Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics

Status:	Re-Review for Panel Review
Release Date:	March 7, 2016
Panel Meeting Date:	March 31-April 1, 2016

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.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Laura N. Scott
Senior Scientific Writer
Date: March 7, 2016
Subject: Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics

Enclosed is the Re-Review of the Amended Safety Assessment of Sodium Sulfate as Used in Cosmetics (identified as *SodSul032016rep* in the pdf document). In 2000, the Panel concluded that Sodium Sulfate is safe as used in rinse-off formulations and safe for use up to concentrations of 1% in leave-on formulations (original assessment identified as *SodSul032016prev*).

Concentrations of use data were received from the Council and are included in this package (*SodSul032016data*). Also included are VCRP data (*SodSul032016FDA*). Frequency of use significantly increased from 2000 (28 reported uses) to 2016 (777 reported uses). The following categories, for which frequency of use were not reported in the original assessment, now have reported uses in 2016: eye area, incidental ingestion, deodorant, hair non-coloring, hair coloring, nail, and baby products. Concentrations reported in the original assessment are not necessarily a comprehensive representation of use at that time; the concentrations were from two separate submissions of unpublished data from industry and not from the FDA or a Council survey. In addition to the increase in frequency of use, the 2015-2016 concentrations of use Council survey data indicate product categories for which no concentration data were originally reported, namely, eye area, incidental ingestion, incidental inhalation, deodorant, hair coloring, nail, and baby products. Currently, concentration of use in leave-on cosmetic products is reported up to 2% in hair tonics and other hair grooming aids.

The Panel is now being asked to consider whether the original conclusion should be reaffirmed, or if the new data warrant re-opening the review.

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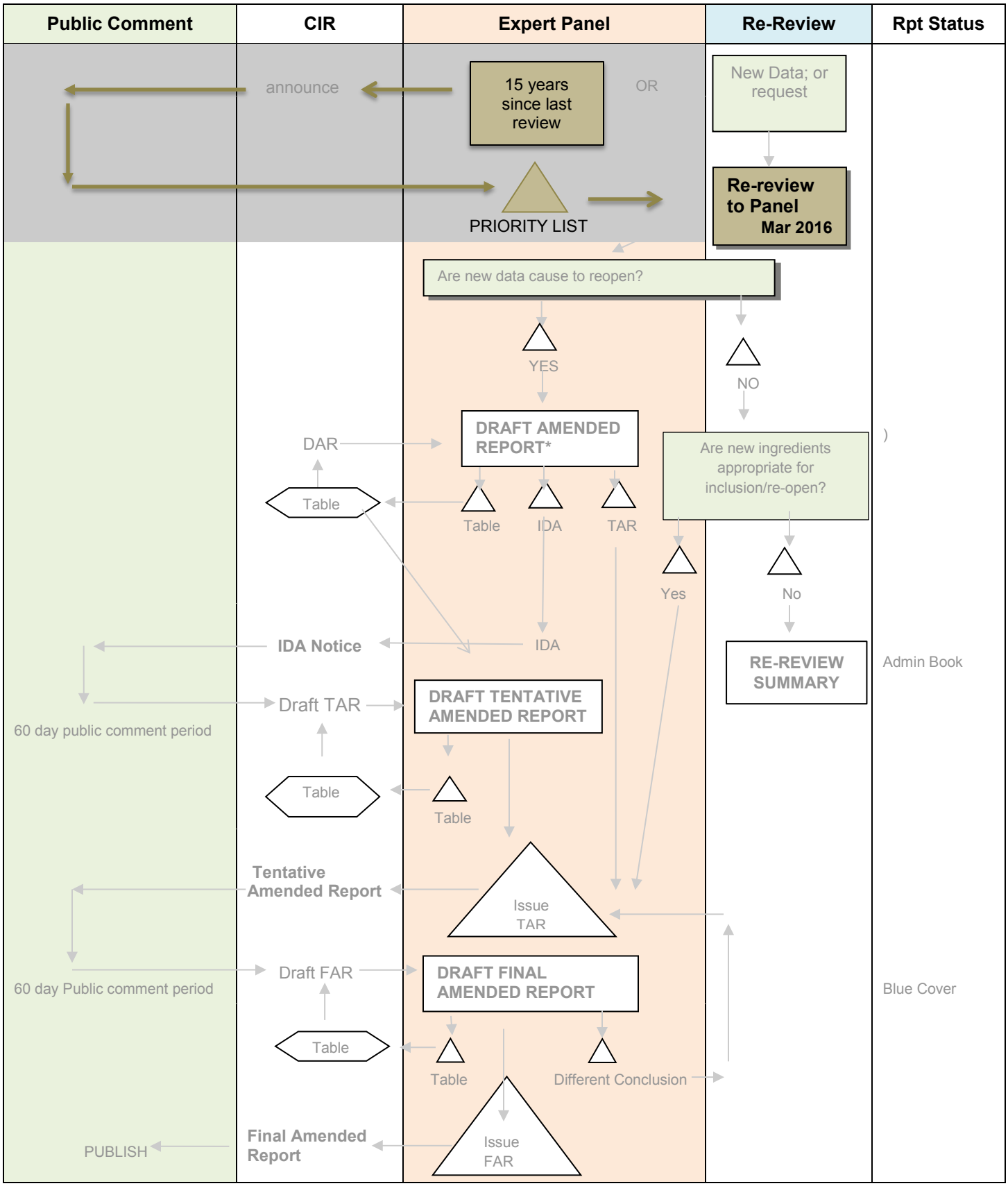
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Sodium Sulfate

MEETING Mar 2016



*If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

Report History-Sodium Sulfate

June 1996-Insufficient Data Announcement issued; Concentration of use and human skin irritation study at concentration of use were requested

December 1996-The Panel unanimously agreed to issue a Tentative Report with the conclusion that Sodium Sulfate is safe at concentrations up to 1.0% in leave-on products and safe as used in rinse-off products. This conclusion was based on negative results in the sensitization study included in the Draft Report.

June 1997-The Panel voted unanimously in favor of issuing a Final Report with the conclusion that Sodium Sulfate is safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.

2000-The Panel concluded that Sodium Sulfate (both anhydrous and decahydrate forms) is safe as used in rinse-off formulations, and safe up to 1% in leave-on formulations.

March, 2016-

Sodium Sulfate Data Profile for **March 31, 2016**. Writer – Laura Scott																										
		ADME				Acute Toxicity				Repeated Dose Toxicity				Irritation					Sensitization							
	Reported Use	Oral-Human	IV-Human	Oral-Animal	Parenteral-Animal	Inhale-Human	Parenteral-Animal	Oral-Animal	Inhale-Animal	Oral-Human	Oral-Animal	Dermal	Inhale-Human	Ocular Animal	Ocular-*In Vitro*	Dermal-Animal	Dermal-Human	Dermal-*In Vitro*	Dermal-Animal	Dermal-Human	*In Vitro*	Repro/Devel	Genotox-*in vitro*	Carcinogenicity	Phototoxicity
Sodium Sulfate: Original Report, 2000	X	X	X	X	X	X	X		X	X	X		X	X			X			X		X	X	X	
Sodium Sulfate: Re-Review Report, 2016	X							X			X					X			X			X	X		

Sodium Sulfate Re-Review Search Info

	Cas No.	Prev Rev	in Use	NTIS	FDA/CFR	NTP	ECHA	HPVIS	SIDS	EU	NICNAS	Web
Sodium Sulfate	7727-73-3 7757-82-6	2000	VCRP	(no recent data available)	X	(no recent data available)	X	X	X	X	X	X

X-indicates data were available

PubMed (August 27, 2015):

CAS #: (7727-73-3) OR 7757-82-6 766 hits/0 useful; ((7727-73-3) AND 7757-82-6) AND "toxicity" 56 hits/0 useful; (sodium sulfate) AND cosmetics 15 hits/0 useful

Email updates are received when new articles (using similar search parameters as above) become available.

SciFinder (August 27, 2015):

CAS #: (7727-73-3) from 1995-2015 317 hits/0 useful; "7757-82-6 and toxicity" from 1995-2015 525 hits/0 useful; "7757-82-6 and cosmetics" 1995-2015 25 hits/0 useful

"Keep Me Posted" email updates are received when new articles (using similar search parameters as above) become available.

ECHA Citations (first link below cited in RR report)

Sodium Sulfate (CAS # 7757-82-6) access date 2/22/16: http://echa.europa.eu/registration-dossier/-/registered-dossier/15539

TOXNET (not cited in RR)

Sodium Sulfate (CAS # 7757-82-6) search date 8/26/15 in GENE-TOX: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~c5J38F:5

Sodium Sulfate (CAS # 7757-82-6) search date 8/26/15 in HSDB: http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~PwwGns:3

PubChem (not cited in RR)

Sodium Sulfate, search date 8/31/15: https://pubchem.ncbi.nlm.nih.gov/compound/sodium_sulfate#section=Top

ILO-ICSC (not cited in RR)

Sodium Sulfate, search date 9/2/15: http://www.ilo.org/dyn/icsc/showcard.display?p_card_id=0952

InChem (WHO Series 44 report, not cited in RR)

Sodium Sulfate, searched Google 8/31/15: http://www.inchem.org/documents/jecfa/jecmono/v44jec07.htm

NICNAS (not cited in RR)

Sodium Sulfate, (CAS# 7757-82-6, 7727-73-3) search date 8/31/15 http://www.nicnas.gov.au/chemical-information/imap-assessments/imap-assessments/tier-i-human-health-assessments

EU Citation (not cited in RR)

Sodium Sulfate, (CAS# 7757-82-6, 7727-73-3) searched 8/31/15: http://ec.europa.eu/health/archive/ph_risk/committees/sccp/documents/out123cm_en.pdf

SIDS Citation (primary source obtained from this link is cited in RR report)

Sodium Sulfate, (CAS# 7757-82-6) searched 8/31/15: http://www.chem.unep.ch/irptc/sids/OECDSIDS/7757826.pdf

HPVIS/EPA (not cited in RR)

Sodium Sulfate, searched "toxicity and sodium sulfate" 8/31/15: http://www2.epa.gov/sites/production/files/2015-03/documents/tri_chemical_list_changes_2_27_15.pdf

Technical Data Sheets (not cited in RR)

Sodium Sulfate, Google search "Technical Data Sheets Sodium Sulfate" 8/31/15: 2010, (CAS# 7757-82-6) Santa Cruz Biotechnology http://datasheets.scbt.com/sc-212945.pdf

Sodium Sulfate, Google search "Technical Data Sheets Sodium Sulfate" 8/31/15: 2002, (CAS# 7727-73-3) J.M. Loveridge plc http://www.jmloveridge.com/cosh/Sodium%20Sulphate.pdf

FDA/CFR (EAFUS last updated 4/23/13, cited in RR report)

Sodium Sulfate, searched 9/1/15: http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=eafusListing&id=1956

National Institute of Health, National Library of Medicine-"Daily Med" (cited in RR report)

Sodium Sulfate, searched 9/24/15: http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=human&query=sodium+sulfate&pagesize=200&page=1

CFR Citations

21CFR186.1797: Part 186-Indirect Food Substances Affirmed As Generally Recognized As Safe; Subpart B-Listing of Specific Substances Affirmed as GRAS; Section 186.1797 Sodium sulfate; (a) Sodium sulfate (Na2SO4, Cas Reg. No. 7757-82-6), also known as Glauber's salt, occurs naturally and exists as colorless crystals or as a fine, white crystalline powder. It is prepared by the neutralization of sulfuric acid with sodium hydroxide. (b) The ingredient is used as a constituent of paper and paperboard used for food packaging, and cotton and cotton fabric used for dry food packaging. (c) The ingredient is used at levels not to exceed good manufacturing practice in accordance with 186.1 (b) (1). (d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

21CFR177.1200: Part 177-Indirect Food Additives: Polymers; Subpart B-Substances For Use as Basic Components of Single and Repeated Use Food Contact Surfaces; Section 177.1200 Cellophane; Cellophane may be safely used for packaging food in accordance with the following prescribed conditions: (b) Subject to any limitations prescribed in this part, the optional substances used in the base sheet and coating may include: (4) Substances named in this section and further identified as required. (c) List of substances: Sodium sulfate.

21CFR172.615: Part 172-Food Additives Permitted For Direct Addition To Food For Human Consumption; Subpart G-Gums, Chewing Gum Bases and Related Substances; Section 172.615 Chewing gum base; The food additive chewing gum base may be safely used in the manufacture of chewing gum in accordance with the following prescribed conditions: (a) The food additive consists of one or more of the following substances that meet the specifications and limitations prescribed in this paragraph, used in amount not to exceed those required to produce the intended physical or other technical effect. Miscellaneous. Sodium sulfate.

21CFR173.310: Part 173-Secondary Direct Food Additives Permitted In Food For Human Consumption; Subpart D-Specific Usage Additives; Section 173.310 Boiler water additives. Boiler water additives may be safely used in the preparation of steam that will contact food, under the following conditions: (a) The amount of additive is not in excess of that required for its functional purpose, and the amount of steam in contact with food does not exceed that required to produce the intended effect in or on the food. (b) The compounds are prepared from the substances identified in paragraphs (c) and (d) of this section, and are subject to the limitations, if any, prescribed: (c) List of substances: Sodium sulfate.

21CFR73.85: Part 73-Listing of Color Additives Exempt From Certification; Subpart A-Foods; Section 73.85 Caramel. (a) Identity. (2) The food-grade acids, alkalis, and salts listed in this subparagraph may be employed to assist caramelization, in amounts consistent with good manufacturing practice. (iii) Salts: Amonium, sodium, or potassium carbonate, bicarbonate, phosphate (including dibasic phosphate and monobasic phosphate), sulfate, and sulfite.

MINUTES FROM ORIGINAL REVIEW OF SODIUM SULFATE

June 1996

Drs. Belsito and Schroeter noted that there had been no response to the informal data request that was issued at the December 11-12, 1995 Panel meeting.

The Panel voted unanimously in favor of issuing an Insufficient Data Announcement on Sodium Sulfate with the following data requests:
(1) Human skin irritation study at concentration of use
(2) Concentrations of use

December 1996

Dr. Schroeter recalled that an Insufficient Data Announcement on Sodium Sulfate was issued at the June 3-4, 1996 Panel meeting, and that data addressing each request for information were received. The data requested were as follows: (1) Concentration of use and (2) Human dermal irritation at concentration of use. Dr. Schroeter also noted that his Team concluded that Sodium Sulfate is safe as used in cosmetics.

Dr. Belsito stated that his Team concluded that Sodium Sulfate is safe at concentrations up to 1.0% in leave-on products (based on negative results in the sensitization study included in the Draft Report) and safe as used in rinse-off products.

Dr. McEwen noted that, actually, a 1.25% aqueous solution of a bubble bath containing 80.8% Sodium Sulfate (effective concentration = 1.01%) was tested in the sensitization study. He recommended that the concentration limit for Sodium Sulfate in leave-on products should be stated accurately in the report conclusion based on this calculation.

Dr. McEwen confirmed with the Panel that the proposed concentration limit is based on negative results for skin irritation (Panel=s original concern) in the human repeated insult patch test.

The Panel unanimously concluded that Sodium Sulfate is safe at concentrations up to 1.0% in leave-on products and safe as used in rinse-off products, and voted in favor of issuing a Tentative Report with this conclusion.

Dr. Andersen noted that the derivation of the 1.0% concentration limit (actually 1.01% test concentration from sensitization study rounded off to nearest tenth) will be included in the report discussion.

June 1997

The Panel voted unanimously in favor of issuing a Final Report with the following 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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INTRODUCTION

In 2000, the Cosmetic Ingredient Review (CIR) Expert Panel (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 in cosmetic formulations.[2] 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), 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.[1]

The original safety assessment addressed both the anhydrous and decahydrate forms of Sodium Sulfate.

A current search of published literature indicated several journal articles with relevant information, which are subsequently referred to in this document (un-italicized text). For ease of comparison, italicized text throughout this report are from the original safety assessment. Additionally, updated frequency of use 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.[3] 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]

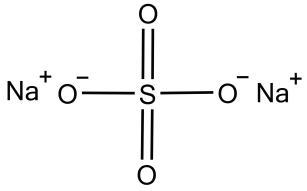

Figure 1. Sodium Sulfate

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, in a 200 mg sample, NMT 0.003% (selenium) in Sodium Sulfate used in food.[4]

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 on the basis of the expected use in cosmetics and potential exposure. The Panel utilizes expected use and exposure data received from the U.S. Food and Drug Administration (FDA) and from the cosmetics industry in determining ingredient safety. The data received from the FDA are those collected from manufacturers on the use of individual ingredients in cosmetics, by product category, in its Voluntary Cosmetic Registration Program (VCRP). Data from the cosmetic industry are

submitted in response to a survey of maximum use concentrations, by product category, conducted by the Personal Care Products Council (Council).

VCRP data obtained from the FDA in 2016[5] indicate that Sodium Sulfate is used in cosmetic formulations. Sodium Sulfate is reported to be used in 777 cosmetic formulations[5] compared to 28 uses reported originally[1] (Table 1). Frequencies of use notably increased compared to originally reported values as follows (reported uses in 2016[5] vs. originally reported uses[1]): leave-on (86 vs. 13), rinse-off (661 vs. 3), diluted for bath use (30 vs. 12), incidental inhalation (35 vs. 7), dermal contact (304 vs. 28), and mucous membrane (215 vs. 15) (Table 1). Uses not reported in the original assessment were reported in 2016[5] as follows: eye area (11 uses), incidental ingestion (1 use), deodorant (2 uses), hair non-coloring (127 uses), hair coloring (325 uses), nail (11 uses), and baby products (7 uses) (Table 1).

The concentrations of use reported in the original safety assessment were not received from the FDA or the Council industry survey; they are not necessarily a comprehensive representation of concentrations in use at that time. The concentrations reported originally were from two separate submissions of unpublished data from industry.[1] The results of the concentration of use survey (Table 1) conducted by the Council in 2015-2016[6] indicate Sodium Sulfate is used at up to 96.4% (96.3% in original report[1]) in diluted for-bath use formulations. In rinse-off formulations the maximum concentration of use for Sodium Sulfate in 2015-2016 is 6%[6] (5% reported originally[1]). 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 aids[6] (0.5% in facial lotion and facial toner reported originally[1]). In the product category, hair non-coloring, the maximum concentration of use reported increased from 1%[1] (original report) to 2.5% in 2015-2016.[6] There was no substantial increase in concentration of use from the original report compared to 2015-2016 reported use for the product categories dermal contact and mucous membrane. 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%).[6]

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 hair preparation formulations[5], 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 survey[6]. Therefore, it should be presumed that there is at least one use in every category for which a concentration is reported.

Sodium Sulfate was reported to be used in cosmetic sprays and powders in 2015-2016 including, face powders (up to 0.5%), fragrance preparations (up to 0.03%), hair tonics (up to 2.0%), and other propellant and pump spray products, and could possibly be inhaled.[6] 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.[7-10] 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.[7,8]

Sodium Sulfate anhydrous (7757-82-6) is not restricted from use in any way under the rules governing cosmetic products in the European Union.[3]

Non-Cosmetic

According to the Code of Federal Regulations section on indirect food additives that are GRAS, Sodium Sulfate's use is noted 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 with no limitations as an indirect food additive 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.[4]

Sodium Sulfate is listed as an ingredient on drug labels associated with colonic preparations because of its laxative effect.[11]

TOXICOKINETICS

Animal

Oral studies conducted in rats showed that Sodium Sulfate was absorbed by the gut. One experiment noted 57-74% of radioactive Sodium Sulfate was excreted in the urine within 24 hours post-administration.[1] In another study 90% of the dose of Sodium Sulfate was recovered in the urine within 24 hours of oral administration. A test in which radioactive Sodium Sulfate 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. 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

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. A test in subjects receiving an intravenous dose of 1.1 Mbq (30μCi) radiolabeled Sodium Sulfate revealed that 88% was recovered in the urine by 24 hours.

TOXICOLOGICAL STUDIES

Single Dose (Acute) Toxicity

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.[3] 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 LD_{50} > 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/m^3 Sodium Sulfate) and rabbits (1 hour exposure to 2000 μg/m^3 Sodium Sulfate) without notable adverse effects.

Repeated-Dose Toxicity

Oral

Animal

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 orally administered in the pigs' water at 600, 1200, or 1800 mg/L *ad libitum*. In the fourth week there was an increase in body weight gain with increasing water sulfate concentrations (either Sodium Sulfate alone or Magnesium Sulfate alone) at 600 or 1800 mg/L as compared to the control group. When Sodium Sulfate and Magnesium Sulfate were administered concurrently in the same test group this trend was not

observed at any of the above concentrations (e.g. Sodium Sulfate and Magnesium Sulfate each at 600 mg/L in one test group; Sodium Sulfate and Magnesium Sulfate each at 1200 mg/L in another test group, etc.). There were no changes in feed consumption or feed-to-body weight gain ratios compared to the control group. At 1800 mg/L sulfate concentration (combined Sodium Sulfate and Magnesium Sulfate) an increase in water consumption was observed. Increased incidence of diarrhea was correlated with sulfate concentrations 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 diarrhea did not negatively impact growth rate, increase mortality, or increase post-weaning pathogens.

Human

There was a 14 day study in subjects (with a history of colonic polyps) that were 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/m^3 *no abnormalities associated with long-term exposure were found.*[1]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Oral

Studies were conducted in Wistar rats to evaluate the effect of Sodium Sulfate on reproduction.[3] 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), 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 for either sex during the length of study. For females, endpoints including 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.[3] Similar parameters were monitored as in the first experiment 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

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.[3] The results were negative for genotoxicity. No cytotoxicity was noted up to 5000 mg/L.

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.[3] The test was performed with and without metabolic activation. The exposure time of experiment 1 was 4 hours with and without metabolic activation. The exposure times 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.[3] 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.[3] 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 duration was 24 hours without metabolic activation and 4 hours with metabolic activation. Test concentrations used for 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 presence of metabolic activation. Therefore, Sodium Sulfate was not found to induce mutations in the mouse lymphoma thymidine kinase locus assay (cell line L5178Y).

COCARCINOGENICITY

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 mmoles/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-dimethylaminoazobenzine) 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 equimolar ratios resulted in partially restoring leukemogenicity of N-[4-(5-nitro-2-furyl)-2-thiazolyl]acetamide (NFTA). A test in which rats had consumed 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.

IRRITATION AND SENSITIZATION

Dermal Irritation and Sensitization

Animal

A 3-month dermal toxicity study was conducted using OECD Guideline 411-Subchronic Dermal Toxicity: 90-Day Study, to determine the effects of Sodium Sulfate on New Zealand White rabbits (n=5 males/5 females per test group).[3] Sodium Sulfate was administered as a positive control in 65 treatments spanning 91 days percutaneously (no further details on exposure route or administration 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) established for Sodium Sulfate in this experiment was 16% (w/w) Sodium Sulfate solution administered 2 mL/kg/day.

An *in vivo* (GLP) study was conducted in accordance with OECD Guideline 404-Acute Dermal Irritation/Corrosion, evaluating the effect of Sodium Sulfate on rabbits (n=3).[3] Occlusive patches containing 500 mg Sodium Sulfate in

polyethyleneglycol 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.

A Guinea Pig Maximization Test (GLP) in male albino Dunkin-Hartley guinea pigs was conducted to determine the cutaneous allergenic potential of Sodium Sulfate.[3] 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 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 were 1:1 (v/v) Freund's Complete Adjuvant and physiological saline mixture, 25% Sodium Sulfate in PEG 300, and 25% Sodium Sulfate in a 1:1 (v/v) mix of Freund's Complete Adjuvant and physiological saline. Control groups were 1:1 (v/v) mix of Freund's Complete Adjuvant and physiological saline, PEG 300, and 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.[3] 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.[3] 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

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 ± on a 0 to 4± 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 (±). 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 35subjects in a 21 day study. Overall the formulation was deemed to be mildly irritating. 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 61subjects. The only notable result was a mild erythema reaction in one subject with no reactions noted during challenge.

Ocular Irritation

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

In 2000, the CIR Expert Panel 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 when 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 in 2000. 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 in 2016 vs. uses in 2000): leave-on (86 vs. 13), rinse-off (661 vs. 3), and diluted for bath use (30 vs. 12). The product categories for which no uses were reported in the original assessment, have reported uses in 2016 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 not necessarily a comprehensive 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 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 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 2%. The product categories for which no concentrations were reported in the original assessment, have concentrations reported in 2015-2016 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 LD_{50} > 2000 mg/kg/ in female rats.

In a 4-week repeated-dose study in nursery pigs orally administered Sodium Sulfate 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 mg/L, 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. Guinea pigs cutaneously exposed to 3% Sodium Sulfate in PEG 300 in a Guinea Pig Maximization Test were observed to have discrete/patchy to moderate and confluent erythema and scaling reported at 24 and 48-hours. Sodium Sulfate was deemed to be non-sensitizing to guinea pig skin as a result of this test.

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[5]	**2000[1]**	**2015-2016[6]**	**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

REFERENCES

1. Madhaven BN. Final Report on the Safety Assessment of Sodium Sulfate. *International Journal of Toxicology*. 2000;19(Suppl. 1):77-87. www.cir-safety.org/ingredients.

2. Nikitakis J and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 15 *ed*. Washington, D.C.: Personal Care Products Council, 2014.

3. European Chemical Agency (ECHA). sodium sulphate (CAS # 7757-82-6). http://echa.europa.eu/registration-dossier/-/registered-dossier/15539. Last Updated 2016. Date Accessed 2-22-2016.

4. United States Pharmacopeia (USP). Food Chemicals Codex. 8th *ed*. Baltimore: United Book Press, Inc., 2012.

5. Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database.* 2016.

6. Personal Care Products Council. 2016. Concentration of Use by FDA Product Category: Sodium Sulfate (Dated Feb 8).

7. Rothe H, Fautz R, Gerber E, Neumann L, Rettinger K, Schuh W, and Gronewold C. Special Aspects of Cosmetic Spray Safety Evaluations: Principles on Inhalation Risk Assessment. *Toxicology Letters*. 2011;205(2):97-104.

8. Bremmer HJ, Prud'homme de Lodder LCH, and van Engelen JGM. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. 2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Date Accessed 8-24-2011. Report No. RIVM 320104001/2006. pp. 1-77.

9. Rothe H. 2011. Special Aspects of Cosmetic Spray Safety Evaluation. Unpublished information presented to the 26 September CIR Expert Panel. Washington, D.C.

10. Johnson MA. The Influence of Particle Size. *Spray Technology and Marketing*. 2004. (November): pp.24-27.

11. National Institute of Health National Library of Medicine Daily Med (Daily Med). Sodium Sulfate. http://dailymed.nlm.nih.gov/dailymed/search.cfm?labeltype=human&query=sodium+sulfate&pagesize=200&page=1. Last Updated 2015. Date Accessed 9-24-2015.

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 $Na_2SO_4 \cdot 10H_2O$.

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

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[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Bindu Nair Madhaven, former Scientific Analyst and Writer, prepared this report. Address correspondence to Dr. F. Alan Andersen, Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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1071-7544/00 $12.00 + .00

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.

REFERENCES

Amdur, M. O., J. Bayles, V. Ugro, and D. W. Underhill. 1978. Comparative irritant potency of sulfate salts. *Environ. Res.* 16:1–8.

Arcuri, P. A., and R. F. Gautieri. 1973. Morphine-induced fetal malformations 3: Possible mechanism of action. *J. Pharm. Sci.* 62:1626–1634.

Balchum, O. J., J. Dybicki, and G. R. Meneely. 1960. Dynamics of sulfur dioxide inhalation. *A.M.A. Arch. Ind. Health* 21:564–569.

Blunck, J., and C. Crowther. 1975. Enhancement of azo dye carcinogenesis by dietary sodium sulphate. *Eur. J. Cancer* 11:23–32.

Boström, H., and S. Aqvist. 1952. Utilization of S35-labeled sodium sulfate in the synthesis of chondroitin sulfuric acid, taurine, methionine, and cystine. *Acta. Chem. Scand.* 6:1557–1559.

Brookfield, R. W. 1934. The effect of injecting some calcium and magnesium salts, as well as inorganic phosphate, on rabbit serum. *Biochem. J.* 28:725–733.

Budavari, S., ed. 1989. *The Merck index. An encyclopedia of chemicals, drugs and biologicals.* 10th ed., 1368. Rahway, NJ: Merck and Co., Inc.

Burke, B. J., and G. E. Staddon. 1983. The radiation dose to man following the intravenous injection of radiosulphate ($Na_2(35)SO_4$). *Int. J. Appl. Radiat. Isot.* 34:1139–1141.

Campbell, N. R., R. S. Sundaram, P. G. Werness, and J. Van Loon. 1985. Sulfate and methyldopa metabolism: Metabolite patterns and platelet phenol sulfotransferase activity. *Clin. Pharmacol. Ther.* 37:308–315.

Casto, B. C., J. Meyers, and J. A. Dipaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. *Cancer Res.* 39:193–198.

Chabrol, E., and M. Maximin. 1929. Research experiments on intravenously administered chologogues. *Presse Med.* 37:666–669.

Chemline. 1995. Chemical tradenames. *Chemline Database.* Bethesda: National Library of Medicine.

Cocchetto, D. M., and G. Levy. 1981. Absorption of orally administered sodium sulfate in humans. *J. Pharm. Sci.* 70:331–333.

Cohen, S. M., and G. T. Bryan. 1978. Effect of p-hydroxyacetanilide, sodium sulfate, and L-methionine on the leukemogenicity of N-(4-(5-nitro-2-furyl)-2-thiazolyl) lacetamide. *Cancer Res.* 38:1398–1405.

Cosmetic, Toiletry and Fragrance Association (CTFA). 1976. Allergic contact sensitization test: Sodium Sulfate. No. 003-76. Submission of unpublished data by The Cosmetic, Toiletry and Fragrance Association (CTFA). Received June 19, 1996. (9 pages.)[2]

CTFA. 1985. Human patch test: Sodium Sulfate. Submission of unpublished data by CTFA. Received June 19, 1996. (1 page.)[2]

CTFA. 1990. Modified Chamber patch test results: Sodium Sulfate. Test No. 677-90. Submission of unpublished data by CTFA. Received June 19, 1996. (4 pages.)[2]

CTFA. 1996a. Use levels for various ingredients. Submission of unpublished data by CTFA. Received September 5, 1996. (1 page concerning Sodium Sulfate.)[2]

CTFA. 1996b. Concentration of Sodium Sulfate in Company products. Submission of unpublished data by CTFA. Received September 24, 1996. (1 page.)[2]

Dohlman, C.-H. 1957. Incorporation of radioactive sulfate into the rabbit eye. *Acta Ophthalmol.* 35:115–130.

Duhm, J., B. Deuticke, and E. Gerlach. 1969. Metabolism of 2,3-diphosphoglycerate and glycolysis in human erythrocytes. The influence of sulfate, tetrathionate and disulfite. *Hoppe-Seyler's Zeitschrit Physiol. Chem.* 350:1008–1016.

Dziewiatkowski, D. D. 1949. Rate of excretion of radioactive sulfur and its concentration in some tissues of rat after intraperitoneal administration of labeled sodium sulfate. *J. Biol. Chem.* 178:197–202.

Food and Drug Administration (FDA). 1978. Sulfuric Acid and Ammonium, Calcium, Potassium, and Sodium Sulfates; proposed affirmation of GRAS status as direct and indirect human food ingredients. Proposed Rule. *Fed. Register* 43:12874–12876.

FDA. 1980. Sulfuric Acid and Ammonium, Calcium, Potassium, and Sodium Sulfates; affirmation of GRAS status. Final rule. *Fed. Register* 45:6084–6086.

FDA. 1992. Modification in Voluntary Filing of Cosmetic Product Ingredient and Cosmetic Raw Composition Statements. Final rule. *Fed. Register* 57:3128–3130.

FDA. 1997. Frequency of use of cosmetic ingredients. *FDA database.* Washington: FDA.

Food and Agriculture Organization of the United Nations/World Health Organization (FAO/WHO). *1994 Summary of evaluations performed by the Joint FAO/WHO Expert Committee on Food Additives (JECFA).* Washington D.C.: International Life Sciences Institute.

[2]Available for review: Director, Cosmetic Ingredient Review, 1101 17th St., NW, Suite 310, Washington, DC 20036-4702, USA.

Franklin Institute Research Laboratories. 1973. GRAS (Generally Recognized as Safe) food ingredients-sulfates. NTIS/order No. PB-221-234. Springfield, VA: NTIS.

Foulks, J. G. 1955. Homeostatic adjustment in the renal tubular transport of inorganic phosphate in the dog. *Can. J. Biochem. Physiol.* 33:638–650.

Galinsky, R. E., and G. Levy. 1984. Evaluation of activated charcoal-sodium sulfate combination for inhibition of acetaminophen absorption and repletion of inorganic sulfate. *J. Toxicol. Clin. Toxicol.* 22:21–30.

Galinsky, R. E., J. T. Slattery, and G. Levy. 1979. Effect of sodium sulfate on acetaminophen elimination by rats. *J. Pharm. Sci.* 68:803–805.

Griffith, J. F., G. A. Nixon, R. D. Bruce, P. J. Reer, and E. A. Bannan. 1980. Dose-response studies with chemical irritants in the albino rabbit eye as a basis for selecting optimum testing conditions for predicting hazard to the human eye. *Toxicol. Appl. Pharmacol.* 55:501–513.

Hill Top Research, Inc. 1985. Report of a human skin test of cumulative irritation: Sodium Sulfate. Report No. 85-1248-72E. Submission of unpublished data by CTFA. Received September 16, 1996. (18 pages.)[2]

Hill Top Research, Inc. 1989. Primary irritation patch test: Sodium Sulfate. Report No. 89-1889-74. Submission of unpublished data by CTFA. Received September 16, 1996. (20 pages.)[2]

Hjelle, J. J., E. A. Brzeznicka, and C. D. Klaassen. 1986. Comparison of the effects of sodium sulfate and N-acetylcysteine on the hepatotoxicity of acetaminophen in mice. *J. Pharmacol. Exp. Ther.* 236:526–534.

Hwang, K. 1966. Mechanism of the laxative effect of sodium sulfate, sodium cyclamate and calcium cyclamate. *Arch. Int. Pharmacodyn. Ther.* 163:302–340.

Kashtan, H., R. C. Gregoire, W. R. Bruce, K. Hay, and H. S. Stern. 1990. Effects of sodium sulfate on fecal pH and proliferation of colonic mucosa in patients at high risk for colon cancer. *J. Natl. Cancer Inst.* 82:950–952.

Kelada, F., and L. E. Euinton. 1978. Health effects of long-term exposure to sodium sulfate dust. *J. Occup. Med.* 20:812–814.

Keller, W. C., and R. A. Yeary. 1980. A comparison of the effects of mineral oil, vegetable oil, and sodium sulfate on the intestinal absorption of DDT in rodents. *Clin. Toxicol.* 16:223–231.

Kezhou, W., H. D. Stowe, A. M. House, K. Chou, and T. Thiel. 1987. Comparison of cupric and sulfate ion effects on chronic selenosis in rats. *J. Anim. Sci.* 64:1467–1475.

Knight, E., J. Van Wart, and D. A. Roe. 1978. Effect of salicylamide on the placental transfer and fetal tissue distribution-sulfur-35-labeled sulfate in the rat. *J. Nutr.* 108:216–225.

Kowarski, A., C. Kowarski, and S. E. Berman. 1961. Inhibition of calcium absorption from milk by sodium sulfate. A metabolic balance study in rats. *Bull. Res. Counc. Isr. Set. E. Exp. Med.* 9E:181.

Krijgsheld, K. R., H. Frankena, E. Scholtens, J. Zweens, and G. J. Mulder. 1979. Absorption, serum levels and urinary excretion of inorganic sulfate after oral administration of sodium sulfate in the conscious rat. *Biochim. Biophys. Acta* 586:492–500.

Lewis, R. J., Sr. 1993a. *Hazardous chemicals desk reference*, 3rd ed., 1173. New York: Van Nostrand Reinhold Co.

Lewis, R. J., Sr. 1993b. *Hawley's condensed chemical dictionary*, 12th ed., 1069–1070. New York: Van Nostrand Renhold.

Lin, J. H., and G. Levy. 1986. Effect of prevention of inorganic sulfate depletion on the pharmacokinetics of acetaminophen in rats. *J. Pharmacol. Exp. Ther.* 239:94–98.

Mattila, M. J., S. Takki, and J. Jussila. 1974. Effect of sodium sulfate and castor oil on drug absorption from the human intestine. *Ann. Clin. Res.* 6:19–24.

Moinuddin, J. F., and H. W.-T. Lee. 1960. Alimentary, blood and other changes due to feeding $MnSO_4$, $MgSO_4$ and Na_2SO_4. *Am. J. Physiol.* 199:77–83.

Morris, M. E., and G. Levy. 1983. Serum concentration and renal excretion by normal adults of inorganic sulfate after acetaminophen, ascorbic acid, or sodium sulfate. *Clin. Pharmacol. Ther.* 33:529–536.

National Academy of Sciences (NAS). 1981. *Food chemicals codex*, 3rd ed., 302–303. Washington, DC: National Academy Press.

Nikitakis, J. M., and G. N. McEwen Jr., eds. 1990. *CTFA compendium of cosmetic ingredient composition—specifications*. Washington, DC: CTFA.

Odeblad, E., and H. Boström. 1952. An autoradiographic study of the incorporation of S35-labeled sodium sulfate in different organs of adult rats and rabbits. *Acta Pathol. Microbiol. Scand* 31:339–344.

Registry of Toxic Effects of Chemical Substances (RTECS). 1995. Online printout on Sodium Sulfate from the Toxnet System. Bethesda, MD: National Library of Medicine.

Rempe, J. M., and L. G. Santucci. 1997. *CTFA list of Japanese cosmetic ingredients*, 3rd ed., 118. Washington, DC: CTFA.

Rossman, T. G., M. Molina, L. Meyer, P. Boone, C. B. Klein, Z. Wang, F. Li, W. C. Lin, and P. L. Kinney. 1991. Performance of 133 compounds in the lambda prophage induction endpoint of the Microscreen assay and a comparison with *S. typhimurium* mutagenicity and rodent carcinogenicity assays. *Mutat. Res.* 260:349–367.

Rothschild, D. L., Jr. 1990. *The Food Chemical News Guide*. Washington, DC: author.

Sackner, M. A., G. A. Chapman, J. Cipley, M. Kwoka, M. Reinhart, M. Brito, R. Schreck, and R. L. Dougherty. 1981. Effects of brief and intermediate exposures to sulfate submicron aerosols and sulfate injections on cardiopulmonary function of dogs and tracheal mucous velocity of sheep. *J. Toxicol. Environ. Health* 7:951–972.

Sackner, M. A., D. Ford, and C. Kim. 1979. Effect of brief exposure to high concentrations of sodium chloride and sodium sulfate aerosols with mass median aerodynamic diameter of 0.5 micrometers on pulmonary function of normal and asthmatic adults. *Am. Rev. Resp. Dis.* 119(4 part 2): 233.

Samelson, S. L., R. L. Nelson, and L. M. Nyhus. 1985. Protective role of faecal pH in experimental colon carcinogenesis. *J. R. Soc. Med.* 78:230–233.

Sax, N. I. 1979. *Dangerous properties of industrial materials*, 5th ed., 989. New York: Van Nostrand Reinhold Co.

Schlesinger, R. B. 1984. Comparative irritant potency of inhaled sulfate aerosols—effects on bronchial mucociliary clearance. *Environ. Res.* 34:268–279.

Seidenberg, J. M., D. G. Anderson, and R. A. Becker. 1986. Validation of an in vivo developmental toxicity screen in the mouse. *Teratog. Carcinog. Mutagen* 6:361–374.

Seidenberg, J. M., and R. A. Becker. 1987. A summary of the results of 55 chemicals screened for developmental toxicity in mice. *Teratog. Carcinog. Mutagen* 7:17–28.

Seldin, D. W., A. J. Coleman, N. W. Carter, and F. C. Rector. 1967. The effect of Na_2SO_4 on urinary acidification in chronic renal disease. *J. Lab. Clin. Med.* 69:893–903.

Slattery, J. T., and G. Levy. 1977. Reduction of acetaminophen toxicity by sodium sulfate in mice. *Res. Commun. Chem. Pathol. Pharmacol.* 18:167–170.

Taylor, E. J., ed. 1988. *Dorland's illustrated medical dictionary*, 27th ed. Philadelphia, PA: WB Saunders Co.

USP. 1995. *The United States pharmacopeia: the national formulary*, 23rd rev. Rockville, MD: United States Pharmacopeial Convention, Inc.

Wenninger, J. A., R. C. Canterbery, and G. N. McEwen., eds. 2000. *International cosmetic ingredient dictionary and handbook*, 8th ed., Vol. 2, 1398. Washington, DC: CTFA.

Yamamoto, R. S., G. M. Williams, H. L. Richardson, E. K. Weisburger, and J. H. Weisburger. 1973. Effect of p-hydroxyacetanilide on liver cancer induction by N-hydroxy-N-2-fluorenylacetamide. *Cancer Res.* 33:454–457.

VCRP Data For Sodium Sulfate-2016

7727733	SODIUM SULFATE	01A - Baby Shampoos	5
7727733	SODIUM SULFATE	01C - Other Baby Products	2
7727733	SODIUM SULFATE	02A - Bath Oils, Tablets, and Salts	11
7727733	SODIUM SULFATE	02B - Bubble Baths	8
7727733	SODIUM SULFATE	02D - Other Bath Preparations	4
7727733	SODIUM SULFATE	03D - Eye Lotion	1
7727733	SODIUM SULFATE	03F – Mascara	9
7727733	SODIUM SULFATE	03G - Other Eye Makeup Preparations	1
7727733	SODIUM SULFATE	05A - Hair Conditioner	36
7727733	SODIUM SULFATE	05C - Hair Straighteners	1
7727733	SODIUM SULFATE	05F - Shampoos (non-coloring)	71
7727733	SODIUM SULFATE	05G - Tonics, Dressings, and Other Hair Grooming Aids	10
7727733	SODIUM SULFATE	05I - Other Hair Preparations	4
7727733	SODIUM SULFATE	06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	320
7727733	SODIUM SULFATE	06D - Hair Shampoos (coloring)	3
7727733	SODIUM SULFATE	06H - Other Hair Coloring Preparation	2
7727733	SODIUM SULFATE	07C – Foundations	1
7727733	SODIUM SULFATE	07D - Leg and Body Paints	1
7727733	SODIUM SULFATE	08A - Basecoats and Undercoats	1
7727733	SODIUM SULFATE	08C - Nail Creams and Lotions	2
7727733	SODIUM SULFATE	08E - Nail Polish and Enamel	5
7727733	SODIUM SULFATE	08G - Other Manicuring Preparations	3
7727733	SODIUM SULFATE	10A - Bath Soaps and Detergents	128
7727733	SODIUM SULFATE	10B - Deodorants (underarm)	2
7727733	SODIUM SULFATE	10E - Other Personal Cleanliness Products	53
7727733	SODIUM SULFATE	11E - Shaving Cream	2
7727733	SODIUM SULFATE	11G - Other Shaving Preparation Products	1
7727733	SODIUM SULFATE	12A – Cleansing	29
7727733	SODIUM SULFATE	12C - Face and Neck (exc shave)	4

VCRP Data For Sodium Sulfate-2016 (con't)

7727733	SODIUM SULFATE	12D - Body and Hand (exc shave)	9
7727733	SODIUM SULFATE	12F - Moisturizing	19
7727733	SODIUM SULFATE	12H- Paste Masks (mud packs)	6
7727733	SODIUM SULFATE	12I - Skin Fresheners	4
7727733	SODIUM SULFATE	12J - Other Skin Care Preps	6
7727733	SODIUM SULFATE	13B - Indoor Tanning Preparations	2
7757826	SODIUM SULFATE, ANHYDROUS	02A - Bath Oils, Tablets, and Salts	5
7757826	SODIUM SULFATE, ANHYDROUS	02B - Bubble Baths	2
7757826	SODIUM SULFATE, ANHYDROUS	09A-Dentifrices	1
7757826	SODIUM SULFATE, ANHYDROUS	10A - Bath Soaps and Detergents	2
7757826	SODIUM SULFATE, ANHYDROUS	10E - Other Personal Cleanliness Products	1

Concentration of Use by FDA Product Category – Sodium Sulfate

Product Category	Maximum Concentration of Use
Baby shampoo	0.05-0.29%
Baby lotions, oils and creams	
Not powder	0.000065-0.01%
Other baby products	0.000002-0.035%
Bath oils, tablets and salts	0.00053-96.4%
Bubble baths	0.094-3.5%
Other bath preparations	0.12%
Eyeliners	0.0005-0.0012%
Eye lotions	0.000046%
Eye makeup removers	0.0064%
Mascara	0.005%
Other eye makeup preparations	0.00025%
Colognes and toilet waters	0.01%
Other fragrance preparations	0.03%
Hair conditioners	0.0002-0.044%
Hair straighteners	0.00014%
Shampoos (noncoloring)	0.0000002-2.5%
Tonics, dressings and other hair grooming aids	0.03-2%
Not spray	0.013%
Hair dyes and colors	0.000054-3.3%
Hair tints	0.0002%
Hair rinses (coloring)	0.000051%
Hair bleaches	0.16-3.8%
Other hair coloring preparations	0.12%
Face powders	0.5%
Foundations	0.0005-0.48%
Makeup fixatives	0.005%
Basecoats and undercoats (manicuring preparations	0.5%
Cuticle softeners	0.2%
Nail creams and lotions	0.015%
Nail extenders	0.005%
Nail polish and enamel	0.001%
Other manicuring preparations	0.001%
Dentifrices	0.00024-0.83%
Mouthwash and breath fresheners	0.00015-0.0063%
Other oral hygiene products	0.037-0.68%
Bath soaps and detergents	0.00022-4.3%
Deodorants	
Not spray	0.000014-0.3%
Other personal cleanliness products	0.05-0.077%
Aftershave lotions	0.000067-0.03%
Shaving cream	0.0027-0.25%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.03-6%

Face and neck products	
Not spray	0.0051-0.54%
Spray	0.0088%
Body and hand products	
Not spray	0.00023-0.08%
Foot products	0.006%
Moisturizing products	
Not spray	0.0001-0.03%
Night products	
Not spray	0.005%
Skin fresheners	0.5%
Other skin care preparations	0.0002-0.54%
Suntan gels, creams and liquids	
Not spray	0.38%

Information collected 2105-2016

Table prepared February 8, 2016