
Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics

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date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

ABSTRACT

This is a safety assessment of Sodium Sulfate as used in cosmetics. Sodium Sulfate is reported to function in cosmetics as a viscosity increasing agent – aqueous. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed the relevant new data for the ingredient. The Panel relied on relevant new data, including concentration of use, and considered data from the previous CIR report. The Panel concluded that Sodium Sulfate is safe in cosmetics in the present practices of use and concentrations described in this safety assessment when formulated to be non-irritating.

INTRODUCTION

In 2000, the Panel published a safety assessment of Sodium Sulfate,¹ an ingredient that is reported in the *International Cosmetic Ingredient Dictionary and Handbook* to function as a viscosity increasing agent – aqueous in cosmetic formulations.² In the original safety assessment (published in 2000), the Panel determined that Sodium Sulfate is safe as used in rinse-off formulations and safe for use up to concentrations of 1% in leave-on formulations, based on the data presented in the safety assessment and the standing that Sodium Sulfate is Generally Recognized as Safe (GRAS) when used as an indirect food additive (21CFR186.1797).¹ The original safety assessment addressed both the anhydrous and decahydrate forms of Sodium Sulfate.

A current search of published literature revealed one journal article with relevant information³, which is summarized in this safety assessment (un-italicized text). For ease of comparison, *italicized text* throughout this report are data summarized from the original safety assessment. Additionally, updated frequency of use (2016) and updated concentration of use (2015-2016) data are reported here.

The original safety assessment is available at <http://www.cir-safety.org/ingredients>.

Report summaries and unpublished data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.⁴ The ECHA website provides summaries of information submitted by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Sodium Sulfate (CAS no. 7727-73-3 decahydrate; 7757-82-6 anhydrous) is the inorganic salt depicted in Figure 1.²

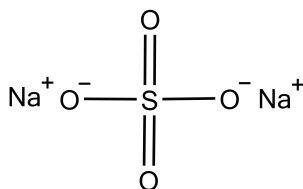


Figure 1. Sodium Sulfate

Chemical and Physical Properties

Sodium Sulfate (anhydrous) is odorless and has the appearance of white crystals or powder. The decahydrate form is hydrated with 10 equivalents of water per sulfate ion. The formula weight of the anhydrous form is 142.04 Da and of the decahydrate form is 322.19 Da. Sodium Sulfate is soluble in water and glycerin and insoluble in alcohol.

Method of Manufacture

*Neutralizing sulfuric acid with sodium hydroxide yields Sodium Sulfate.*¹

Impurities

According to United States Pharmacopeia's *Food Chemical Codex*, lead and selenium impurities are acceptable at not more than (NMT) 2 mg/kg (lead) and NMT 0.003% (selenium) in Sodium Sulfate used in food.⁵

Natural Occurrence

*In nature, Sodium Sulfate exists as the minerals thenardite and mirabilite.*¹

USE

Cosmetic

The safety of the cosmetic ingredient included in this assessment is evaluated based on the expected use and potential exposure of the ingredient in cosmetics. The Panel evaluates data received from the U.S. Food and Drug Administration (FDA) and from the cosmetics industry to determine the expected cosmetic use. The data received from the FDA are collected from manufacturers through the FDA's Voluntary Cosmetic Registration Program (VCRP), and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category.

VCRP data obtained from the FDA in 2016⁶ indicate that Sodium Sulfate is used in cosmetic formulations. Sodium Sulfate is reported to be used in 777 cosmetic formulations⁶ compared to 28 uses reported originally¹ (**Table 1**). Frequencies of use notably increased compared to originally reported values as follows (uses reported in 2016⁶ vs. originally reported uses¹): 86 vs. 13 leave-on; 661 vs. 3 rinse-off; 30 vs. 12 diluted for bath use; 35 vs. 7 incidental inhalation; 304 vs. 28 dermal contact; 215 vs. 15 mucous membrane (**Table 1**). Uses not reported in the original assessment were reported in 2016⁶ as follows: 11 eye area uses; 1 incidental ingestion use; 2 deodorant uses; 127 hair non-coloring uses; 325 hair coloring uses; 11 nail uses; and 7 baby product uses (**Table 1**).

The concentrations of use reported in the original safety assessment were not received from the FDA or the Council survey; they were reported from two separate submissions of unpublished data from industry.¹ These data are considered to be a limited representation of concentrations in use at that time. The results of the concentration of use survey (**Table 1**) conducted by the Council in 2015-2016⁷ indicate that Sodium Sulfate is used at up to 96.4% (96.3% in original report¹) in diluted for-bath use formulations. In rinse-off formulations the highest maximum concentration of use for Sodium Sulfate based on the results of the 2015-2016 survey is 6%⁷ (5% reported originally¹). The highest maximum concentration of use reported for products resulting in leave-on dermal exposure is 2.0% in hair tonics and other hair grooming aids⁷ (0.5% in facial lotion and facial toner reported originally¹). In the product category, hair non-coloring, the highest maximum concentration of use reported increased from 1%¹ (original report) to 2.5% in 2015-2016.⁷ There was no substantial increase in concentration of use from the original report compared to 2015-2016 reported use for the product categories associated with dermal contact and mucous membrane exposure. Highest maximum use concentrations not reported in the original assessment have been reported in 2015-2016 as follows: eye area (in eye make-up remover up to 0.0064%), incidental ingestion (in dentifrices up to 0.83%), deodorant (up to 0.3%), hair coloring (up to 3.8%), nail (up to 0.5%), and baby products (in baby shampoos up to 0.29%).

In some cases, reports of uses were received in the VCRP, but concentrations of use data were not provided. For example, Sodium Sulfate is reported to be used in 4 "other hair preparation" formulations (no further details provided)⁶, but no use concentration data were reported. In other cases, no uses were reported in the VCRP, but concentration of use data were received from industry; Sodium Sulfate had no reported uses in the VCRP, but a use concentration in hair bleach at up to 3.8% was provided in the industry survey⁷. Therefore, it should be presumed that there is at least one use in every category for which a concentration or a frequency of use is reported.

Sodium Sulfate was reported to be used in cosmetic sprays and powders including, face powders (up to 0.5%), fragrance preparations (up to 0.03%), and hair tonics (up to 2.0%) and could possibly be inhaled.⁷ In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm , with propellant sprays yielding a greater fraction of droplets/particles below 10 μm compared with pump sprays.⁸⁻¹¹ Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.^{8,9} Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.¹²⁻¹⁴

Sodium Sulfate anhydrous (7757-82-6) is not restricted from use in any way under the rules governing cosmetic products in the European Union.¹⁵

Non-Cosmetic

The Code of Federal Regulations section on indirect food additives that are GRAS indicates that Sodium Sulfate is used in components of paper and paperboard used in food packaging, as well as in the cotton and cotton fabric in dry food wrapping (21CFR186.1797). Sodium Sulfate is listed as an indirect food additive with no limitations in

substances used as “basic components in single and repeated use food contact surfaces” in the section referring to cellophane (21CFR177.1200). It is a direct food additive that appears under “Miscellaneous” in the section referring to chewing gum base substances (21CFR172.615); it is recorded as a secondary direct food additive with no limitations for use in boiler water additives used to prepare steam that comes into contact with food (21CFR173.310). Mentioned as a color additive that is exempt from certification, Sodium Sulfate can be utilized as a food-grade salt, in accordance with good manufacturing practice, to assist in caramelization (21CFR73.85).

The *Food Chemicals Codex* lists Sodium Sulfate as an agent used in caramel production.⁵

Sodium Sulfate is listed as an ingredient on drug labels for colonic preparations because of its laxative effect.¹⁶ Sodium Sulfate is included as an inactive ingredient in FDA approved drug products at the following concentrations (exposure routes noted in parenthesis): up to 1.2% (ophthalmic), up to 0.03% (inhalation), up to 182 mg (oral), and up to 1.14% (intravenous).¹⁷

TOXICOKINETIC STUDIES

Absorption, Distribution, Metabolism, and Excretion (ADME)

Sulfate-Mediated Drug Metabolism

Sodium Sulfate can increase the elimination rate of high doses of acetaminophen by providing inorganic sulfate to reduce acetaminophen toxicity, as shown in some animal studies.¹ In humans, the liver, primarily, and the kidneys and intestines, secondarily, metabolize acetaminophen.¹⁸ In the body, acetaminophen is mostly converted to metabolites, which are excreted in the urine as: inactive acetaminophen glucuronide (52-57% of dose), inactive acetaminophen sulfate conjugates (30-44% of dose), and very reactive N-acetyl-p-benzoquinone imine (NAPQI, 5-10% of dose). NAPQI is the main metabolite that causes acetaminophen-induced hepatotoxicity. NAPQI binds to glutathione and is excreted in the urine as cysteine and mercapturic acid conjugates. At extremely high doses of acetaminophen (> 4 g/day in humans) the sulfation pathway, and eventually the glucuronidation pathway, become saturated, leading to the depletion of glutathione and the accumulation of NAPQI. The excess unconjugated NAPQI interacts with critical proteins to cause ion-channel imbalances, loss of cellular energy production and, ultimately, cell death. The antidote for acetaminophen poisoning is N-acetylcysteine (NAC) administered orally or intravenously, because it delivers glutathione and facilitates the sulfation pathway to elevate the elimination rate of NAPQI from the body.

Animal

Oral

Oral studies conducted in rats showed that Sodium Sulfate was absorbed by the gut. One experiment noted 57-74% of radioactive Sodium Sulfate ($\text{Na}_2^{35}\text{SO}_4$) was excreted in the urine within 24 hours post-administration.¹ In another study 90% of the dose of Sodium Sulfate ($\text{Na}_2^{35}\text{SO}_4$) was recovered in the urine within 24 hours of oral administration.

Intraperitoneally

A test in which radioactive Sodium Sulfate ($\text{Na}_2^{35}\text{SO}_4$) was intraperitoneally administered (180-330 g) to rats, 85% of the dose was detected in urine and, with the inclusion of fecal excretion, 95% of the dose was recovered in 120 hours.¹ Nearly complete elimination of the dose was observed by 48 hours in blood, liver, and brain. In bone and bone marrow tissue samples substantial concentrations were still present up to 120 hours after administration.

Human

Oral

In human subjects, experiments have been conducted to measure the recovery of free sulfate in the urine after oral administration of Sodium Sulfate.¹ The sulfate detected in urine 24 and 72 hours after dosing (18.1 g of decahydrate Sodium Sulfate administered in a single dose or 4 equally divided doses) was 36.4% and 53.4% (single dose) and 43.5% and 61.8% (divided dose), respectively. Subjects who were administered a single dose of 18.1 g Sodium Sulfate reported severe diarrhea between 2-24 hours following dosing.

Intravenous

A test in subjects receiving an intravenous dose of 1.1 Mbq (30 μ Ci) radiolabeled Sodium Sulfate ($\text{Na}_2^{35}\text{SO}_4$) revealed that 88% was recovered in the urine by 24 hours.¹

TOXICOLOGICAL STUDIES

Acute (single exposure) Toxicity

Animal

Oral

A study following Organization for Economic Co-operation and Development (OECD) Guideline 423-Acute Oral Toxicity-Acute Toxic Class Method, using Good Laboratory Practice (GLP), was conducted to evaluate the acute oral toxicity of Sodium Sulfate in Wistar rats.⁴ After fasting (17-20 hours), 1 group of 3 female rats (no controls) was administered one dose of 2000 mg/kg Sodium Sulfate in polyethylene glycol (PEG 300) by gavage. No pertinent clinical signs or Sodium Sulfate associated deaths were noted 48 hours following administration, therefore another group of 3 female rats (no controls) were dosed the same as the first group. All 6 rats were observed for 15 days. No effects on body weight or gross pathology were observed. One rat died as a result of the gavage procedure immediately after dosing; this was not Sodium Sulfate treatment related. An LD₅₀ > 2000 mg/kg Sodium Sulfate for female rats was reported.

Inhalation

Research on intubated anesthetized dogs breathing aerosol generated from a 0.1% Sodium Sulfate solution (particles size 0.1-0.2 µm) for 7.5 minutes in one study, and 0.5% Sodium Sulfate solution for 4 hours in another experiment, resulted in no significant change in respiratory functions.¹ In sheep exposed to 0.1% Sodium Sulfate solution for 20 minutes or those exposed to a 0.5% Sodium Sulfate solution for 4 hours, no significant changes were observed. Studies were also conducted on guinea pigs (1 hour exposure to 0.90 mg/m³ Sodium Sulfate, 0.1 µm particle size) and rabbits (1 hour exposure to 2000 µg/m³ Sodium Sulfate) without notable adverse effects.

Human

Inhalation

Human subjects (n=5 healthy, n=5 asthmatic) were exposed to Sodium Sulfate aerosol (mass median aerodynamic diameter of 0.5 µm) up to 3 mg/m³ for 10 minutes. Results indicated no difference in pulmonary function up to 1 hour after exposure to Sodium Sulfate compared to sodium chloride (control) except in 2 asthmatics showing a 15-20% reduction in forced exhalation volume (FEV₁).¹ In a subsequent test in human subjects (n=6 healthy, n=6 asthmatic) exposed to Sodium Sulfate aerosol (3 mg/m³ for 10 minutes; lung function measurements recorded for 3 hours post-exposure) there were no adverse effects on pulmonary function compared to sodium chloride (control). Two asthmatics exhibited a 15-20% drop in FEV₁ following exposure to Sodium Sulfate or sodium chloride.

Short-Term Toxicity

Animal

Dermal

A 90-day dermal toxicity study was conducted using methods similar to OECD Guideline 411-Subchronic Dermal Toxicity to determine the effects of Sodium Sulfate on New Zealand White rabbits (n=5 males/5 females per test group).⁴ During the study Sodium Sulfate was administered percutaneously as a positive control in 65 treatments (no further details on dermal-exposure method were provided) at 2 mL/kg/day (16% w/w Sodium Sulfate solution). The control (water) was administered percutaneously at 2 mL/kg/day. Results indicated that clinical signs and mortality, body weight and weight gain (animals were reported to gain weight in this study), organ weights, and gross pathology were unaffected by treatment. Hematology tests revealed no statistically significant differences in results between control and test groups, except for a statistically significant increase in MCV (mean corpuscular volume) and MCH (mean corpuscular hemoglobin) measurements for test group females compared to control females. However, the researchers concluded this was not “biologically significant” because the rabbits’ individual values were within normal ranges. Histopathology results were non-neoplastic with the only test-related lesion noted to be subacute dermatitis (see Irritation and Sensitization section for further details). Observations were normal, related to spontaneous disease, or incidental lesions.

Oral

An experiment, lasting 4 weeks, in weanling rats fed up to 138 mmol Sodium Sulfate/kg basal diet showed no significant differences between the control group with regards to: weight gain, feed in-take, feed-gain ratio, water intake, hemoglobin levels, red blood cell count, white blood cell count, serum protein, alkaline phosphatase, and

inorganic phosphatase concentrations.¹ Small intestine length and color and gastrointestinal organ weights were also unaffected.

A study was conducted in 28-day old weaned crossbred pigs (Landrace or Yorkshire cross, n = 415 tested in study including controls) for 4 weeks to evaluate the effects of Sodium Sulfate and Magnesium Sulfate.³ Sodium Sulfate or Magnesium Sulfate or both were administered orally in drinking water at 600, 1200, or 1800 mg/L *ad libitum*. In the fourth week of exposure, there was a statistically significant body weight gain increase with increasing sulfate concentrations to pigs administered either 600 mg/L or 1800 mg/mL Sodium Sulfate or 600 mg/L or 1800 mg/L Magnesium Sulfate (results for 1200 mg/L Sodium Sulfate or 1200 mg/L Magnesium Sulfate are not reported during the fourth week) compared to the control group. When Sodium Sulfate and Magnesium Sulfate were administered in the same test group this trend was not observed at any of the concentrations tested (e.g. combined Sodium Sulfate and Magnesium Sulfate at 600 mg/L in one test group; combined Sodium Sulfate and Magnesium Sulfate at 1200 mg/L in another test group, etc.). There were no differences in feed-to-body-weight gain ratios in treated groups compared to the control group. At 1800 mg/L total sulfate concentration (combined Sodium Sulfate and Magnesium Sulfate; distribution not specified) a statistically significant increase in water consumption was observed. A statistically significant increase in incidence of diarrhea was correlated with total sulfate concentrations (combined Sodium Sulfate and Magnesium Sulfate; distribution not specified) of 600, 1200, and 1800 mg/L and determined not to be attributed to high concentrations of common post-weaning pathogens. This high-sulfate-content water consumption, resulting in increased incidence of diarrhea, did not negatively impact growth rate, increase mortality, or increase post-weaning pathogens. The deaths of 4 pigs (mortality rate 0.96%) during the study were not attributed to sulfate treatment; 3 died of enterotoxigenic *Escherichia coli* and 1 was euthanatized because of weight loss and lack of response to therapeutic interventions.

Human

Oral

There was a 14 day study in subjects (with a history of colonic polyps) that were orally administered 4-6 g/day of Sodium Sulfate. Results yielded no adverse effects.¹

Inhalation

For workers with occupational exposure to Sodium Sulfate dust at concentrations up to 150 mg/m³ no abnormalities associated with long-term exposure were found.¹

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

Experiments conducted in pregnant ICR/SIM mice orally administered (via intubation) 2800 mg/kg/day Sodium Sulfate on days 8 through 12 of gestation showed no maternal toxicity.¹ No resorptions were observed in treated or control groups; all neonates in the treated group survived from days 1-3. Average birthweight of treated neonates was statistically significantly greater than controls. The researchers considered this to be a positive result for Sodium Sulfate, despite the lack of maternal toxicity in the treated group. However, the researchers acknowledged that, with the absence of published teratogenic data for orally administered Sodium Sulfate, they could not confirm the validity of the positive results.

Studies were conducted in Wistar rats to evaluate the effect of Sodium Sulfate on reproduction.⁴ The first study (non-GLP) was used to determine the exposure concentrations for the second (OECD Guideline 421-Reproduction/Developmental Toxicity Screening Test, GLP), more comprehensive experiment. Groups of 3 male and 3 female rats were dosed with 0, 100, 300, and 1000 mg/kg/day Sodium Sulfate. Both sexes were dosed by gavage for 14 days pre-pairing, during pairing (14-day max), and up to 1 day before necropsy for males and up to day 13 of gestation for females. Males were killed after at least 28 days of dosing and females were killed on day 14 of gestation. No rats died prior to necropsy. Endpoints including food consumption, body weights, reproductive performance, and gross pathology were unaffected by Sodium Sulfate in either sex during the duration of study. For females, endpoints including number of corpora lutea, pre- and post-implantation loss, and number of live embryos were also unaffected by treatment with Sodium Sulfate. The only clinical observation to note, at 1000 mg/kg/day Sodium Sulfate, was soft feces in both sexes on day 11 of the pre-pairing period through day 3 after pairing (males) and days 2 or 3 of gestation (females). Gross examination yielded no abnormal findings.

Another experiment was conducted to determine the effects of Sodium Sulfate on reproductive performance of Wistar rats.⁴ Similar parameters were monitored as in the first experiment summarized above (same dose rates, i.e.,

0, 100, 300, 1000 mg/kg/day Sodium Sulfate) with the following exceptions: each group contained 10 males and 10 females; males were killed after at least 28 days of treatment, females were allowed to give birth and rear their litters for 4 days post-partum, and females and pups were killed on day 4 post-partum. If the females did not give birth when expected (day 21 of gestation) they were killed by day 25 of gestation. Parental endpoints of clinical signs, body weight, food consumption, reproductive function (sperm measures), reproductive performance, fertility index, conception rate, organ weights, gross pathology, and histopathology were unaffected by Sodium Sulfate. No parental deaths were reported prior to scheduled necropsies. The duration of gestation, corpora lutea count, implantation rate, post-implantation loss, duration of gestation, and litter size at first litter check were unaffected by Sodium Sulfate. One pup from the control group died on day 3. Offspring endpoints of viability, clinical signs, body weight, and gross pathology were unaffected by Sodium Sulfate. Upon gross examination of the pups no abnormal findings were reported. A general no observed effect level (NOEL), as well as reproduction/developmental toxicity NOEL, was reported to be 1000 mg/kg/day.

GENOTOXICITY STUDIES

In Vitro

An experiment examining Sodium Sulfate for genotoxicity was negative in a microscreen assay (275 µg/well Sodium Sulfate) evaluating bacterial DNA damage by measuring prophage induction into Escherichia coli.¹ Another test evaluating Sodium Sulfate on Syrian hamster embryo cells was determined to be negative for enhanced transformation of the cells by a simian adenovirus (SA7).

An Ames test was conducted to evaluate the effect of Sodium Sulfate (312.5 to 5000 µg per plate with 4 dilutions) on *Salmonella typhimurium* TA1535, TA1537, TA100, and TA98, both with and without metabolic activation.⁴ The results were negative for genotoxicity. No cytotoxicity was observed at the concentrations tested.

An *in vitro* mammalian chromosome aberration test (GLP compliant) was performed in Chinese hamster lung fibroblasts (V79) in accordance with OECD Guideline 473 – *in vitro* Mammalian Chromosome Aberration Test.⁴ The test was performed with and without metabolic activation. The exposure duration of experiment 1 was 4 hours with and without metabolic activation. The exposure durations of experiment 2 were 4 hours with metabolic activation and 18 hours without metabolic activation. Both experiments used deionized water as the vehicle. Test concentrations with and without metabolic activation in experiment 1 were 11.1, 22.2, 44.4, 88.8, 177.5, 355.0, 710.0, and 1420.0 µg/mL Sodium Sulfate. In experiment 2 with activation, concentrations tested were 177.5, 355.0, 710.0, and 1420.0 µg/mL Sodium Sulfate. Test concentrations without metabolic activation in experiment 2 were 22.2, 44.4, 88.8, 177.5, 355.0, 710.0, and 1420.0 µg/mL Sodium Sulfate. Negative solvent/vehicle controls and positive controls were used.

Outcomes revealed that Sodium Sulfate did not induce structural chromosome aberrations in V79 cells of the Chinese hamster *in vitro* (non-clastogenic) up to 1420.0 µg/mL.⁴ No cytotoxic effects or biologically relevant increase in the number of cells containing structural chromosome aberrations were noted (with or without metabolic activation). No biologically relevant increase in the rate of polyploid cells was found. Appropriate vehicle and positive controls yielded expected results.

An *in vitro* mammalian cell gene mutation assay test (GLP compliant) was conducted in mouse lymphoma L5178Y cells in accordance with OECD Guideline 476 – *in vitro* Mammalian Cell Gene Mutation Test.⁴ The test was performed with and without metabolic activation. The exposure duration of experiment 1 was 4 hours with and without metabolic activation. Experiment 2 exposure durations were 24 hours without metabolic activation and 4 hours with metabolic activation. The concentrations tested in experiments 1 and 2, both with and without metabolic activation, were 88.8, 177.5, 355, 710, and 1420 µg/mL Sodium Sulfate (deionized water was vehicle/solvent used). Negative solvent/vehicle controls and appropriate positive controls were used. Results were negative for genotoxicity and negative for cytotoxicity, whether in the absence or the presence of metabolic activation. Therefore, Sodium Sulfate was not found to induce mutations in the mouse lymphoma thymidine kinase locus assay (cell line L5178Y).

CARCINOGENICITY STUDIES

Co-Carcinogenicity

Oral

In one study Sodium Sulfate was shown to inhibit the carcinogenicity of N-hydroxy-N-2-fluorenylacetamide (N-OH-FAA) or increase the inhibitory effect of p-hydroxyacetanilide in rats fed 0.89 mmole/kg N-OH-FAA concurrently

with 3 equivalents of Sodium Sulfate.¹ However, another experiment with rats fed 1.34 mmole/kg N-OH-FAA and 3 equivalents of Sodium Sulfate showed no additional effect on the inhibitory actions of *p*-hydroxyacetanilide. A test in rats that were fed a carcinogen (0.06% 3'-methyl-4-dimethylaminoazobenzene) and Sodium Sulfate (0.84%) resulted in increased risks of developing multiple neoplasms and metastatic neoplasms. A study in mice that were co-administered Sodium Sulfate and an inhibitor in their diet in equimolar ratios resulted in partially restoring leukemogenicity of N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA). A test in which rats were fed Sodium Sulfate and had been injected with dimethylhydrazine (DMH) results showed fewer colon tumors in rats treated with Sodium Sulfate plus DMH compared to those treated with only DMH.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

A 90-day dermal toxicity study was conducted using methods similar to OECD Guideline 411-Subchronic Dermal Toxicity to determine the effects of Sodium Sulfate on New Zealand White rabbits (n=5 males/5 females per test group).⁴ Sodium Sulfate was percutaneously administered as a positive control in 65 treatments spanning 91 days (no further details on dermal-exposure method were provided) at 2 mL/kg/day (16% w/w Sodium Sulfate solution). Water was administered percutaneously as the control at 2 mL/kg/day. An effect occurred in 3 control-group rabbits showing mild subacute dermatitis and in the 16% Sodium Sulfate-group in 8 rabbits showing mild to moderate subacute dermatitis. The lowest observed adverse effect level (LOAEL) for Sodium Sulfate in this study was 2 mL/kg/day of a 16% (w/w) aqueous Sodium Sulfate solution.

An *in vivo* (GLP) study was conducted in accordance with OECD Guideline 404 – Acute Dermal Irritation/Corrosion, to evaluate the effect of Sodium Sulfate on rabbits (n=3).⁴ Occlusive patches containing 500 mg Sodium Sulfate in polyethylene glycol (PEG) 400 were applied for 4 hours. Dermal application sites were examined for up to 14 days post-exposure (no further details provided). Results showed that Sodium Sulfate was non-irritating.

Human

Several occlusive patch tests containing Sodium Sulfate were conducted in human subjects. One patch test using the equivalent of 9.7% Sodium Sulfate in a bath bead formulation yielded results with only 1 of 19 subjects reacting with \pm (first non-zero grade on a 0 to 4 \pm scale)¹ Three 24-hour patches of a bar soap flake formulation containing 5.84% Sodium Sulfate (effective concentration of 0.1168%) resulted in mild irritation in 11 out of 13 subjects. An experiment containing 1.8% Sodium Sulfate patch concentration, comparable to 200 times the expected use of a children's powdered bubble bath preparation, showed 7 subjects had mild erythema and 8 had dryness (\pm) out of 20 subjects tested. A test with a Sodium Sulfate patch concentration corresponding to 0.004% in an aqueous solution cleansing bar base resulted in various exposures to all 35 subjects in a 21 day study. Overall the formulation was deemed to be mildly irritating.

Sensitization

Animal

A Guinea Pig Maximization Test (GLP) in male albino Dunkin-Hartley guinea pigs was conducted to determine the allergenic potential of dermal exposure to Sodium Sulfate.⁴ The OECD Guideline 406 – Skin Sensitization was followed. Appropriate negative and positive controls were used yielding expected results. Three phases of the experiment included: intradermal induction (25% Sodium Sulfate in PEG 300), epidermal induction (75% Sodium Sulfate in PEG 300), and epidermal occlusive challenge (50% Sodium Sulfate in PEG 300). There were 5 control animals, 10 test animals, 1 animal used for the intradermal pretest, and 2 animals used for the epidermal pretest. On Test Day 1 there were 3 pairs of intradermal injections (0.1 mL/site) given within the 4 x 6 cm clipped, hair-free zone of scapular region dorsal skin. Test groups received 1:1 (v/v) Freund's Complete Adjuvant and physiological saline mixture, 25% Sodium Sulfate in PEG 300, or 25% Sodium Sulfate in a 1:1 (v/v) mix of Freund's Complete Adjuvant and physiological saline. Control groups received 1:1 (v/v) mix of Freund's Complete Adjuvant and physiological saline, PEG 300, or 1:1 (w/w) mix of PEG 300 in a 1:1 (v/v) mix of Freund's Complete Adjuvant and physiological saline.

The epidermal induction was conducted on Test Day 8.⁴ A week following intradermal injections, a 2 x 4 cm occlusive 48-hour patch with 75% Sodium Sulfate in PEG 300 (~0.3 g Sodium Sulfate) was placed on each injection

site. The control group guinea pigs were treated similarly except no Sodium Sulfate was present in the PEG 300 (~0.3 mL) solution. The injection sites were examined for erythema and edema 24 and 48 hours after injection.

The challenge was performed on test and control group guinea pigs on test day 22, following a 2 week non-treatment period after the completion of the induction phase.⁴ Two 24-hour occlusive patches (3 x 3 cm) with 0.2 mL of 50% Sodium Sulfate in PEG 300 were placed on the left flank and PEG 300 only (~0.2 mL) placed on the right flank. Results indicated no toxic signs or local skin effects in the surviving guinea pigs of the control or test group. During this study there were no deaths attributable to Sodium Sulfate exposure and no control or test group animals showed toxic signs; animals were not necropsied. One animal was euthanized because of a prolapsed anus and blood loss, which were not treatment related. Body weight and clinical signs were unaffected by Sodium Sulfate. Concluding remarks were that Sodium Sulfate was not classified as a skin sensitizer (in accordance with Regulation EC No. 1272/2008).

Human

In an experiment on sensitization using a Sodium Sulfate effective concentration of 1.01% (100 times greater than normal use levels) from an aqueous bubble bath solution was tested via insult patches on 61 subjects.¹ The only notable result was a mild erythema reaction in one subject during induction with no reactions noted during challenge.

OCULAR IRRITATION STUDIES

Animal

Direct application of up to 0.1 mL sodium carbonate-Sodium Sulfate granular mixture (1:1, w/w) to the corneas of 3 rabbits resulted in moderate ocular irritation.¹

SUMMARY

The CIR Expert Panel originally concluded that Sodium Sulfate was safe as used in cosmetic rinse-off formulations and safe up to 1% in leave-on formulations. This conclusion was based on several factors, including the GRAS status of Sodium Sulfate used as an indirect food additive, data submitted by the cosmetics industry addressing dermal irritation and sensitization, and results from a clinical sensitization study evaluating repeated, prolonged exposure in which 1 in 61 subjects exhibited mild erythema in response to a 1.01% sodium-sulfate-containing patch applied for 24 hours.

The current frequency of use of Sodium Sulfate reported in cosmetic formulations (777 uses) is a considerable increase from the 28 uses reported originally. The highest reported frequencies of use are in hair dyes and colors (320 uses) in the current VCRP data and were in bubble baths (11 uses) in the original report. The frequencies of use in cosmetic formulations reported for the following categories are (uses reported in 2016 vs. uses reported in originally): 86 vs. 13 leave-on; 661 vs. 3 rinse-off; 30 vs. 12 diluted for bath use. The product categories for which no uses were reported in the original assessment have reported uses in the 2016 survey for: eye area, incidental ingestion, deodorant, hair non-coloring, hair coloring, nail, and baby products.

The concentrations of use reported in the original safety assessment are a limited representation of concentrations in use at that time; the concentrations originally reported were from two separate submissions of unpublished data from industry and not from the FDA VCRP or the Council industry survey. The original report specifies concentrations of use up to 5% in rinse-off formulations and up to 96.3% in cosmetic formulations diluted for bath use. The current reported highest maximum concentrations of use are up to 6% in rinse-off formulations and up to 96.4% in products diluted for bath use. The original safety assessment reported a concentration of use in leave-on dermal exposure cosmetic products to be 0.5%, as compared to the currently reported highest maximum use concentration of 2%. The product categories for which no concentrations were reported in the original assessment, have concentrations reported in the 2015-2016 survey for: eye area, incidental ingestion, incidental inhalation, deodorant, hair coloring, nail, and baby products.

In an acute oral toxicological study conducted in rats, no significant effects from Sodium Sulfate were noted in test animals administered Sodium Sulfate at 2000 mg/kg; this study reported an LD₅₀ > 2000 mg/kg/ in female rats.

During a 3-month repeated-dose dermal toxicity study in rabbits, clinical signs and mortality, body weight and weight gain, organ weights, and gross pathology were unaffected by percutaneously administered Sodium Sulfate (2 mL/kg/day; 16% w,w). Hematology results were not biologically significant; histopathology findings were non-neoplastic. In a 4-week repeated-dose study in nursery pigs orally administered Sodium Sulfate in their water *ad*

libitum the observations noted were: increased water intake at 1800 mg/L Sodium Sulfate, increased incidence of diarrhea at 600, 1200, and 1800 mg/L Sodium Sulfate, but no negative effect on growth rate nor increased mortality at any of these concentrations.

Reproductive and developmental toxicity experiments in rats (administration by gavage) reported no abnormal results other than soft feces in both male and female rats administered Sodium Sulfate by gavage at dose rates up to 1000 mg/kg/day. Another study in rats dosed with Sodium Sulfate up to 1000 mg/kg/day by gavage concluded no abnormal findings, and reported a 1000 mg/kg/day NOEL for both general and reproductive/developmental toxicity endpoints.

Genotoxicity studies conducted on *S. typhimurium*, Chinese hamster lung fibroblasts (V79), and mouse lymphoma L5178Y cells testing Sodium Sulfate up to 5000 µg per plate (with 4 dilutions), 1420.0 µg/mL, and 1420 µg/mL, respectively, were negative for genotoxicity and cytotoxicity. The test on Chinese hamster lung fibroblast cells was also negative for polyploid cells.

In dermal irritation and sensitization experiments, 8 rabbits exhibited mild to moderate subacute dermatitis when percutaneously exposed to 16% (w/w) Sodium Sulfate at 2 mL/kg/day, which was the reported LOAEL. Three control rabbits exhibited mild subacute dermatitis in this study. In an occlusive coverage test, 4 hour duration, 500 mg Sodium Sulfate was determined to be non-irritating to rabbits. Sodium Sulfate was deemed to be non-sensitizing to guinea pig skin in a Guinea Pig Maximization test using a challenge dose of 50% Sodium Sulfate (in PEG 300).

DISCUSSION

The Panel decided to reopen the Final Report on the Safety Assessment of Sodium Sulfate based on the significant increase in reported frequency of use (777 uses reported in 2016 compared to 28 uses originally) and the increase in highest maximum use concentration reported for leave-on products (to up to 2% in hair tonics and other hair grooming aids), which exceeds the leave-on use concentration noted in the original conclusion (safe up to 1% in leave-on formulations).

The dermal irritation data presented in this safety assessment, including data summarized from the original report, show mixed results. In rabbits, a 16% aqueous solution was mildly to moderately irritating, but 500 mg was not irritating in an occlusive patch test. The original report includes 4 dermal irritation studies, and one sensitization study (in which irritation was noted at induction in 1 of 61 subjects), in human subjects exposed to Sodium Sulfate at concentrations ranging from 0.004% to 9.7% (occlusive patches used) with test results indicating no irritation to mild irritation. Given these results, the Panel specified that cosmetics that contain this ingredient should be formulated to be non-irritating.

Moderate ocular irritation was observed in an experiment in which Sodium Sulfate (1:1, w/w, granular mixture of Sodium Sulfate: sodium carbonate) was instilled into the corneas of rabbits. The highest reported maximum use concentration of Sodium Sulfate in cosmetic products used in the eye area (up to 0.0064% in eye make-up removers) is orders of magnitude less than Sodium Sulfate concentration reported to be used as an inactive ingredient in FDA-approved ophthalmic drug products (up to 1.2%) and concentrations that produced moderate eye irritation in the rabbits tested. Thus, the potential for ocular irritation from exposure to Sodium Sulfate in cosmetic products is very low.

The Panel discussed the issue of incidental inhalation exposure from fragrance sprays, hair tonics, and face powders. The Panel considered pertinent data from the original report, for test animals and human subjects, indicating that incidental inhalation exposures to Sodium Sulfate in such cosmetic products would not cause adverse health effects. Several acute inhalation toxicity studies evaluating the effects of Sodium Sulfate (up to 0.5% or up to 2000 µg/m³; particle sizes 0.1-0.2 µm, when specified) in animals reported no significant changes in respiratory functions.

Healthy and asthmatic human subjects exposed to respirable Sodium Sulfate aerosol at concentrations up to 3 mg/m³ in an acute toxicity study indicated no difference in pulmonary function compared to exposure to sodium chloride (control), except in 2 asthmatics showing a 15-20% reduction in FEV₁; when the test was repeated in a subsequent experiment, 2 asthmatics exposed to Sodium Sulfate and 2 asthmatics exposed to sodium chloride (control) also showed a 15-20% reduction in FEV₁. For workers with occupational exposure to Sodium Sulfate dust (up to 150 mg/m³) no abnormalities were associated with long-term exposure. Although particles appear to have reached the lungs in these studies, the sizes of the particles used were either clearly within the respirable range (i.e., ≤ 10 µm) or were not reported.

Sodium Sulfate is reportedly used at concentrations up to 2% in cosmetic products that may be aerosolized and up to 0.5% in face powder that may become airborne. The Panel noted that droplets/particles produced in cosmetic aerosols and loose-powder cosmetic products would not be respirable to any appreciable amount. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

Data presented in this safety assessment show an absence of substantial systemic toxicity for Sodium Sulfate administered at high doses in acute oral and repeated-dose dermal and oral exposure studies. Sodium Sulfate was non-toxic in development and reproductive tests. Genotoxicity was negative in an Ames test and in experiments evaluating chromosome aberrations and gene mutations. Sodium Sulfate was found to be non-sensitizing in a Guinea Pig Maximization Test. These results are in agreement with toxicity data reported in the original safety assessment and affirm the lack of toxicity of Sodium Sulfate for use in cosmetics.

CONCLUSION

The CIR Expert Panel concluded that Sodium Sulfate is safe in cosmetics in the present practices of use and concentrations described in this safety assessment when formulated to be non-irritating.

TABLE

Table 1. Current and historical frequency and concentration of use of Sodium Sulfate according to duration and exposure

	# of Uses		Max Conc of Use (%)	
	2016 ⁶	2000 ¹	2015-2016 ⁷	2000 ¹
Totals*	777	28	0.0000002-96.4	0.1-96.3
Duration of Use				
Leave-On	86	13	0.000002-2.0	0.5
Rinse-Off	661	3	0.0000002-6.0	0.1-5.0
Diluted for (Bath) Use	30	12	0.00053-96.4	3.5-96.3
Exposure Type				
Eye Area	11	NR	0.000046-0.0064	NR
Incidental Ingestion	1	NR	0.00015-0.83	NR
Incidental Inhalation-Spray	possible: 35 ^a ; 13 ^b	possible: 7 ^a ; 3 ^b	spray: 0.0088-0.03 possible: 0.00015-2.0 ^a ; 0.006 ^b	NR
Incidental Inhalation-Powder	possible: 13 ^b	possible: 3 ^b	powder: 0.5 possible: 0.006 ^b ; 0.00023-0.54 ^c	NR
Dermal Contact	304	28	0.000002-96.4	0.5-96.3
Deodorant (underarm)	2 ^a	NR	0.000014-0.3 ^d	NR
Hair - Non-Coloring	127	NR	0.0000002-2.5	0.1-1.0
Hair-Coloring	325	NR	0.000051-3.8	NR
Nail	11	NR	0.001-0.5	NR
Mucous Membrane	215	15	0.00015-96.4	1.0-96.3
Baby Products	7	NR	0.000002-0.29	NR

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

^a Includes products that can be sprays, but it is not known whether the reported uses are sprays

^b Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

^c Includes products that can be powders, but it is not known whether the reported uses are powders

^d Deodorant products reported here are *not* sprays

NR – no reported use

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