Final Report on the Safety Assessment of Ammonium, Potassium, and Sodium Persulfate[1]

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/m^3 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.

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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 $(NH_4)_2S_2O_8$ (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; Ammoniumperoxydodisulfate; 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 $K_2S_2O_8$ (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 $Na_2S_2O_8$ (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 (Budavari 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

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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, Canterbery, 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 1
Cosmetic product formulation data on Ammonium, Potassium, and Sodium Persulfate (FDA 1998)

Product category	Total no. of formulations in category	Total no. of formulations containing ingredient
	Ammonium Persulfate	
Hair dyes and colors	1572	1
Hair bleaches	113	23
Other hair-coloring preparations	59	5
Other skin care preparations	692	1
1998 total for Ammonium Persulfate		**30**
	Potassium Persulfate	
Hair straighteners	63	1
Hair dyes and colors	1572	2
Hair lighteners with color	6	1
Hair bleaches	113	27
Other hair-coloring preparations	59	5
1998 total for Potassium Persulfate		**36**
	Sodium Persulfate	
Hair straighteners	63	1
Hair dyes and colors	1572	2
Hair lighteners with color	6	1
Hair bleaches	113	21
Other hair-coloring preparations	59	1
1998 total for Sodium Persulfate		**26**

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 Ca^{2+} ionophore A23187 (which bypasses membranous signal transduction) resulted in a dose-dependent decrease in the amount of total generated leukotriene B_4 (LTB_4); the decrease was significant at all test concentrations. A similar decrease was also observed with Sodium Persulfate. A decrease in LTB_4 was also observed after incubation with Ammonium Persulfate and activation with the tripeptide formylmethionylleucylphenylalanine (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 Ca^{2+} ionophore, LTB_4-enriched supernatants were obtained, and Ammonium Persulfate was then added. LTB_4 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 LTB_4.

The effect of priming PMNs with Ammonium Persulfate was also examined. Cells were pretreated with Ammonium Persulfate, washed, and stimulated with the Ca^{2+} 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 Ca^{2+} ionophore (Köller, Hilger, and König 1996).

Effect on Smooth Muscle Tone

The effect of Ammonium Persulfate on smooth muscle tone was examined using an in vitro guinea pig tracheal preparation (Mensing, Marek, and Baur 1996). Ammonium Persulfate (9×10^{-5} to 9×10^{-2} M) dilated the trachea and caused a concentration-dependent decrease in intratracheal pressure. The acutely elicited tracheal muscle dilatation was mediated by nitric oxide.

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 ^{45}Ca 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 LD_{50} 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 LD_{50} was 600 mg/kg and 495 mg/kg, respectively (CTFA 1994). The oral LD_{50} 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 LD_{50} 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 LC_{50} 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 LC_{50} 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_{50} 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^3 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^3 Ammonium Persulfate. However, at concentrations of 4 to 20 mg/m^3, Ammonium Persulfate caused a significant reduction in body weight and a significant increase in the wet weight of the right apical of the lung lobe. The greatest increase in wet weight was 164% with 20 mg/m^3 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 Cooperation 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 unrinsed eyes and was considered minimally irritating to these eyes. Ammonium Persulfate was practically nonirritating to rinsed 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 hamster 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 a week 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 premanently 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

(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 hair dressers, 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 (Frosch and Kligman 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-cm^2 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

Case studies	Reference
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.	Brubaker (1972)
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.	Fisher and Dooms-Goossens (1976)
A 46-year-old woman developed redness and slight crustiness 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."	Fisher and Dooms-Goossens (1976)
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.	Fisher 1977
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.	Fisher 1977
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.	Fisher (1985a)
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.	Fisher (1985a)
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.	Fisher (1993)

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 dermal 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/m^3 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 5 mg/m^3, measured as persulfate (ACGIH 1986). However, the ACGIH recommends a TLV of 2 mg/m^3 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 LD_{50} of Ammonium Persulfate was 2 and 10 g/kg for rats and rabbits, respectively. For rats, the reported oral LD_{50} of Ammonium Persulfate ranged from 600 to 820 mg/kg and for Potassium Persulfate was 802 mg/kg. The inhalation LC_{50} 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 LD_{50} 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/m^3 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; signficant 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

Reaction	Study description	Reference
	Hairdressers	
Contact dermatitis	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.	Fisher and Dooms-Goossens (1976)
Contact dermatitis	Twelve of 49 hairdressers patch tested with 2.5% Ammonium Persulfate in petrolatum had positive reactions, compared to 1 of 118 nonhairdressers tested.	Kellett and Beck (1985)
Contact dermatitis	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.	Van Joost and Roesyanto (1991)
Contact dermatitis	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.	Guerra, Tosti, and Bardazzi (1992b)
Contact dermatitis	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.	Frosch et al. (1993)
Contact dermatitis	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.	Sutthipisal, McFadden, Cronin 1993
Contact dermatitis	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.	van der Walle and Brunsveld 1994
Contact dermatitis	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.	Katsarou et al. 1995
Asthma	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.	Fisher and Dooms-Goossens (1976)

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TABLE 3
Occupational exposure to Persulfate Salts *(Continued)*

Reaction	Study description	Reference
Asthma	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.	Pepys, Hutchcroft, and Breslin (1976)
Asthma	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.	Davies and Blainey (1983)
Asthma	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.	Blainey et al. (1986)
Asthma	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.	Gamboa et al. (1989)
Contact dermatitis and asthma	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.	Pepys, Hutchcroft, and Breslin (1976)
Contact dermatitis and asthma	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.	Widstrom(1977)

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TABLE 3
Occupational exposure to Persulfate Salts *(Continued)*

Reaction	Study description	Reference
Contact dermatitis and asthma	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.	Parra et al. (1992)
Rhinoconjunctivitis and asthma	A hairdresser developed rhinoconjunctivitis and bronchial asthma associated with hair bleach containing persulfate after 2 years. A prick test was positive for the persulfate.	Pankow et al. (1989)
	Bakers	
Contact dermatitis	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.	Grosfeld (1951)
Contact dermatitis	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.	Nava et al. (1983)
	Industrial workers	
Contact dermatitis	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.	White, Catchpole, and Rycroft (1982)
Asthma	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	Wrbitzky, Drexler, and Letzel 1995

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TABLE 3
Occupational exposure to Persulfate Salts *(Continued)*

Reaction	Study description	Reference
	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.

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