
Amended Safety Assessment of Persulfates as Used in Cosmetics

Status: Final Amended Report
Release Date: February 15, 2018
Panel Date: December 4-5, 2017

The 2017 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 Executive Director is Bart Heldreth, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst.

ABSTRACT: The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reassessed the safety of 3 persulfates, which function as oxidizing agents in cosmetic products. The Panel reviewed relevant data relating to the safety of these ingredients and concluded that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and hair lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel also concluded that the available data are insufficient for determining the safety of these persulfates in leave-on products and dentifrices.

INTRODUCTION

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are inorganic salts that are used as oxidizing agents in cosmetic products. The Panel concluded in a final report (published in 2001), 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.¹ 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. The source of much of the new data included is the European Chemicals Agency. 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.

This safety assessment includes relevant published and unpublished data for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A list of the typical search engines and websites used, sources explored, and endpoints that CIR evaluates is available on the CIR website (<https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <https://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the 2001 safety assessment on the previously reviewed ingredients are disseminated throughout the text of this re-review document, as appropriate. For complete and detailed information, please refer to the original report, which is available on the CIR website (<https://www.cir-safety.org/ingredients>).

CHEMISTRY

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are inorganic salts. Definitions and structures of these ingredients are presented in Table 1.² The structure of Ammonium Persulfate is also presented below.

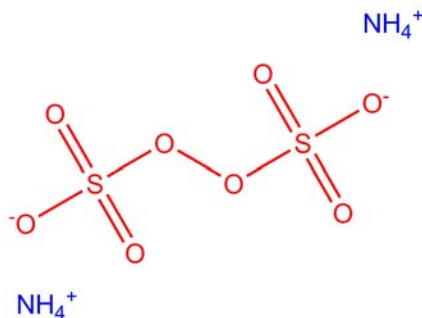


Figure 1. Ammonium Persulfate

Physical and Chemical Properties

Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are soluble in water. When persulfate salts are dissolved in water, they dissociate nearly instantaneously to form hydrated K^+ , Na^+ , NH_4^+ , SO_4^{2-} and persulfate dianion.³ Additional chemical/ physical properties of these ingredients are presented in Table 2.¹

Method of Manufacture

Ammonium Persulfate

Ammonium Persulfate is prepared by electrolysis of a concentrated solution of ammonium sulfate.¹

Potassium Persulfate

Potassium Persulfate is prepared by electrolysis of a concentrated solution of potassium sulfate.¹

Sodium Persulfate

Sodium Persulfate is manufactured by the conversion of Ammonium Persulfate with lye.¹

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 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).^{4,5}

According to 2017 VCRP data, the greatest reported use frequency is for Potassium Persulfate (73 product formulations, mostly rinse-off products), followed by Sodium Persulfate (48 product formulations; all rinse-off products, and most of the uses are in hair coloring products).⁴ It should be noted that 2017 VCRP data indicate that, of the 3 persulfates that are being used in cosmetics (most of which are rinse-off product uses), Ammonium Persulfate and Potassium Persulfate are also being used in leave-on products (i.e., product types that are not hair coloring preparations [rinse-off products]). The results of a concentration of use survey conducted in 2015 reported use in various types of hair coloring preparations, and 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).⁵ Of the many product categories surveyed for persulfate ingredient uses, only uses in various types of hair coloring preparations were reported in this survey. Ingredient use concentrations and use frequencies that were included in the CIR Final Report on Ammonium, Potassium, and Sodium Persulfates (published in 2001) are also presented in Table 3.¹

According to 1998 use frequency data provided by the FDA, Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate were being used in hair coloring/hair bleaching products, and Ammonium Persulfate was also being used in a skin care preparation at the time of the original assessment.¹ However, according to 2017 VCRP data, these persulfates are still being used in hair coloring/hair bleaching products, and use in additional product categories is being reported for Ammonium Persulfate (in eye makeup preparations and in tonics, dressings and other hair grooming aids), Sodium Persulfate (in dentifrices), and Potassium Persulfate (in tonics, dressings and other hair grooming aids).⁴ The following differences in maximum ingredient use concentrations in hair coloring/hair bleaching products are apparent when 1995 concentration of use data and 2015 data are compared:^{1,5} Ammonium Persulfate - 60% in 1995, 44.1% in 2015; Potassium Persulfate - 60% in 1995, 72.5% in 2015; and Sodium Persulfate - 60% in 1995, 33.4% in 2015.

Cosmetic products containing Ammonium Persulfate may be applied to the skin or used near the eyes; all three persulfates are used in hair products. Products containing these ingredients may be used as frequently as daily (dentifrices; 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.

The concentrations of particles that hairdressers are exposed to during hair bleaching have been measured.⁶ Two different types of bleaching powders were used, i.e., dust-free and regular. Particles that were < 10 µm were emitted, specifically when regular powder was prepared. Super coarse powders (> 10 µm) were emitted during bleaching when both the regular and dust-free powders were used. The measured level of persulfate sampled in the breathing zone of the hairdressers was 26 µg/m³ (average value) when the regular powder was used, and was 11 µg/m³ (average value) when the dust-free powder was used. Study results indicated that the point of sampling and orientation of the hairdresser toward the

hair that is being bleached are important in the exposure assessment of persulfates, influencing the observed results. Furthermore, it was predicted that, by using dust-free bleaching products and separate mixing areas, the total persulfate exposure in hairdresser salons can be lowered because the emission of particles < 10 µm would be minimized. The persulfate concentrations (average values) in the breathing zone of hairdressers may be compared to the American Conference of Governmental Industrial Hygienists (ACGIH) occupational exposure limit for persulfates of 0.1 mg/m³ (i.e., 100 µg/m³) as a time-weighted average.⁷

The ingredients reviewed in this safety assessment do not appear on the list of substances that are prohibited in cosmetic products that are marketed within the European Union and are not subject to any restrictions relating to their use in these products.⁸

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 the US FDA as generally recognized as safe (GRAS) as a component of coatings on fresh citrus fruit.⁹ 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.¹⁰

Persulfates are also used in denture cleansers (medical device).¹¹ In 2008, the FDA issued a public health notification alerting the public to the risk of allergic reactions in users of denture cleansers, and the risks of misusing these products. The FDA noted that the literature and research suggest that the ingredient in denture cleansers responsible for these reactions is persulfate, a known allergen.

TOXICOKINETIC STUDIES

Persulfates rapidly dissociate and hydrolyze upon contact with water.³ These substances dissociate upon dissolution to form the corresponding hydrated cations (i.e., ammonium, potassium, or sodium) and persulfate anions. The persulfate anion, independent of the cation, quickly dissociates under aqueous conditions, cross-associating to form other sulfates and, possibly, reacting to form other sulfur-containing anions with strong oxidant character (e.g., peroxymonosulfate), that will invariably be reduced by other chemicals in formulation. Based on the fundamental properties of persulfates, they are not likely to be systematically available, whether by inhalation, ingestion, or skin exposure.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Ammonium Persulfate

*The dermal LD₅₀ of Ammonium Persulfate was 2000 and 10,000 mg/kg in studies involving rats and rabbits, respectively.*¹

Ammonium Persulfate was tested for acute dermal toxicity in Sprague-Dawley rats (group of 10; 5 males, 5 females) in a single dose test in accordance with guideline EPA OPP 81-2.³ An occlusive patch (2" x 2") containing the test substance (in saline) was applied for 24 h. In this test, the acute LD₅₀ was reported to be 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 in 4 male rabbits (strain not stated).³ The test material was applied (undiluted) in a single application at a dosage 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 reported to be 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.¹

Ammonium Persulfate was tested for acute oral toxicity in groups of 10 Sprague-Dawley rats (5 males, 5 females/dose group) in accordance with Organization for Economic Co-operation and Development (OECD) guideline 401.³ Males received dosages (by stomach tube) of 300, 500, 660, or 750 mg/kg body weight. Females received dosages (by stomach tube) of 300, 660, or 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. Animal deaths were reported as follows: 750 mg/kg dose group (3 males and 3 females), 660 mg/kg dose group (2 females), and 500 mg/kg dose group (2 males and 1 female). 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.

The acute oral toxicity of Ammonium Persulfate was evaluated in accordance with OECD Guideline 423 using 9 female specific pathogen free (SPF) Sprague-Dawley (SD) rats.¹² 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. The Globally Harmonized Classification System (GHS) was used to categorize the acute oral toxicity of Ammonium Persulfate.¹³ In this system, Category 1 is the most severe toxicity category, and Category 4 is the least severe. Based on these study results, Ammonium Persulfate was calculated as GHS 4 (LD₅₀ cutoff = 500 mg/kg).

Potassium Persulfate

Potassium Persulfate was tested for acute oral toxicity in male rats (strain not stated).³ The test article was administered by oral gavage as a suspension in corn oil in dosages of 500 mg/kg body weight, 1000 mg/kg body weight, and 2500 mg/kg body weight. Each test group contained six male animals. The clinical signs observed were described as mild depression and weak, rapid breathing. Animal deaths were reported as follows: 2500 mg/kg dose group (6 rats), 1000 mg/kg dose group (2 rats), and 500 mg/kg dose group (1 rat). The acute oral LD₅₀ was determined to be 1130 mg/kg body weight.

Sodium Persulfate

Sodium Persulfate was tested for toxicity by oral exposure in male and female Sprague Dawley rats.³ Ten male and 10 female Sprague-Dawley rats per group were dosed, by gavage, with 215, 464, 562, 681, 852, 1000, 1210, or 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), 464 mg/kg group, or 562 mg/kg group. Mortalities in the remaining dose groups were as follows: 1 male and 1 female at 681 mg/kg doses, 5 males and 5 females at 852 mg/kg doses, 2 males and 7 females at 1000 mg/kg doses, 9 males and 7 females at 1210 mg/kg doses, and 20 rats at 1470 mg/kg doses. Death occurred within 60 minutes through 6 days after the initiation of 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.¹

Potassium Persulfate was tested for acute inhalation toxicity in 7 male rats (strain not specified).³ 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 LC_{50} 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 aqueous hydrogen peroxide) or aqueous hydrogen peroxide could induce airway hyperresponsiveness and/or an obstructive ventilation pattern in a rabbit model (male and female New Zealand white rabbits; groups of 8).¹⁴ When nebulized, the total aerosol concentrations were 12, 120, or 1200 mg/m³ in air, corresponding to the inhalation of 2.3, 23, or 230 mg hair bleach in 4 h, respectively. Changes in airway response to aerosols composed 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 aqueous hydrogen peroxide in air caused airway hyperresponsiveness to acetylcholine after 4 h of exposure. Aerosolized aqueous hydrogen peroxide (37 mg/m³ in air) did not influence airway responsiveness to acetylcholine. The results demonstrate that hair bleaching products containing persulfates dissolved in aqueous hydrogen peroxide cause airway hyperresponsiveness to acetylcholine in rabbits.

Short-Term Toxicity Studies

Oral

Ammonium Persulfate

*In a short-term feeding study (28 days) of Ammonium Persulfate using rats, the lowest observed adverse effect level (LOAEL) was determined to be 600 ppm, the highest concentration that was administered in the study. No deaths occurred during dosing at this concentration, and gross lesions were not observed at necropsy.*¹

Ammonium Persulfate was tested for oral toxicity in groups of 10 male rats in a 28-day study.¹⁵ 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. Decreased relative adrenal weight was observed at the highest dose. The no-observed adverse effect level (NOAEL) was determined to be 41.1 mg/kg body weight/day.

Potassium Persulfate

Potassium Persulfate was tested for toxicity in rats in a 28-day study in accordance with OECD Guideline 407.³ In this study, the test substance was administered (in 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

*In a study involving rats, inhalation exposure to aerosolized Ammonium Persulfate at concentrations ranging from 4 mg/m³ to 20 mg/m³ for 7 days caused a significant increase in the wet weight of the right apical portion of the lung lobe.¹ 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. These changes were attributed to pulmonary edema and/or inflammation. No change in the lung wet-to-dry weight ratio was observed at any concentration tested.*¹

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 in the diet for 5 months or 16 months, respectively.*¹

A 90-day oral toxicity study on Ammonium Persulfate was performed in accordance with OECD Guideline 408 using groups of 20 SPF rats (10 males, 10 females/group).¹² The test substance was administered orally (in distilled water) at 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 statistically significant difference in daily mean food consumption (21.08 ± 1 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 statistically 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 was true for ovary weights (significant increase) when 20 mg/kg dose group (females) were compared with controls. 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 among 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.

Sodium Persulfate

*Local damage to the mucous membrane in the gastrointestinal tract of rats, but no other systemic effects, was observed in a 13-week (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).*¹

Sodium Persulfate was administered in the diet of rats (CR strain; groups of 40 (20 males, 20 females/group)) for 13 weeks.³ Observations included body weight, food consumption, and blood and urine parameters. 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 concentration 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. Whether or not the significant changes in body weight and food consumption were increases or decreases was not stated. 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 females received 50 percent more test material than the males 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 8 weeks, followed by 5000 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/m³.¹⁶ The average mass median aerodynamic diameters and geometric standard deviations of samples taken from the 5-, 10.3-, and 25-mg/m³ exposure levels were 2.5 ± 1.85 , 2.7 ± 1.83 , and 2.5 ± 1.80 μ m, respectively. 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/m³ group, and in a few animals in the 10.3 mg/m³ 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/m³ 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 increased in the 25 mg/m³ 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 exposure to 25 mg/m³. These lesions were not observed at 6 weeks post-exposure. Based on the results of this study, the NOAEL for exposure of rats to a dust aerosol of Ammonium Persulfate was 10.3 mg/m³, while the no-observed-effect level (NOEL) was 5.0 mg/m³.

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) in accordance with OECD guideline 421.³ 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 CrI:CD (SD)IGS BR rats at dosages 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. The NOAEL for male and female toxicity, the NOAEL for male and female fertility performance and the NOAEL for F₁ viability and development were reported to be ≥ 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 10,000 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 tested 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 intraperitoneally with 85, 169 or 338 mg/kg Sodium Persulfate at a dose volume of 10 mL/kg.¹⁷ 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 indicate that Sodium Persulfate did induce bone marrow toxicity. No significant increases in micronucleated polychromatic erythrocytes were observed at 24 h, 48 h, or 72 h post-dosing in males or females. There were no changes in the ratio of polychromatic erythrocytes to total erythrocytes at 85

mg/kg Sodium Persulfate. The results of the assay indicate 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).¹

Tumor Promotion

Dermal

Ammonium Persulfate

There was no significant evidence of tumor promotion in a study in which rats were initiated with dimethylbenzanthracene (DMBA) and then received topical applications of Ammonium Persulfate (200 mg/ml biweekly for 51 weeks).¹

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

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 in accordance with OECD Test Guideline 404.³ The test substance (> 99% pure (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 skin irritation persisted with same intensity over the 14-day observation period. The first day after application of the test material, eschar formation occurred (circular cavities with a depth of 1 to 2 mm). The eschar sloughed during the second observation week. Ammonium Persulfate was considered irritating to the skin.

Sodium Persulfate

Sodium Persulfate was tested as an aqueous solution (pH of 1.1, concentration not stated) for skin corrosion effects in 6 New Zealand rabbits (3 males, 3 females).³ One intact and one abraded skin test site per rabbit were selected for dermal application (4 h). Each test site was treated with 0.5 mL of the test material applied, 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.

Sensitization

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 EC₃ value for Ammonium Persulfate was 1.9 %. Based on the EC₃ 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 on 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 naive animals received 0.30 g of the test material (challenge control group). 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 SI of 6.4 +/- 1.2 at the highest concentration tested (5 %). Applying a 5% solution of Sodium Persulfate caused a three-fold increase in the lymph node weight (LNW) and a 6.5 -fold increase in total lymph node cell (LNC) number when compared with the dimethylsulfoxide control. From the calculated SI values, the estimated EC₃ of Sodium Persulfate is 0.9. Based on the EC₃ 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

Risk Assessment

A National Industrial Chemicals Notification and Assessment Scheme (NICNAS) on Ammonium, Sodium, and Potassium Persulfate was published in 2001.¹⁵ This assessment of persulfate salts in hair bleaching preparations 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 material safety data sheets (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.

OCULAR IRRITATION STUDIES

Ammonium Persulfate

*Ammonium Persulfate (0.1 g) was slightly irritating to the eyes of the 3 rabbits that were tested. In a study involving 9 rabbits, Ammonium Persulfate (concentration/dose not stated) 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 specified).¹⁵ The test material (concentration not stated) was applied to the intact eyes 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.¹⁸ 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%), 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) were reviewed.¹⁹ 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 (14.4%), 4-aminoazobenzene (13.4%), and pyrogallol (9.1%).

Patch test results of 399 hairdressers and 1995 matched controls with contact dermatitis were analyzed.²⁰ 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 ($n = 2067$) have also been analyzed.²¹ 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).

In hairdressers ($n = 200$) patch tested from 1994 to 2003, an increase in skin sensitization reactions caused by Ammonium Persulfate (7.9% [1980 to 1993] to 14.3% [1994 to 2003]) was observed.²² According to results from another study involving 164 hairdressers and trainees with occupational dermatitis, Ammonium Persulfate was responsible for positive patch test reactions in 48% of the patients tested.²³ In a larger population of hairdressers ($n = 729$; ~ 30% with history of atopic eczema) patch tested, positive reactions were observed in 10% of the hairdressers.²⁴

Other Clinical Reports

Ammonium Persulfate, Potassium Persulfate, and Persulfate Salts

Clinical reports, most of which are on Ammonium Persulfate, relating to persulfate-induced allergenicity are summarized in Table 4.

Case Reports

Ammonium Persulfate and Potassium Persulfate

Case reports on Ammonium Persulfate and Potassium Persulfate, mostly involving hairdressers, are summarized in Table 4. Frequently, positive patch/prick test reactions to these ingredients were observed.

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 inorganic 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 2017 VCRP data, the greatest reported use frequency is for Potassium Persulfate (73 product formulations, mostly rinse-off products), followed by Sodium Persulfate (48 product formulations; all rinse-off products, and most of the uses are in hair coloring products). It should be noted that the 2017 VCRP data indicate that, of the 3 persulfates that are being used in cosmetics (most of which are rinse-off product uses), Ammonium Persulfate and Potassium Persulfate are also being used in leave-on products (i.e., eye makeup preparations, tonics, dressings, and other hair grooming aids). Of the 157 ingredient uses of persulfates that were reported to the FDA’s VCRP, 151 relate to use in hair coloring products. The results of a concentration of use survey conducted in 2015 reported use in various types of hair coloring preparations, and 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). Only uses in various types of hair coloring preparations were reported in this survey on Ammonium, Potassium, and Sodium Persulfate.

Persulfates rapidly dissolve upon contact with water. The substances dissociate and form the corresponding cations (ammonium, potassium, sodium) and persulfate anions. The persulfate anion, independent of the cation, may cross-associate in aqueous environments to form other salts. Based on these fundamental properties of persulfates, they are not likely to become bioavailable, whether by inhalation, ingestion, or contact by skin.

In an acute dermal toxicity study involving male and female rats, Ammonium Persulfate was considered non-toxic ($LD_{50} > 2000$ mg/kg body weight). In an acute dermal toxicity study involving male rabbits, an $LD_{50} > 10,000$ mg/kg body weight was reported.

An acute oral LD_{50} 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 LD_{50} was determined to be 500 mg/kg body weight. The acute oral LD_{50} for Potassium Persulfate in male rats was determined to be 1130 mg/kg body weight. LD_{50} 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 LC_{50} 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 in rabbits 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, respectively, 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. Regarding human exposure, it has been predicted that, by using dust-free bleaching products and separate mixing areas, the total persulfate exposure in hairdresser salons can be lowered because the emission of particles < 10 µm would be minimized.

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 F₀ parents of either sex or in F₁ pups at any treatment level. The NOAEL for male and female fertility performance and the NOAEL for F₁ 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 allergenicity 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

The CIR Expert Panel concluded in a final report (published in 2001) on the Safety Assessment of Ammonium, Potassium, and Sodium Persulfate, 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. In that safety assessment, the Panel was concerned with the sensitization and urticarial potential of persulfates because these ingredients caused both delayed-type and immediate skin reactions. The Panel noted that one of the studies reviewed was a sensitization study on 17.5% Ammonium, Potassium, and Sodium Persulfate that also examined the incidence of urticarial reactions. It was determined that, at this concentration, a mixture of these persulfates was not sensitizing, and that the application of Ammonium, Potassium, and Sodium Persulfate did not result in an urticarial reaction.

In that 2001 final report, the Panel also expressed concern that the greatest concentration of persulfates tested was 17.5%, yet data submitted to CIR reported that persulfates were used in hair lighteners at concentrations of 60%. Because the test materials were applied under occlusive patches during testing, it was assumed that, in normal use (i.e., not occluded and rinsed off), a concentration greater than 17.5% would also be safe. However, given the clinical reports of urticarial reactions, the Panel concluded that manufacturers and formulators should be aware of the potential for urticarial reactions at concentrations of persulfates greater than 17.5%.

Regarding more recent use concentration data, the results of a Personal Care Products Council concentration of use survey conducted in 2015 only reported use of persulfates in various types of hair coloring preparations, and indicated that

Potassium Persulfate had the highest maximum concentration of use, i.e., 72.5% in hair coloring preparations (rinse-off products). The Panel agreed that the increased use concentration of persulfates in hair coloring preparations from 60% to 72.5% does not warrant any safety concerns, taking into consideration that the 72.5% concentration relates to ingredient use in rinse-off products. Accordingly, the Panel agreed that their original conclusion relating to the use of persulfates in rinse-off products (all hair coloring preparations) remains valid. While these ingredients are not themselves hair dye couplers or precursors, these persulfates are commonly used in conjunction with such hair dye components to formulate a final mixed hair dye product for application. Regarding the safety of hairdressers and consumers exposed to these products, it should be noted that FDA has issued certain safety precautions to be followed,

<https://www.fda.gov/Cosmetics/ResourcesForYou/Consumers/ucm167436.htm>.

Unlike the results of the Personal Care Products Council survey indicating that persulfates are only being used in hair coloring preparations, ingredient use-frequency data provided by the FDA in 2017 indicate that persulfates are being used in hair coloring preparations, leave-on products (i.e., eye makeup preparations, tonics, dressings, and other hair grooming aids), and in dentifrices (rinse-off). Regarding the latter product category, the Panel considered that an FDA public health notification was issued regarding the risk of allergic reactions in users of denture cleansers containing Sodium Persulfate, and the risks of misusing these products. They noted the literature and research suggesting that the ingredient in denture cleansers responsible for these reactions is persulfate, which is a known allergen. Given the use of persulfates in leave-on products and dentifrices and the safety concerns that have been expressed, the Panel determined that the following data are needed in order to evaluate the safety of persulfates in these types of products:

- No-Observed-Effect-Level (NOEL) for sensitization and urticaria
- Concentrations of use in leave-on products and dentifrices

CONCLUSION

The CIR Expert Panel concluded that Ammonium, Potassium, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and hair lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel also concluded that the available data are insufficient for determining the safety of these persulfates in leave-on products and dentifrices. This conclusion supersedes the conclusion that was published in 2001.

TABLES

Table 1. Definitions, structures, and functions of the ingredients in this safety assessment.²

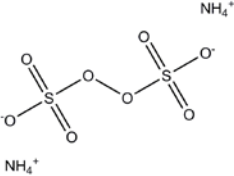
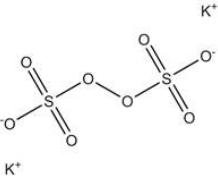
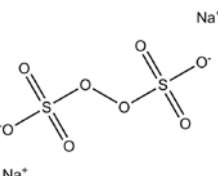
Ingredient CAS No.	Definition & Structure	Function
Ammonium Persulfate 7727-54-0	Ammonium Persulfate is the inorganic salt that conforms to the formula: 	Oxidizing agent
Potassium Persulfate 7727-21-1	Potassium Persulfate is the inorganic salt that conforms to the formula: 	Oxidizing agent
Sodium Persulfate 7775-27-1	Sodium Persulfate is the inorganic salt that conforms to the formula: 	Oxidizing agent

Table 2. Properties of Persulfates.¹

Property	Value	Background Information
Ammonium Persulfate		
Form/Odor	Yellow to white crystalline material with a slight acid odor	Strong oxidizing agent. Decomposes at 120°C, and sulfur dioxide and sulfur trioxide are dangerous decomposition products
Formula Weight (Da)	228.20	
Solubility (g/l at temperature, °C)	Readily dissolves in water. Solubility in water of 1% solution: 559 (at 20) and 510 (at 25)	
Potassium Persulfate		
Form	White, odorless, crystalline material	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.
Formula Weight (Da)	270.3	
Solubility	Soluble in ~50 parts water	Acidic in aqueous form
Sodium Persulfate		
Form	White crystalline powder	Gradually decomposes, and decomposition is promoted by moisture and higher temperatures
Formula Weight (Da)	238.13	
Solubility	Soluble in water; decomposes in alcohol	

Table 3. Current Frequency and Concentration of Use According to Duration and Type of Exposure.^{1,4,5}

	Ammonium Persulfate		Ammonium Persulfate		Potassium Persulfate	
	Conc. (%)		Conc. (%)		Conc. (%)	
	# of Uses (2017)	(2015)	# of Uses (1998)	(1995)	# of Uses (2017)	(2015)
Totals/Conc. Range	36	5.8-44.1	30	NR	73	6-72.5
Duration of Use						
<i>Leave-On</i>	2	NR	1	NR	1	NR
<i>Rinse off</i>	34	5.8-44.1	29	≤4-60	72	6-72.5
<i>Diluted for (bath) Use</i>	NR	NR			NR	NR
Exposure Type						
<i>Eye Area</i>	1	NR	1	NR	NR	NR
<i>Incidental Ingestion</i>	NR	NR	NR	NR	NR	NR
<i>Incidental Inhalation- Sprays</i>	NR	NR	NR	NR	NR	NR
<i>Incidental Inhalation- Powders</i>	NR	NR	NR	NR	NR	NR
<i>Dermal Contact</i>	1	NR	1	NR	NR	NR
<i>Deodorant (underarm)</i>	NR	NR	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	1*	NR	NR	NR	1	NR
<i>Hair-Coloring</i>	34	5.8-44.1	29	1-60	72	6-72.5
<i>Nail</i>	NR	NR	NR	NR	NR	NR
<i>Mucous Membrane</i>	NR	NR	NR	NR	NR	NR
<i>Baby Products</i>	NR	NR	NR	NR	NR	NR
	Potassium Persulfate		Sodium Persulfate		Sodium Persulfate	
	Conc. (%)		Conc. (%)		Conc. (%)	
	# of Uses (1998)	(1995)	# of Uses (2017)	(2015)	# of Uses (1998)	(1995)
Totals/Conc. Range	36	≤8-60	48	0.67-33.4	26	1-60
Duration of Use						
<i>Leave-On</i>	NR	NR	NR	NR	NR	NR
<i>Rinse off</i>	36	≤8-60	48	0.67-33.4	26	1-60
<i>Diluted for (bath) Use</i>	NR	NR	NR	NR	NR	NR
Exposure Type						
<i>Eye Area</i>	NR	NR	NR	NR	NR	NR
<i>Incidental Ingestion</i>	NR	NR	2	NR	NR	NR
<i>Incidental Inhalation- Sprays</i>	NR	NR	NR	NR	NR	NR
<i>Incidental Inhalation- Powders</i>	NR	NR	NR	NR	NR	NR
<i>Dermal Contact</i>	NR	NR	NR	NR	NR	NR
<i>Deodorant (underarm)</i>	NR	NR	NR	NR	NR	NR
<i>Hair - Non-Coloring</i>	NR	NR	NR	NR	NR	NR
<i>Hair-Coloring</i>	36	1-60	45	0.67-33.4	26	1-60
<i>Nail</i>	NR	NR	NR	NR	NR	NR
<i>Mucous Membrane</i>	NR	NR	2	NR	NR	NR
<i>Baby Products</i>	NR	NR	NR	NR	NR	NR

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.

Table 4. Other Clinical Reports and Case Reports

Ingredient Test Concentration	Test Protocol	Subjects	Results
<i>Ammonium Persulfate</i>			
Not stated	Prick test and nasal provocation test (NPT)	40 hairdressers with work-related rhinitis	1 of 40 subjects had a positive prick test; subject also had asthma and contact urticaria. 1 of 35 subjects with uncertain reaction in the NPT. ²⁵
Not stated	Prick test, patch test, and lung function test	355 female hairdressers. 189 with work-related skin and respiratory symptoms and lifetime prevalence of 16.9% for hand dermatoses, 16.9% for allergic rhinitis, and 4.5% for asthma. 130 of the 189 underwent prick, patch, and lung function tests.	In clinical investigations, 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. ²⁶
Not stated	Patch test	200 hairdressers (93% female) patch-tested in Spain from 1994 to 2003. Results compared with those from previous study on hairdressers patch-tested from 1980 to 1993.	Significant increase in skin sensitization caused by Ammonium Persulfate (7.9% [1980 to 1993] to 14.3% [1994 to 2003]). ²²
Not stated	Patch test	139 apprentice hairdressers. 43.9% of hairdressers with present or past work-related skin conditions affecting the hands. Such conditions diagnosed in 25.9% of hairdressers during dermatological examination.	Ammonium Persulfate was one of the more frequent allergens, with allergic contact dermatitis in 8.3% of the 139 hairdressers patch-tested. ²⁷
Not stated	Patch test/prick test	44 hairdressers with hand dermatitis.	Ammonium Persulfate was one of the more common causative allergens, with hand dermatitis in 13.63% of the 44 hairdressers patch-tested. ²⁸
Not stated	Patch test	164 hairdressers and trainees with occupational dermatitis. Allergic contact dermatitis more common in apprentices than in hairdressers.	Ammonium Persulfate was responsible for positive patch test reactions in 48% of the 164 patients tested. ²³
Not stated	Pre-specific inhalation challenge-induced sputum challenge test (22 of 26 patients). Nasal secretion collection and processing 24 of 26)	26 patients with respiratory allergy caused by Ammonium Persulfate.	12 of 26 with respiratory occupational asthma only. 14 of 26 with occupational rhinitis. ²⁹
Not stated	Systematic review of studies in PubMed (1966 to 2010) studying allergens in children. 49 studies with available data on 170 allergens included. Proportions of positive reactions for each allergen combined with random effects models across studies.	At least 100 children enrolled in each study.	Ammonium Persulfate was among the top 5 allergens, with positive reactions exceeding 10%. ³⁰

Table 4. Other Clinical Reports and Case Reports

Ingredient Test Concentration	Test Protocol	Subjects	Results
20 mg/ml (prick test). Doses up to 0.6 mg in specific inhalation challenge (SIC)	Patch test (4 subjects), Prick test (7 subjects) and 2 SIC protocols (4 subjects per protocol)	7 female hairdressers	SIC positive in 4 patients. Prick test results positive in 1 SIC- positive patient (2 mm wheal) and in 2 SIC-negative patients (3 and 4 mm wheal). Positive reaction in all 4 subjects patch- tested; 3 were SIC-positive. ³¹
<u>Inhalation Study</u>			
Not stated	Pre-specific inhalation challenge-induced sputum challenge test (22 of 26 patients). Nasal secretion collection and processing 24 of 26)	26 patients with respiratory allergy caused by Ammonium Persulfate.	12 of 26 with respiratory occupational asthma only. 14 of 26 with occupational rhinitis. ²⁹
<i>Ammonium Persulfate and Potassium Persulfate</i>			
2% solution of each	Prick test and open application test	138 patients. 6 had symptoms of urticaria, eczema, or angioedema due to contact with hair bleaches	7 patients with positive prick test reaction to at least 1 persulfate salt. 3 of 4 subjects in open application test developed urticaria. Mechanism of immediate hypersensitivity to persulfates seemed to have been IgE-mediated, at least in some patients. ³²
<i>Potassium Persulfate</i>			
Not stated	Test to study pathogenesis of persulfate-associated rhinitis. Changes in nasal lavage fluid proteome monitored after challenge with Potassium Persulfate	Hairdressers with bleaching powder-associated rhinitis.	Major finding was increased abundance of apolipoprotein A- 1 at 20 minutes post-challenge, detected in group of symptomatic hairdressers. ³³
Not stated	Prick test	17 female hairdressers with work-related rhinitis, mainly due to persulfate bleaching powder exposure.	Negative prick test. ³⁴
<i>Persulfate Salts</i>			
Not stated	Skin prick tests, bronchial challenge tests, performed at least 3 years prior to enrollment in study, and spirometry.	10 patients with occupational asthma attributable to exposure to persulfate salts. At time of follow-up evaluation, 7 of 10 had avoided workplace exposure to persulfates.	Bronchial hyperresponsiveness in 3 of the 7 improved significantly. No improvement in patients who continued to be exposed to persulfates. Skin prick tests became negative in 3 patients who were no longer exposed at time of follow-up examination. 1 patient with worsening of symptoms in spite of avoidance of exposure. Thus, asthma and bronchial hyperresponsiveness conditions seemed to improve after avoidance of persulfate salt exposure. ³⁵
<i>Case Reports</i>			
Ammonium Persulfate (2.5%)	Skin prick test and radioallergosorbent (RAST) test	Hairdresser with rhinitis and asthma	Positive (++) reaction. Reaction 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 RAST test. ³⁶

Table 4. Other Clinical Reports and Case Reports

Ingredient Test Concentration	Test Protocol	Subjects	Results
Ammonium Persulfate (1%)	Patch test	Hairdresser with rhinorrhea and dyspnea	++ reaction (erythema and wheals). Dyspnea and nasal obstruction; forced expiratory volume (FEV ₁) progressively decreased, with maximal fall of 49% at 150 minutes. Conclusion: anaphylactoid reaction to patch testing. ³⁷
Ammonium Persulfate (2.5% and 0.1%); Potassium Persulfate (0.1%)	Patch and prick tests	Hairdresser with hand eczema and asthma	Positive patch test to 2.5% Ammonium Persulfate. Positive prick test reaction to 0.1% Ammonium Persulfate, but not 0.1% Potassium Persulfate. ³⁸
Ammonium Persulfate and Potassium Persulfate	Intradermal tests (0.1% Ammonium Persulfate and 0.1% Potassium Persulfate). Prick tests with up to 2% aqueous Potassium Persulfate or 2% aqueous Ammonium Persulfate. Patch tests with Potassium Persulfate (2.5% aqueous) or Ammonium Persulfate (2.5% in petrolatum).	Hairdresser with severe asthma and a hairdresser's client with anaphylaxis.	<p>Intradermal tests on client yielded positive results (wheal and flare) after 15 minutes for 0.1% aqueous Ammonium Persulfate (wheal of 20 mm) and 0.1% aqueous Potassium Persulfate (wheal of 14 mm).³⁹</p> <p>Prick tests on hairdresser yielded positive results (wheal and flare) for both 1.0% aqueous Ammonium Persulfate (wheal of 8 mm) and 1.0% aqueous Potassium Persulfate (wheal of 9 mm; no specific IgE detected in serum. Prick tests with Ammonium and Potassium Persulfate (0.1%) yielded negative results in 4 controls.³⁹</p> <p>Positive (+) patch test reaction to Ammonium Persulfate (2.5% in petrolatum) in client. For the hairdresser, positive patch tests for Ammonium Persulfate (2.5% in petrolatum) and Potassium Persulfate (2.5% aqueous), producing a wheal of more than 12 mm and flare.³⁹</p>
Ammonium Persulfate (1%) and Potassium Persulfate (1%)	Prick test	Hairdresser with hand eczema and asthma	Positive prick tests and immediate-type allergy to both ingredients. ⁴⁰
Ammonium Persulfate	Patch test	Boy with pruritic and eczematous eruption over trunk and extremities	Positive (1+ to 2+) reaction to Ammonium Persulfate. ⁴¹

REFERENCES

1. Andersen, F. A. Final report on the safety assessment of ammonium, potassium, and sodium persulfate. *International Journal of Toxicology*. 2001;20(3):7-21.
2. Nikitakis, J. and Lange B. International Cosmetic Ingredient Dictionary and Handbook Online Version (wINCI). <http://webdictionary.personalcarecouncil.org/jsp/Home.jsp>. Washington, DC. Last Updated 2017. Date Accessed 3-6-2017.
3. European Chemicals Agency. Registration dossier. Toxicokinetics/toxicity data on ammonium persulfate, potassium persulfate, and sodium persulfate. <http://www.echa.europa.eu/>. Last Updated 2016. Date Accessed 3-23-2016.
4. Food and Drug Administration (FDA). Information supplied to FDA by industry as part of the VCRP FDA database. 2017. Washington, D.C.: FDA.
5. Personal Care Products Council. Concentration of use by FDA product category. Persulfates. Unpublished data submitted by the Personal Care Products Council on 10-15-2015. 2015. pp.1
6. Nilsson, P. T. Marini S. Wierzbicka A. Karedal M. Blomgren E. Nielsen J. Buonanno G. and Gudmundsson A. Characterization of hairdresser exposure to airborne particles during hair bleaching. *Ann.Occup.Hyg.* 2015;60(1):90-100.
7. National Institute for Occupational Safety and Health (NIOSH). Occupational exposure limits. Persulfates. <https://www.cdc.gov/niosh/ipcsneng/neng0632.html>. Last Updated 2015. Date Accessed 6-14-2017.
8. European Commission. CosIng database; following Cosmetic Regulation No. 1223/2009. <http://ec.europa.eu/growth/tools-databases/cosing/>. Last Updated 2017. Date Accessed 5-11-0017.
9. Food and Drug Administration (FDA). Direct food additives. Ammonium persulfate and potassium persulfate. 21 CFR 172.892 and 21 CFR 172.210. <http://www.fda.gov/>. Last Updated 2015. Date Accessed 4-13-2016.
10. Food and Drug Administration (FDA). Indirect food additives. Ammonium persulfate, potassium persulfate, and sodium persulfate. 21 CFR 175.1056, 21 CFR 175.210, 21 CFR 176.170, 21 CFR 177.1200, 21 CFR 177.1210, and 21 CFR 177.2600. <http://www.fda.gov/>. Last Updated 2016. Date Accessed 4-13-2016.
11. U.S.Food and Drug Administration (FDA). Public Health Notification: Denture cleanser allergic reactions and misuse. <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062012.htm>. Last Updated 2008. Date Accessed 12-1-2016.
12. Kim, Y. S. Baek M. W. Sung J. H. Ryu H. Y. Kim M. S. Cho H. S. Choi B. G. Song M. S. Song M. Y. Baik E. J. Choi Y. K. Kim J. K. Yu I. J. and Song K. S. Acute and subchronic oral toxicity study of ammonium persulfate in Sprague-Dawley rats. *Toxicol.Res.* 2009;25(3):132-139.
13. United Nations. Globally Harmonized System of Classification and labeling of Chemicals (GHS). http://www.unece.org/trans/danger/publi/ghs/ghs_rev00/00files_e.html. Last Updated 2003. Date Accessed 6-14-2017.
14. Mensing, T., Marek, W, Raulf-Heimsoth, M, and Baur, X. Acute exposure to hair bleach causes airway hyperresponsiveness in a rabbit model. *European Respiratory Journal*. 1998;12(6):1371-1374.
15. National Industrial Chemicals Notification and Assessment Scheme (NICNAS). NICNAS on Ammonium, Sodium, and Potassium Persulfate. http://www.nicnas.gov.au/_data/assets/pdf_file/0005/4379/PEC_18_Ammonium-Potassium-and-Sodium-Persulfate_Full_Report_PDF.pdf. Last Updated 2001.
16. Signorin, J. Ulrich C. E. Butt M. T. and D'Amato E. A. 13-week inhalation toxicity study (including 6- and 13-week recovery periods) with ammonium persulfate dust in albino rats. *Inhal.Toxicol.* 2001;13(11):1033-1045.
17. Organisation for Economic Co-operation and Development (OECD). SIDS Initial Assessment Report for SIAM 20. Paris, France, 19-21 April, 2005. Persulfates. <http://ncis.nier.go.kr/data/sids/f11-2017727-21-1.pdf>. Last Updated 2005.
18. Kiec-Swierzczynska, M. Krecisz B. and Chomiczeewska D. Results of patch test in hairdressers examined in the Institute of Occupational Medicine in Lodz. *Medycyna Pracy*. 2009;60(6):459-467.
19. Wang, M. Z., Farmer, SA, Richardson, DM, and Davis, MD. Patch-testing with hairdressing chemicals. *Dermatitis*. 2011;22(1):16-26.

20. Schwensen, J. F., Johansen, JD, Veien, NK, Funding, AT, Avnstorp, C, Osterballe, M, Andersen, KE, Paulsen, E, Mortz, CG, Sommerlund, M, Danielsen, A, Andersen, BL, Thormann, J, Kristensen, O, Kristensen, B, Vissing, S, Nielsen, NH, Thyssen, JP, and Sisted, H. Occupational contact dermatitis in hairdressers: an analysis of patch test data from the Danish contact dermatitis group, 2002-2011. *Contact Dermatitis*. 2014;70(4):233-237.
21. Uter, W., Gefeller, O, John, SM, Schnuch, A, and Geier, J. Contact allergy to ingredients of hair cosmetics - a comparison of female hairdressers and clients based on IVDK 2007-2012 data. *Contact Dermatitis*. 2014;71(1):13-20.
22. Valks, R., Conde-Salazar, L, Malfeito, J, and Ledo, S. Contact dermatitis in hairdressers, 10 years later: patch-test results in 300 hairdressers (1994 to 2003) and comparison with previous study. *Dermatitis*. 2005;16(1):28-31.
23. Lyons, G., Roberts, H, Palmer, A, Matheson, M, and Nixon, R. Hairdressers presenting to an occupational dermatology clinic in Melbourne, Australia. *Contact Dermatitis*. 2013;68(5):300-306.
24. O'Connell, R. L., White, IR, Mc Fadden, JP, and White, JM. Hairdressers with dermatitis should always be patch tested regardless of atopy status. *Contact Dermatitis*. 2010;62(3):177-181.
25. Hytonen, M., Leino, T, Sala, E, Kanerva, L, Tupasela, O, and Malmberg, H. Nasal Provocation Test in the Diagnostics of Hairdressers' Occupational Rhinitis. *Acta Oto-Laryngologica*. 1997;529:133-136.
26. Leino, T., Tammilehto, L, Hytonen, M, Sala, E, Paakkulainen, H, and Kanerva, L. Occupational skin and respiratory diseases among hairdressers. *Scandinavian Journal of Work Environment & Health*. 1998;24(5):398-406.
27. Krecisz, B., Kiec-Swierczynska, M, and Chomiczewska, D. Dermatological screening and results of patch testing among Polish apprentice hairdressers. *Contact Dermatitis*. 2011;64(2):90-95.
28. Tresukosol, P. and Swasdivanich, C. Hand contact dermatitis in hairdressers: clinical and causative allergens, experience in Bangkok. *Asian Pac J Allergy Immunol*. 2012;30(4):306-312.
29. Moscato, G., Pala, G, Perfetti, L, Frascaroli, M, and Pignatti, P. Clinical and inflammatory features of occupational asthma caused by persulphate salts in comparison with asthma associated with occupational rhinitis. *Allergy*. 2010;65(6):784-790.
30. Bonitsis, N. G., Tatsioni, A, Bassioulas, K, and Ioannidis, JP. Allergens responsible for allergic contact dermatitis among children: a systematic review and meta-analysis. *Contact Dermatitis*. 2011;64(5):245-257.
31. Hagemeyer, O., Marek, E, van, K, V, Sander, I, Raulf, M, Merget, R, and Bruning, T. Specific Inhalation Challenge in Persulfate Asthma. *Adv Exp Med Biol*. 2015;861:85-91.
32. Aalto-Korte, K. and Kinen-Kiljunen S. Specific immunoglobulin E in patients with immediate persulfate hypersensitivity. *Contact Dermatitis*. 2003;49:22-25.
33. Karedal, M. H. Mortstedt H. Jeppsson M. C. Diab K. K. Nielsen J. Jonsson B. A. G. and Lindh C. H. Time-dependent proteomic iTRAQ analysis of nasal lavage of hairdressers challenged by persulfate. *Journal of Proteome Research*. 2010;9:5620-5628.
34. Diab, K. K. Jonson B. A. G. Axmon A. and Nielsen J. Work-related airway symptoms, nasal reactivity and health-related quality of life in female hairdressers: a follow-up study during exposure. *Int.Arch.Occup.Environ.Health*. 2014;87:61-71.
35. Munoz, X., Gomez-Olles, S, Cruz, MJ, Untoria, MD, Orriols, R, and Morell, F. [Course of bronchial hyperresponsiveness in patients with occupational asthma caused by exposure to persulfate salts]. *Arch Bronconeumol*. 2008;44(3):140-145.
36. Borelli, S. and Wuthrich, B. Immediate and delayed hypersensitivity to ammonium persulfate. *Allergy (Copenhagen)*. 1999;54(8):893-894.
37. Perfetti, L., Galdi, E, Biale, C, Garbelli, N, and Moscato, G. Anaphylactoid reaction to patch testing with ammonium persulfate. *Allergy*. 2000;55(1):94-95.
38. Bregnhøj, A. and Sosted, H. Type I ammonium persulfate allergy with no cross reactivity to potassium persulfate. *Contact Dermatitis*. 2009;61(6):356-357.
39. Hoekstra, M., van der Heide, S, Coenraads, PJ, and Schuttelaar, ML. Anaphylaxis and severe systemic reactions caused by skin contact with persulfates in hair-bleaching products. *Contact Dermatitis*. 2012;66(6):317-322.

40. Hougaard, M. G., Menn, T, and Sisted, H. Occupational eczema and asthma in a hairdresser caused by hair-bleaching products. *Dermatitis*. 2012;23(6):284-287.
41. Salvaggio, H. L. Scheman A. J. and Chamlin S. L. Shock treatment: Swimming pool contact dermatitis. *Pediatric Dermatology*. 2013;30(4):494-495.