Amended Safety Assessment of Persulfates as Used in Cosmetics

Status: Re-Review for Panel Review
Release Date: May 13, 2016
Panel Date: June 6-7, 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 report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst and Bart Heldreth, Ph.D., Chemist.

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: May 13, 2016
Subject: Re-review on Persulfates

At the September 10-11, 1998 Expert Panel meeting, the Panel issued a Final Report with the conclusion that Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Final Report was published in 2001. The current safety assessment is a re-review of Persulfates, and contains updated use concentration data and data that have entered the published literature since the Final Report was issued in 1998.

Included in this package for your review is the Re-review document on Persulfates (persul062016rep), the CIR report history (persul062016hist), Literature search strategy (persul062016strat), Ingredient Data profile (persul062016prof), the minutes from prior Panel meetings on Persulfates (persul062016min), 2016 FDA VCRP data (persul062016FDAdata), the 2001 published Final Report on Persulfates (persul062016final), and updated use concentration data on Persulfates (persul062016data 1 and persul062016data2).

After considering the data included in this Re-review document, the Panel will need to determine whether the new data present a reason to reopen the Final Report on Persulfates or if the data reaffirms the original conclusion, in which case the review would not be re-opened.
**RE-REVIEW FLOW CHART**

**INGREDIENT/FAMILY**  Persulfates

**MEETING**  June 2016

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

Ammonium, Potassium, and Sodium Persulfate


The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: The CIR Expert Panel concludes that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief, discontinuous use followed by thorough rinsing from the hair and skin.

**Re-Review, Belsito and Marks Teams/Panel: June 6-7, 2016 (135th)**

Updated use concentration data were received from the Council.
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Literature Searches on Persulfates (1/6-7/2016)

SciFinder/PubMed Searches (Years 1996-2016)

Search Terms

Ammonium Persulfate  
+ (7727-54-0)
Potassium Persulfate  
+ (7727-21-1)
Sodium Persulfate  
+ (7775-27-1)

Search Updates

Search updated on 4-23-2016
Dr. Bergfeld noted that new data on this group of ingredients had been received.

Dr. Belsito said that the new data merely support the studies that are already referenced in the Draft Report, and add very little to the Panel's data needs. He noted that his Team concluded that the available data on the Persulfates are still insufficient for determining safety, and that an Insufficient Data Announcement should be issued. This conclusion is based on the following data that are needed: (1) Concentration of use and length of exposure. Specifically, whether concentrations of > 50% (1984 FDA data) or 20% (as referenced in article by Fisher [198]) are being used in cosmetics needs to be clarified; (2) Human data on the incidence of dermal sensitization, immediate contact urticarial reactions to products at intended concentrations of use; and (3) There was some concern about the lack of teratogenicity data. However, relative to dermal teratogenicity, Dr. Belsito's Team agreed that the Persulfates probably are not teratogens, but would like to review any dermal teratogenicity studies that are available.

Dr. Belsito restated his Team's data requests as follows: (1) Concentration of use and length of exposure, (2) Dermal sensitization, together with immediate urticarial hypersensitivity reactions in humans at use concentrations, and (3) Dermal teratogenicity, if available.

Dr. Shank wanted to know if the sensitization study should be on the pure compound or on a formulation. He noted that the Persulfates become much less active when mixed with other ingredients, and that the Panel already has human sensitization data on Sodium Persulfate indicating that it is a sensitizer at a concentration of 5,000 ppm, but not at 100 ppm.

Dr. Belsito was convinced that a formulation should be tested in the dermal sensitization study.

Dr. Shank noted that Dr. McEwen provided the following concentration of use data on the preceding day: Ammonium Persulfate (8%), Potassium Persulfate (10%), and Sodium Persulfate (6%). Dr. McEwen also mentioned that these ingredients are supplied in powder form. Dr. Shank noted that Dr. McEwen did not provide information on length of exposure.

Dr. Schroeter recalled that the concentration of use data were not provided in writing.

Mr. Heinz Eiermann noted that exposure to Persulfates in hair dyes or hair bleaching products would amount to anywhere from 20 to 40 minutes.

Dr. Belsito noted that according to current frequency of use data received from FDA, Ammonium Persulfate is used in products (categorized as other skin care preparations) other than hair products.

Dr. Bergfeld said that the Panel could restrict the use of Persulfates to hair products in its conclusion.

Dr. Andersen recalled that it had been indicated during discussions on the preceding day that data on use concentrations and length of exposure will likely be made available at a later date. With this in mind, he asked that the Panel's requests for data on use concentrations and length of exposure remain on the list of data requests.

The Panel voted unanimously in favor of issuing an Insufficient Data Announcement on Ammonium, Potassium, and Sodium Persulfates with the following data requests:

(1) Concentration of use and length of exposure
(2) Human sensitization and immediate contact urticarial reactions at use concentrations in formulation
(3) Dermal teratogenicity, if available
Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Belsito noted that current concentration of use data on the Persulfates were received along with correspondence asserting that dermal teratogenicity data are not essential because Persulfates are allowed in foods. Furthermore, in response to the Panel's request for dermal sensitization data of the delayed type and immediate hypersensitivity type, the Panel was informed by industry that these data are not necessary because the number of consumer complaints on products containing Persulfates is not above those reported for other products.

Dr. Belsito agreed that teratogenicity data are no longer needed. However, he disagreed with industry's argument against the need for sensitization data. Dr. Belsito restated the Panel's need for dermal sensitization data as follows: (1) Human delayed-type hypersensitivity testing of contact dermatitis at concentration of use and (2) Human contact urticaria immediate hypersensitivity testing at concentration of use.

Dr. Bergfeld asked Dr. Belsito to clarify his Team's reason for requesting contact urticaria data.

Dr. Belsito noted that the Persulfates clearly are histamine releasers and that the mechanism for this is unclear. However, he said that some individuals may be reacting based upon IgE-mediated hypersensitivity, developing wheal and flare type reactions and asthmatic reactions. Others may be reacting simply on the basis of Persulfate-induced release of histamine from skin mast cells, on a non-immunologic basis (non-immunologic contact urticaria). Dr. Belsito also said that he has no personal knowledge of any data on the dose-response release of histamine by Persulfates or any information on the incidence of Persulfate-induced contact urticaria in the general population.

Dr. Belsito noted that the dose-response release of histamine by Persulfates and the incidence of Persulfate-induced contact urticaria are of concern, even though the Persulfates act primarily as a booster in hair dyes, where use is brief and discontinuous. He also recalled that the Persulfates are strong sensitizers in guinea pigs, hence, the need for more delayed-type testing, and noted that brief exposure is sufficient for the induction of severe contact urticaria by an urticant.

Regarding the information relating to consumer complaints that were submitted, Dr. Belsito said that these data are not useful, because products containing Persulfates are used primarily in hairdressing salons.

Dr. Shank called the Panel's attention to the human RIPT in which concentrations of 10, 100, and 5,000 ppm Sodium Persulfate were applied during induction and challenge phases, respectively. He noted that sensitization was noted at 5,000 ppm, but not at 100 ppm, and wanted to know if these results would alleviate Dr. Belsito's concerns about sensitization.

Dr. Belsito noted that the RIPT was not conducted at use concentrations, and that a 100 ppm concentration limit would not satisfy industry in terms of its use of Persulfates.

Dr. McEwen noted that human data on contact urticaria, human RIPT data (occlusive patches), and consumer complaints data on the Persulfates had been reviewed by the Panel. He said that these data support the conclusion that the Persulfates are safe for use in products designed for brief, discontinuous use, followed by thorough rinsing from the skin.

Dr. Schroeter agreed with Dr. McEwen's conclusion.

Dr. Belsito said that the problem with using repeated insult patch testing to detect contact urticaria is that at the time at which one would expect to see the urticaria, any resulting lesions would be concealed by the patch. Furthermore, when the patches are removed 24 or 48 h later, the urticarial reaction will not be present.

Dr. Schroeter noted that contact urticaria is a rare phenomenon.

Dr. Belsito said that contact urticaria is a well-reported phenomenon; however, its incidence is not known. He also noted that Persulfates have been removed from flour bleaches in Europe because of this problem.
Dr. McEwen said that if further testing of Persulfates is being proposed, then testing will have to be done at exposures that would be expected to occur. He was concerned that the exposures in such a test would not be considered long enough in duration by the Panel, and that the results would be rejected.

Dr. Belsito proposed the following sensitization test protocol, which would simulate actual use conditions of Persulfate products: Subjects for this type of study would include 100 women who are in the process of having their hair bleached. Following product use, the scalp of each subject would be examined by a dermatologist for evidence of an urticarial reaction. Furthermore, patch test an additional group of 100 women who have been exposed to Ammonium Persulfate (e.g. hair color changed to light shades of blonde) at the standard patch test concentration of 2.0% aqueous and determine the incidence of sensitization. Dr. Belsito emphasized that it is likely that contact urticaria could be observed under conditions of brief, discontinuous use.

Dr. Bergfeld noted that patch testing is recommended for hair dyes, and that it may be reasonable to suggest in the report discussion that products containing Persulfates should be patch tested. She recalled that Persulfates act as a booster in hair dyes.

Dr. McEwen said that relative to hair dye use, Persulfates are used to promote the hair lightening process prior to dye application. He said that he does not see the need for a warning statement concerning the use of Persulfate bleaching products.

Dr. Bergfeld noted that the Panel has the option of either tabling its review of Persulfates and referring the Draft Report back to Teams or issuing a Tentative Report with an insufficient data conclusion.

Dr. McEwen said that the Panel also has the option of concluding that the Persulfates are safe for use in products designed for brief, discontinuous use, followed by thorough rinsing from the skin.

In response to the Panel's request, Dr. Belsito restated his original motion as follows: The data are insufficient for ruling on the safety of Ammonium, Potassium, and Sodium Persulfate. Thus, the following data are needed: (1) Human delayed-type hypersensitivity (i.e. allergic contact dermatitis) data, under the concentrations and conditions of use and (2) Human contact urticaria data, under the concentrations and conditions of use. In other words, results indicating the incidences of these two types of diseases (human delayed-type hypersensitivity and contact urticaria) are needed.

The Panel voted unanimously in favor of issuing a Tentative Report on Ammonium, Potassium, and Sodium Persulfate with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of these ingredients (mentioned in preceding paragraph) will be listed in the discussion section of the report.
Day 2 of the December 11-12, 1995 (57th) CIR Expert Panel Meeting

**Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate**

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: The CIR Expert Panel concludes that the available data are insufficient to support the safety of Ammonium, Sodium, and Potassium Persulfate for use in cosmetic products. The following data that are needed in order for the Panel to complete its safety assessment are included in the report discussion as follows:

1. Human delayed-type hypersensitivity data, i.e. allergic contact dermatitis, at use concentrations and conditions
2. Human immediate contact urticaria reactions at use concentrations and conditions

Day 2 of the March 4-5, 1996 (58th) CIR Expert Panel Meeting

**Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate**

Dr. Bergfeld noted that the Panel voted in favor of issuing a Final Report, with an insufficient data conclusion, on the Persulfates at the December 1995 Panel meeting. Dr. Andersen was asked to present Dr. Bergfeld's administrative decision relative to this action.

Dr. Andersen noted that, relative to the insufficient data conclusion that was approved, the Panel determined that the following data are needed for completion of the safety assessment of Ammonium, Sodium, and Potassium Persulfate: (1) Human delayed-type hypersensitivity data, i.e. allergic contact dermatitis, at use concentrations and conditions and (2) Human immediate contact urticaria reactions at use concentration and conditions. He then recalled that during the Panel's discussion on Persulfates at the December 1995 Panel meeting, an offer by industry to develop and provide these data was accidentally overlooked. With this in mind, any final decision concerning the safety of Persulfates should have been tabled (pending data) at that meeting. Thus, Dr. Andersen recommended and Dr. Bergfeld agreed that CIR would not issue the Final Report on Persulfates that was approved.

The Panel agreed with Dr. Bergfeld's action and based on industry's commitment to provide data, the Panel voted unanimously in favor of rescinding its previous decision and tabling the report on Persulfates pending data.

Day 2 of the September 19-20, 1996 (60th) CIR Expert Panel Meeting

**Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate**

Dr. Andersen noted that the testing of Ammonium, Potassium, and Sodium Persulfate has begun. He anticipated that a progress report on these ongoing tests will be given at the December Panel meeting.

Day 2 of the December 16-17, 1996 (61st) CIR Expert Panel Meeting

**Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate**

Dr. Andersen informed the Panel that the clinical studies on Ammonium, Potassium, and Sodium Persulfate promised by industry are ongoing and that the study results will be made available in 1997.
Day 2 of the April 3-4, 1997 (62nd) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Andersen said that CIR has received a commitment from industry to perform the necessary studies on Ammonium, Potassium, and Sodium Persulfate. He urged industry to complete these studies in a timely fashion.

Dr. McEwen noted that the study is underway.

Day 2 of the June 5-6, 1997 (63rd) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Andersen reported that these ingredients are under test by industry. He said that he is hopeful that the studies can be completed and made available for consideration at the September 22-23, 1997 Panel meeting.

Day 2 of the September 22-23, 1997 (64th) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Andersen reported that these ingredients are under test by industry. He said that he is hopeful that the studies can be completed and made available for consideration at the December 8-9, 1997 Panel meeting.

Day 2 of the December 8-9, 1997 (65th) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Andersen informed the Panel that the studies on these ingredients have been completed and data are being analyzed in preparation for submission.

Day 2 of the March 19-20, 1998 (66th) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Schroeter noted that at the December 11, 1995 Panel meeting, the last time this group of ingredients was reviewed, the Panel expressed concern over the human delayed hypersensitivity data (allergic contact dermatitis at ingredient use concentrations and conditions) and immediate contact urticaria reactions at use concentrations and conditions. He also said that industry has provided the Panel with data (from Dr. Jordan's laboratory), which is more than adequate to answer these issues. Dr. Schroeter said that his Team recommended that these data be incorporated into the current report (in text and in report discussion), and that the Persulfates are safe as used at the current concentrations of use.

Dr. Belsito said his Team concluded that each of the Persulfates is safe for use as an oxidizing agent in hair colorants and lighteners designed for brief, discontinuous use followed by thorough rinsing from the skin.
Dr. Belsito also said that it should be pointed out in the discussion that while urticaria was not seen at a use concentration of 17.5%, information in the CIR report indicates that the Persulfates can be used at concentrations up to 60%. He added that the Panel does not know the threshold for inducing urticaria, and that in using the Persulfates at concentrations > 17.5%, manufacturers should be aware of the clinical case reports of urticaria.

Dr. Bergfeld noted that both Teams are in agreement with Dr. Belsito’s comments for the report discussion.

The Panel voted unanimously in favor of issuing a Revised Tentative Report with the following conclusion: The CIR Expert Panel concludes that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin.

It is important to note that the Panel issued a Tentative Report with an insufficient data conclusion on the Persulfates at the August 28-29, 1995 Panel meeting and a Final Report with the same conclusion at the December 10-11, 1995 Panel meeting. Because the Final Report discussion and conclusion have been revised, the report must now be reissued as a Revised Tentative Report.

Day 2 of the September 10-11, 1998 (68th) CIR Expert Panel Meeting

**Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate**

The Panel voted unanimously in favor of issuing a Final Report with the following conclusion: The CIR Expert Panel concludes that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief, discontinuous use followed by thorough rinsing from the hair and skin.

Dr. McEwen expressed concern over the inclusion of a statement on the Panel’s prior data needs on this group of ingredients in the report discussion, taking into consideration that these data have been received and incorporated into the current document.

Dr. Andersen proposed that this type of language remain in a document up to the Tentative Report stage, so that those reviewing it will be knowledgeable of the review history. He agreed that information on the review history should not be included in the discussion section of the Final Report.

Dr. Bergfeld indicated that the Final Report discussion will be revised based on the preceding comments.
Amended Safety Assessment of Persulfates as Used in Cosmetics

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INTRODUCTION

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are inorganic salts that are used as oxidizing agents in cosmetic products. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) issued a final report (published in 2001) with the conclusion that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. Additional safety test data have entered the literature since this final report was published, and the safety of these ingredients in cosmetics is re-reviewed in this report. Chemistry and safety test data from the final report are italicized in the text of this re-review document. Only data that were not included in the published final report are included in the report summary. The report summary is followed by the discussion and conclusion sections from the published final report.

CHEMISTRY

Definition and Structure

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are inorganic salts, and definitions and structures of these ingredients are presented in Table 1. The structure of Ammonium Persulfate is also presented below.

![NH₄⁺]

NH₄⁺

Additional chemical/physical properties of these ingredients are presented in Table 2.

Method of Manufacture

Ammonium Persulfate

Ammonium Persulfate is prepared by electrolysis of a concentrated solution of ammonium sulfate.

Potassium Persulfate

Potassium Persulfate is prepared by electrolysis of a concentrated solution of potassium sulfate.

Sodium Persulfate

Sodium Persulfate is manufactured by the conversion of Ammonium Persulfate with lye.
Composition/Impurities

Ammonium Persulfate

The following specifications for Ammonium Persulfate have been reported: sulfate ash (0.05%), arsenic (3 ppm), iron (5 ppm), and lead (20 ppm).¹

USE

Cosmetic

The safety of the persulfates included in this safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA’s Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data indicate that Ammonium, Potassium, and Sodium Persulfate are currently being used in cosmetic products (Table 3).⁵,⁶

According to 2016 VCRP data, the greatest reported use frequency is for Potassium Persulfate (67 product formulations, all rinse-off products), followed by Sodium Persulfate (42 product formulations: all rinse-off products, and most of the uses are in hair coloring products) (Table 3).⁵ The results of a concentration of use survey provided in 2015 indicate that Potassium Persulfate has the highest maximum concentration of use; it is used at concentrations up to 72.5% in rinse-off products (hair coloring preparations) (Table 3).⁶ Ingredient use concentrations and use frequencies that were included in the 2001 report on persulfates are also presented in Table 3.¹ The maximum use concentration of Ammonium Persulfate decreased from 60% in 1998 to 44.1% in 2015. The maximum use concentration of Potassium Persulfate increased from 60% in 1998 to 72.5% in 2015. The maximum use concentration of Sodium Persulfate decreased from 60% in 1998 to 33.4% in 2015.

Cosmetic products containing persulfates may be applied to the skin and hair or, incidentally, may come in contact with the eyes (e.g., Ammonium Persulfate). Products containing these ingredients may be applied as frequently as daily (dentrifrices; tonics, dressings, and other hair grooming aids) or monthly (hair coloring preparations) and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Non-Cosmetic

Ammonium Persulfate has been approved by FDA as a component of food starch-modified, which is an approved direct food additive. Potassium Persulfate has been classified by FDA as generally recognized as safe as a component of coatings on fresh citrus fruit.⁷ Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate have been approved by FDA as components of articles intended for use in packaging, transporting, or holding food.⁸

TOXICOKINETIC STUDIES

Persulfates rapidly hydrolyze upon contact with water.³ The substances degrade and will eventually form the corresponding cations (ammonium, potassium, sodium) and persulfate anions. The persulfate anion, independent of the cation, undergoes further decomposition upon contact with water to form sulfate species. Based on these fundamental properties of persulfates, they are not likely to become bioavailable, neither by inhalation, ingestion, or contact by skin.
A National Industrial Chemicals Notification and Assessment Scheme (NICNAS) on Ammonium, Sodium, and Potassium Persulfate was published in 2001. It was concluded that this assessment of Persulfate salts in hair bleaching preparations has identified the following health and safety issues: (1) Persulfate salts in hair bleaching preparations are hazardous chemicals, and all of the products that are available for consumer and salon use are harmful if swallowed, irritating to the skin and eyes, and able to cause allergic responses such as dermatitis and asthma; (2) The majority of formulations are not optimal for minimizing exposure due to dust formation; (3) Most of the MSDS and labels for salon products are deficient in several areas; (4) Most hair salons would benefit from a workplace assessment and health surveillance program; and (5) The training of salon workers in the safe use of chemicals used in hairdressing appears inadequate.

Many of the studies included in the NICNAS on Persulfates are included in this re-review of Ammonium, Sodium and Potassium Persulfates.

Acute Toxicity Studies

Dermal

Ammonium Persulfate

The dermal LD₅₀ of Ammonium Persulfate was 2 and 10 g/kg in studies involving rats and rabbits, respectively.

Ammonium Persulfate was tested for acute dermal toxicity in Sprague-Dawley rats (group of 10; 5 males, 5 females) in a single dose test according to guideline EPA OPP 81-2. An occlusive patch (2” x 2”) containing the test substance (in saline) was applied for 24 h. In this test, the acute LD₅₀ was greater than 2000 mg/kg body weight (practically nontoxic). There were no test substance-related findings or gross internal lesions at necropsy. Under the conditions of this study, Ammonium Persulfate was considered non-toxic to both male and female rats when topically applied.

Potassium Persulfate

Potassium Persulfate was tested for acute dermal toxicity to 4 male rabbits (strain not stated). The test material was applied (undiluted) in a single application at a dose of 10,000 mg/kg body weight. The post-exposure observation period was 14 days. None of the four test animals died during the 14-day observation period. Slight erythema that was observed at the site of application disappeared after a few days. The LD₅₀ was greater than 10,000 mg/kg body weight.

Oral

Ammonium Persulfate

For rats, the reported oral LD₅₀ of Ammonium Persulfate ranged from 600 to 820 mg/kg, and, for Potassium Persulfate, the LD₅₀ was 802 mg/kg.

Ammonium Persulfate was tested for acute oral toxicity in groups of 10 Sprague-Dawley rats (5 males, 5 females/dose group) according to OECD guideline 401. Males received dosages (oral gavage) of 300, 500, 660, 750 mg/kg body weight. Females received dosages (oral gavage) of 300, 660, 750 mg/kg body weight. Dosing was followed by a 14-day observation period. The predominant clinical signs were abdominal gripping, abdominogenital staining, ataxia, anorexia, chromodacryorrhoea, chromorhinorrhoea, diarrhea, decreased feces, decreased locomotion, dehydration, hypothermia, lacrimation, no feces, oral discharge, and tremors. All rats recovered by study day 8 and remained healthy until study termination. No gross lesions were found during necropsy. The oral LD₅₀ was calculated to be 742 mg/kg body weight (male rats) and 700 mg/kg body weight (female rats). The test substance was considered slightly toxic by oral administration to rats.

Potassium Persulfate

The acute oral toxicity of Ammonium Persulfate was evaluated according to OECD Guideline 423 using 9 female specific pathogen free (SPF) Sprague-Dawley (SD) rats. The test substance was formulated in a 30 mg/ml suspension in distilled water, and then administered at a dosage of 300 mg/kg body weight to each animal. This procedure was repeated in a second study involving 9 rats of the same strain. In both studies, none of the animals died and gross lesions were not found in any of the organs at necropsy. Based on these negative results, an oral dosage of 2000 mg/kg (200 mg/ml distilled water suspension) was administered to 6 rats. All 6 animals died within 6 h post-dosing; discoloration in the lung and marginal region of liver were observed at necropsy. Based on these study results, the LD₅₀ for Ammonium Persulfate was determined to be 500 mg/kg body weight.
Potassium Persulfate

Potassium Persulfate was tested for acute oral toxicity in male rats (strain not stated). The test article was administered by oral gavage as a suspension in corn oil in dosages of 2500 mg/kg body weight, 1000 mg/kg body weight, and 500 mg/kg body weight. Each test group contained six male animals. The acute oral LD₅₀ was determined to be 1130 mg/kg body weight.

Sodium Persulfate

Sodium Persulfate was tested for toxicity by oral application in male and female Sprague Dawley rats. Ten male and 10 female Sprague-Dawley rats per group were dosed with 215, 464, 562, 681, 825, 1000, 1210 and 1470 mg/kg body weight Sodium Persulfate and were observed for 4 weeks. Clinical signs and mortalities were recorded. All animals were subjected to gross necropsy after termination of the study. No animal died in the lowest dose group (215 mg/kg body weight), two rats (one male and one female rat) died in the intermediate dose group (681 mg/kg body weight) and all rats died in the highest dose group (1470 mg/kg body weight). Death occurred within 60 minutes after the initiation of dosing through 6 days after initial dosing. Surviving animals had recovered 48 hours after dosing. Clinical signs included sedation, dyspnea, diarrhea, muscular hypotension, reduced feed intake and face-down position. LD₅₀s of 930 mg/kg body weight (males) and 920 mg/kg body weight (females) were determined after a 14-day observation period.

Inhalation

Ammonium Persulfate and Potassium Persulfate

The inhalation LC₅₀ of Ammonium Persulfate for rats was 2.95 mg/l after a 4-h exposure. For 1 h of exposure to a 25% water suspension of Ammonium Persulfate, the LC₅₀ was 520 mg/l in rats. Potassium Persulfate was tested for acute inhalation toxicity in 7 male rats (strain not stated). The test substance was administered at a nominal chamber concentration of 42.9 mg/l for 1 h. None of the seven test animals died during the 14-day observation period. Clinical signs included hyperexcitability and slight irritation. Enlarged livers and spleens were found in all test animals. The LC₅₀ for inhalation toxicity was estimated to be greater than 42.9 mg/l.

A study was performed to determine whether exposure for 4 h to a hair bleach composition (containing Ammonium Persulfate, Potassium Persulfate and H₂O₂) or H₂O₂ could induce airway hyperresponsiveness and/or an obstructive ventilation pattern in a rabbit model (male and female New Zealand white rabbits; groups of 8). When nebulized, the total aerosol concentrations were 1,200, 120 or 12 mg/m³ in air, corresponding to the inhalation of 230, 23 or 2.3 mg hair bleach in 4 h, respectively. Changes in airway response to aerosols of 0.2% and 2% acetylcholine solutions in saline, generated by a commercial nebulizer, were investigated. Control animals were exposed to aerosolized saline. Exposure to the aerosols did not alter baseline airway resistance, dynamic elastance, slope of inspiratory pressure generation or arterial blood pressure and blood gas measurements. Hair bleach aerosols containing $10.9$ mg/m³ persulfate (ammonium and potassium salt) in air and $1.36$ mg/m³ H₂O₂ in air caused airway hyperresponsiveness to acetylcholine after 4 h of exposure. Aerosolized H₂O₂ (37 mg/m³ in air) did not influence airway responsiveness to acetylcholine. The results demonstrate that hair bleaching products containing persulfates dissolved in H₂O₂ cause airway hyperresponsiveness to acetylcholine in rabbits.

Intraperitoneal

Sodium Persulfate

In an intraperitoneal dosing study, the minimal lethal dose for Sodium Persulfate was 226 mg/kg in rabbits.

Intravenous

Sodium Persulfate

In an intravenous dosing study, the minimal lethal dose for Sodium Persulfate was 178 mg/kg in rabbits.
Short-Term Toxicity Studies

Oral

Ammonium Persulfate

*In a short-term feeding study of Ammonium Persulfate using rats, the lowest observed adverse effect level (LOAEL) was 600 ppm.*

Ammonium Persulfate was tested for oral toxicity in groups of 10 male rats in a 28-day study. In this study, the test substance was administered to male weanling albino rats in the diet at concentrations of 0 ppm (control), 100 ppm (13.30 mg/kg body weight/day), 300 ppm (41.05 mg/kg body weight/day) and 600 ppm (82.08 mg/kg body weight/day). All test animals showed normal body weight gain and survived the study period. No significant pathology was observed. The no-observed adverse effect level (NOAEL) was determined to be 41.1 mg/kg body weight/day.

A 90-day oral toxicity study on Ammonium Persulfate was performed according to OECD Guideline 408 using groups of 20 SPF rats (10 males, 10 females/group). The test substance was administered orally (in distilled water) at dose rates of 5, 20, or 80 mg/kg body weight/day. The control group received vehicle (filtered tap water) only. None of the animals died during the study, and there were no signs of toxicity or gross behavioral changes in test or control groups. Additionally, there were no abnormal clinical observations. A significant difference in daily mean food consumption (21.08 ± 1.90 vs. 18.75 ± 1.04 g) between the 5 mg/kg dose group (females) and control female rats was observed at week 9, but it was noted that this finding was a transitional phenomenon. A significant increase (p < 0.05) in mean absolute right adrenal gland weight between the 5 mg/kg dose group (females) and female controls was observed, and the same as true for ovary weights (significant increase) when control females were compared with the 20 mg/kg dose group (females). Microscopic examination did not reveal any dose-related changes. Nonspecific histopathological changes (slight to mild grade inflammation) in the liver (mild vacuolation also observed), kidneys, and lungs were observed in some of the animals of all groups. All changes observed were about equally distributed between the controls and groups dosed with the test substance. Because body weight changes, food consumption, and hematological, biochemical, and pathological examinations did not show any noticeable and significant differences between the administered (5, 20, 80 mg/kg body weight) and control (vehicle only) group animals, the authors concluded that the NOAEL was > 80 mg/kg body weight.

Potassium Persulfate

Potassium Persulfate was tested for toxicity in rats in a 28-day study according to OECD Guideline 407. In this study, the test substance was administered in the diet to groups of 10 male weanling albino rats at concentrations of 0 ppm (control), 100 ppm (12.62 mg/kg body weight/day), 316 ppm (41.15 mg/kg body weight/day) and 1000 ppm (131.50 mg/kg body weight/day). All test animals showed normal body weight gain and survived the study period. No significant pathology was observed. The NOAEL was estimated to be 131.5 mg/kg body weight/day.

Inhalation

Ammonium Persulfate

*Inhalation toxicity was observed in a short-term toxicity study in which rats were exposed to aerosolized Ammonium Persulfate at concentrations of 4 mg/cm² and greater.*

Subchronic Toxicity

Oral

Ammonium Persulfate

*In subchronic feeding studies, no signs of toxicity were observed in rats or dogs fed Ammonium Persulfate-treated flour or bread.*

Sodium Persulfate

*Local damage to the mucous membrane in the gastrointestinal tract of rats, but no other systemic effects, was observed in a subchronic feeding study of Sodium Persulfate (dose of 30 mg/kg/day). Lesions were not observed in another subchronic study of Sodium Persulfate (same dose).*
Sodium Persulfate

Sodium Persulfate was administered in the diet of rats (CR strain; groups of 40 [20 males, 20 females/group]) for 13 weeks. Observations included body weight, food consumption, and blood and urine parameters. Further ophthalmologic examinations and gross and microscopic examinations were carried out. The concurrent control group was of the same age, sex distribution and derivation. One group of animals received only the basal diet (control group). Others received 300 and 3000 ppm of the test material in the diet. The fourth group received 1000 ppm of the test material in the diet for 8 weeks and 5000 ppm of the test material in the diet for the final 5 weeks. The dose was increased to 5000 ppm for the remaining 5 weeks because, after 8 weeks at 1000 ppm, it appeared unlikely that there would be any adverse effects at this concentration. All animals survived the study. Significant differences were seen among the groups in body weights and food consumption. No statistically significant differences were seen among groups in hematological blood chemical, and urine analytical parameters, and organ weight and body weight ratios. Organ weights, organ-to-body weight ratios and type and frequency of grossly observable lesions seen during necropsy were comparable among the four groups. Intestinal changes were noted in the rats which received 3000 ppm of Sodium Persulfate for 13 weeks. These changes were seen more frequently among females than males. The former received 50 percent more test material than the latter on a dose per body weight basis. No statistically significant changes were seen among the controls or the groups that received 300 ppm in the diet for 13 weeks or 1000 ppm in the diet for the remainder of the study. No other microscopic changes were noted on comparison among these three groups. A LOAEL and a NOAEL of 200 and 91 mg/kg body weight/day (3000 and 1000 ppm), respectively, were determined.

Inhalation

Ammonium Persulfate

The subchronic inhalation toxicity of Ammonium Persulfate was characterized using Sprague-Dawley rats (20/sex/group) at respirable dust concentrations of 0, 5.0, 10.3, and 25 mg/m$^3$. Whole-body exposures were conducted 6 h/day, 5 days/week for 13 weeks. Gravimetric airborne test material samples were taken daily and particle size samples were taken weekly from each exposure chamber for analysis. Ten animals/sex/group were necropsied after 13 weeks of exposure, and 5 animals/sex/group were held for 6- and 13-week recovery periods. Animals were observed for clinical signs. Effects on body weight, food consumption, clinical chemistry and hematology, ophthalmologic parameters, organ weights, gross lesions, and histopathology were evaluated. There were no exposure-related deaths during the study. Rales and increased respiration rate were noted in both males and females in the 25 mg/m$^3$ group, and in a few animals in the 10.3 mg/m$^3$ group. The incidence of these clinical signs decreased to zero during the first few weeks of the recovery period. Body weights for both males and females in the 25 mg/m$^3$ group were significantly depressed during most of the exposure period compared to the control group. By the end of the recovery period, body weights for the exposed animals were similar to the control group values. Lung weights were elevated in the 25 mg/m$^3$ group after 13 weeks of exposure, but were similar to controls at 6 weeks post-exposure. Irritation of the trachea and bronchi/bronchiole was noted microscopically after 13 weeks of exposure to 25 mg/m$^3$. These lesions had recovered by 6 weeks post-exposure. Based on the results of this study, the NOAEL was 10.3 mg/m$^3$, while the no-observed-effect level (NOEL) for exposure of rats to a dust aerosol of Ammonium Persulfate was 5.0 mg/m$^3$.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Ammonium Persulfate

Ammonium Persulfate was tested for oral reproductive/developmental toxicity in a screening test with rats (groups of 12; 6 males, 6 females/group) according to OECD guideline 421. The purpose of this study was to obtain initial information on the possible effects of the test item on reproduction and development when administered orally in the diet to Crl:CD (SD)IGS BR rats at dose rates of 40, 100 and 250 mg/kg body weight/day compared to control animals (plain diet only). There were no treatment-related clinical signs of toxicity observed in F0 parents of either sex or in F1 pups at any treatment level. Remarkable clinical signs in the F0 parents and F1 pups were not attributed to treatment with Ammonium Persulfate, as they occurred sporadically, were of short duration, and did not demonstrate a dose response. No significant changes were observed in male and female reproductive performance such as gonadal function, mating behavior, conception, pregnancy, parturition and in development of the F1 offspring from conception to day 4 postpartum. In conclusion, under the conditions of this study, the NOAEL for male and female toxicity, the NOAEL for male and female fertility performance and the NOAEL for F1 viability and development were ≥ 250 mg/kg/day.
GENOTOXICITY

In Vitro

Ammonium Persulfate

Results for Ammonium Persulfate were negative in the Ames test.¹

Sodium Persulfate

The genotoxicity of Sodium Persulfate was evaluated in the Ames test using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, TA1537 and TA1538.³ Sodium Persulfate was tested at five dose levels ranging from 100 to 10000 μg/plate. The assay was conducted in the presence and absence of metabolic activation. During the tests, positive and negative controls were run concurrently. The reference mutagens (sodium azide, 9 - aminoacridine, 2 -nitrofluorene, 2 -anthramine) showed a distinct increase in induced relevant colonies. Sodium Persulfate did not cause a positive response in any of the tester strains with or without metabolic activation, and was considered non-genotoxic.

Sodium Persulfate was tested in the rat hepatocyte unscheduled DNA synthesis assay.³ The test substance was tested at eight concentrations ranging from 1.5 to 500 μg/mL and was fully evaluated at five concentrations of 5.0, 15, 50, 150 and 250 μg/mL. Thus, the test substance was considered not mutagenic. The positive control, 7,12-dimethylbenz(a)anthracene (DMBA), induced significant increases in the mean number of net nuclear grain counts over that in the solvent control.

In Vivo

In the mouse micronucleus assay, male and female ICR mice were dosed i.p. with 85, 169 or 338 mg/kg Sodium Persulfate at a volume of 10 ml/kg. Bone marrow cells, collected 24 h, 48 h, and 72 h after dosing, were examined microscopically for micronucleated polychromatic erythrocytes. A reduction in the ratio of polychromatic erythrocytes to total erythrocytes was observed in female mice at 72 h post-administration of 169 mg/kg and in male and female mice at 72 h post-administration of 338 mg/kg. These results indicated that Sodium Persulfate did induce bone marrow toxicity. No statistically significant increases in micronucleated polychromatic erythrocytes were observed at 24 h, 48 h, or 72 h post-dosing in males or females. The results of the assay indicated that Sodium Persulfate did not induce a significant increase in micronucleated polychromatic erythrocytes in male or female ICR mice. It was concluded that the results were negative in the mouse micronucleus assay, and that Sodium Persulfate was non-clastogenic.

CARCINOGENICITY STUDIES

Dermal

Ammonium Persulfate

There was no significant evidence of carcinogenicity in a study in which rats received topical applications of Ammonium Persulfate (200 mg/ml biweekly for 51 weeks).³

Tumor Promotion

Dermal

Ammonium Persulfate

There was no significant evidence of tumor promotion in a study in which rats received topical applications of Ammonium Persulfate (200 mg/ml biweekly for 51 weeks).³

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation
Ammonium Persulfate

Ammonium Persulfate (99% pure) was not irritating to intact rabbit skin.\(^1\)

Ammonium Persulfate was tested for skin irritation on 3 Albino – White Russian rabbits according to OECD Test Guideline 404.\(^1\) The test substance (0.5 g; vehicle = water) was applied under an occlusive patch to scarified skin for 4 h. Reactions were scored for up to 72 h. Severe irreversible erythema and slight edema were observed. Erythema was present one hour after removal of the occlusive bandage from the scarified epidermis and was evaluated with the rating 3 and 4 (moderate and severe erythema, eschar formation with profound damage). The irritations persisted with same intensity over the 14 day observation period. The first day after application of the test material, eschar formation occurred, and loss of substance became visible at the location of application, which showed circular cavities with a depth of 1 to 2 mm. The eschar sloughed during the second observation week. The reparation process started with scar formation without reaching the level of the health skin area completely. Based on these results Ammonium Persulfate was considered irritating to the skin.

Sodium Persulfate

Sodium Persulfate was tested as an aqueous solution for skin corrosion effects in 6 New Zealand rabbits (3 males, 3 females).\(^3\) For dermal application (4 h), there was one intact and one abraded skin test site per rabbit. Each test site was treated with 0.5 mL of actual undiluted test material by introducing the test material at room temperature beneath a surgical gauze patch (occlusive patch) measuring 1" x 1" and two single layers thick. The patches were secured in place with strips of adhesive tape and the entire trunk of each animal was wrapped with polyethylene film. Destruction or irreversible alteration of the skin did not occur on any of the test sites. Neither skin irritation nor corrosion was produced by the test material.

Animal

Ammonium Persulfate

Ammonium Persulfate induced skin sensitization in guinea pigs. All 20 animals reacted to intradermal administration of a 0.1% solution in physiological saline; 16 animals reacted to epicutaneous application of a 1% solution in demineralized water.\(^1\)

Ammonium Persulfate was tested for skin sensitizing potential in the mouse local lymph node assay (LLNA).\(^3\) Exposure to the test substance resulted in a maximal mean Stimulation Index (SI) of 6.8 +/- 1.8 at the highest concentration tested (5 %). From the calculated SI values, the estimated EC\(_3\) value for Ammonium Persulfate was 1.9 %. Based on the EC\(_3\) value, Ammonium Persulfate was classified as a moderate skin sensitizer.

Sodium Persulfate

Sodium Persulfate was applied topically (0.30 g on occlusive patch [Hill top chamber]) to the left shoulders of 10 male and 10 female Hartley guinea pigs.\(^3\) The test material was left in contact with the skin for approximately 6 hours. The animals received three induction treatments one week apart. Fourteen days after the third induction treatment, the animals were challenged with the test material at a virgin skin site. An additional five male and female naïve animals received 0.30 g of the test material (challenge control group). Observations for skin reactions were recorded at 24 h and 48 h after each application. Slight to moderate erythema, slight edema and desquamation were noted on the test sites during the induction period. Under the conditions of this study, the test material was considered to be non-sensitizing when applied to Hartley guinea pigs.

Sodium Persulfate was tested for skin sensitizing potential in the mouse LLNA.\(^3\) Exposure to the test substance resulted in a maximal mean stimulation index (SI) of 6.4 +/- 1.2 at the highest concentration tested (5 %). Applying a 5% solution of Sodium Persulfate caused an increase of 3 times in the lymph node weight (LNW) and increase of 6.5 -fold in total lymph node cell (LNC) number when compared with the DMSO control. From the calculated SI values, the estimated EC\(_3\) of Sodium Persulfate is 0.9. Based on the EC\(_3\) value, Sodium Persulfate was classified as a strong skin sensitizer.
Human

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate

In a study examining the sensitization potential and the incidence of urticarial reactions to 17.5% Ammonium, Potassium, and Sodium Persulfate in a lightener/developer mixture, the Persulfate mixture was not a sensitizer in the 46 subjects tested and none of the Persulfates caused an urticarial reaction; significant skin irritation was induced by the vehicle during induction.¹

In a clinical patch test, 5 of 26 subjects had positive sensitization reactions to 5000 ppm Sodium Persulfate. These reactions were confirmed in two subjects when rechallenged.¹

In another study, it was noted that reactions to Ammonium Persulfate were more severe when the ingredient was scratched into the skin. Noting a characteristic wheal and flare response, the investigators concluded that histamine release was involved. This is supported by results of in vitro and in vivo animal studies. However, it could not be determined whether Ammonium Persulfate works directly on mast cells or whether histamine release is due to immediate-type immune hypersensitivity.¹

**OCULAR IRRITATION STUDIES**

Ammonium Persulfate

Ammonium Persulfate was slightly irritating to the eyes of the 3 rabbits that were tested. In a study involving 9 rabbits, Ammonium Persulfate was practically nonirritating to rinsed eyes, but caused slight to mild conjunctivitis and iritis (considered minimally irritating reactions) in unrinsed eyes.¹

Sodium Persulfate

Sodium Persulfate was tested for eye irritation/corrosion in rabbits (strain not stated).³ The test material was applied to the intact eye of eight rabbits. Examinations of cornea, iris and conjunctivae were performed after 24, 48 and 72 hours. Slight irritation effects, which were fully reversible within 24 h, were observed in 5 of 8 test animals. Sodium Persulfate was considered non-irritating to the eyes of rabbits.

**CLINICAL STUDIES**

Ammonium Persulfate and Potassium Persulfate

The persulfates cause both delayed-type and immediate skin reactions. These reactions include irritant dermatitis, allergic eczematous dermatitis, localized contact urticarial, generalized urticarial, rhinitis, asthma, and syncope. The most common causes of allergic dermatitis in hairdressers are the active ingredients in hair dyes, and Ammonium Persulfate has been identified as a frequent allergen. A number of occupational case studies document these types of reactions, but no incidence data were available.¹

Multicenter Studies

Ammonium Persulfate

A group of 121 hairdressers (106 women, 6 men) was selected from 4523 patients with suspected occupational skin disease who were referred to the Nofer Institute of Occupational Medicine, Lodz, in 1995-2008.¹³ At least one positive patch test reaction was found in 69.7% of the patients; patch tests were negative in 30.3%. The most frequent allergens included Ammonium Persulfate (23.2%), as well as nickel sulfate (40% of females), p-phenylenediamine (25% of study group), cobalt chloride (21.4%), 2,5-diaminotoluene sulfate (9.8%), formaldehyde (9.8%), ammonium thioglycolate (7.1%), and glyceryl monothioglycolate (7.1%).
Results for patients who underwent patch testing with a standard allergen series (including 15 hairdressing chemicals) and a supplementary “hairdresser series” (18 additional hairdressing chemicals) at Mayo Clinic (Rochester, MN; Scottsdale, AZ; and Jacksonville, FL) from January 1, 2000 through December 31, 2008 were reviewed. Two hundred ten patients were patch-tested. The most common sites of dermatitis were the scalp, face, and hands. Patients had widely varying occupations. The most common occupations were cosmetologist (10.5%), housewife (9.5%), and beautician (5.2%). 14.3% were retired. The hairdresser series detected 13 additional patients with allergies (6.4%; 204 patients tested with both series) who would not have been detected with the standard allergen series alone. The highest allergic patch-test rates in the supplemental hairdresser series were with Ammonium Persulfate (4.4%), 4-aminoazobenzene (13.4%), and pyrogallol (9.1%).

Patch test results of 399 hairdressers and 1995 matched controls with contact dermatitis, registered by the Danish Contact Dermatitis Group between January 2002 and December 2011, were analysed. All patients were patch tested with the European baseline series, and hairdressers were additionally tested with the hairdressing series. Sensitization (positive patch test) reactions to Ammonium Persulfate were observed in 43 of the 397 hairdressers patch tested with this ingredient (10.8% incidence; 95% CI 7.8–13.9). Ammonium Persulfate was among the most common sensitizers for hairdressers. In Europe and Australia, the prevalence of sensitization to Ammonium Persulfate has been reported to be between 8% and 21.7%.

Patch test results with the ‘hairdresser series’ in female hairdressers (n = 824) and clients (n = 2067) patch tested in 2007–2012 in the departments of the Information Network of Departments of Dermatology have also been analyzed. The patients were either currently working as hairdressers and had been diagnosed with occupational dermatitis, or those who had previously suffered from work-related dermatitis when working as hairdressers. Clients included those female patients in whom hair cosmetics were regarded as a cause of dermatitis, and who had never worked as hairdressers, according to the case documentation. Of the 696 hairdressers patch tested with 2.5% Ammonium Persulfate, results were positive (contact sensitization) for 148 (18.7% incidence). Of the 1692 clients patch tested with 2.5% Ammonium Persulfate, results were positive for 32 (2.1% incidence).

Case Reports

Ammonium Persulfate and Potassium Persulfate

A 20-year-old hairdresser developed rhinitis and asthma during her work at the reception desk of a hairdressers' shop. She had also developed hand eczema, caused by delayed-type hypersensitivity to p-phenylenediamine, p-tolyuendiamine, and Ammonium Persulfate. Skin prick testing of a bleaching agent used in the hairdressers' shop gave a positive reaction (++++). Further investigation revealed that this bleaching agent contained Ammonium Persulfate and Potassium Persulfate. Therefore, skin prick testing of a hairdressers' panel used in patch testing was performed, revealing a positive reaction (+++) to Ammonium Persulfate (2.5%). This reaction could be confirmed by negative testing of Ammonium Persulfate (2.5%) in 10 nonatopic and 10 atopic volunteers. No specific IgE to Ammonium Persulfate could be detected in an external laboratory with a commercially unavailable RAST.

Six years after starting her job, a 21-year-old hairdresser developed work-related rhinorrhea, sneezing, dry cough, dyspnea, wheezing, and occasionally neck erythema, which appeared 15 minutes after starting work, improved on the weekly rest, and disappeared over holidays. Her history was negative for atopy. Patch tests showed a positive reaction to Ammonium Persulfate (++), which the patient was exposed to at the workplace; on such occasions, rhinitis and dyspnea occurred some hours after patch application. Skin prick test and specific IgE to common Aeroallergens and latex were negative. On day 1, a patch with Ammonium Persulfate 1% in petrolatum was applied on the back, and spirometry was performed hourly. By 90 min after the application, cough, dyspnea, nasal obstruction, itching at the site of the patch, and wheals on neck and face had occurred. The patch was removed, showing erythema and wheals. FEV1 progressively decreased, with a maximal fall of 49% at 150 minutes. These results were indicative of an anaphylactoid reaction to patch testing with Ammonium Persulfate. Furthermore, in this case, the development of a systemic reaction was indicative of cutaneous absorption of Ammonium Persulfate.

A 29-year-old female hairdresser presented with occupation-related hand eczema and asthmatic symptoms. She had previously been patch tested, with positive reactions to p-phenylenediamine (1.0%) and Ammonium Persulfate (2.5%). In this case report, prick tests on Ammonium Persulfate (0.1%) and Potassium Persulfate (0.1%) were performed. A positive prick test reaction to Ammonium Persulfate, but not Potassium Persulfate, was reported.

Two cases with severe systemic reactions because of skin contact with persulfates in hair-bleaching products have been reported. The first case (female client of hairdresser) had anaphylaxis, and the second case (hairdresser) had severe asthma. The 2 patients were patch tested with Potassium Persulfate (2.5% aqueous) or Ammonium Persulfate (2.5% in petrolatum). They were also prick tested with up to 2% aqueous Potassium Persulfate or 2% aqueous Ammonium
Provocation tests (NPTs) can be applied in diagnostics. The study subjects were 40 hairdressers having work-related rhinitis and known previous exposure to Ammonium Persulfate.

Ammonium Persulfate and Persulfate Salts

Metabisulfite, and Ammonium Persulfate. Prick test sites were read at 20 minutes with no wheal and flare reaction, indicating no evidence of immediate hypersensitivity. Patches placed on his lower back were removed at 48 hours and read at 48 and 96 hours. At 96 hours he had a 1+ to 2+ reaction to Ammonium Persulfate. Controls were not patch tested to control for irritancy. The authors noted that the culprit pools and water park were periodically shocked with potassium peroxymonosulfate, a persulfate shown to cross-react with Ammonium Persulfate. It was also noted that this child had no symptoms, results from the peak flow measurements, and a positive prick test to persulfate salts.

A female hairdresser apprentice presented with occupational-related hand eczema and asthma. She had been in apprenticeship for 2 years and exposed to hair bleaching products. After 15 months of apprenticeship, she developed a vesicular hand eczema bilaterally on the dorsal side of her hands and fingers and interdigitally. The patient had positive prick test reactions to both Potassium Persulfate and Ammonium Persulfate at a concentration of 1.0%. Immediate-type allergy toward Ammonium Persulfate and Potassium Persulfate was concluded, and the patient was diagnosed with allergic occupational asthma caused by persulfate salts on the basis of a diagnosis of asthma, clinical history of work-related symptoms, results from the peak flow measurements, and a positive prick test to persulfate salts.

An 11-year-old boy presented to the pediatric dermatology clinic for evaluation of a pruritic and eczematous eruption over the trunk and extremities that had been occurring periodically for 4 years. The child and his family related the eruptions to swimming in certain indoor and outdoor pools and to the water park that his family visited each summer. Prick and patch testing were performed to look for evidence of immediate and delayed hypersensitivity reactions to four swimming pool-related allergens: chlorine (1% aqueous), 1-bromo-3-chloro-5,5-dimethylhydantoin (1% aqueous), sodium metabisulfite, and Ammonium Persulfate. Prick test sites were read at 20 minutes with no wheal and flare reaction, indicating no evidence of immediate hypersensitivity. Patches placed on his lower back were removed at 48 hours and read at 48 and 96 hours. At 96 hours he had a 1+ to 2+ reaction to Ammonium Persulfate. Controls were not patch tested to control for irritancy. The authors noted that the culprit pools and water park were periodically shocked with potassium peroxymonosulfate, a persulfate shown to cross-react with Ammonium Persulfate. It was also noted that this child had no known previous exposure to Ammonium Persulfate.

Other Clinical Reports

Ammonium Persulfate and Persulfate Salts

A study was performed to investigate the work-related rhinitis symptoms of hairdressers, and to study whether nasal provocation tests (NPTs) can be applied in diagnostics. The study subjects were 40 hairdressers having work-related rhinitis symptoms. Detailed work and exposure histories and work-related symptoms were inquired of using a questionnaire. Prick tests were done. Altogether 35 NPTs on Ammonium Persulfate were performed. Of the two Ammonium Persulfate-skin-prick-test positive patients, one (patient A) had a positive and the other (patient B) an uncertain reaction in NPT. Patient A was also diagnosed as having asthma and contact urticaria.

The occurrence and causes of hairdressers' occupational skin and respiratory diseases were studied. Of a random sample of 500 female hairdressers, 355 were available for study. Of the 189 reporting work-related skin and respiratory symptoms in a computer-aided telephone interview on exposure and health, 130 underwent lung function tests and prick and patch testing. The telephone interview revealed a life-time prevalence of 16.9% for hand dermatoses, 16.9% for allergic rhinitis, and 4.5% for asthma among the hairdressers. In the clinical investigations, the prevalence was 2.8% for occupational dermatoses, 1.7% for occupational rhinitis, and 0.8% for occupational asthma. Ammonium Persulfate caused 90% of the respiratory diseases and 27% of the hand dermatoses.

Prick testing with persulfate salts (2% Ammonium and Potassium Persulfate solutions) was performed in a total of 138 patients. Seven patients had a positive reaction to at least 1 persulfate salt. 6 of the patients had had skin symptoms, urticaria, eczema or angioedema, because of contact with hair bleaches. Open application on healthy skin was performed in 4 patients, and 3 out of them had urticarial reactions. The sera of 5 patients were investigated with immunospot and RAST. On immunospot, specific binding of IgE to human serum albumin (HSA)- conjugated Ammonium and Potassium Persulfate was found in 2 patients. One immunospot-positive patient also had a positive RAST to Ammonium Persulfate–HSA conjugate. The mechanism of immediate hypersensitivity to persulfates thus seems to be IgE-mediated at least in some patients.

Three-hundred hairdressers who were seen in a dermatology department in Spain from 1994 to 2003 were studied, and the results were compared with those of a previous study involving hairdressers who attended the dermatology
Hairdressers are frequently exposed to bleaching powder containing persulfates, a group of compounds that may induce hypersensitivity in the airways, and the mechanism causing this reaction is not clear. A study was performed to identify changes in the nasal lavage fluid proteome after challenge with Potassium Persulfate in hairdressers with bleaching powder-associated rhinitis. Furthermore, an objective was to compare their response to that of hairdressers without nasal symptoms, and atopic subjects with pollen-associated nasal symptoms. To study the pathogenesis of persulfate-associated rhinitis, the response in protein expression from the upper airway was assessed by time-dependent proteomic expression quantitation (iTRAQ) and analyzed by online 2D-nanoLC-MS/MS. Differences in the protein pattern between the three analysis of nasal lavage fluids. Samples were prepared by pooling nasal lavage fluids from the groups at different time points after challenge. Samples were depleted of high-abundant proteins, labeled with isobaric tags for relative and absolute quantitation (iTRAQ) and analyzed by online 2D-nanoLC-MS/MS. Differences in the protein pattern between the three groups were observed. Most proteins with differentially expressed levels were involved in pathways of lipid transportation and antimicrobial activities. The major finding was increased abundance of apolipoprotein A-1, 20 min post-challenge, detected solely in the group of symptomatic hairdressers. These results suggest there may be differences between the mechanisms responsible for the rhinitis in the symptomatic and atopic group.

A study was performed to describe the course of bronchial hyperresponsiveness and immunologic test results in patients with occupational asthma due to persulfate salts. Ten patients with occupational asthma attributable to exposure to persulfate salts were studied. Diagnosis was based on specific bronchial challenge tests performed at least 3 years before enrollment. An exhaustive medical and work history was taken during interviews with all patients, and all underwent spirometry and nonspecific bronchial challenge testing. Total immunoglobulin E levels were determined and skin prick tests to several persulfate salts were performed. Study results were as follows: At the time of evaluation, 7 patients had avoided workplace exposure to persulfate salts. The bronchial hyperresponsiveness of 3 of those 7 patients had improved significantly. No improvement was observed in patients who continued to be exposed. Specific skin prick tests became negative in 3 patients who were no longer exposed at the time of the follow-up evaluation. Most of the patients continued to report symptoms, although improvements were noted. One patient, however, reported worsening of symptoms in spite of avoidance of exposure. It was concluded that, although asthma symptoms and bronchial hyperresponsiveness may persist for patients with occupational asthma from exposure to persulfate salts, their condition seems to improve if they avoid exposure to these salts.

Hairdressers are frequently exposed to bleaching powder containing persulfates, a group of compounds that may induce hypersensitivity in the airways, and the mechanism causing this reaction is not clear. A study was performed to identify changes in the nasal lavage fluid proteome after challenge with Potassium Persulfate in hairdressers with bleaching powder-associated rhinitis. Furthermore, an objective was to compare their response to that of hairdressers without nasal symptoms, and atopic subjects with pollen-associated nasal symptoms. To study the pathogenesis of persulfate-associated rhinitis, the response in protein expression from the upper airway was assessed by time-dependent proteomic expression analysis of nasal lavage fluids. Samples were prepared by pooling nasal lavage fluids from the groups at different time points after challenge. Samples were depleted of high-abundant proteins, labeled with isobaric tags for relative and absolute quantitation (iTRAQ) and analyzed by online 2D-nanoLC-MS/MS. Differences in the protein pattern between the three groups were observed. Most proteins with differentially expressed levels were involved in pathways of lipid transportation and antimicrobial activities. The major finding was increased abundance of apolipoprotein A-1, 20 min post-challenge, detected solely in the group of symptomatic hairdressers. These results suggest there may be differences between the mechanisms responsible for the rhinitis in the symptomatic and atopic group.

A study was performed to investigate the frequency of work-related skin disorders among apprentice hairdressers, and to identify the factors contributing to the development of dermatoses during vocational training. One hundred thirty-nine hairdressers were included in the study. Present or past work-related skin conditions affecting the hands were reported by 43.9% of individuals, and diagnosed in 25.9% during dermatological examination. Positive patch test results were found in 38.1%. The most frequent allergens were nickel (29.3% of all tested) and Ammonium Persulfate (8.3%). Allergic contact dermatitis was recorded in 27.3%, and was of occupational origin in 87.9% of all tested individuals. Irritant contact dermatitis was diagnosed in 51.1% of participants.

Forty-four hairdressers who were diagnosed with hand dermatitis in a dermatological outpatient department were included and investigated by patch testing with standard and hairdressing related allergens and/or prick test. Allergic contact dermatitis was diagnosed with a positive patch test reaction in 33 cases (75%), irritant contact dermatitis was found in 11 cases (25%). The clinical manifestations were mostly scaly plaques (68.18%) or vesicles (50%). The most common site of involvement was the palms (38.63%). The common causative allergens included Ammonium Persulfate (13.63%), as well as p-phenylenediamine (45.45%), nickel (31.18%), fragrance mix (20.45%), p-toluenediamine sulfate (18.18%), p-aminophenol (13.63%).
Work-related rhinitis (WR) is often a complaint of hairdressers, and they are infrequently sensitized to persulfates. The cause and mechanism of the symptoms and the effects on their health-related quality of life (HRQoL) remains unclear. Female hairdressers (17) with WR, mainly from bleaching powder regarding nasal reactivity to persulfate, were studied. Skin prick tests were performed on the hairdressers, and HRQoL questionnaires were completed. Skin prick tests to Potassium Persulfate were negative. Although the nasal reactivity to persulfate did not change a steady increase in nasal symptoms, especially blockage, and in eosinophil cationic protein in nasal lavage fluid was noticed in the symptomatic hairdressers. The HRQoL deteriorated in the symptomatic hairdressers indicating an effect on their working situation and daily life. The atopics had more, but varying symptoms (itching, sneezing and secretion).

The clinical charts of 26 subjects diagnosed as respiratory allergy caused by Ammonium Persulfate, confirmed by specific inhalation challenge (SIC), were reviewed. Twenty-two out of 26 patients underwent pre-SIC-induced sputum challenge test (IS) and 24/26 underwent nasal secretion collection and processing. Twelve out of 26 patients received a diagnosis of occupational asthma (OA)-only and 14/26 of occupational rhinitis (OAR). Duration of exposure before diagnosis, latency period between the beginning of exposure and asthma symptom onset, basal FEV1, airway reactivity to methacholine and asthma severity did not differ in the two groups. Eosinophilic inflammation of upper and lower airways characterized both groups. Eosinophil percentage in IS tended to be higher in OAR [11.9 (5.575–13.925)%] than in OA-only [2.95 (0.225–12.5)%] (P = 0.31). Eosinophilia in nasal secretions was present both in subjects with OAR [55 (46–71)%] and in subjects with OA-only [38 (15–73.5)%], without any significant difference. These study results indicate that OA because of Ammonium Persulfate coexists with occupational rhinitis in half of the patients. Unexpectedly, rhinitis did not seem to have an impact on the natural history of asthma.

A total of 729 hairdressers who had been patch tested at a clinic in London were retrospectively identified. Allergic reactions to relevant allergens from the extended European baseline series and hairdressing series were analyzed against history of atopic eczema. Of the total, 29.9% of patients had a current or past history of atopic eczema. The most frequent positive allergens from the European baseline series were nickel sulfate (32.1%) and p-phenylenediamine (19.0%) and from the hairdressing series were glyceryl monothioglycolate (21.4%) and Ammonium Persulfate (10.6%). There was no significant difference between people with or without a history of atopic eczema, except for fragrance mix I and nickel sulfate.

A systemic review of studies in PubMed (1966–2010) investigating allergens in at least 100 enrolled children was done to evaluate the proportion of positive reactions for allergens tested in children and to identify allergens with positive reactions in at least 1% of them. Forty-nine studies with available data on 170 allergens were included. Each study tested a median of two allergens. Proportions of positive reactions for each allergen were combined with random effects models across studies. Among the 94 allergens evaluated by at least two studies, 58 had estimates of positive reactions of at least 1% by random effects calculations, and for 21 of them the 95% confidence interval ensured that the proportion of positive reactions was at least 1%. The top five allergens tested by at least two studies included nickel sulfate, Ammonium Persulfate, gold sodium thiosulfate, thimerosal, and toluene-2,5-diamine (p-toluenediamine). Only nickel sulfate and Ammonium Persulfate exceeded 10%.

Specific inhalation challenge (SIC) may be considered the ‘gold standard’ for the diagnosis of occupational asthma due to persulfate salts. A study was performed to develop a safe SIC protocol. Between 2003 and 2014, eight patients with suspected occupational asthma due to persulfate salts were examined (7 females, all hairdressers). SIC was done with a dosimeter and a nebulizer using Ammonium Persulfate dissolved in phosphate buffer. Until 2009, a four-step-protocol (doses: 0.0004, 0.0045, 0.045, 0.45 mg; cumulative: 0.5 mg) was used, afterwards a six-step-protocol (doses: 0.0004, 0.0018, 0.007, 0.028, 0.113, 0.45 mg; cumulative: 0.6 mg). With each SIC protocol, four subjects were tested. Skin prick tests with Ammonium Persulfate (20 mg/mL) were performed in all and patch tests in four subjects. In total, four subjects showed a positive SIC, two with each protocol. All subjects showed an isolated late reaction. The greatest decrease of volume in 1 s was 35% about 3.5 h after the last inhalation (four-step-protocol). Skin prick test with Ammonium Persulfate was positive in one SIC positive (2 mm wheal) and in two SIC negative patients (3 and 4 mm wheal). All four subjects tested with patch tests showed a positive reaction; three of them were SIC positive. The authors recommended including patch-testing in the diagnosis of suspected occupational asthma due to persulfate salts. Isolated late asthmatic reactions may occur after SIC.

**SUMMARY**

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are inorganic salts that are used as oxidizing agents in cosmetic products. A CIR final report with the following conclusion on these ingredients was published in 2001: The Cosmetic Ingredient Review (CIR Expert Panel concludes that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing.
from the hair and skin. Additional safety test data have entered the literature since this final report was published, and the safety of these ingredients in cosmetics is re-reviewed in this report.

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are water-soluble organic salts. Collectively, data on use frequency from FDA and use concentrations from a Council survey indicate that all 3 persulfates are being used in cosmetic products. According to 2016 VCRP data, the greatest reported use frequency is for Potassium Persulfate (67 product formulations, all rinse-off products), followed by Sodium Persulfate (42 product formulations, all rinse-off products). The results of a concentration of use survey provided in 2015 indicate that Potassium Persulfate has the highest maximum concentration of use; it is used at concentrations up to 72.5% in rinse-off products (hair coloring preparations).

Persulfates rapidly hydrolyze upon contact with water. The substances degrade and will eventually form the corresponding cations (ammonium, potassium, sodium) and persulfate anions. The persulfate anion, independent of the cation, undergoes further decomposition upon contact with water to form sulfate species. Based on these fundamental properties of persulfates, they are not likely to become bioavailable, neither by inhalation, ingestion, or contact by skin.

In an acute dermal toxicity study involving male and female rats, Ammonium Persulfate was considered non-toxic (LD50 > 2000 mg/kg body weight). In an acute dermal toxicity study involving male rabbits, an LD50 of > 10,000 mg/kg body weight was reported.

An acute oral LD50 of 742 mg/kg body weight was calculated for Ammonium Persulfate in a study involving male and female rats. In another study in which Ammonium Persulfate was tested at doses up to 2000 mg/kg body weight in female rats, the acute oral LD50 cut-off was determined to be 500 mg/kg body weight. The acute oral LD50 for Potassium Persulfate in male rats was determined to be 1130 mg/kg body weight. LD50 values of 930 mg/kg body weight (male rats) and 920 mg/kg body weight (female rats) were reported in an acute oral toxicity study on sodium Persulfate.

The LC50 value for inhalation toxicity was estimated to be greater than 42.9 mg/l in an acute inhalation toxicity study on Potassium Persulfate involving male rats. Hair bleach aerosols containing Ammonium Persulfate and Potassium Persulfate caused airway hyperresponsiveness to acetylcholine after 4 h of exposure.

In a 28-day oral toxicity study on Ammonium Persulfate involving male rats receiving doses up to 82.08 mg/kg body weight per day, no significant pathology was observed and the NOAEL was determined to be 41.1 mg/kg body weight per day. No significant pathology was observed and the NOAEL was estimated to be 131.5 mg/kg body weight per day in a 28-day oral toxicity study on Potassium Persulfate involving male rats.

Microscopic examination did not reveal any dose-related changes and the NOAEL was > 80 mg/kg body weight in a 90-day oral toxicity study of Ammonium Persulfate in male and female rats. All nonspecific histopathological changes were equally distributed between test and control groups.

Sodium Persulfate was administered in the diet (up to 3000 or 5000 ppm Sodium Persulfate) of rats for 13 weeks. LOAEL and NOAEL values of 200 and 91 mg/kg body weight per day were determined. The frequency of grossly observable lesions was comparable between test and control groups.

In a 13-week inhalation toxicity study (whole-body exposure) on Ammonium Persulfate (concentrations of 5, 10.3, and 25 mg/m3) involving male and female rats, the NOAEL was 10.3 mg/m3. The NOEL for the exposure of rats to a dust aerosol of Ammonium Sulfate was 5 mg/m3.

Ammonium Persulfate was tested for oral reproductive/developmental toxicity in a test involving rats receiving daily doses up to 250 mg/kg body weight/day. There were no treatment-related clinical signs of toxicity observed in F_0 parents of either sex or in F_1 pups at any treatment level. The NOAEL for male and female fertility performance and the NOAEL for F_1 viability and development were ≥ 250 mg/kg/day.

Sodium Persulfate was non-genotoxic in the in vitro Ames test, with and without metabolic activation, and in the in vitro rat hepatocyte unscheduled DNA synthesis assay. Results for Sodium Persulfate were also negative in the in vivo mouse micronucleus assay.

Ammonium Persulfate (0.5 g in water) was irritating to the skin of rabbits when applied for 4 h. Neither skin irritation nor corrosion was observed in rabbits when undiluted Sodium Persulfate (0.5 ml) was applied for 4 h.

Ammonium Persulfate (5%) and Sodium Persulfate (5%) were classified as a moderate sensitizer and strong sensitizer, respectively, in the mouse LLNA.
Sodium Persulfate (0.3 g on occlusive patch) was applied to the skin of guinea pigs during induction (three 4-h applications) and the 24-h challenge. The test substance caused skin irritation, but not sensitization.

In a multicenter study, positive patch test reactions were observed in 43 of 397 hairdressers (10.8% sensitization incidence) patch tested with Ammonium Persulfate. In another multicenter study, of the 696 hairdressers patch tested with 2.5% Ammonium Persulfate, results were positive (contact sensitization) for 148 (18.7% incidence). Of the 1692 clients patch tested with 2.5% Ammonium Persulfate, results were positive for 32 (2.1% incidence). Skin sensitization reactions/asthma were reported in case reports and other clinical reports on Ammonium Persulfate and Persulfate salts.

Sodium Persulfate was non-irritating to the eyes of rabbits.

**DISCUSSION (From Final Report)**

The Expert Panel was concerned with the sensitization and urticarial potential of persulfates. A sensitization study that also examined the incidence of urticarial reactions was performed with 17.5% Ammonium, Potassium, and Sodium Persulfate. At this concentration, a mixture of these persulfates was not sensitizing, and application of Ammonium, Potassium, and Sodium Persulfate did not result in an urticarial reaction.

Also, the Expert Panel was concerned that the greatest concentration of persulfates tested was 17.5%, yet data submitted to CIR reported that persulfates are used in hair lighteners at concentrations of 60%. Because the test materials were applied under occlusive patches, it was assumed that, in normal use (i.e., not occluded and rinsed off), a concentration greater than 17.5% would also be safe. Given the clinical reports of urticarial reactions, the Expert Panel concluded that manufacturers and formulators should be aware of the potential for urticarial reactions at concentrations of persulfates greater than 17.5%.

**CONCLUSION (From Final Report)**

The CIR Expert Panel concludes that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin.
Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.  

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<thead>
<tr>
<th>Ingredient</th>
<th>CAS No.</th>
<th>Definition &amp; Structure</th>
<th>Function</th>
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<tr>
<td>Ammonium Persulfate</td>
<td>7727-54-0</td>
<td>Ammonium Persulfate is the inorganic salt that conforms to the formula:</td>
<td>Oxidizing agent</td>
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<td>Value</td>
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<tr>
<td><strong>Ammonium Persulfate</strong></td>
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<tr>
<td>Form/Odor</td>
<td>Yellow to white crystalline material with a slight acrid odor</td>
<td>Strong oxidizing agent. Decomposes at 120°C, and sulfur dioxide and sulfur trioxide are dangerous decomposition products</td>
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<tr>
<td>Formula Weight</td>
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<td>Readily dissolves in water.</td>
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<td>Solubility in water of 1% solution: 559 g/l (at 20°C) and 510 g/l (at 25°C)</td>
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<td><strong>Potassium Persulfate</strong></td>
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<td></td>
</tr>
<tr>
<td>Form</td>
<td>White, odorless, crystalline material</td>
<td>Loses oxygen with time and with greater rapidity at higher temperatures, completely decomposing at 100°C. Incompatible with combustible materials, sulfur, metallic dust, aluminum dust, chlorates, and perchlorates.</td>
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<tr>
<td>Formula Weight</td>
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<tr>
<td>Solubility</td>
<td>Soluble in ~50 parts water</td>
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<td><strong>Sodium Persulfate</strong></td>
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<td>Form</td>
<td>White crystalline powder</td>
<td>Gradually decomposes, and decomposition is promoted by moisture and higher temperatures</td>
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<td>Formula Weight</td>
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<td>Solubility</td>
<td>Soluble in water; decomposes in alcohol</td>
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<tr>
<td>Duration of Use</td>
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<td>Conc. (%)</td>
<td># of Uses</td>
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<td>Hair - Non-Coloring</td>
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<td>Hair-Coloring</td>
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<th>Conc. (%)</th>
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<table>
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<tr>
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<td>Eye Area</td>
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<td>Hair - Non-Coloring</td>
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<td>Hair-Coloring</td>
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<td>0.67-33.4</td>
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<td>Mucous Membrane</td>
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<tr>
<td>Baby Products</td>
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<td>NR</td>
</tr>
</tbody>
</table>

NR = Not Reported; Totals = Rinse-off + Leave-on + Diluted (for Bath) Product Uses.

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


Ammonium, Potassium, and Sodium Persulfate are inorganic salts used as oxidizing agents in hair bleaches and hair-coloring preparations. Persulfates are contained in hair lighteners at concentrations up to 60%, in bleaches and lighteners at up to 22% and 16%, respectively, and in off-the-scalp products used to highlight hair strands at up to 25%. They are used in professional product bleaches and lighteners at similar concentrations. Much of the available safety test data are for Ammonium Persulfate, but these data are considered applicable to the other salts as well. Acute dermal, oral, and inhalation toxicity studies are available, but only the latter are remarkable, with gross lesions observed in the lungs, liver, stomach, and spleen. In short-term and subchronic feeding studies the results were mixed; some studies found no evidence of toxicity and others found local damage to the mucous membrane in the gastrointestinal tract, but no other systemic effects. Short-term inhalation toxicity was observed when rats were exposed to aerosolized Ammonium Persulfate at concentrations of 4 mg/m³ and greater. Ammonium Persulfate (as a moistened powder) was not an irritant to intact rabbit skin, but was sensitizing (in a saline solution) to the guinea pig. It was slightly irritating to rabbit eyes. Ammonium Persulfate was negative in the Ames test and the chromosomal aberration test. No significant evidence of tumor promotion or carcinogenicity was observed in studies of rats receiving topical applications of Ammonium Persulfate. The persulfates were reported to cause both delayed-type and immediate skin reactions, including irritant dermatitis, allergic eczematous dermatitis, localized contact urticaria, generalized urticaria, rhinitis, asthma, and syncope. The most common causes of allergic dermatitis in hairdressers are the active ingredients in hair dyes, and Ammonium Persulfate has been identified as a frequent allergen. A sensitization study that also examined the incidence of urticarial reactions was performed with 17.5% Ammonium, Potassium, and Sodium Persulfate under occlusive patches. At this concentration and exposure conditions, a mixture of these Persulfates was not sensitizing, and application of Ammonium, Potassium, and Sodium Persulfate did not result in an urticarial reaction. In normal use (i.e., not occluded and rinsed off), it was expected that a concentration greater than 17.5% would also be safe. Given the clinical reports of urticarial reactions, however, manufacturers and formulators should be aware of the potential for urticarial reactions at concentrations of Persulfates greater than 17.5%. Based on the available data, the Cosmetic Ingredient Review (CIR) Expert Panel concluded that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin.

INTRODUCTION

Ammonium, Potassium, and Sodium Persulfate are inorganic salts used as oxidizing agents in hair bleaches and hair coloring preparations. The following report reviews the safety data on these ingredients.

CHEMISTRY

Definition and Structure

Ammonium Persulfate (CAS No. 7727-54-0) is the inorganic salt that conforms to the formula (NH₄)₂S₂O₈ (Wenninger, Canterbery, and McEwen 2000). It is also known as Ammonium Peroxydisulfate; Peroxydisulfuric Acid, Diammonium Salt (Wenninger, Canterbery, and McEwen 2000); Diammonium Persulfate; Diammonium Peroxydisulfate (Registry of Toxic Effects of Chemical Substances [RTECS] 1994); Ammoniumperoxodisulfate; Ammoniumperoxydisulfate; and Ammoniumperoxysulfate (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1994).

Potassium Persulfate (CAS No. 7727-21-1) is the inorganic salt that conforms to the formula K₂S₂O₈ (Wenninger, Canterbery, and McEwen 2000). It is also known as Peroxydisulfuric Acid, Dipotassium Salt (Wenninger, Canterbery, and McEwen 2000); Potassium Peroxydisulfate; and Dipotassium Persulfate (RTECS 1994).

Sodium Persulfate (CAS No. 7775-27-1) is the inorganic salt that conforms to the formula Na₂S₂O₈ (Wenninger, Canterbery, and McEwen 2000). It is also known as Sodium Peroxydisulfate and Peroxydisulfuric Acid, Disodium Salt (Wenninger, Canterbery, and McEwen 2000).

Physical and Chemical Properties

Ammonium Persulfate is a yellow to white crystalline material that has a slight acrid odor (Nikitakis and McEwen 1990). It has a molecular weight of 228.20 Da and readily dissolves in water (Budvani 1989). Water solubility values are 559 g/l at 20°C, pH 2 to 2.5 at 250 g/l, and 510 g/l at 25°C, pH 4 to 6 for 1% solution (CTFA 1994). Ammonium Persulfate...
decomposes at 120°C (Lewis 2000). Dangerous decomposition products of Ammonium Persulfate are sulfur dioxide and sulfur trioxide (CTFA 1994). Ammonium Persulfate is a strong oxidizing agent, and aqueous solutions of this ingredient are acidic and lose active oxygen with time, especially at elevated temperatures (Budavari 1989; Nikitakis and McEwen 1990). CTFA specifications for Ammonium Persulfate list the maximum allowable concentration for sulfated ash as 0.05% (Nikitakis and McEwen 1990). The following impurities and their maximum concentrations were also listed: arsenic (3 ppm), iron (5 ppm), and lead (20 ppm).

Potassium Persulfate is a white, odorless, crystalline material with a molecular weight of 270.3 Da (Budavari 1989). Like Ammonium Persulfate, it loses oxygen with time and with greater rapidity at higher temperatures, completely decomposing at 100°C. Potassium Persulfate is soluble in about 50 parts water and is acidic in aqueous form. This ingredient is incompatible with combustible materials, organic materials and other oxidizable materials, sulfur, metallic dust, aluminum dust, chlorates, and perchlorates.

Sodium Persulfate is a white crystalline powder with a molecular weight of 238.13 Da. It gradually decomposes, and decomposition is promoted by moisture and higher temperatures (Budavari 1989). This ingredient is soluble in water, and decomposes in alcohol (Lewis 2000).

**Manufacture and Production**

Ammonium Persulfate and Potassium Persulfate are prepared by electrolysis of concentrated solutions of ammonium sulfate and potassium sulfate, respectively (Lewis 1999). Merget et al. (1996) reported that Ammonium Persulfate is produced by anodic oxidation of a concentrated ammonium sulfate solution, and that Sodium Persulfate is made by conversion of Ammonium Persulfate with lye.

In 1986, a cosmetic supplier/manufacturer sold 141 tons of bleaching powder, corresponding to 5.5 million applications (CTFA 1987).

**USE**

**Cosmetic**

Ammonium, Potassium, and Sodium Persulfate are oxidizing agents used in hair bleaches, hair-coloring preparations, and/or hair lighteners with color (Wenninger, Canterbury, and McEwen 2000) and are used to decolorize or lighten hair (CTFA 1995a). The product formulation data submitted to the Food and Drug Administration (FDA) in 1998 reported that Ammonium Persulfate was used in a total of 30 cosmetic product formulations, Potassium Persulfate was used in 36 formulations, and Sodium Persulfate in 26 formulations (Table 1) (FDA 1998).

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tr>
<td>Cosmetic product formulation data on Ammonium, Potassium, and Sodium Persulfate (FDA 1998)</td>
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<table>
<thead>
<tr>
<th>Product category</th>
<th>Total no. of formulations in category</th>
<th>Total no. of formulations containing ingredient</th>
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<tbody>
<tr>
<td><strong>Ammonium Persulfate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hair dyes and colors</td>
<td>1572</td>
<td>1</td>
</tr>
<tr>
<td>Hair bleaches</td>
<td>113</td>
<td>23</td>
</tr>
<tr>
<td>Other hair-coloring preparations</td>
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<tr>
<td>Other skin care preparations</td>
<td>692</td>
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</tr>
<tr>
<td><strong>1998 total for Ammonium Persulfate</strong></td>
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<td>30</td>
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<tr>
<td><strong>Potassium Persulfate</strong></td>
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<td></td>
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<tr>
<td>Hair straighteners</td>
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<td>Hair dyes and colors</td>
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<td>2</td>
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<tr>
<td>Hair lighteners with color</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Hair bleaches</td>
<td>113</td>
<td>27</td>
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<tr>
<td>Other hair-coloring preparations</td>
<td>59</td>
<td>5</td>
</tr>
<tr>
<td><strong>1998 total for Potassium Persulfate</strong></td>
<td></td>
<td>36</td>
</tr>
<tr>
<td><strong>Sodium Persulfate</strong></td>
<td></td>
<td></td>
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<tr>
<td>Hair straighteners</td>
<td>63</td>
<td>1</td>
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<tr>
<td>Hair dyes and colors</td>
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<tr>
<td>Hair lighteners with color</td>
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<td>Hair bleaches</td>
<td>113</td>
<td>21</td>
</tr>
<tr>
<td>Other hair-coloring preparations</td>
<td>59</td>
<td>1</td>
</tr>
<tr>
<td><strong>1998 total for Sodium Persulfate</strong></td>
<td></td>
<td>26</td>
</tr>
</tbody>
</table>
Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992). One data submission to Cosmetic Ingredient Review (CIR) states that liquid and gel lighteners for general (all over the head) hair lightening contain ≤12% (on-head) Persulfates, usually comprised of ≤4% Ammonium and ≤8% Potassium Persulfate, and off-the-scalp products used to highlight hair strands generally contain ≤25% (on-head) Persulfates, usually comprised of ≤10% Ammonium and ≤15% Potassium Persulfate (CTFA 1995a). Professional-use lightening products contain the same maximum on-head concentrations as just given, but often contain a mixture of Ammonium (5%), Potassium (15%), and Sodium (5%) Persulfates.

Another submission to CIR by CTFA states that Ammonium, Potassium, and Sodium Persulfates are used in hair lighteners at a concentration of 60% and that the three Persulfates are contained in bleaches and lighteners at concentrations of 12% to 22% (use concentration of 4% to 8%) and 2% to 16% (use concentration of 1% to 6%) (CTFA 1995b). This submission also stated that the Persulfates are used in bleaches and lighteners that are professional products involving off-scalp use (on the hair shaft only), and in these products the Persulfates may be used at a concentration of 10% to 18%. Product formulation data submitted to the FDA in 1984 stated all three ingredients were used at concentrations greater than 50% (FDA 1984).

In general, the strong oxidizing action of persulfates is used to accelerate the bleaching process of peroxide hair bleaches (Fisher 1985a). These ingredients make the hair “porous,” making it more receptive to dyes or toners that provide the final hair shade.

International

Ammonium, Potassium, and Sodium Persulfates are used in Europe to decolorize or lighten hair (CTFA 1995a).

None of these ingredients are listed in the Comprehensive Licensing System (CLS) categories, in which ingredients are listed that have a precedent for use in Japan (Santucci 1999). According to Notification 990 of the Pharmaceutical and Medical Safety Bureau of the Japan Ministry of Health and Welfare, issued September 29, 2000, these ingredients are not prohibited or restricted in its use beyond a basic obligation of manufacturers to use all ingredients in a manner which guarantees safety (Japan Ministry of Health and Welfare 2000).

Noncosmetic

Ammonium Persulfate is cleared for use as a bleaching agent for food starch at ≤0.075%; as an industrial starch modifier and as an alkaline starch reactant at ≤0.3% and ≤0.6%, respectively; in adhesives; as a component of paper and paperboard in contact with aqueous, fatty, and dry foods; and in cellophane and water-insoluble hydroxyethylcellulose film (Rothschild 1990). Ammonium Persulfate is used as a reducer and retarder in photography, as an oxidizer for copper (Budavari 1989), and as an etchant for printed circuit boards (Lewis 1997). It is also used in electroplating, the manufacture of other persulfates, deodorizing and bleaching oils, aniline dyes; preserving foods, depolarizer in batteries, and washing infected yeast.

Potassium Persulfate is cleared for use in certain types of coatings for fresh citrus fruits; in adhesives; in acrylate ester copolymer coating; in resinous and polymeric coatings at 1%; as a component of paper and paperboard in contact with aqueous, fatty, and dry foods; in closures with sealing gaskets for food containers when ≤1% by weight of the gasket composition; and in rubber articles intended for repeated use (Rothschild 1990). Potassium Persulfate is used as a reducing agent in photography, as an analytical reagent, as a polymerization promoter, in pharmaceuticals, in the modification of starch, as a flour maturing agent, and in de-sizing of textiles (Lewis 1997).

Sodium Persulfate is cleared for use as components of paper and paperboard in contact with aqueous, fatty, and dry food; in closures with sealing gaskets for food containers when ≤1% by weight of the gasket composition; and at a concentration of less than 1% in can-end cements for resinous and polymeric coatings (Rothschild 1988). Additionally, it is cleared as a denuding agent of mucous membranes in tripe. Sodium Persulfate is used as a bleaching agent for fats, oils, fabrics, and soaps. It is also used in battery depolarizers and in emulsion polymerization (Lewis 1997).

GENERAL BIOLOGY

Immunological Effects

The histamine-releasing potential of Ammonium Persulfate was investigated using skin slices obtained from Dunkin-Hartley guinea pigs, CFY rats, and Rhesus monkeys (Mahzoon, Yamamoto, and Greaves 1977). Triplicate samples (one to three slices per sample) were incubated with 1 to 1000 µg/ml Ammonium Persulfate for 15 to 30 minutes. No significant histamine release was observed at any of the concentrations tested with guinea pig or monkey skin. With the rat skin, 1000 µg/ml Ammonium Persulfate released 20% to 24% of the histamine from the skin.

Parsons, Goodwin, and Safford (1979) reported that both Ammonium and Potassium Persulfate caused histamine release from isolated rat peritoneal mast cells and from guinea pig skin in vitro and in vivo. In studies with mast cells, both persulfates (0.33 to 2.7 mg/ml) caused dose-dependent releases of histamine. Histamine release induced by Potassium Persulfate was characterized by degranulation of the mast cell with no disruption of the cell membrane. However, with Ammonium Persulfate, alterations in the granules were observed but no apparent degranulation or disruption of the cell membrane occurred. In in vitro studies with slices of guinea pig skin, Potassium Persulfate, but not Ammonium Persulfate, appeared to release histamine selectively. At concentrations ranging from 0.1 to 8 mg/0.5 ml, Ammonium Persulfate induced a dose-related mean histamine release of 1.11% to 14.42% and Potassium Persulfate induced a dose-related mean release of 0.45% to 24.33%. In
in vivo studies, intradermal injections of Potassium Persulfate (4 to 16 mg/ml saline) into guinea pigs caused a dose-dependent release of histamine. Because pretreatment with mepyramine maleate reduced histamine release, the investigators speculated that the vascular permeability changes were due in part to an indirect action mediated by histamine released from skin mast cells. However, because histamine release was not completely inhibited by mepyramine maleate, mediators other than histamine are probably also involved. The investigators concluded that Potassium Persulfate induced the release of histamine by a slow, dose-dependent, noncytolytic mechanism, whereas Ammonium Persulfate appeared to work through both this mechanism and a rapid cytolytic mechanism.

Human polymorphonuclear neutrophil granulocytes (PMNs) were treated with 0.1 to 10 mM Ammonium Persulfate and activated with different stimuli (Köller, Hilger, and König 1996). Stimulation with Ca²⁺ ionophore A23187 (which bypasses membrane signal transduction) resulted in a dose-dependent decrease in the amount of total generated leukotriene B₄ (LTB₄); the decrease was significant at all test concentrations. A similar decrease was also observed with Sodium Persulfate. A decrease in LTB₄ was also observed after incubation with Ammonium Persulfate and activation with the tripeptide formyl-methionyl-leucyl-phenylalanine (fMLP) (which activates cellular responses via ligand-receptor coupling) and sodium fluoride (which directly stimulates heterotrimeric G proteins). Lymphocytes monocytes/basophils were also treated with 0.1 to 10 mM Ammonium Persulfate. A dose-dependent histamine release was observed without additional cellular stimulation; the amount of released histamine ranged from 6% to 20% at 1 mM to 40% at 10 mM Ammonium Persulfate. Coincubation of basophils with fMLP resulted in a significant histamine release with 10 mM Ammonium Persulfate, but not at lower concentrations.

The stability of leukotrienes in a cell-free system was examined. PMNs were stimulated with the Ca²⁺ ionophore, LTB₄-enriched supernatants were obtained, and Ammonium Persulfate was then added. LTB₄ was significantly decreased at concentrations of 1 and 10 mM. The addition of Ammonium Persulfate to resting cells also resulted in a significant decrease in LTB₄.

The effect of priming PMNs with Ammonium Persulfate was also examined. Cells were pretreated with Ammonium Persulfate, washed, and stimulated with the Ca²⁺ ionophore, fMLP, or sodium fluoride. An increase in leukotriene release was observed when the cells were stimulated with fMLP or sodium fluoride; the priming effect was primarily achieved by stimulation with fMLP. The increase in leukotriene formation was generally greatest at a concentration of 0.1 mM Ammonium Persulfate. The priming effect of Ammonium Persulfate was not observed after stimulation with the Ca²⁺ ionophore (Köeller, Hilger, and König 1996).

**Effects on Cardiomyocytes**

The effects of Ammonium Persulfate on the calcium uptake in cardiomyocytes isolated from the hearts of male Sprague-Dawley rats was investigated (Kaminishi, Yanagishita, and Kako 1989). Ammonium Persulfate caused both a concentration- and time-dependent increase in the number of cells in contracture. A concentration of 55 mM Ammonium Persulfate caused contracture of 50% of the cells following 90 minutes of exposure. The Ca²⁺ concentration in the cardiomyocytes decreased in proportion to the concentration of Ammonium Persulfate. The half-maximal decrease was observed at a concentration of 20 mM. The investigators concluded that Ammonium Persulfate "...inhibited intracellular uptake of calcium and accelerated calcium release, thus raising the cytosolic calcium concentration and causing cell contracture."

**Antimicrobial Activity**

Loveless, Spoerl, and Weisman (1954) reported that 2000 μg/ml Potassium Persulfate reduced the growth of Saccharomyces cerevisiae by about 50%, but had no effect on average cell size.

**ANIMAL TOXICOLOGY**

**Acute Toxicity**

**Oral**

The oral LD₅₀ of Ammonium Persulfate, when intubated at a concentration of 200 mg/ml, was 820 mg/kg (Smyth et al. 1969) for rats. When administered in distilled water to male rats and as a 25% w/v solution in tap water to female Sprague-Dawley rats, the oral LD₅₀ was 600 mg/kg and 495 mg/kg, respectively (CTFA 1994). The oral LD₅₀ values of Ammonium and Potassium Persulfate were 689 and 802 mg/kg, respectively, for rats (American Conference of Governmental Industrial Hygienists, Inc. [ACGIH] 1986).

**Dermal**

The dermal LD₅₀ of Ammonium Persulfate was 2 g/kg when applied to the intact skin of 10 Sprague-Dawley rats and 10 g/kg when applied undiluted to four male rabbits (CTFA 1994).

**Inhalation**

The LC₅₀ of Ammonium Persulfate was 2.95 mg/l (the maximum attainable dust concentration via gravimetric method) for Sprague-Dawley rats with a 4-hour exposure time (CTFA 1994). Ninety-seven percent of the particles were <10 μm in diameter. The LC₅₀ of Ammonium Persulfate in a 25% water suspension was 520 mg/l for male rats with a 1-hour exposure
time. At necropsy 14 days after dosing, gross lesions were observed in the liver, stomach, lungs, and spleen.

Parenteral
The intravenous minimum lethal dose and the intraperitoneal LD<sub>50</sub> of Sodium Persulfate for rabbits were 178 and 226 mg/kg, respectively (ACGIH 1986).

Short-Term Toxicity
Oral
Groups of 10 male CR-CD rats were fed 100, 300, or 600 ppm Ammonium Persulfate in the diet for 28 days (CTFA 1994). No deaths occurred during dosing and no gross lesions were observed at necropsy. The lowest-observed-adverse-effect level (LOAEL) was 600 ppm.

Inhalation
Groups of six Sprague-Dawley rats were exposed to 1, 4, 9, 17, and 20 mg/m<sup>3</sup> of aerosolized Ammonium Persulfate for 23.5 hours a day for 7 days (Last et al. 1982). The mass median aerodynamic diameter of the aerosol ranged from 0.8 to 1.3 μm. Control groups of rats were exposed to filtered air. No significant changes were observed with 1 mg/m<sup>3</sup> Ammonium Persulfate. However, at concentrations of 4 to 20 mg/m<sup>3</sup>, Ammonium Persulfate caused a significant reduction in body weight and a significant increase in the wet weight of the right apical part of the lung lobe. The greatest increase in wet weight was 164% with 20 mg/m<sup>3</sup> Ammonium Persulfate. However, no change in the wet-to-dry weight ratio was observed at any of the concentrations tested. Protein and DNA concentrations were significantly increased in the lungs, and tracheal mucus glycoprotein secretion rates tended to be greater than that observed in the control animals. The investigators attributed these changes to pulmonary edema and/or inflammation.

Subchronic Oral Toxicity
No signs of toxicity were observed when six dogs were fed a diet of flour containing 15 g/45 kg Ammonium Persulfate 6 days a week for 3 months (Arnold 1949).

No gross or microscopic alterations were seen in rats and dogs fed Ammonium Persulfate--treated flour or bread in the diet for 5 or 16 months, respectively (BGChemie 1994).

Rats were fed 30 mg/kg/day Sodium Persulfate for 13 weeks (BGChemie 1994). Local damage to the mucous membrane of the gastrointestinal tract occurred, but other systemic effects were not observed. No adverse effects were observed with administration of 30 mg/kg/day Sodium Persulfate for 13 weeks or 100 mg/kg/day for 8 weeks with subsequent administration of 500 mg/kg/day for 5 weeks (BGChemie 1994).

Dermal Irritation
To determine the irritation potential of 99% pure Ammonium Persulfate, 0.5 g moistened with 0.1 ml of water was applied under an occlusive patch to the intact and abraded skin of three white Russian rabbits for 4 hours (BGChemie 1994). Slight edema, which disappeared within 24 hours, was observed in intact skin, whereas moderate to severe erythema, moderate edema, and scab formation followed by cicatrization were observed at the abraded sites. Ammonium Persulfate was considered nonirritating to intact skin.

The dermal irritation potential of Ammonium Persulfate was determined according to Organisation for Economic Co-operation and Development (OECD) Guideline No. 404 using six male and female New Zealand White rabbits (CTFA 1994). No irritation was noted within 72 hours following application. Ammonium Persulfate (dose not specified) was applied to an intact and abraded site on six rabbits, and the sites were scored by the Draize method at 24 and 72 hours (CTFA 1994). Ammonium Persulfate was not irritating.

Dermal Sensitization
The sensitization potential of Ammonium Persulfate was determined in an optimization test (OECD Guideline No. 406) using 10 male and 10 female Pirbright White guinea pigs (BGChemie 1994). All of the animals reacted to intradermal administration of a 0.1% solution in physiological saline, whereas 16 of the animals reacted to epicutaneous application of a 1% solution in demineralized water. Ammonium Persulfate was considered sensitizing to the guinea pig.

Inhalation Sensitization
Wass and Belin (1990) developed an in vitro method for predicting sensitizing properties of inhaled chemicals. Sodium Persulfate (50 μL) was mixed with a lysine-containing peptide (500 μL) at neutral pH and 37°C. The reaction was monitored by means of high-performance liquid chromatography. A peptide reactivity index was determined, ranging from 0, for no detectable reaction, to 10, for complete reactivity. In general, simple acids, bases, and solvents did not react with the peptide, whereas chemicals known for their sensitizing and asthma-inducing properties, such as isocyanates, anhydrides, and chloramine-T, did react. The peptide reactivity index was 0 for Sodium Persulfate.

Ocular Irritation
Ammonium Persulfate, 0.1 g, was instilled into the conjunctival sac of the eye of three white Russian rabbits (BGChemie 1994). Severe diffuse reddening and swelling with hypersecretion subsided within 72 hours; however, clouding of the cornea was still present at this time. The irritation index was 10.5 and Ammonium Persulfate was considered slightly irritating to the eye.

The ocular irritation potential of Ammonium Persulfate was determined according to OECD Guideline No. 405 using nine New Zealand White rabbits; the eyes of six animals were not rinsed whereas the eyes of three animals were rinsed 30 seconds after instillation (CTFA 1994). Ammonium Persulfate caused
slight to mild conjunctivitis and iritis in the unirused eyes and was considered minimally irritating to these eyes. Ammonium Persulfate was practically nonirritating to ringed eyes.

In a Draize test using eight rabbits, Ammonium Persulfate (dose not specified) was not irritating to the eye (CTFA 1994).

**GENOTOXICITY**

Ammonium Persulfate, 1 to 1000 μg/plate, was evaluated for mutagenic activity in an Ames test using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 (Huntingdon Research Centre 1977). Tests were performed with and without metabolic activation and in triplicate. Positive and negative controls were used. Ammonium Persulfate was not mutagenic at any of the concentrations tested.

Ammonium Persulfate was evaluated for mutagenic potential in the Ames test at concentrations up to 10.0 mg/plate using *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA1537 (Ishidate et al. 1984). Tests were conducted both with and without metabolic activation with S9 mix and in duplicate. Ammonium Persulfate was not mutagenic in either protocol at any of the concentrations tested.

Ammonium Persulfate was also negative in the chromosomal aberration test (Ishidate et al. 1984; Ishidate 1988). Chinese hamaster fibroblasts exposed to Ammonium Persulfate at concentrations up to 0.25 mg/ml for 48 hours had no increase in the incidences of polyploid cells or cells with structural aberrations.

*Salmonella* strain TA97 was incubated in triplicate at either 25°C or 37°C with Ammonium Persulfate (concentration not specified) for 30 minutes at pH 5.0 (Pagano, Zeiger, and Stark 1990). Following incubation, the mean number of his+ revertants was determined. Ammonium Persulfate was toxic but not mutagenic at both temperatures.

**TUMOR PROMOTION AND CARCINOGENICITY**

In a skin tumor-promotion test, a single topical application of 20 nmol dimethylbenzanthracene (DMBA) in 0.2 ml acetone was applied to the shaved backs of 20 female Sencar mice, followed 1 week later by biweekly applications of 200 mg/ml Ammonium Persulfate for 51 weeks (Kurokawa et al. 1984). Positive- and vehicle-control groups of mice were also initiated with DMBA, followed by treatment with 12-O-tetradecanoylphorbol-13-acetate (TPA) and acetone, respectively. All of the animals were examined for tumors weekly and body weight was recorded monthly. At necropsy, samples of the skin and major organs were removed and prepared for microscopic examination.

No significant change in body weight or mean survival time was observed for the mice treated with Ammonium Persulfate. At week 52, three of the mice had skin tumors. None of the acetone-treated mice developed tumors, whereas all of the mice treated with TPA had skin tumors. It was noted that there was a relatively high incidence of tumors of the mammary glands, lungs, and uterus in the treated group, but such incidences were also observed in both the positive- and negative-control groups. The investigators concluded that Ammonium Persulfate was inactive as a skin tumor promoter.

The carcinogenic potential of Ammonium Persulfate was also investigated (Kurokawa et al. 1984). Twenty female Sencar mice were topically treated with 200 mg/ml Ammonium Persulfate twice a week for 51 weeks. A control group of mice was treated with acetone alone. All of the mice were examined for skin tumors weekly, and the skin and major organs were examined microscopically at the end of the study. No significant change in body weight or mean survival time was observed for the mice treated with Ammonium Persulfate. Two mice developed epidermal hyperplasia at week 51, whereas none of the mice treated with acetone had skin tumors. As seen in the tumor-promotion study, the incidence of tumors of the mammary glands, lungs, and uterus was similar in both the treated and the vehicle-control groups. The investigators concluded that Ammonium Persulfate was not a dermal carcinogen.

**CLINICAL ASSESSMENT OF SAFETY**

**Dermal Irritation and Sensitization**

The most common causes of allergic contact dermatitis in hairdressers are the active ingredients in hair dyes (Fisher 1989). Ammonium Persulfate has been identified as a frequent allergen in hairdressers’ hands (Beck 1990).

The sensitization potential of Ammonium, Potassium, and Sodium Persulfate was determined in a study that was initiated with 57 subjects, 2 males and 55 females, and completed by 46 subjects, 2 males and 44 females (Jordan 1998). For induction, a lightener/developer mixture with 17.5% Ammonium, Potassium, and Sodium Persulfate was applied to the left inner forearm under an occlusive patch for 4 hours. The mixture without the Persulfates was used as a control. The patches were originally to be applied to the same sites three times for 3 weeks. However, due to strong irritant reactions to the vehicle, patches 3 through 9 were applied for 1 hour instead of 4 hours, and the sites were rotated on the same forearm. Following a 2-week nontreatment period, two challenge applications, applied 48 hours apart, of occlusive patches containing 0.2 ml of 2% Ammonium, 2% Potassium, and 2% Sodium Persulfate were applied to the right inner forearm, examined after 1 hour, replaced, and removed at 24 hours. The sites were evaluated at 1 and 48 hours. One subject had an “irritant response that precluded the use of the same site for the second period,” so the second set of patches was applied at an adjacent site on the same arm for 30 minutes using 1% of each Persulfate.

Eight subjects were prematurely removed from the study during induction because of irritation. Ammonium, Potassium, and Sodium Persulfate were not sensitizers (Jordan 1998).

Sodium Persulfate was tested at concentrations of 10, 100, and 5000 ppm in a human patch test using 26 subjects
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AMMONIUM, POTASSIUM, AND SODIUM PERSULFATE

(E.I. DuPont de Nemours and Company 1992). Each dose was placed under an occlusive patch four times a week for 3 weeks. After a 1-week nontreatment period, each subject was challenged with the same concentration as used for induction. No sensitization reactions were observed in subjects of the 10- and 100-ppm treatment groups. However, 5 of 26 subjects treated with 5000 ppm Sodium Persulfate developed grade 4 skin reactions, which included redness, induration, swelling, papules, and vesicles, following the challenge application. These five subjects were rechallenged with either 100 or 2500 ppm Sodium Persulfate for 24 or 48 hours. Two of the subjects had grade 4 reactions at the site treated with 2500 ppm Sodium Persulfate, and one of these also had reactions at the 100 ppm site.

Van Joost et al. (1984) analyzed data from 242 patients who had one or more positive reactions to a routine battery of test antigens and who were also tested with 2% aqueous Ammonium and Potassium Persulfate. Six patients had delayed-type responses to Ammonium Persulfate and 11 had positive responses to Potassium Persulfate. The incidences of delayed-type response at 48 and 72 hours were subjected to studies of shifts (48 vs. 72 hours) and statistically analyzed. Neither of the ingredients had a negative shift over the time interval studied, increasing from the low value of 0.12 at 48 hours to 1.82 at 72 hours. In general, the persulfates had a significantly higher confidence limit for the mean value of shifts as compared to that of the routine battery as a whole. The investigators speculated that this may indicate that the persulfates behave differently in early delayed-type responses.

Ammonium Persulfate proved to fulfill classification criteria for a contact allergen and a sensitizer by inhalation in a project of the Nordic Council of Ministers. The conclusion on criteria documents from national research in Norway also stated that Ammonium Persulfate may cause allergy by skin contact (Nordic Council of Ministers, 1991).

Guerra, Bardazzi, and Tosti (1992a) reported that of 49 clients of hairdressers, only 7 (2.7%) had a positive patch test to 2.5% Ammonium Persulfate in petrolatum. One of these subjects, who had complained of generalized urticaria after exposure to a hair bleach, had a positive reaction to an open patch that confirmed the diagnosis of an immediate contact reaction caused by Ammonium Persulfate.

Ammonium Persulfate was used in a comparison of test results using Duhring and Finn chambers (Frosh and Kilgman 1979). (Details of the testing were not provided.) A 1% aqueous Ammonium Persulfate solution produced a reaction of 2+ using the Duhring chamber and a reaction of 0 using the Finn chamber. A 10% solution produced reactions of 3+ and 1+ using the Duhring and Finn chambers, respectively.

A number of case studies of dermal and respiratory problems associated with persulfates have been reported in the literature. All of the cases were associated with the use of hair bleaches containing these ingredients. See Table 2 for a further description of these cases.

Urticarial Reactions

In the study performed by Jordan (1998) described earlier, the incidence of contact urticaria was examined by removing the challenge patches 1 hour after application and evaluating the test site. Application of Ammonium, Potassium, and Sodium Persulfate did not result in urticarial reactions.

Calnan and Shuster (1963) studied reactions to Ammonium Persulfate in five women with hand dermatitis. Saturated solutions of Ammonium Persulfate were applied topically or scratched into the skin. Wheals were produced in all of the women after 15 minutes; the wheals were larger when the solution was scratched into the skin. A 1:10 solution of Ammonium Persulfate was the lowest concentration at which these reactions were observed after the solution was scratched into the skin. Intradermal injections (0.05 ml) of a 1:100 solution of Ammonium Persulfate caused wheals greater than 15 mm in diameter. The investigators noted that skin responses were delayed by 15 to 30 minutes after topical exposure and by 10 to 15 minutes following intradermal exposure. The subsequent wheal and flare were indicative of a histamine response.

In order to investigate this further, four of the patients were tested using antihistamines. Ammonium Persulfate was applied to the skin both before and after antihistamines were injected. One patient's response was unchanged, two patients had reduced wheals, and one patient had no response. The investigators concluded that the characteristic cutaneous reactions caused by Ammonium Persulfate were due to histamine being slowly released from the skin.

This conclusion was also supported by results of a study in which Ammonium Persulfate had no effect upon skin that had been depleted of histamine. Four patients were injected with compound 48/80 in the forearm at each corner of a 2-cm² area of skin on the forearm. Twenty-four hours later a saturated solution of Ammonium Persulfate was scratched into the center of the square, as well as sites both proximal and distal to the square. No reactions occurred at the center of the square, but distal sites treated with Ammonium Persulfate had reactions.

The investigators were unable to conclude whether Ammonium Persulfate works directly on mast cells or whether histamine release is due to immediate-type immune hypersensitivity. Seven of 57 subjects developed wheals after being scratch tested with Ammonium Persulfate. This number was considered low and was not consistent with the idea that Ammonium Persulfate initiated histamine release. Slow absorption did not appear to be a factor because no reactions were observed when normal subjects were injected with Ammonium Persulfate. Additionally, the cutaneous responses could not be attributed to increased sensitivity to histamine because wheals induced by histamine acid phosphate were of similar size in normal individuals. Thus, the investigators surmised that the reactions observed in the five patients were due to increased sensitivity to Ammonium Persulfate (Calnan and Shuster 1963).
TABLE 2
Case studies of dermal reactions to Persulfates in hair bleaches

<table>
<thead>
<tr>
<th>Case studies</th>
<th>Reference</th>
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<tbody>
<tr>
<td>A 54-year-old woman developed itchiness of the face and became red and swollen on the upper part of her body within .5 hour of having a hair bleach applied. She went into shock and had generalized erythema and urticaria. Patch tests with 2% Ammonium Persulfate were negative. However, direct application of a supersaturated solution of Ammonium Persulfate caused a 1+ response, and when the solution was rubbed in the skin, a 4+ response. A freshly prepared hair bleach caused a response of 1+ when applied to the skin and a 2+ urticarial wheal when rubbed into the skin.</td>
<td>Brubaker (1972)</td>
</tr>
<tr>
<td>The face of a 49-year-old woman became red and edematous immediately following exposure to a hair bleach containing a persulfate-peroxide mixture. This condition lasted for several hours. Generalized urticaria persisted for 24 hours. Patch tests with 2% and 5% aqueous Ammonium Persulfate were negative, but tests with 5% aqueous Ammonium Sulfate were positive.</td>
<td>Fisher and Dooms-Goossens (1976)</td>
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<td>A 46-year-old woman developed redness and slight crusting on the anterior portion of the scalp and forehead one day after treatment with a hair bleach containing Ammonium Persulfate. Erythema and crusting were apparent on day 3. Patch tests with 2% and 5% Ammonium Persulfate were negative. The authors believed that the reaction was due to “...excessive concentrations of Ammonium Persulfate producing a strongly irritating alkaline effect.”</td>
<td>Fisher and Dooms-Goossens (1976)</td>
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<tr>
<td>The face of a 49-year-old woman became red and edematous, her eyelids could not be opened, and generalized urticaria developed immediately upon her first-time application of a persulfate-peroxide hair bleach. Edema lasted for several hours and generalized urticaria persisted for 24 hours. An open patch test with 2% aqueous Ammonium Persulfate applied to the forearm produced a large urticarial wheal within 7 minutes for the woman but not in three controls. The author believed this was a severe histamine reaction because it was a first time exposure and that Ammonium Persulfate is not primarily urticariogenic because the controls did not have a reaction.</td>
<td>Fisher 1977</td>
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<td>A 45-year-old woman stated that on several occasions immediately upon application of Ammonium Persulfate hair bleach, a burning sensation and diffuse erythema developed on the forehead, back of the neck, and upper back, followed by a mild crusted dermatitis of the scalp and back of the neck the next day. The use of prednisone and Chlor-Trimeton prior to bleaching resulted in minimal symptoms.</td>
<td>Fisher 1977</td>
</tr>
<tr>
<td>A 72-year-old woman developed erythema and edema of the face 1 hour following exposure to hair bleach containing 5% aqueous Ammonium Persulfate. The following day, her cheeks and forehead were sharply demarcated and she had marked edematous urticaria on her face and forehead. When she was tested with 5% Ammonium Persulfate, an immediate wheal was produced. However, a 48-hour patch test with 2% aqueous Ammonium Persulfate was negative.</td>
<td>Fisher (1985a)</td>
</tr>
<tr>
<td>A 70-year-old woman developed pruritic edema on her cheeks and forehead 3 hours after the application of a hair bleach containing Ammonium Persulfate.</td>
<td>Fisher (1985a)</td>
</tr>
<tr>
<td>A 69-year-old woman experienced facial flushing following exposure to a hair bleaching formulation containing 2% Ammonium Persulfate. She reported a stinging and burning sensation of the scalp and her forehead and face were erythematous with no itching. This condition persisted for 48 hours. Patch tests with 2% Ammonium Persulfate were negative.</td>
<td>Fisher (1993)</td>
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</table>

It was reported that a wheal developed after a patient was scratch tested with Ammonium Persulfate powder "as is" (Fisher and Dooms-Goossens 1976). A different patient who was tested in the same manner developed a large wheal, asthma, and erythema of the face. Other patients tested with 5% Ammonium Persulfate developed large pruritic wheals without any systemic reaction. The investigators noted that although patch tests with Ammonium Persulfate in dermatitic patients indicated that reactions were allergic in nature and were of the delayed variety, the results of the scratch tests and the fact that a few control subjects also had positive responses indicated that Ammonium Persulfate may also be a primary urticariogenic agent and that some immediate reactions could be due to a nonallergic release of histamine.

Patients with urticarial reactions or asthma after exposure to Ammonium Persulfate may have immediate reactions to patch
tests (Fisher and Dooms-Goossens 1976). One subject patch tested with 5% aqueous Ammonium Persulfate developed a large urticarial wheal within 10 minutes of exposure, which was followed by an urticarial reaction of the head and neck that persisted for 16 hours.

Adverse Reaction Reporting
The FDA Consumer Experience Reporting System aggregates all consumer complaints received by cosmetic companies that participate in the FDA voluntary program by number of complaints received (not by complaint type). Information is submitted for both retail and professional use. The 1990 to 1993 annual rate for all adverse experiences reported for hair lighteners was 8.79 complaints/million units sold, with a mean of 8.46 complaints reported for 1.07 million units sold on average per year (CTFA 1995a). The mean complaint rate for hair lighteners with dyes was 2.60 complaints/million units sold, with a mean of 167 complaints reported for 130,000 units sold on average per year. (These complaint rates are lower than those reported for shampoos, baby shampoos, bath soaps, and permanent waves.)

Occupational Studies
A number of occupational studies regarding dermatologic problems associated with exposure to persulfates have also been reported. Fisher (1985a) reports that “The persulfates are unique chemicals that can produce not only irritant dermatitis and allergic eczematous dermatitis of the delayed ‘Type IV’ variety but also ‘immediate’ reactions including localized contact urticaria, generalized urticaria, rhinitis, asthma and syncope.” In general, reactions such as severe, immediate localized, and generalized urticaria and possibly syncope are associated with formulations containing 10% to 20% Ammonium Persulfate, whereas delayed localized urticaria is associated with preparations containing 2% to 5% Ammonium Persulfate. However, the ACGIH (1986) reported that, based on 20 years experience with persulfates in one industry, even when the threshold value of 15 mg/m³ for nuisance dust was employed for control purposes, no cases of occupational illness occurred. They also stated no “significant cases of dermatitis have occurred from skin contact when good personal hygiene practices were being followed.”

Adverse effects are most commonly reported in the hairdressing industry. Reports of dermatitis in the manufacturing of persulfates exist, but are limited due to the preventive measures taken to limit exposure. In the past, dermatitis was also associated with the baking industry in Europe, which used persulfates in the making of bread. Several countries banned the use of persulfates in baking, and in general, potassium bromate has replaced persulfates in the baking industry (Fisher 1985b).

See Table 3 for the details of these occupational studies.

Threshold Limit Value
The persulfates are assigned a time-weighted average threshold limit value (TLV) of 2 mg/m³, measured as persulfate (ACGIH 1986). However, the ACGIH recommends a TLV of 2 mg/m³ for Potassium Persulfate (Sullivan 1992).

SUMMARY
Ammonium, Potassium, and Sodium Persulfate are inorganic salts used as oxidizing agents in hair bleaches and hair-coloring preparations. In 1998, it was reported to the FDA that Ammonium, Potassium, and Sodium Persulfate used in 30, 36, and 26 formulations, respectively. Data submitted to CIR state that Persulfates are contained in hair lighteners at concentrations up to 60%, in bleaches and lighteners at up to 22% (use concentration up to 8%) and up to 16% (use concentration up to 6%), respectively, and in off-the-scalp products used to highlight hair strands at up to 25% (on-head); they are used in professional product bleaches and lighteners at similar concentrations.

The dermal LD₅₀ of Ammonium Persulfate was 2 and 10 g/kg for rats and rabbits, respectively. For rats, the reported oral LD₅₀ of Ammonium Persulfate ranged from 600 to 820 mg/kg and for Potassium Persulfate was 802 mg/kg. The inhalation LC₅₀ of Ammonium Persulfate for rats was 2.95 mg/l after a 4-hour exposure, and for a 25% water suspension and a 1-hour exposure, it was 520 mg/l. The intravenous minimal lethal dose and the intraperitoneal LD₅₀ of Sodium Persulfate were 176 and 226 mg/kg, respectively. In a short-term feeding study of Ammonium Persulfate using rats, the LOAEL was 600 ppm. In a subchronic feeding studies, no signs of toxicity were observed in rats or dogs fed Ammonium Persulfate–treated flour or bread. Local damage to the mucous membrane in the gastrointestinal tract, but no other systemic effects, was observed in one subchronic feeding study with Sodium Persulfate, but no lesions were observed in another study. Inhalation toxicity was observed when rats were exposed to aerosolized Ammonium Persulfate at concentrations of 4 mg/m³ and greater. Ammonium Persulfate was not an irritant to intact rabbit skin, but was sensitizing to the guinea pig. It was slightly irritating to rabbit eyes.

Ammonium Persulfate was negative in the Ames test and the chromosomal aberration test. No significant evidence of tumor promotion or carcinogenicity were observed in studies of rats receiving topical applications of Ammonium Persulfate. In a study examining the sensitization potential of and the incidence of urticarial reactions to 17.5% Ammonium, Potassium, and Sodium Persulfate in a lightener/developer mixture, the Persulfate mixture was not a sensitizer and none of the Persulfates caused an urticarial reaction; significant irritation to the vehicle was observed during induction. In a clinical patch test, 5 of 26 subjects had positive sensitization reactions to 5000 ppm Sodium Persulfate. These reactions were confirmed in two subjects when rechallenged. In another study, it was noted that reactions to Ammonium Persulfate were more severe when the ingredient was scratched into the skin. Noting a characteristic wheal and flare response, the investigators concluded that histamine release was involved. This is supported by results of in vitro and in vivo animal studies. However, it could not be determined
### TABLE 3
Occupational exposure to Persulfate Salts

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Study description</th>
<th>Reference</th>
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<tr>
<td><strong>Hairdressers</strong></td>
<td>A 32-year-old hairdresser developed acute eczematous dermatitis on both hands following exposure to hair bleaches containing Ammonium Persulfate. Patch tests with 2% Ammonium Persulfate were positive.</td>
<td>Fisher and Dooms-Goossens (1976)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Twelve of 49 hairdressers patch tested with 2.5% Ammonium Persulfate in petrolatum had positive reactions, compared to 1 of 118 nonhairdressers tested.</td>
<td>Kellett and Beck (1985)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Over a 5-year period, 2320 patients with reactions to one or more allergens in a standard series were also tested with 2.5% pet. Ammonium Persulfate and 2% aqueous Potassium Persulfate. A total of 22 individuals had positive reactions to these persulfates. Retrospectively, 14 of these patients were hairdressers, of which 11 reacted to both persulfates and 3 reacted to only Ammonium Persulfate. Of the remaining eight nonhairdressers, five reacted to both persulfates and three reacted to only Ammonium Persulfate. The investigators noted that the hand dermatitis of four of these nonhairdressers was exacerbated by their personal use of hair bleaches.</td>
<td>Van Joost and Roesyanto (1991)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>A multicenter study was performed in Italy in order to evaluate the frequency and source of contact sensitization in hairdressers. Of the 302 hairdressers studied, 11.3% tested positively to 2.5% Ammonium Persulfate in petrolatum.</td>
<td>Guerra, Tosti, and Bardazzi (1992b)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Patch test results from nine European centers were evaluated in order to determine the frequency of sensitization among European hairdressers. Of the 809 hairdressers tested, 8% had positive patch test results with 2.5% petrolatum Ammonium Persulfate. Of 104 clients who were patch tested because of suspected contact sensitization, none reacted to Ammonium Persulfate.</td>
<td>Frosch et al. (1993)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Over a 5-year period, 143 atopic and nonatopic hairdressers with hand eczema were patch-tested with a hairdressers and standard series of allergens. The subjects were divided into three groups: 45 were eczematous atopics, 32 were mucous membrane atopics, and 66 were nonatopic. Seven (16%), 4 (13%), and 10 (15%) of the subjects of each group, respectively, were sensitized to Ammonium Persulfate.</td>
<td>Sutthipisal, McFadden, Cronin 1993</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>One hundred three hairdressers were patch-tested with a number of allergens over a 4-year period. Thirty-seven hairdressers reacted to 2.5% Ammonium Persulfate in petrolatum. One patient had a type 1 reaction, with airways obstruction, in addition to allergic contact dermatitis.</td>
<td>van der Walle and Brunsveld 1994</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Over a 9-year period, 106 hairdressers were patch-tested with a hairdressers and standard series of allergens. Nineteen subjects (17.9%) had a positive reaction to 2.5% Ammonium Persulfate in petrolatum.</td>
<td>Katsarou et al. 1995</td>
</tr>
<tr>
<td>Asthma</td>
<td>A 29-year-old woman acquired rhinitis and asthma while working in a beauty salon. A scratch test performed using 1% aqueous Ammonium Persulfate immediately produced a wheal, followed by a mild asthma attack.</td>
<td>Fisher and Dooms-Goossens (1976)</td>
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<th>Reaction</th>
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<tr>
<td>Asthma</td>
<td>A 21-year-old hairdresser had a nonimmediate asthmatic reaction to hair bleach containing persulfates. This type of reaction was reproduced by exposure to the bleach and was blocked by inhalation of beclomethasone dipropionate but not by sodium cromoglycate. Patch tests with Potassium Persulfate and the bleach were negative. The investigators noted that at the time of these tests, the subject had changed jobs and was no longer being exposed to the bleach.</td>
<td>Pepys, Hutchcroft, and Breslin (1976)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Eleven of 23 employees of a hair salon complained of upper or lower respiratory tract symptoms. Four of six with asthma had cases that were occupationally related. These subjects developed late type asthmatic reactions after exposure to bleach powder. Bronchial provocation tests with the components of the bleach indicated that Potassium Persulfate was the cause.</td>
<td>Davies and Blainey (1983)</td>
</tr>
<tr>
<td>Asthma</td>
<td>Four of 23 employees of one hairdressing salon had occupational asthma due to inhalation of bleach powders containing persulfate salts. One of the four was positive in a skin prick test to persulfate salts. When specific bronchial provocation tests were conducted on 14 of the employees, as well as 8 other individuals, the investigators reported that only those with a history of work related asthma and bronchial hyperreactivity had positive reactions. They concluded that the response to the bleach powder was specific. Further studies indicated that the response was caused by changes in airway caliber rather than lung volumes and that mast cells may play a part in the pathogenesis of persulfate induced asthma.</td>
<td>Blainey et al. (1986)</td>
</tr>
<tr>
<td>Asthma</td>
<td>A 21-year-old hairdresser suffered from rhinitis and wheezing dyspnea during 5.5 years of employment when she was exposed to hair bleaches and hair dyes containing bleaches. She had elevated total IgE in allergy tests and a provocation test with 10 mg/ml histamine was positive. Exposure tests with a hair bleaching product and 1% Ammonium Persulfate caused wheezing and dyspnea 3 to 4 hours following exposure. These responses were partially inhibited when disodium cromoglycate was inhaled 15 minutes prior to exposure, and completely inhibited when betamethasone was administered. The investigators concluded that the patient suffered from late onset bronchial asthma due to sensitivity to Ammonium Persulfate.</td>
<td>Gamboa et al. (1989)</td>
</tr>
<tr>
<td>Contact dermatitis and asthma</td>
<td>A 21-year-old hairdresser developed rhinitis from exposure to commercial bleaches, had urticarial reactions when she applied the bleach to her own hair, and eventually developed conjunctivitis and edema of the eyelids. Patch tests were positive for Potassium and Sodium Persulfate, and inhalation tests with the hair bleach produced an immediate asthmatic reaction within 1 minute.</td>
<td>Pepys, Hutchcroft, and Breslin (1976)</td>
</tr>
<tr>
<td>Contact dermatitis and asthma</td>
<td>A 23-year-old hairdresser developed acute pruritus and rashes on her hands and forearms after using hair bleach containing Ammonium Persulfate. An open test with 5% aqueous Ammonium Persulfate caused slight reddening and pruritus after 20 minutes. A scratch test with 1% aqueous Ammonium Persulfate caused erythema and wheal information after 5 minutes. A closed patch test with 2% aqueous Ammonium Persulfate was positive at 72 hours.</td>
<td>Widstrom (1977)</td>
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## TABLE 3
Occupational exposure to Persulfate Salts (Continued)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Study description</th>
<th>Reference</th>
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<tr>
<td>Contact dermatitis and asthma</td>
<td>A hairdresser who developed cutaneous and respiratory symptoms after 1 year of employment was tested in clinical and immunological studies. Skin prick tests with 1:5 w/v Potassium and Sodium Persulfate were positive, but were negative with 10 control subjects. The hairdresser had no reaction to a 2% concentration of either of the persulfates in an open patch test. Hyperreactivity was observed in a methacholine inhalation test. A bronchial provocation test with 1:50 w/v Potassium Persulfate elicited a nonimmediate asthmatic response, which was followed by a recurrent nocturnal fall in airflow that was resolved after 3 days. Plethysmography indicated air trapping due to increased airway resistance. Histamine release tests were not conclusive and determinations of specific immunoglobins against persulfate salts were negative.</td>
<td>Parra et al. (1992)</td>
</tr>
<tr>
<td>Rhinoconjunctivitis and asthma</td>
<td>A hairdresser developed rhinoconjunctivitis and bronchial asthma associated with hair bleach containing persulfate after 2 years. A prick test was positive for the persulfate.</td>
<td>Pankow et al. (1989)</td>
</tr>
<tr>
<td>Bakers</td>
<td>Forty-two of 400 bakers examined had positive patch test reactions to Ammonium Persulfate. However, only one of 150 individuals not in the baking industry reacted to this ingredient.</td>
<td>Grosfeld (1951)</td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>Five bakers with occupational eczematous dermatitis were tested with a variety of baking ingredients using on-off and patch tests to determine the cause of their dermatitis. Two of the workers were sensitive to persulfates.</td>
<td>Nava et al. (1983)</td>
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<tr>
<td>Industrial workers</td>
<td>Over a 5-year period, the incidence of rashes among persulfate workers in one factory was determined. Although 15 workers comprised the production staff, the turnover rate was such that up to 25 new workers were involved in 1 year. Over the 5-year period, 20% to 70% of the new employees developed rashes within 1 month of employment. The rashes were characterized by itchy red papules and eczematous patches on the wrists and forearms, hands, neck, and face. It was predominantly the workers involved in the manufacture of Potassium Persulfate that were affected rather than those working with Ammonium Persulfate. The affected workers fell into two classes: those who after removal from the persulfate did not relapse after reexposure and those who rapidly relapsed after reexposure.</td>
<td>White, Catchpole, and Rycroft (1982)</td>
</tr>
<tr>
<td>Asthma</td>
<td>A cross-sectional study of 52 employees of a plant that produced Persulfates was performed; 12 subjects were directly involved in Persulfate production, the remaining 40 subjects had indirect contact. Thirteen persons from the medical profession were used as controls. Questionnaires were administered, skin prick tests were performed with 1% and 5% (w/v) Ammonium and Potassium Persulfate, atopy screening was done, and lung function was assessed. Three, two, and three test subjects reacted to Ammonium, Potassium, and both Ammonium and Potassium Persulfate, respectively; of these eight reactors, only three had direct contact with Persulfates. Six of the</td>
<td>Wrbitzky, Drexler, and Letzel 1995</td>
</tr>
</tbody>
</table>

(Continued on next page)
eight reactors reported workplace-related breathing difficulties; 9 of the 44 nonreactor test subjects also reported breathing difficulties. None of the controls reacted to the prick test. The mean total IgE was increased in 16 subjects; a Phadiatop test reported positive results in 12 test subjects. Test subjects that had positive results to the prick test had decreased lung function values compared to those subjects that had negative results.

Asthma
A cross-sectional study of 32 employees of a chemical plant that produced Persulfates was performed. Eighteen workers at the plant who were not exposed to Persulfates were used as the controls. Questionnaires were used, skin prick tests were performed with 80 mg/ml buffered Ammonium (pH 3.1) and Sodium Persulfate (pH 3.9), total IgE and specific IgE were measured, and lung function and bronchial responsiveness to histamine were assessed. Work-related rhinitis was reported by one test subject, and work-related conjunctivitis and bronchitis were reported by two control subjects. Early and/or late skin reactions to Persulfates were not observed for test or control subjects. Lung function, total IgE, and response to histamine were similar for test and control subjects. Bronchial hyperresponsiveness was present in four nonatopic test subjects and in one nonatopic and one atopic control worker. It was noted that 7 of 36 exworkers left because of medical reasons; 6 had work-related contact dermatitis and 1 reported asthma. Merget et al. (1996)

Contact dermatitis and asthma
Of 106 workers in a hydrogen-peroxide factory, 34% had eczematous dermatitis and 15% had asthmatic bronchitis thought to be occupational in nature. Patch tests with Ammonium Persulfate were positive in 32 of 46 workers. None of the workers had positive responses to Potassium Persulfate, sulfuric acid, or hydrogen peroxide. It was noted that inhalation tests with aerosolized Ammonium Persulfate exacerbated the symptoms. The investigators concluded that the observed reactions were allergic in nature. Barsotti, Parmeggiani, and Sassi (1951)

Contact dermatitis and asthma
Two industrial workers developed dermatitis, rhinitis, bronchitis, and asthma following occupational exposure to the dust of persulfate salts. Patch tests induced late cutaneous reactions and occupational exposure to the workplace for 8 hours induced a pathological increase in airway resistance. Baur, Fruhmann, and Leibe (1979)

whether Ammonium Persulfate works directly on mast cells or whether histamine release is due to immediate-type immune hypersensitivity.

The persulfates caused both delayed-type and immediate skin reactions. These reactions include irritant dermatitis, allergic eczematous dermatitis, localized contact urticaria, generalized urticaria, rhinitis, asthma, and syncope. The most common causes of allergic dermatitis in hairdressers are the active ingredients in hair dyes, and Ammonium Persulfate has been identified as a frequent allergen. A number of occupational case studies document these types of reactions, but no incidence data were available.

DISCUSSION
The Expert Panel was concerned with the sensitization and urticaria potential of Persulfates. A sensitization study that also examined the incidence of urticarial reactions was performed with 17.5% Ammonium, Potassium, and Sodium Persulfate. At this concentration, a mixture of these Persulfates was not sensitizing, and application of Ammonium, Potassium, and Sodium Persulfate did not result in an urticarial reaction.

Also, the Expert Panel was concerned that the greatest concentration of Persulfates tested was 17.5%, yet data submitted to CIR reported that Persulfates are used in hair lighteners at concentrations of 60%. Because the test materials were applied
under occlusive patches, it was assumed that, in normal use (i.e., not occluded and rinsed off), a concentration greater than 17.5% would also be safe. Given the clinical reports of urticarial reactions, the Expert Panel concluded that manufacturers and formulators should be aware of the potential for urticarial reactions at concentrations of Persulfates greater than 17.5%.

CONCLUSION

The CIR Expert Panel concludes that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin.

REFERENCES


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Unpublished data submitted by CTFA. (11 pages.)


Available for review. Director, Cosmetic Ingredient Review, 1101 17th St., N.W., Suite 310, Washington, DC 20036, USA.


2016 FDA VCRP Data

**Ammonium Persulfate**

- 03G - Other Eye Makeup Preparations: 1
- 05G - Tonics, Dressings, and Other Hair Grooming Aids: 1
- 06A - Hair Dyes and Colors (all types requiring caution statements and patch tests): 11
- 06F - Hair Lighteners with Color: 3
- 06G - Hair Bleaches: 16
- 06H - Other Hair Coloring Preparation: 6
- **Total**: 38

**Sodium Persulfate**

- 06A - Hair Dyes and Colors (all types requiring caution statements and patch tests): 3
- 06F - Hair Lighteners with Color: 3
- 06G - Hair Bleaches: 33
- 06H - Other Hair Coloring Preparation: 3
- 09A - Dentifrices: 2
- **Total**: 44

**Potassium Persulfate**

- 05G - Tonics, Dressings, and Other Hair Grooming Aids: 1
- 06A - Hair Dyes and Colors (all types requiring caution statements and patch tests): 14
- 06F - Hair Lighteners with Color: 4
- 06G - Hair Bleaches: 42
- 06H - Other Hair Coloring Preparation: 7
- **Total**: 68
Memorandum

TO: Lillian Gill, D.P.A.
   Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Beth A. Lange, Ph.D.
      Industry Liaison to the CIR Expert Panel

DATE: October 15, 2015

SUBJECT: Concentration of Use by FDA Product Category: Persulfates
## Concentration of Use by FDA Product Category – Persulfates

**Ammonium Persulfate**

- Hair dyes and colors: 5.8-10%
- Hair bleaches: 7-44.1%
- Other hair coloring preparations: 12.5%

**Potassium Persulfate**

- Hair dyes and colors: 6-14.4%
- Hair tints: 72.5%
- Hair bleaches: 10.8-70%
- Other hair coloring preparations: 42.8%

**Sodium Persulfate**

- Hair dyes and colors: 0.67-1.9%
- Hair bleaches: 6-33.4%
- Other hair coloring preparations: 15.5%

Information collected in 2015
Table prepared October 13, 2015