfate ingestion were noted.

Oral Toxicity

In a study to determine the role of fecal pH on the risk of colon cancer, 27 patients with a history of colonic polyps received a mean dose of 4 g/day of Sodium Sulfate for 14 days (Kashtan et al. 1990). A control group of 25 patients received placebo. The panelists were instructed to self-adjust the daily dose (not to exceed 6 g/day) such that two to three soft stools were produced each day. No adverse effects were noted.

Inhalation Toxicity

Sackner, Ford, and Kim (1979) exposed for 10 minutes five healthy and five asthmatic adults to 1, 2, and 3 mg/m^3 Sodium Sulfate aerosol with a mass median aerodynamic diameter (MMAD) of 0.5 μm. Respiratory parameters were measured for up to 1 hour following exposure. Mean values for the measured respiratory parameters were similar to the values obtained for exposure to equivalent amounts of sodium chloride (control). Two asthmatics had a 15% to 20% fall in forced exhalation volume (FEV_1); however, the response did not worsen with exposure to higher concentrations. In a subsequent experiment, six normal and six asthmatic adults were exposed for 10 minutes to 3 mg/m^3 Sodium Sulfate aerosol. Lung function measurements were made for 3 hours following exposure. Again, mean values for Sodium Sulfate when compared to sodium chloride indicated no adverse effect on pulmonary function. An immediate 15% to 20% fall in FEV_1 was noted in two of six asthmatics after breathing either Sodium Sulfate or sodium chloride.

Kelada and Euinton (1978) found no abnormality attributable to long-term occupational exposure to Sodium Sulfate dust in 119 workers from five sodium sulfate surface solution mines. Dust exposure concentrations ranged from <5 mg/m^3, 40 mg/m^3 in the main plant, and up to 150 mg/m^3 during loading of the final product. The workers had between 2 months to 31 years of exposure. The workers were not distinguishable from the general population with regards to parameters measured in the cardiorespiratory, gastrointestinal, or hepatorenal systems. Lung function, serum sulfate, calcium and electrolytes were within normal limits. There were no significant differences in the serum sulfate concentrations of workers with >10 years experience as compared to those from workers with <10 years experience.

Dermal Irritation

A single 24-hour occlusive patch containing an effective Sodium Sulfate concentration of 9.7% (10% aqueous solution of a bath bead formulation containing 97.0% Sodium Sulfate) was applied to 19 panelists. No reactions were noted in 18 panelists. One panelist had a reaction scored as ± (first nonzero grade on scale from 0 to 4±) (CTFA 1985).

An effective Sodium Sulfate concentration of 0.1168% (2% solution of a bar soap flake formulation containing 5.84% Sodium Sulfate) was applied in three 24-hour occlusive patches to the lateral arm of 13 panelists. Mild irritation (score 0.5–1.0: maximum possible score 4.00) was noted in 11 panelists. Of these, seven reacted to all three exposures, two reacted to the second and third exposure, and two reacted to the third patch only. The group average was 0.410 and the formulation was classified as mildly irritating (Hill Top Research Inc. 1989).

An effective Sodium Sulfate concentration of 1.8% was applied in a 4-hour patch on each of 4 days to 20 panelists. The test material was a children's powdered bubble bath and the exposure concentration was 200 times the expected consumer use level. Sites were scored after the fourth exposure. Thirteen panelists had no incidence of erythema and 11 had no incidence of dryness. Mild erythema and dryness (scored ±, the first nonzero grade) were noted in seven and eight panelists, respectively. Dryness in the twentieth panelist was scored 1 on a 0 to 2+ scale (CTFA 1990).

A 24-hour occlusive patch containing an effective Sodium Sulfate concentration of 0.004% (a 0.25% aqueous solution of a cleansing bar base containing 1.75% Sodium Sulfate) was applied to the back of 35 panelists on each of 21 consecutive days. Components of the formulation other than water included: sodium alkyl glyceryl sulfonate (10–60%), stearic acid (1–20%), lauric acid (1–15%), sodium lauroyl sarcosinate (1–10%), unsulfonated alcohols (1–8%), and sodium chloride (1–5%). Reactions were noted after various exposures in all panelists. Most reactions indicated moderate irritation (score 2 or 2.5 on a scale to 4). Mild to slightly irritating reactions (score between 0.5–1.0) and severely irritating reactions (score of 3) were noted in three panelists, respectively. The group mean score was 1.571 and the formulation was considered mildly irritating (Hill Top Research, Inc. 1985).

Dermal Sensitization

An effective Sodium Sulfate concentration of 1.01% (1.25% aqueous solution of a bubble bath containing 80.8% Sodium Sulfate) was tested in a repeated insult patch test on 61 panelists. The concentration tested was a 100-fold exaggeration of normal use levels. The first induction patch was left in place on the back for 48 hours and the remaining eight patches were applied for 24 hours of exposure. Every third patch (i.e., patches 1, 4, 7 and 2, 5, 8) was applied to the same site on the back. Following a 3-week nontreatment period, panelists were challenged on a previously unexposed site with a 48-hour patch. One panelist had a single incidence of mild erythema after exposure to induction patch 4. No reactions were observed at challenge (CTFA 1976).

SUMMARY

Sodium Sulfate is a GRAS ingredient that is used in cosmetic formulations as a viscosity increasing agent. In 1997 there were 28 reported cosmetic uses. Data from two sources indicated use at a variety of concentrations, with a maximum use of almost 97% in bath formulations. Sodium Sulfate is rapidly absorbed and excreted following oral intake.

No significant adverse effects were noted in rats following short-term oral dosing or in anesthetized dogs or conscious sheep following brief or intermediate inhalation exposures. A granular

sodium carbonate–Sodium Sulfate mixture produced moderate ocular irritation in rabbits.

No developmental changes were noted in rat fetuses whose dams had received an intramuscular injection of Sodium Sulfate on gestation day 17. An oral-dose study found increased neonate birth weight in fetuses of mice which had received Sodium Sulfate during gestation.

Sodium Sulfate was negative in mutagenicity assays. Results of various oral cocarcinogenicity assays were dependent on the carcinogen administered with Sodium Sulfate (and an inhibitor).

Clinical studies reported no significant adverse effects following oral or inhalation exposure to Sodium Sulfate. Mild-to-no irritation and no sensitization were noted in dermal studies that tested Sodium Sulfate–containing bath formulations at exaggerated-use concentrations and conditions.

DISCUSSION

In assessing the safety of Sodium Sulfate, the CIR Expert Panel relied on its GRAS status to preclude the need for many studies. Further, the submission of clinical dermal irritation and sensitization data by the cosmetics industry addressed the Panel's concerns about the lack of such studies in the published literature. The submitted data showed Sodium Sulfate induced no-to-mild irritation and no sensitization when tested in bath formulations. The Panel decided that these data were sufficient to conclude that Sodium Sulfate was safe as used in rinse-off formulations.

However, because some of these formulations produced irritation under patch test conditions, the Panel restricted the use of Sodium Sulfate in leave-on products. Results from a clinical sensitization study were considered particularly useful because the testing protocol specified repeated prolonged exposure. An induction period in which nine 24-hour insult patches containing 1.01% Sodium Sulfate were applied noted one isolated incidence of mild erythema in 1 of 61 panelists. The Panel rounded the figure to 1% to arrive at the limit for use in leave-on products.

CONCLUSION

Based on the available data, the CIR Expert panel concludes Sodium Sulfate to be safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.

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