
Amended Safety Assessment of Persulfates as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 10, 2017
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.



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Wilbur Johnson, Jr.
Senior Scientific Analyst
Date: November 10, 2017
Subject: Draft Final Amended Report on Persulfates

At the June 12-13 Expert Panel meeting, the Panel issued a Tentative Amended Report with a conclusion stating that Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel also concluded that the available data are insufficient for determining the safety of these persulfates in leave-on products and dentifrices. The Panel determined that the following data are needed in order to evaluate the safety of persulfates in leave-on and dentifrice products:

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

To date, the data stated above have not been received. Comments on the Tentative Amended Report that were received from the Council (*persul122017pcpc1*, *persul122017pcpc2*, *persul122017pcpc3*, and *persul122017pcpc4*) have been addressed and are attached for the Panel's review.

Also included in this package for review are the Draft Final Amended Report on Persulfates (*persul122017rep.docx*), the CIR report history (*persul122017hist.docx*), Flow chart (*persul122017flow.docx*), Literature search strategy (*persul122017strat.docx*), Ingredient Data profile (*persul122017prof.docx*), the minutes from prior Panel meetings on Persulfates (*persul122017min*), 2017 FDA VCRP data (*persul122017FDAdata.xlsx*), and the 2001 published Final Report on Persulfates (*persul122017prev.pdf*).

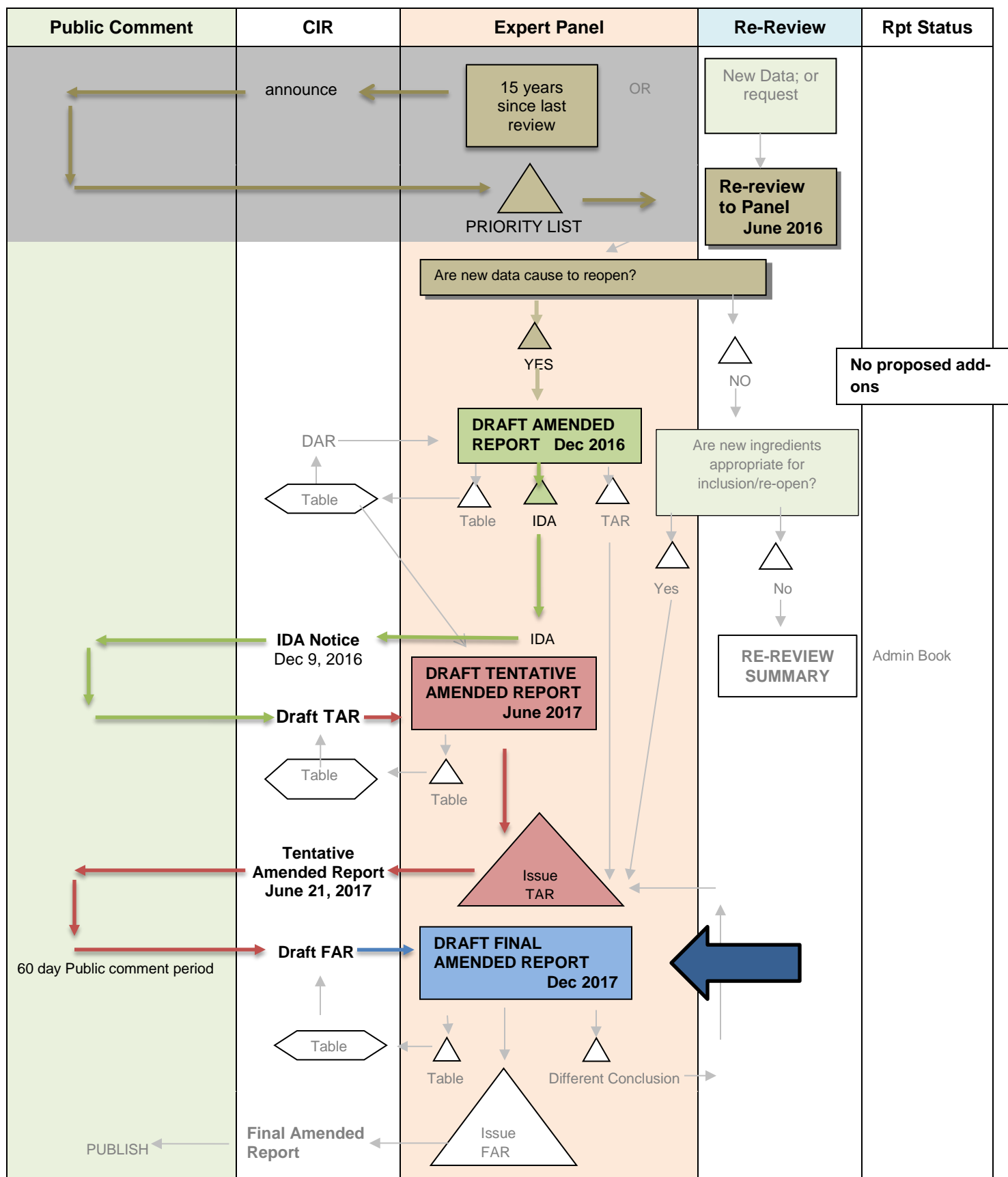
The discussion section of the Tentative Amended Report contained a link to the coal-tar hair dye safety checklist at the FDA's website. However, the Draft Amended Final Report points to a more general FDA precautionary statement to instruct consumers on the safe use of all types of hair dyes that could be formulated with these persulfates.

After reviewing these documents, the Panel should review the Abstract, Discussion, and Conclusion, and be prepared to issue a Final Amended Report.

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Persulfates

MEETING Dec 2017



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

CIR History of:

Ammonium, Potassium, and Sodium Persulfate

Draft Final Report, Teams/Panel: September 10-11, 1998 (68th)

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

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

Updated use concentration data were received from the Council and have been incorporated.

The Panel agreed that the Final Report on Persulfates should be reopened to determine whether or not these ingredients are currently being used in product categories other than hair coloring products, i.e., tonics, dressings and other hair grooming aids (Ammonium and Potassium Persulfates), dentifrices (Sodium Persulfate), and in other eye makeup preparations (Ammonium Persulfate). The Panel asked FDA to confirm whether or not the reported uses of Persulfates in the 3 product categories are valid, and the Council was asked to survey their member companies for the availability of any use concentration data relating to these product categories.

Draft Report, Belsito and Marks Teams/Panel: December 5-6, 2016

Comments that were received from the Council prior to the June 2016 Panel meeting have been addressed.

Results from a 2016 Council survey were received and indicate that Ammonium, Potassium, and Sodium Persulfates are not being used in product categories other than hair coloring products. An FOIA request for current frequency of use data on the 3 Persulfates was submitted to FDA after the Panel meeting, and the data requested were received on October 24, 2016. The updated frequency of use data indicate that the reported uses of Persulfates in product categories other than hair coloring products (i.e., leave-on products and dentifrices) remain valid.

Review of the Draft Amended Report resulted in the Panel's issuance of an Insufficient Data Announcement with the following data requests on the 3 persulfates:

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

Draft Tentative Amended Report, Belsito and Marks Teams/Panel: June 12-13, 2017

To date, responses to the data requested at the December 2016 Panel meeting have not been received.

Comments on the safety assessment (Draft Amended Report) that were received from the Council prior to the December 2016 Panel meeting have been addressed. Additionally, 2017 VCRP data on persulfates were received from the FDA, and these data are identical to the 2016 data that were reviewed at the December Panel meeting.

The Panel issued a tentative amended report and confirmed their original conclusion (published in 2001) that Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin. The Panel also concluded that the available data are insufficient for determining the safety of these ingredients in leave-on products and dentifrices.

In 2016 Panel, the Panel reopened the original report on Ammonium Persulfate, Potassium Persulfate, and Sodium Persulfate to evaluate the safety of these ingredients for the newly reported uses. At the December 2016 Panel meeting, the Panel issued an insufficient data announcement for these 3 ingredients. The additional data needed to evaluate the safety of these ingredients in leave-on products and dentifrices are:

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

Specific to dentifrices, an FDA public health notification was issued concerning the risk of allergic reactions in users of denture cleansers containing Sodium Persulfate, and the risks of misusing these products. To date, these data have not been received and the data needs remain unchanged.

Draft Final Report, Belsito and Marks Teams/Panel: December 4-5, 2017

Comments that were received from the Council have been addressed. To date, the data that the Panel has determined are needed for completion of the safety assessment of Ammonium, Potassium, and Sodium Persulfate have not been received.

Persulfates Check List for December 4-5, 2017 Panel. Analyst – Wilbur Johnson																				
			Acute toxicity				Repeated dose toxicity			Irritation			Sensitization							
			ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Human	Sensitization Animal	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Ammonium Persulfate			X	X		X	X	X			X	X	X	X	X	X	X	X	X	
Potassium Persulfate			X	X			X							X	X					
Sodium Persulfate			X		X			X				X	X	X	X	X		X		

Literature Searches on Persulfates (1/6-7/2016)

SciFinder/PubMed Searches (Years 1996-2016)

Search Terms

Ammonium Persulfate

+ (7727-54-0)

Potassium Persulfate

+ (7727-21-1)

Sodium Persulfate

+ (7775-27-1)

Search Updates

Search updated on 4-23-2016

Search updated on 10/21/2016

Search updated on 5/4/2017

Search updated on 10/20/2017

Day 2 of the March 16-17, 1995 (54th) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Bergfeld noted that new data on this group of ingredients had been received.

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

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

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

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

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

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

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

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

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

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

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

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

Day 2 of the August 28-29, 1995 (56th) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

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

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

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

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

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

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

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

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

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

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

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

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

Dr. Belsito said that contact urticaria is a well-reported phenomenon; however, its incidence is not known. He also noted that Persulfates have been removed from flour bleaches in Europe because of this problem.

Dr. McEwen said that if further testing of Persulfates is being proposed, then testing will have to be done at exposures that would be expected to occur. He was concerned that the exposures in such a test would not be considered long enough in duration by the Panel, and that the results would be rejected.

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

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

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

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

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

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

The Panel voted unanimously in favor of issuing a Tentative Report on Ammonium, Potassium, and Sodium Persulfate with an insufficient data conclusion. The data needed in order for the Panel to complete its safety assessment of these ingredients (mentioned in preceding paragraph) will be listed in the discussion section of the report.

Day 2 of the December 11-12, 1995 (57th) CIR Expert Panel Meeting

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

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

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

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

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

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

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

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

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

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

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

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

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

Dr. Andersen informed the Panel that the clinical studies on Ammonium, Potassium, and Sodium Persulfate promised by industry are ongoing and that the study results will be made available in 1997.

Day 2 of the April 3-4, 1997 (62nd) CIR Expert Panel Meeting

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

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

Dr. McEwen noted that the study is underway.

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

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

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

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

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

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

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

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

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

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

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

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

Dr. Belsito said his Team concluded that each of the Persulfates is safe for use as an oxidizing agent in hair colorants and lighteners designed for brief, discontinuous use followed by thorough rinsing from the skin.

Dr. Belsito also said that it should be pointed out in the discussion that while urticaria was not seen at a use concentration of 17.5%, information in the CIR report indicates that the Persulfates can be used at concentrations up to 60%. He added that the Panel does not know the threshold for inducing urticaria, and that in using the Persulfates at concentrations > 17.5%, manufacturers should be aware of the clinical case reports of urticaria.

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

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

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

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

Ammonium Persulfate, Potassium Persulfate and Sodium Persulfate

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

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

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

Dr. Bergfeld indicated that the Final Report discussion will be revised based on the preceding comments.

Day 1 of the June 6-7, 2016 CIR Expert Panel Meeting – Dr. Belsito's Team

Persulfates

If not, we move on to the persulfates. So this is a re-review of ammonium, potassium, and sodium persulfate. They were reviewed in 2001. We found them safe as used in oxidation agents and hair color and some lighteners for brief discontinuous use and thorough rinsing.

The uses have increased and the concentration of use data has also increased for potassium persulfate from 60 to 72.5 percent. There have been information that have been taken from the ECHA website, and the question is does this new information or does this increased use or slight increase in concentration of use for the ammonium change our feelings about what we need to say about this, and I thought that none of the data differs from what we previously had known.

We certainly labored over the idea that the persulfates can cause probably non-immunologic urticaria. That was all outlined in our original assessment, and I did not think we needed to reopen this report based upon the information we received now.

DR. LIEBLER: Yes, I agree.

SPEAKER: Agree.

DR. BERGFELD: I agree.

DR. BELSITO: And just one -- page 23 of the PDF -- just to make sure the -- under ammonium persulfate and potassium persulfate case reports, the first word in the third line on a 20-year-old hair dresser, you say talualang diamine. I think you mean paratalumine diamine?

DR. JOHNSON: Yes.

DR. BELSITO: Okay. I had nothing else.

DR. JOHNSON: Dr. Belsito, I might mention that if you look at the 2015 FDA data that the persulfates are used in dentifrices, tonics, dressings, and other hair grooming products, and an eye shadow product, and that's -- those are FDA data, but all of the use concentration data received from industry indicate use in hair coloring products.

DR. BELSITO: Right. I think that we've already said that they're safe for brief discontinuous use, and that was part of the argument we used to say we were less concerned about the ability to induce this what we believed to be non-immunologic urticaria, so those products at least the way I interpret the data. Otherwise I would like a whole bunch more information on this contact urticaria thing is that the data are insufficient to support those uses. So I don't know. Do we have to re-open it to address that?

DR. BERGFELD: How much of a problem is it clinically? I haven't seen --

DR. BELSITO: You know, we've been testing ammonium persulfate for about a year as part of the North American Contact Dermatitis Group Standard tray primarily to pick up reactions to the potassium mono-persulfate that's used in spas, swimming pools, and hot tubs. One of the trade names is Shock.

I've seen some pretty significant delay-type hypersensitivity reactions to it. I haven't had anyone bothered by urticaria, but I mean we're -- it's 8mm thin chamber, you know, 15 microliters, so there's not a lot on there. I mean it's reported in the literature. All of the data on the case reports urticaria are there, but I mean, again, our argument at least back when we first looked at this in 2001 was that it was for brief discontinuous use and therefore -- you know, you're right. I just totally zoned on that.

DR. JOHNSON: But then again, Dr. Belsito, as I said if you look at the --

DR. BELSITO: We have concentrations of use, right, so are these correct reports, but we say at the beginning of our text that their VCR reports which have no concentration of use and then there are some where there's no VCR report, but there is a concentration of use and therefore we assume it's being used. I mean, I think the flip works as well. If there's a VCR report but we have no concentration of use, we have to assume that the VCR report might also be correct, so I -- you know, again, I wasn't even thinking in that mode when I looked at this because I was simply looking at these as being used in hair dyes and bleaches.

DR. LIEBLER: So the issue is dentifrice?

DR. BELSITO: No, eye area for ammonium persulfate. There's one reported there.

DR. LIEBLER: Oh, eye make-up and there's two --

DR. JOHNSON: And then dentifrices for sodium persulfates and tonics, dressings, and other hair grooming aids for potassium persulfate and ammonium persulfate.

DR. BERGFELD: Well, hair dressing would not be considered a temporary exposure. It would be a long-term exposure.

DR. BELSITO: Hair tonic you mean.

DR. JOHNSON: Yes.

DR. BELSITO: No, no, I agree. So these are new reported uses.

DR. BERGFELD: (inaudible) has to open it up again and present the data.

DR. BELSITO: Yes, I mean, I think that based upon that --

DR. JOHNSON: Would FDA need to confirm that those uses actually exist?

DR. BELSITO: Well, --

DR. JOHNSON: Well, they sort of already did with the concentration data.

DR. BELSITO: Well, yeah, see, the issue becomes -- so we said the expert panel in our discussion from the prior final report, we had a sensitization study at 17.5 percent ammonium potassium and sodium persulfate in a mixture, and that application did not result in urticarial reactions. I don't know what the number was, and then --

DR. BERGFELD: That's the original.

DR. BELSITO: That's the original. And then we said that we're concerned because the concentration of persulfates was up to 60 percent but these were rinse-off products, so really, I mean if it's being used in those types of products then I think we need to go and re-open it to get some sense of the concentration of use. I mean -- or we can simply say that it's insufficient.

DR. EISENMANN: You did have one --

DR. BELSITO: But that would still change our conclusion, so I think we need to re-open.

DR. EISENMANN: In the original report there was one dermal -- I don't know what it was, but there was one dermal contact use of ammonia persulfate in the original report. In other words, your conclusion already is saying --

DR. BELSITO: It shouldn't be used in that?

DR. EISENMANN: Right, right.

DR. BELSITO: But we specifically -- I mean typically now with a conclusion we say it's -- in the data are insufficient for its use in, and we didn't in that report -- in the persulfate report. We just said it's safe for brief discontinuous use, and we didn't continue that conclusion to say that it is insufficient for that dermal contact use and here are the insufficiencies which is -- again, I think --

DR. EISENMANN: Right, right.

DR. BELSITO: And we missed it. I mean, I guess. I don't --

DR. GILL: And that dermal contact didn't say

(inaudible) at that time (inaudible) at least as I had read it.

DR. BELSITO: And we wouldn't have had a concentration range, right? That was when we weren't getting concentrations or there was none reported. I mean I'm wondering if that eye area -- wasn't there something about these persulfates being used for eyebrow dyes in Europe, for dyes in the eyebrow in Europe? Am I recalling that correctly?

SPEAKER: Women do use dye on their eyebrows when they have (inaudible).

DR. LIEBLER: So you're not worried about the toothpastes?

DR. BELSITO: Yes, I mean --

DR. LIEBLER: Okay.

DR. BELSITO: I wasn't even -- I think the toothpastes are probably even more of concern.

DR. LIEBLER: Okay.

DR. BELSITO: Just want to go back and see what you have here.

DR. BERGFELD: Carol, would the industry be interested in coming back with their concentrations with some evidence?

DR. EISENMANN: I went out. I don't think that -- and as for concentration of

use, I didn't get any information. I mean I can go out again, but I doubt that I'll get any information.

DR. BELSITO: But I think that --

DR. BERGFELD: (inaudible) expected it to be insufficient for the other uses.

DR. BELSITO: But we have to re-open it though to be able to say that, right?

DR. BERGFELD: No, just re-endorse your 17.5 percent as the upper limit of approved concentration.

DR. BELSITO: We didn't have -- we didn't set an upper limit.

DR. BERGFELD: Well, we set it in our discussion, I believe; the 17.5 percent was there somewhere.

DR. BELSITO: Yes, we said it in the discussion that 17.5 percent did not cause evidence of delayed (inaudible) hypersensitivity or urticaria, but we remain concerned that it was used at a higher amount; however this was brief discontinuance.

We never addressed the issue in the discussion or our conclusion about whether we felt these were safe for a dentifrice or a leave-on hair tonic. I mean it's almost like what I just zoned -- when I was looking at this I was simply thinking of it as a bleaching agent prior to a hair dye rather than as any other function, and it's being reported for other functions, so I think we need to -- I think what will happen is we'll re-open it and we'll say insufficient for these leave-on and oral uses on the basis of lack of no-L for the urticarial reactions because we won't have a concentration range for them.

I think you need to do due diligence and go back and re-survey industry, and say listen, VCRP says there's this use, this use, and this use, and who's reporting this to FDA, and are these reports correct because if I recall we've sometimes gotten reports that it's been reported and then the company goes "Oh, no. I'm sorry. We made a mistake. We're not using it in a dentifrice." So, I think we just need to clarify that, and if in fact it's being used then I think we need to issue a new conclusion that's safe as used in hair dyes for brief discontinuous rinse-off use and insufficient for leave-on and oral dentifrice.

DR. LIEBLER: Yes, I'm okay with that.

DR. BERGFELD: I'm sorry to go back to the discussion from the final report, but it is on 28, reference 28, so it was repeated in this new document, the discussion from the original final.

DR. BELSITO: I understand, Wilma, but --

DR. BERGFELD: I'm just saying that it does point out 17.5 and indicates sort of in a backwards way that that was the limit of concentration that was approved. We didn't say it as distinctly as we have said it very early on in other documents. Is it 48?

DR. BELSITO: Yes, but our conclusion simply was that it was safe as used in oxidizing agents and hair color and lighteners. We said nothing about its use in dentifrices or leave-ons --

DR. BERGFELD: No, we didn't.

DR. BELSITO: -- so I think we have to go back and re-open it and say something in our conclusion about those uses.

DR. BERGFELD: Fine. We have two choices.

DR. BELSITO: I mean we can't rely on the idea that -- I mean we really haven't -- I mean I think how many animals were done in that 17.5 study, et cetera? Does it justify -- so we have non-hair coloring uses.

DR. BERGFELD: Two.

DR. BELSITO: Right. Including dental orifice --

DR. SNYDER: I think the process allows us to re-open and get more information without formally -- we can go to the next step by (inaudible).

DR. BELSITO: We can always re-open and then -- yes.

DR. SNYDER: So let's get clarification on those.

DR. GILL: There have been meetings in the past where FDA has been able to clarify this before end of the meeting so we would know by day 2 whether or not we should re-open it, so if FDA could do that.

SPEAKER: The clarification?

DR. GILL: The clarification on whether or not it is used in these -- used for

other things other than hair colorants. If FDA could clarify that before tomorrow's meeting we might be able to make a determination of how we go forward with this report.

DR. SADRIEH: I'm not sure what you mean by clarification.

DR. GILL: I'm sorry. Go ahead.

DR. SNYDER: There are some uses that are reported that fall outside of the non -- that fall in the category of non-hair coloring.

DR. SADRIEH: Right, but this is how it's been listed. We just provide the information based on -- people fill out the 2511, 2512 form, and whatever's provided in there, that's what we provide to CIR, so we don't have any -- nobody explains to us. We just basically take information as provided to us, and then we just report it back.

DR. GILL: But sometimes FDA is able to go back and say this was reported. It's either in the correct category or not. It's older data. You'll give us a range of when it was reported, so if we could get some of that clarification?

DR. SADRIEH: We can try to look at that but by tomorrow, no.

DR. SNYDER: So we are tentatively going to re-open and go insufficient?

DR. BELSITO: Well, yes, I mean at this point we need to re-open to further assess whether in fact they're used in non-hair coloring uses; the dental and the hair tonics. If so, at what concentration, and then I don't know that we can -- if they're used at .000 percent, you know, then I think we can go safe as used based upon the 17.5 study. If they're used -- and I think we need to go back and re-assess the -- how solid that data at 17.5 percent is. So, we just need to re-look at the data much more closely certainly than I looked at it based upon the new data we were getting and the thought that these were simply used in hair dyes.

DR. SNYDER: Well, either way it's going to result in a change in the conclusion.

DR. BELSITO: Right, it will.

DR. SNYDER: It's either going to include leave-ons or (inaudible) or it's going to (inaudible).

DR. BELSITO: Right, or we'll find out that it's not used in any of these leave-ons, and it won't change the conclusion, and then we'll go not to open it. We'll just change how it's used, but I think at this point we need to re-open.

DR. SNYDER: Right, I agree.

DR. BERGFELD: Are the dental products handled by OTC panel of the FDA?

DR. SADRIEH: It depends on the indication. If it's for -- if it's got fluoride in it and it's for prevention of cavities, then yes. But if it's for cleansing, it would be a cosmetic.

DR. BERGFELD: Okay.

DR. LIEBLER: And the reason that this chemical would probably be included in a toothpaste is for whitening. It's kind of a hydrogen peroxide with training wheels essentially, so.

DR. BELSITO: Would whitening be considered --

DR. SADRIEH: Tooth whitenings right now -- it's not clear what's going on with tooth whiteners. I think it's being passed between centers.

DR. BELSITO: So it could be OTC or it could be cosmetic?

DR. SADRIEH: It could, depending on the claims that are made, and possibly if one were to look at more the mechanism of action because the question is how does it actually work. Does it have an effect on the structure and function because if it actually affects certain structural features of the tooth enamel, then that's one thing, but if it just changes how it reflects light then that might be something else because of just some sort of surface property.

DR. LIEBLER: (inaudible) change how it reflects light by changing the structure.

DR. SADRIEH: Well, that's why it's being passed around because, you know, we feel one way about it and then Cedar feels another way about it, so.

DR. LIEBLER: So, if something falls between the cracks and teeth, does that bring floss into play then?

DR. SADRIEH: It's a device.

DR. BELSITO: Okay, so we're going to recess.

(Recess)

DR. BELSITO: Okay, so we are going to reopen to get further information about these non-hair coloring uses, concentrations. And then make a decision at that point that will go into our conclusion.

DR. GILL: Are there any other data points that you need for the insufficient list?

DR. BELSITO: At this point we just need clarification as to whether they are used and what their concentration is. And then depending upon that, we may need more information about sensitization and irritation at those use concentrations.

DR. SADRIEH: So the VCRP's not going to have concentration of use information. I just -- yeah, --

DR. BELSITO: No, I understand.

DR. SADRIEH: Yeah.

DR. BELSITO: That's why we're asking Carol to go back up and get it. And if we don't get it, then we'll go insufficient for concentration of use. And -- I'm sorry, I'm having major issues here. Okay, anything else on the persulfates?

Day 1 of the June 6-7, 2016 CIR Expert Panel Meeting -- Dr. Marks' Team

Persulfates

And the next one is persulfates. And we have a lot of -- so this is a re-review on persulfates. In '98, the expert panel issued a final report with a conclusion that ammonium persulfate, potassium persulfate, and sodium persulfate are used -- are safe as used -- are safe as used as oxidizing agents -- a lot of as's there -- in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin.

So, just a little bit of background. The original report highlights the issues of sensitization (inaudible) reactions rhinitis and asthma reactions in the client and the worker. That was page 44 of this report, which is confirmed in studies since then. The discussion should emphasize the conclusion for both the client and the worker, the hairdresser. I'm not sure it was in the original report -- emphasize the worker, the hairdresser -- their issues.

We look at uses in page 31. There should not be leave-on. There are a couple leave-ons in the table. And if we look -- and, again, more recent data -- if we look at the local lymph node assay, ammonium and sodium persulfate are sensitizers. I knew that. At five percent, however, it's rinse off. But my feeling is it's not a big problem. So I felt not reopen, but I --

DR. SHANK: So did I. If you reopen, what you change the conclusion to?

DR. MARKS: No. I'd put -- you wouldn't. I agree. I think the only thing I would do in the discussion and not reopening is emphasize that the conclusion is not only aimed at the client, but also aimed at the hairdresser, because that's where I've seen a significant number of problems with allergic contact dermatitis of the hands and some contact to carry the hands of the hair dressers. And if I read this without knowing that, I might think it's only directed to the client themselves, not to the hairdresser. Okay.

DR. SLAGA: Not reopen.

DR. MARKS: Not reopen. Yeah. I just highlighted those, Wilbur, to be in the discussion.

MR. JOHNSON: Yeah. Just one question, Dr. Marks. I know the original conclusion really related to rinse-off products. And now, as you mention, we have uses in tonics, dressings and other grooming aids, dentifrices and other eye makeup preparations. And I know that the other eye makeup preparations and the tonics, dressings and other hair grooming aids are leave-on product uses.

DR. MARKS: Well, it says only -- at least, what I - - when I looked at the table, in only had three. I just highlighted is -- let me see here, where were they? There was --

MR. JOHNSON: There was one for ammonium persulfate.

DR. MARKS: Leave-on -- yeah. Ammonium persulfate two leave-on and --

MR. JOHNSON: Okay.

DR. MARKS: -- the most recent. And ammonium persulfate one leave-on and I would just -- I would comment that a brief discontinuous exposure isn't a leave-on.

DR. HILL: Yeah.

MR. ANSELL: That's not going to change the conclusion --

DR. MARKS: Right.

MR. ANSELL: -- that these materials are inconsistent with the existing conclusion.

DR. MARKS: Right. And that's --

DR. SHANK: Those leave-ons would be uses which we did not feel would be necessarily safe.

DR. MARKS: Yes.

DR. SHANK: That's why we said had to be rinsed off.

DR. MARKS: Mm-hmm. So I don't know if that answers you, Wilbur. I just -- again, to me that would be all in the discussion when you say not reopen.

DR. HILL: So really if you -- if you don't reopen, there's nothing on the consumer commitment code that happens, then the really the balls in the FDA's court, isn't it? If they --

DR. MARKS: That's correct. That's my understanding.

DR. HILL: -- concerned with the safety -- yeah.

DR. MARKS: Have an FDA representative -- yeah. We only make the recommendations. We're not the enforcer.

DR. HILL: That was my -- I did have -- well, if we're not going to reopen, then we don't have to tweak their priorities. Just -- but it's a general not report specific issues, which is -- so if you look at -- I'll raise it quickly, because it is quick. This is just a general way of perceiving -- I'm trying to find the chemistry. Where is it? Page 14. I've even got a page number. Why am I having trouble finding it? Yeah, okay. I know what it was.

So when we had -- when you have a statement capture from an old report and there's a technical inaccuracy in there, if we were going to reopen the report and do something with it, how do you capture mistakes in the original language?

DR. MARKS: Yeah, what I do is just put -- if it's significant enough, just capture it in the discussion with a not reopen report that we could share.

DR. HILL: Okay. Great.

DR. MARKS: What -- what was that?

DR. HILL: Well, it says they dissociate and eventually form potassium, sodium, immodium and sulfate and persulfate (inaudible). No, they nearly instantaneously dissociate when you dissolve them in water to get that. And then with the persulfate, other things happen. But, yeah, so -- I'd just --

DR. MARKS: Again, maybe you could --

DR. HILL: It's captured in here, so there shouldn't be any problem.

DR. MARKS: Okay.

DR. HILL: I just wondered what was the procedure.

DR. MARKS: Okay. Any -- so tomorrow, presumably, I'm going to be seconding a motion not to reopen. And we have all these things we discussed about in terms of the discussion in the table. Or I mean in the not reopen report.

MS. FIUME: Dr. Marks?

DR. MARKS: Yes.

MS. FIUME: I think one of the other things we were trying to find out -- and this is for the FDA representative -- is that if we could get clarification on the VCRP data. If there's been any changes or what's in there is correct? In the past, they've been able to look and see if something that was captured in the VCRP is actually correct or not. So --

DR. MARKS: So are you talking about the leave-ons?

MS. FIUME: Yeah.

MR. ANSELL: But it wouldn't change the conclusion.

MS. FIUME: Well, no. Just for clarification of the report that it -- all the information is captured correctly. Because there is a dentifrice use listed and things like that. FDA has been able to go into the VCRP data in the past and see. Can we still find out if uses that are listed in the VCRP are still currently listed in the VCRP or if there's been changes?

MS. DEWAN: The ones which you have in the report is the ones which the data information when you requested it.

MS. FIUME: When we requested it.

MS. DEWAN: Yes, yeah. So those are the correct ones. After that, there could be because I think it's sent in annually. The request is done --

MS. FIUME: January.

MS. DEWAN: -- yes, yes. That comes in January. From January to this time, if there are more additions -- yeah, there may be some changes, but not a significant change in (inaudible).

MS. FIUME: Yeah. We wonder actually if there was deletions from the oral or leave-on (inaudible).

MS. DEWAN: Yeah. So there may be some. But, again, you know, we don't have the update data as of now -- today. Yeah. But that -- I don't think that would throw you way off the numbers.

Day 2 of the June 6-7, 2016 CIR Expert Panel Meeting – Full Panel

Persulfates

DR. BELSITO: Persulfates. So this is a re-review from 2001 where we concluded that they're safe as oxidizing agents in hair colorants and lighteners designed for brief, discontinuous use, followed by thorough rinsing from the hair and skin. In this report, and as it turns out in the last report, there was one use in the last report and more than one use, particularly in dentifrices, that aren't within that category of brief, discontinuous use followed by thorough rinsing of the skin.

And as you may recall, those of us who were here in 2001, there was a great discussion as to the contact urticarial potential of these persulfates, which we thought could be cleared by a study on a hair product that was rinsed off. However, given these non-hair, non-rinse-off potential uses that are reported, we thought we had to reopen it to look at those uses because we never made a comment in our discussion whether a non-hair, non-rinse-off use was safe or insufficient. So reopened. Look at particularly the uses in dentifrices. We need the concentrations and --

DR. BERGFELD: And tonics.

DR. BELSITO: -- of those products.

DR. LIEBLER: Hair tonics.

DR. BERGFELD: And tonics.

DR. BELSITO: And hair tonics. Yep.

DR. BERGFELD: Jim?

DR. MARKS: Our team had a little different slant, as you might imagine we often do. The teams don't come to quite the same conclusion. We felt we did not need to reopen it. We concurred with the original conclusion and just noted that there were three uses, which were not brief and discontinuous and didn't think that we had to justify those three uses. They shouldn't be used for that based on the conclusion.

So I guess there was no new information other than that. We knew it was -- these persulfates are sensitizers. We know that they cause contact urticarial, rhinitis. There are asthma reactions. What I want to emphasize in the discussion is that the conclusion is really applied to not only the client but the worker, in this case, the hairdresser because we know there's a significant number of contact dermatitis, probably contact urticarial occurring in the worker. So it should be brief and discontinuous for them too or have some sort of protection. But I think it's just a difference in addressing the new uses --

DR. BELSITO: But they're not new. There was actually one use that was reported as a leave on, and we simply failed to pick it up, I mean. So we're being told, I mean, you cannot change what we're being told these products are being used as. And then are you saying that they're unsafe and then unsafe based upon what? We don't know what concentration. You know, they may be being used a concentration where they are safe. So at this point, I mean, we can always close the safety assessment later. But we need to go out, have Carol query industry, find out are they in fact being used in tonics and dentifrices, if so, what's the concentration. And then come back and reassess the data because, otherwise, I mean you cannot just simply say we're not going to reopen because the conclusion in 2001 does not address uses we're being told are in current practice today. And if you say that those are unsafe uses, then you need a reason to say that. And we don't have a reason to say that either. I mean we have to open it up and look and see what's going on. We can close it -- we can open and close. We've done that before. We don't have to pursue it. But we at least need that information.

DR. MARKS: Second.

MS. SADRIEH: I just wanted to confirm that two of them are in dentifrices.

DR. BERGFELD: What did you say?

MS. SADRIEH: Two of them are in dentifrices.

DR. BERGFELD: Okay. Yep. Okay. All right. With the --

DR. BELSITO: Then the question becomes are they there as a cosmetic or are they there as an OTC. So, I mean that -- we need to clarify all of that.

DR. MARKS: So, Don, I second the motion and really, in terms of guiding

Wilbur, we really want to know about the dentif --

DR. BERGFELD: And the hair tonics.

DR. MARKS: And the hair tonics.

DR. BELSITO: Right.

DR. MARKS: Those two.

MS. SADRIEH: If they're in VCRP, their -- they would not be for drug use.

DR. BELSITO: Okay.

MS. SADRIEH: So these are two from VCRP --

DR. BELSITO: Okay.

MS. SADRIEH: -- so they are not used for drug purposes.

DR. BERGFELD: Thank you. I'm going to call the question then. To reopen, a motion has been made and seconded. All those in favor to reopen? Thank you. It passed.

Day 1 of the December 5-6, 2016 CIR Expert Panel Meeting – Dr. Belsito's Team

Persulfates

DR. BELSITO: Okay, so persulfates. June meeting, the panel agreed to reopen the final report on persulfates. Examine the current use of three ingredients in the report. Product categories other than hair coloring products. That was tonics, dressings, and other hair grooming aids. Ammonium and potassium persulfate dentifrices, and then other eye makeup preparations.

So, the FDA and industry both went out and looked and did in fact say that these ingredients are not being used in product categories other than hair coloring. But I now understand that they are also used in dentifrices. Right? So, they are used in dentifrices.

MR. JOHNSON: Well, they're used in all those categories --

DR. BELSITO: Right.

MR. JOHNSON: -- that were mentioned.

DR. BELSITO: Right. Okay.

MR. JOHNSON: So, FDA was saying that they are used in leave-on products and dentifrices, whereas industry did not submit new data that suggest, you know, those uses.

DR. BELSITO: Okay. But when I queried, because it just so happened that I had a patient that I was seeing with lip dermatitis last week who was using a denture cleanser that was labeled as antibacterial, that had ammonium persulfate in it, and I queried back to Lilly. And since this had an antibacterial claim, it was an Efferdent plus something or other, that this would be considered an OTC, and was that what we're getting reported. And she said she went back to both FDA and to Carol and was told no, it was used in dentifrices, not without an antibacterial claim. So, that was the response I got back from Lillian.

MR. JOHNSON: And if the --

DR. BELSITO: So, the council, obviously, has information that it is being used in dentifrices as well.

MR. JOHNSON: Yes, and that dentifrice use relates to "real teeth" as opposed to dentures.

DR. BELSITO: Right. Yeah, that's what I mean. Okay. Go back and save this and open that. Okay, that's under persulfates, right? Okay. So, we know that at least when used as bleaching agents

and hair products, they can cause some airway hyper- responsiveness. I don't know if that's an issue based upon hair tonics and dentifrices. I would imagine it shouldn't be because they shouldn't be aerosolized under those conditions. So, I think it takes away the concerns with that. We don't have an NOAEL for irritation, but we can say formulated to be nonirritating.

I guess my biggest issue with these is the fact that we know ammonium persulfate can cause urticaria. We don't whether it's allergic or non-immunologically.

DR. SNYDER: We produced (inaudible) 17.5 percent. Is that still valid?

DR. BELSITO: Well, but that was haircare product. You know, we don't have any data. You know, that was brief discontinuous use on the skin and which we had, I believe, data looking at that at 17.5 percent. But that was not on a leave-on basis.

DR. SNYDER: I thought it was.

DR. BELSITO: No. Study examined sensitization and instance of urticarial reactions to 17.5 ammonium potassium sodium. So, if I can make sure it was not a

(inaudible) and none of the persulfates caused -- yeah. Okay, you're right, we do. So, it's 17.5. But then in a clinical patch test study, 5 to 26 subjects had positive sensitive reactions. These reactions were confirmed and rechallenged. I mean I presume that's delayed-type hypersensitivity. But that's at a very low concentration. You know, it's 0.05 percent, right?

DR. SNYDER: Yeah.

DR. BELSITO: 5000 parts per million. And we also don't know what it would be like with

mucosal exposure because it says that another study was noted that the reactions

to ammonium persulfate were more severe when the ingredient was scratched into the skin. So, bypassing the stratum corneum then that raises a completely different issue for dentifrices where you don't have a stratum corneum. I mean, we have two ocular studies that are negative.

DR. SNYDER: So, we voted to reopen to add --

DR. BELSITO: Right.

DR. SNYDER: -- to other nonhair-coloring uses, but we don't have data to say sufficient for safety because we don't have any data on sensitization or irritation for use -- the new use.

DR. BELSITO: Right.

DR. LIEBLER: I would rephrase that slightly. We voted to reopen it because we were aware of other uses because of the other reported uses, as opposed to, you know, with the intent of --

DR. SNYDER: Yeah.

DR. LIEBLER: -- supporting them because there are insufficient data in my view to support them at this point.

DR. SNYDER: Right.

DR. LIEBLER: So, anyway, yeah, I agree.

DR. BELSITO: Yeah, so I said okay with brief discontinuous use to hair. insufficient for leave-on dentifrices for a NOAEL for sensitization --

DR. LIEBLER: Right.

DR. BELSITO: -- and urticaria.

DR. LIEBLER: I agree.

DR. SNYDER: Yeah, same here.

DR. BELSITO: Okay, as we originally said, with these safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin, the data are insufficient to support the persulfates as leave-on products or in dentifrices. And the data that would be needed would be the NOAEL for sensitization and urticaria.

And do we have the concentration of use for those? I didn't think we did.

DR. LIEBLER: No reported concentrations, I think.

DR. BELSITO: Right. And for the concentration of use because we can't interpret a NOAEL without knowing how they're used.

MR. JOHNSON: Exactly right.

DR. JONAS: We'd also like to make the suggestion in the non-cosmetic use section that there should be a reference that the persulfates are used in denture cleaners and that FDA has a 2008 public health notification concerning the use of this ingredient. So, if we could link to that FDA warning, that would be great or the notification, rather.

DR. BELSITO: Where were you, Beth, I'm sorry?

DR. JONAS: Under non-cosmetic uses, at the beginning.

DR. BELSITO: PDF?

DR. SNYDER: 24.

DR. JONAS: Thank you.

DR. BELSITO: And you want us to state that?

DR. JONAS: State that persulfates are used in denture cleaners as a medical device --

DR. BELSITO: Okay.

DR. JONAS: -- and cite FDA's 2008 public health notification.

DR. BELSITO: Okay. And we're referencing, you said 2008 FDA notification?

DR. JONAS: Correct.

DR. BELSITO: Okay.

MR. JOHNSON: And I'd just like to add that that public health notification alerted the public to the risk of allergic reactions in users of denture cleansers.

DR. BELSITO: Yeah, I mean if you look at this Efferdent Plus Antibacterial, it has like a box. On the outside of the box, it warns about the potential for sensitization. So, it's not quite a black statement, but it's a warning label that exists right on the box of the Efferdent. Now, whether people read it or not, I don't know. But it was interesting that this guy actually happened

to be allergic to persulfates. We'll see whether it was the cause of his cheilitis since I just diagnosed it on Friday, so.
Anything else? Okay.

Day 1 of the December 5-6, 2016 CIR Expert Panel Meeting – Dr. Marks’ Team

Persulfates

let's see. Next is draft amended report on

2 persulfates. Is that correct? Am I in

3 the right order here?

4 DR. SHANK: That's right.

5 DR. MARKS: We're coming down the home

6 stretch, team. Only three more to go. Can we

7 last that long before a potty break?

8 (Discussion off the record.)

9 DR. MARKS: Let me see here. Are you

10 still up here, Wilbur?

11 MR. JOHNSON: Yep.

12 DR. MARKS: Wilbur, you're getting --

13 okay. You've gotten the tail end of things here

14 it looks like.

15 So at the September meeting -- no, yeah,

16 September meeting only back in 1998 -- issued a

17 final report with the conclusion ammonium

18 persulfate, potassium persulfate, and sodium

19 persulfate are safe as used as oxidizing agents in

20 hair colorants and lighteners designed for brief

21 discontinuous use followed by thorough rinsing

22 from the hair and skin. That report was published

221

1 in 2001. And then now what we found, since then
2 that there are other uses of these persulfates.
3 There are other hair grooming aids found in
4 dentifrices if I -- and that was an email back and
5 forth between Don and William as to how much is
6 FDA? If it's a cleaning agent then it's FDA; if
7 it's just a dentifrice, it's a personal care
8 product. It (inaudible), I guess, not a perfume.
9 And then there was, what, one eye makeup use? So
10 the persulfates, from my vantage point, they're
11 well-known sensitizers and contact urticants. So
12 what do we do? It seems to me as I recall we
13 thought don't reopen but then we have these other
14 uses.

15 DR. SHANK: I have don't reopen. The
16 new data don't change the conclusion. There's no
17 need to reopen the report just to add to the
18 conclusion caveat that used as a hair tonic or eye
19 cosmetic.

20 DR. MARKS: Yeah, I guess the only
21 change in the conclusion would be and not -- and
22 insufficient data for the other uses. One could

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1 open it and say insufficient data for the other
2 uses or -- because I have to look at the minutes.
3 I think we were do not reopen but then the other
4 team wanted to reopen.

5 DR. SHANK: They're not used for that
6 though.

7 DR. MARKS: Pardon?

8 DR. SHANK: The FDA says they are.
9 Isn't that right? The counsel stated --

10 DR. EISENMANN: Well, I didn't get any
11 use concentrations. One of the things we're
12 speculating is that it is used in denture
13 cleansers and then FDA issued this public alert on
14 denture cleansers in 2008, which probably should
15 be at least as a minimum be in the use section.
16 That somebody could have misregistered a denture
17 cleanser as a dental --

18 DR. HILL: That makes sense.

19 DR. EISENMANN: And I don't know about
20 the other. I don't know if you could get the name
21 of the product from FDA, if they've come out with
22 that.

1 MR. JOHNSON: Well, I actually
2 communicated with FDA and FDA confirmed that the
3 dentifrice uses relate to the use of toothpaste on
4 real teeth.

5 DR. EISENMANN: Correct.

6 MR. JOHNSON: Yeah.

7 DR. EISENMANN: But we don't know -- in
8 fact, the product name from the VCRP, if the
9 product name would reveal if it was a toothpaste
10 or if it was a --

11 MR. JOHNSON: Well, yeah, they told me
12 that it was a toothpaste that's applied to real
13 teeth, not dentures. That's what they --

14 DR. GILL: Yeah, she said it does not
15 relate to use in denture cleaners for noncosmetic
16 uses, the VCRP data.

17 DR. EISENMANN: Right. It shouldn't.
18 But whether or not somebody made a mistake, I
19 don't know for sure.

20 DR. GILL: And reported it as such?

21 DR. EISENMANN: Right. I mean, those
22 things happen at times. But we can't necessarily

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1 resolve that other than it is clearly use in
2 denture cleansers which is considered a medical
3 device.

4 DR. HILL: So the Freedom of Information
5 Act didn't identify the company?

6 MR. JOHNSON: They didn't identify the
7 company to me. They just, you know, confirmed
8 that that use is in a dentifrice, particularly a
9 toothpaste that's going to be applied to real
10 teeth because that was a concern whether or not
11 this is applied to dentures or real teeth and FDA
12 says real teeth.

13 DR. MARKS: It's not sure to me. Oh, I
14 can see for dentures you can do it outside the
15 mouth.

16 Well, the other for me, I had eye
17 makeup. Somewhere in here it says eye area. So I
18 had, besides dentifrices, it's diluted out, da da
19 da da da da. It's got to be put on straight. Do
20 not reopen because the conclusion doesn't change.

21 DR. SHANK: Change.

22 DR. MARKS: The question is do you amend

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1 the conclusion and say not for other uses? But
2 that's implied.

3 DR. SHANK: Right. If you do that with
4 --

5 DR. MARKS: So our team is going to
6 stick to our guns --

7 DR. SHANK: -- all of them.

8 DR. MARKS: -- and not reopen because
9 I'll be making the motion tomorrow and then we'll
10 see if the Belsito team still wants to -- well, we
11 say don't reopen. I guess now it's been reopened.

12 Close, no change of conclusion is accurate. So
13 I'll move we close this review. No change in
14 conclusion. And then we'll see whether the
15 Belsito wants to wordsmith and say no other -- but
16 not -- or insufficient for other uses. So team,
17 what are we going to do tomorrow when we get that?
18 Because that could be easily rehandled in the
19 re-review discussion --

20 DR. SHANK: Correct.

21 DR. MARKS: -- that we can clarify. I
22 mean, the conclusion is pretty clear.

1 MR. JOHNSON: Now, the other team is
2 requesting no effect level for sensitization and
3 urticaria.

4 DR. MARKS: In what situation? Because
5 --

6 MR. JOHNSON: Taking into consideration
7 --

8 DR. MARKS: -- no effect on the buccal
9 mucosa?

10 MR. JOHNSON: -- the use in leave-on
11 products. That's exactly what that team is
12 requesting.

13 DR. MARKS: Well, we'll find out.

14 MR. JOHNSON: No effect.

15 DR. MARKS: It's going to be an
16 interesting discussion tomorrow.

17 MR. JOHNSON: Yes.

18 DR. MARKS: Because how do you get a no
19 effect? I guess you can get a no effect level for
20 sensitization in the buccal mucosa.

21 DR. HILL: I think I'll get a later
22 flight.

1 DR. MARKS: So team, do you like that
2 move? Close this review, no change in conclusion?

3 DR. SLAGA: Right. Oh, no, this will be
4 fun.

5 DR. MARKS: Okay. Thanks, Wilbur, for
6 calling the FDA.

7 MR. JOHNSON: Okay. You're welcome.

8 DR. MARKS: And clarifying that. And
9 we'll have a meeting of the minds tomorrow.

10 DR. HILL: I did have one question since
11 Ivan was in here in particular, Wilbur, too, about
12 this NICNAS. Where is it over here? I was just
13 there, 31. Page 31.

14 It was, yeah, there were five items and
15 I was confused by why would there be dust from a
16 hair coloring preparation? Because that was one
17 of the items in the NICNAS report. Is that
18 pertaining to industrial production?

19 MR. BOYER: It has to do with
20 occupational exposure.

21 DR. HILL: Occupational. Not
22 occupational to the hair dressers --

1 MR. BOYER: Correct.

2 DR. HILL: Okay. That is what was
3 confusing about the way it was laid out is --
4 because I was trying to figure out how
5 hairdressers would be exposed to persulfate dust.

6 MR. BOYER: Released in manufacturing.

7 DR. HILL: Okay. Yeah. Okay, that now
8 makes sense.

9 MR. JOHNSON: And I guess I should add a
10 statement to that effect that that relates to
11 occupational exposure, not for the hairdresser but
12 in the --

13 DR. HILL: Well, it says assessment of
14 persulfate salts in hair bleaching preparations
15 identified the following health and safety
16 concerns. And then you've got minimizing exposure
17 to dust formation in item two, and then item five
18 is the training of salon workers. So I was trying
19 to figure out how in the context of hair bleaching
20 preparations there would be dust formation that
21 was relevant.

22 MR. BOYER: Well, for that specific item

1 it's very likely in the use in a hair salon you're
2 going to get some evaporation of the other
3 ingredients and so forth, so you might have some
4 significant amounts of dust.

5 DR. HILL: Okay. I wondered if that was
6 what -- and I guess I would like -- if that -- I
7 mean, it's fine to stay in there but I scratched
8 my head. I was puzzled why dust. Is that what
9 they were thinking when they wrote that report? I
10 don't know how we would go about finding that out.
11 It was 2001. But --

12 MR. BOYER: We'll look at the full
13 report.

14 DR. HILL: Well, see if you can get an
15 enlightenment would be great because it just seems
16 like there was a disconnect there. Had we never
17 dealt with Brazilian blowout in the context of
18 pragmatic use I probably wouldn't have paid much
19 more attention to this.

20 DR. MARKS: Okay. It will be
21 interesting. It is going to be fun tomorrow
22 because -- and I'd like to see what their motion

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- 1 is. Are they going to issue a tentative --
- 2 suggest issuing a tentative report with safe and
- 3 insufficient conclusion?
- 4 Okay. Any other comments?

Day 2 of the December 5-6, 2016 CIR Expert Panel Meeting – Full Panel

Persulfates

DR. BERGFELD: Opposed, yes. Thank you. Thank you we'll move on then.
The Persulfates doctor Marks?

DR. MARKS: So in September of 1998 while I have (inaudible), we should have filed a report with a conclusion in it. Ah these three persulfates ammonia; potassium; and sodium. Are safe as used as oxidizing agents in hair colorance and lightener's, designed for brief discontinuance use. Followed by thorough rinsing from the hair and skin. At the June meeting this year we reopened this report of the persulfates because of other uses of these compounds, such as hair grooming aide; dentifrices; and eye makeup. Our team considered those and decided that. There should be no change in the conclusion therefore we move to close this review.

DR. BERGFELD: Is there a second to that, or additional comments?

DR. MARKS: Yeah we would handle the other uses, in the re-review document as there's insufficient data. But we wouldn't reopen it. I should say we would close it at this point. The conclusion does not include other uses.

DR. BELSITO: Well I mean we certainly agree that the original conclusion can be, sustained. We were asked to review this. It's reported to be used out there in hair tonics and in dentifrices. It certainly is used in a non cosmetic denture cleansers. I actually saw a patient last week who had colitis related to persulfate in his Efferdent. So I thought since it's reported to be used out there, we should go on record that we found it to be insufficient for leave on in dentifrices. For concentration of use which weren't told. And for a no effect level for sensitization and urticaria. Because I copied Lillian when I saw that persulfate on the dentifrices and said. I presume that this is an OTC because it was labeled as antibiotic. Are those the reports? And she came back to me and said no. That's actually used in toothpaste. So I mean if we think it's unsafe, or we don't have the data to support that use. I think we need to review it. We can't just say well you know, we don't want to reopen it.

DR. BERGFELD: Other comments

DR. SNYDER: We also felt this was communicated by The FDA publication knowing the 2008 that there public notification on different issues, at a risk of allergic reactions. So that's out there so it (inaudible)

DR. BELSITO: Yeah if you look at the effort in box, there is a box right on it. Warning about allergic reactions to use of that denture cleanser.

DR. SHANK: So the conclusion has changed?

DR. BELSITO: Well the conclusion changes because we now, say that there are other uses. So it's okay with brief discontinuous use to the hair. Insufficient for leave on cosmetics and dentifrices, and the insufficient data are the concentration of use, which were not being told. And in no effect level for sensitization and urticaria.

DR. SHANK: I think that could be handled in the re-review statement. Without reissuing the report.

DR. BELSITO: Well anyway, I don't know the rules and regs here.

DR. GILL: Yeah I think that's a panel decision on whether or not you (inaudible) use is there, and want to address that.

DR. BELSITO: Well the uses.

DR. GILL: Because it is used.

DR. BELSITO: The use is there. You told me

DR. GILL: That's right

DR. BELSITO: Both FDA and Carol got back to you and said that. They checked again and it was being used.

DR. GILL: It's been used in toothpaste your correct.

DR. BELSITO: And if we don't list it as insufficient If we don't reopen it, would those uses go on a two year time clock?

DR. GILL: No, I think it's a new conclusion. I think it would be insufficient on a two year time clock.

DR. BELSITO: But even if we don't open it and just put that in the re-review?

DR. GILL: No. I think you have to because.

DR. BELSITO: So I think we have to open it.

DR. GILL: You're acknowledging there is a different use.

DR. BELSITO: Right. I think we have to open it.

DR. BERGFELD: Doctor Marks you want to reconsider your motion?

DR. MARKS: Absolutely so. Reopen?

DR. BELSITO: Yes

DR. MARKS: Well it's already open

DR. BELSITO: So it is open we don't have to

DR. MARKS: Okay so I'll withdraw my motion and Don if I heard you incorrectly. Again it's the same as we did, in the new conclusion there would be insufficient data for other uses than the brief discontinuous uses. An oxidizing agent and hair color and some lighteners, so even other hair grooming aids would be insufficient?

DR. BELSITO: Right

DR. MARKS: Okay

DR. BERGFELD: And you're seconding that?

DR. BELSITO: Yes

DR. BERGFELD: Okay any further discussion?

DR. BELSITO: The data needs as I stated earlier

DR. BERGFELD: And the data needs. You want to restate those?

DR. BELSITO: Yeah we like to know the concentration of use for those?

DR. BERGFELD: Right

DR. BELSITO: And also a no effect level for sensitization and urticaria.

DR. BERGFELD: So we started out with a motion and we ended up with a insufficient. So I think that is consensus to move forward with an insufficient data announcement.

Day 1 of the June 12-13, 2017 CIR Expert Panel Meeting – Dr. Belsito's Team

DR. BELSITO: So moving on to persulfates. 2001 published a final report the conclusion of ammonium, potassium and sodium persulfates safe as used as oxidizing agents in hair color and some lighteners designed for brief discontinuous use, yada, yada, yada. In 2016 we reopened the report because of reports that the persulfates were being used in leave on products and we are concerned about the, about obtaining an NOL for sensitization and urticaria and also about the concentrations of use on the leave on products and the dentifrices that contained these materials. And we really haven't gotten that information. So I thought that the draft conclusion minus the last sentence should stand that it's okay for brief discontinuous use but we conclude that the available data are insufficient for determining the safety of these persulfates and leave on products and dentifrices and the data needs are as we requested before.

DR. LIEBLER: I agree.

DR. BELSITO: Comments? Okay, that was easy.

DR. BERGFELD: Could I just ask a question? The contact urticaria sits in those leave ons?

DR. BELSITO: Yes. Yes, we had discussed that issue very extensively in the report for the wash offs. Okay.

Day 1 of the June 12-13, 2017 CIR Expert Panel Meeting – Dr. Marks' Team

DR. MARKS: So, this morning, I believe we left off at -- persulfates is our next ingredient. And in 1998, the expert panel issued a final report with conclusion that these three persulfates are safe as used as oxidizing agents in hair colorants and lighteners designed for brief discontinuous use followed by thorough rinsing the hair.

In June of last year, so, now a year ago, the Panel decided to reopen this final report; and then at the December meeting an insufficient data announcement was issued; and in the memo from Wilbur you see the no-affect level for sensitization and urticarial reactions and concentration use in leave-on products and the dentifrices; and that was the big issue why it was reopened.

Our team, actually, was in favor of not reopening it. So, I guess, we're still at the point, do we want to not reopen; do we issue a tentative amended report? Those insufficient data were not received, nothing addressing those; so, we should be proceeding for to either close it or a tentative amended report. And, I guess one could handle it by -- we use the same safe conclusion from 1998, insufficient data conclusion for leave-on and for dentifrices.

Team, how do you want to proceed, or is there another option?

DR. HILL: This is already a tentative amended report, is it not?

DR. HELDRETH: It's a draft.

DR. HILL: Draft tentative report.

DR. HELDRETH: You've already left it to reopen it.

DR. HILL: It's opened to add the ingredients, wasn't it?

DR. MARKS: Yeah, that was the key; is it'd been approved? We had felt it was safe for hair colorants and lighteners, and brief discontinuous use; and then we found out when it was re-reviewed that it was being not only used for that but also being used for leave-on and dentifrices.

Okay; so, there're no sensitizers; there're no irritants. That was known in the first; that's why a restriction for a brief discontinuous use, so. Team, how do you want to proceed?

DR. EISENMAN: The restriction is for use in hair color --

DR. MARKS: Yeah.

DR. EISENMAN: and for lighteners? We're a little concerned about this extension, the use restriction relates to the consumer as well as hairdressers. I think it'd be better in the discussion to have more robust discussion of -- I mean there's a whole list of things you have to do when you're using -- like gloves and skin protectants. I think putting this in the conclusion suggests maybe that's enough.

DR. MARKS: What's that?

DR. EISENMAN: If you get it on your skin, rinse it off.

DR. MARKS: Well, that would be the same conclusion as 1998 --

DR. EISENMAN: Correct.

DR. MARKS: -- if that were the case. As our team suggests the last time, don't reopen it.

DR. EISENMAN: No, but you're still adding the insufficient data for the other uses, or just concerned about the statement that you're extending the hair dye --

DR. MARKS: Mm? (Inaudible).

DR. EISENMAN: -- extending that to hairdressers; and, I think, it would be better to have a better discussion about -- there's a whole list that you should follow package directions, and there's a whole list of things you need to do when you're using these products.

DR. MARKS: Yeah, no, I have no problem including that in the discussion.

DR. EISENMAN: Okay. Take that statement out of the conclusion.

DR. MARKS: Was that in the -- where is the present -- did you have a conclusion on this one, Wilbur, or were you waiting? What page is that?

MR. JOHNSON: PDF page 51. This is a draft conclusion.

DR. MARKS: 51? I'm sorry somehow --

MR. JOHNSON: And, Dr. Marks, I forgot about this but we had distributed a Neilson publication relating to, I guess, breathing zone, concentrations of particles for sulfates with respect to hairdressers; and there's also a supplement supporting information for that particular study; and let me just pass that out.

DR. MARKS: So, Team; move on with this new conclusion? Eliminating -- yeah, somehow I missed this. Eliminating the sentence, use restriction relates to consumers as well as hairdressers. Do you like the new conclusion -- draft conclusion, I should say on page 51? I don't think we can close it again.

DR. SHANK: It has to be the most complex conclusion in CIR (inaudible). There's usually one sentence, maybe two.

DR. MARKS: So, I don't hear anybody saying we should close it again, not reopen it, and handle the issue of the leave-on and the dentifrices in the discussion of the review summary. I get the sense that we want to -- we are at the draft tentative amended report; and, Ron, do you have a different way of wording the conclusion, making it simpler?

DR. SHANK: Yes; but I don't like it -- safe as used when formulated to be non-irritating, non-sensitizing, non-urticarial.

DR. SLAGA: Don't go there.

DR. SHANK: Is there another direction we should go?

DR. MARKS: It is simpler on the surface.

DR. SLAGA: Not to cop-out.

DR. SHANK: Sorry.

DR. SHANK: Actually, I don't find, once we eliminate the sentence you suggested, Carol, I find it pretty straightforward; and we basically endorsed the previous conclusion and just expanded, because now it's being used in other than hair color and some lighteners for brief discontinuous use; and we say it's insufficient for those uses; and that's it. I don't know, Ron, I didn't think it was that complex, but maybe I'm -- I certainly like it better than saying don't formulate it to be toxic to any human being.

DR. MARKS: Yes, formulate it to be non-toxic.

(Inaudible). Then we can all go home. So, I, actually, if we're going to, and we have reopened and we're going to move forward, I actually like that conclusion.

DR. SHANK: Okay.

DR. MARKS: Ron Hill, Tom?

DR. HILL: So, what we're doing is just taking out the sentence that says something about hairdressers.

DR. MARKS: Right, exactly; and that's, well, you're right, there's a lot of protective, and, I think, it's just -- I, actually, just probably brought up that issue at the last meeting is that I felt that it was important that we not just focus on the client because the hairdressers have exposure to this; but, I think, as long as they do protective measures; that's on the package inserts; that's fine with me.

DR. SHANK: Okay.

DR. MARKS: Ron Hill, what -- I haven't heard you.

DR. HILL: I'm fine with deleting that sentence.

DR. MARKS: Let me see, are we seconding or moving? No, we'll second. So, a tentative amended report as on page 51, striking that one sentence.

DR. HILL: So, effectively, that's the same conclusion as the previous report, but it adds in the specific insufficiencies which seem to be good.

DR. MARKS: Yes, and technically speaking, in the first report, shouldn't have been used for leave-ons and dentifrices. Anyway, I think, our team felt that was implied by the conclusion. My sense is that they'll see, though, Team One to be more explicit and say it's insufficient for these other uses. That's how I recall.

DR. HILL: Well, and based on our procedures, if you didn't do that and put it specifically, then it's there in the old report but nothing will happen. They will keep using them for dentifrices and for (inaudible).

DR. MARKS: Okay.

MR. JOHNSON: And, also, in the published filed report, there were leave-on product uses but, I think, that was overlooked, you know, in our generated conclusion because it only relates to rinse-off products.

DR. MARKS: Or, maybe, the Panel at that point felt with this conclusion it stopped being used only once even though there were. That would be another possibility.

MR. JOHNSON: Possibly.

DR. MARKS: Any rate; any other comments? So, we're going to go with a conclusion on page 51, striking that one sentence which will be dealt with in the discussion. And Wilbur, you and Carol can wordsmith that. I don't know that we need to go over that -- what she said -- I think it's quite appropriate; any other comments? If not, presumably, I'll be seconding a motion tomorrow that a tentative amended report be issued, and we'll see if one more time for the final. Okay.

Sorry, Ron, we couldn't go with the non-sensitizing, non-irritating, non-urticarial. You tried. I don't know, Ron, something is happening today, although you got us on that other one.

Day 2 of the June 12-13, 2017 CIR Expert Panel Meeting – Full Panel

DR. BERGFELD: Moving on to the next ingredient, persulfates.

Dr. Belsito?

DR. BELSITO: Okay. So the persulfates. In 2001, we published a final report with a conclusion that ammonium, potassium, and sodium persulfate were 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 2016, we opened the report and issued a draft amended report that was reviewed at the December meeting resulted in us issuing an insufficient data announcement for two requests on three persulfates. A no alpha sensitization in urticaria and concentration of use in leave-on products and dentifrices since we were being told that they were now used in those, and we have not received anything regarding that. We got some information on hairdressers exposed to persulfates, but I don't think it really helped us. So I think our conclusion stands safe for use in oxidizing agents and hair colorants for brief discontinuous use and insufficient for use in leave-on products.

DR. BERGFELD: And that's a motion?

DR. BELSITO: Yes.

DR. BERGFELD: Second?

DR. MARKS: Second.

DR. BERGFELD: Any other discussion?

DR. MARKS: Yes. On page 51 of the conclusion, our team felt we could -- let me get that page up -- that we could -- from the draft conclusion, that we would eliminate the sentence, "this use restriction relates to consumers as well as hairdressers." We felt that could be handled in the discussion. There are many, both instructions in use of these the way hairdressers should use it wearing gloves, et cetera, and so we felt we did not have to have that in the conclusion.

DR. BELSITO: Agree.

DR. BERGFELD: So both teams agree to make that editorial change?

Any other comments?

MR. JOHNSON: I have one question.

DR. BERGFELD: Wilbur?

MR. JOHNSON: Should any information relating to instructions be included in the discussion?

DR. MARKS: I think once you read those, Wilbur, you can decide how much you would like to include in it and then we'll review it in the final draft and proceed from there.

DR. BERGFELD: Good suggestion. Jay, do you have a question? Comment? All right. I'll call the question. All those in

favor then in moving forward with the safe and some insufficient?

Thank you. Approved unanimously.

(The motion passed unanimously.)

Amended Safety Assessment of Persulfates as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 10, 2017
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 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, and are identified by italicized text. 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.

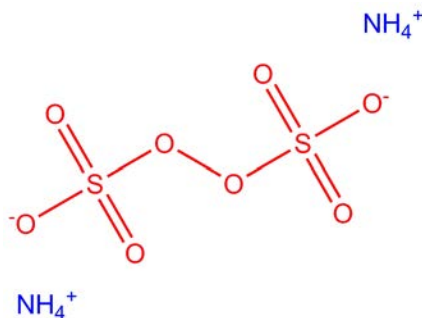


Figure 1. Ammonium Persulfate

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 safety assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by Industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category. Collectively, the use frequency and use concentration data indicate that Ammonium, Potassium, and Sodium Persulfate are currently being used in cosmetic products (Table 3).^{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 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., 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.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 data received from the Cosmetics, Toiletries and Fragrance Association (CTFA, now the Council) and 2015 data received from the Council 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 (Ammonium Persulfate only) 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. Supercoarse 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 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 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 2,000 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 after the initiation of dosing 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 LC₅₀ for inhalation toxicity was estimated to be greater than 42.9 mg/l.

A study was performed to determine whether exposure for 4 h to a hair bleach composition (containing Ammonium Persulfate, Potassium Persulfate and 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.

Intraperitoneal

Sodium Persulfate

In an intraperitoneal dosing study, the minimal lethal dose for Sodium Persulfate was 226 mg/kg in rabbits.¹

Intravenous

Sodium Persulfate

In an intravenous dosing study, the minimal lethal dose for Sodium Persulfate was 178 mg/kg in rabbits.¹

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. Further ophthalmologic examinations and gross and microscopic examinations were carried out. The concurrent control group was of the same age, sex distribution and derivation. One group of animals received only the basal diet (control group). Others received 300 and 3000 ppm of the test material in the diet. The fourth group received 1000 ppm of the test material in the diet for 8 weeks and 5000 ppm of the test material in the diet for the final 5 weeks. The 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. No statistically significant differences were seen among groups in hematological blood chemical and urine analytical parameters, and organ weight and body weight ratios. Organ weights, organ-to-body weight ratios and type and frequency of grossly observable lesions seen during necropsy were comparable among the four groups. Intestinal changes were noted in the rats which received 3000 ppm of Sodium Persulfate for 13 weeks. These changes were seen more frequently among females than males. The former received 50 percent more test material than the latter on a dose per body weight basis. No statistically significant changes were seen among the controls or the groups that received 300 ppm in the diet for 13 weeks or 1000 ppm in the diet for 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 13 weeks of 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).³ The test material 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]).²⁶ 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.²⁹ 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.³¹

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., 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). 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 the published 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, 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 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

Table1. Definitions, structures, and functions of the ingredients in this safety assessment.²

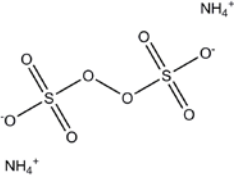
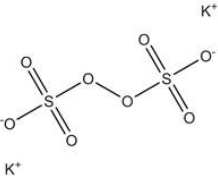
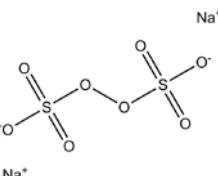
Ingredient CAS No.	Definition & Structure	Function
Ammonium Persulfate 7727-54-0	Ammonium Persulfate is the inorganic salt that conforms to the formula: 	Oxidizing agent
Potassium Persulfate 7727-21-1	Potassium Persulfate is the inorganic salt that conforms to the formula: 	Oxidizing agent
Sodium Persulfate 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	
	# of Uses (2017)	Conc. (%) (2015)	# of Uses (1998)	Conc. (%) (1995)	# of Uses (2017)	Conc. (%) (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	
	# of Uses (1998)	Conc. (%) (1995)	# of Uses (2017)	Conc. (%) (2015)	# of Uses (1998)	Conc. (%) (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. ²⁴
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. ²⁵
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]). ²⁶
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. ²⁹
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. ³⁰
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%. ³²

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. ³³
<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. ³⁰
<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. ³⁴
<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. ³⁵
Not stated	Prick test	17 female hairdressers with work-related rhinitis, mainly due to persulfate bleaching powder exposure.	Negative prick test. ³⁶
<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. ³⁷
<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. ³⁸

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. ³⁹
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. ⁴⁰
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.	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). ⁴¹ 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. ⁴¹ 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. ⁴¹
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. ⁴²
Ammonium Persulfate	Patch test	Boy with pruritic and eczematous eruption over trunk and extremities	Positive (1+ to 2+) reaction to Ammonium Persulfate. ⁴³

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Final Report on the Safety Assessment of Ammonium, Potassium, and Sodium Persulfate¹

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

colorants and lighteners designed for brief discontinuous use followed by thorough rinsing from the hair and skin.

INTRODUCTION

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

CHEMISTRY

Definition and Structure

Ammonium Persulfate (CAS No. 7727-54-0) is the inorganic salt that conforms to the formula (NH₄)₂S₂O₈ (Wenninger, Canterbury, and McEwen 2000). It is also known as Ammonium Peroxydisulfate; Peroxydisulfuric Acid, Diammonium Salt (Wenninger, Canterbury, and McEwen 2000); Diammonium Persulfate; Diammonium Peroxydisulfate (Registry of Toxic Effects of Chemical Substances [RTECS] 1994); Ammoniumperoxydisulfate; 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 K₂S₂O₈ (Wenninger, Canterbury, and McEwen 2000). It is also known as Peroxydisulfuric Acid, Dipotassium Salt (Wenninger, Canterbury, and McEwen 2000); Potassium Peroxydisulfate; and Dipotassium Persulfate (RTECS 1994).

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

Physical and Chemical Properties

Ammonium Persulfate is a yellow to white crystalline material that has a slight acid 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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¹Reviewed by the Cosmetic Ingredient Review Expert Panel. Susan Pang and Monice Zondlo Fiume, former CIR staff members, prepared this report. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

decomposes at 120°C (Lewis 2000). Dangerous decomposition products of Ammonium Persulfate are sulfur dioxide and sulfur trioxide (CTFA 1994). Ammonium Persulfate is a strong oxidizing agent, and aqueous solutions of this ingredient are acidic and lose active oxygen with time, especially at elevated temperatures (Budavari 1989; Nikitakis and McEwen 1990). CTFA specifications for Ammonium Persulfate list the maximum allowable concentration for sulfated ash as 0.05% (Nikitakis and McEwen 1990). The following impurities and their maximum concentrations were also listed: arsenic (3 ppm), iron (5 ppm), and lead (20 ppm).

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

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

Manufacture and Production

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

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

USE

Cosmetic

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

TABLE 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 $\leq 12\%$ (on-head) Persulfates, usually comprised of $\leq 4\%$ Ammonium and $\leq 8\%$ Potassium Persulfate, and off-the-scalp products used to highlight hair strands generally contain $\leq 25\%$ (on-head) Persulfates, usually comprised of $\leq 10\%$ Ammonium and $\leq 15\%$ 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 $\leq 0.3\%$ and $\leq 0.6\%$, 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 $\mu\text{g/ml}$ 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 $\mu\text{g/ml}$ 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 $\text{mg}/0.5\text{ ml}$, 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 formyl-methionylleucylphenylalanine (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 prepara-

tion (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 $\mu\text{g}/\text{ml}$ 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 $<10 \mu\text{m}$ 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 LD₅₀ 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/m³ 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 μ m. Control groups of rats were exposed to filtered air. No significant changes were observed with 1 mg/m³ Ammonium Persulfate. However, at concentrations of 4 to 20 mg/m³, 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/m³ 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 ap-

plied under an occlusive patch to the intact and abraded skin of three white Russian rabbits for 4 hours (BGChemie 1994). Slight edema, which disappeared within 24 hours, was observed in intact skin, whereas moderate to severe erythema, moderate edema, and scab formation followed by cicatrization were observed at the abraded sites. Ammonium Persulfate was considered nonirritating to intact skin.

The dermal irritation potential of Ammonium Persulfate was determined according to Organisation for Economic Co-operation and Development (OECD) Guideline No. 404 using six male and female New Zealand White rabbits (CTFA 1994). No irritation was noted within 72 hours following application.

Ammonium Persulfate (dose not specified) was applied to an intact and abraded site on six rabbits, and the sites were scored by the Draize method at 24 and 72 hours (CTFA 1994). Ammonium Persulfate was not irritating.

Dermal Sensitization

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

Inhalation Sensitization

Wass and Belin (1990) developed an in vitro method for predicting sensitizing properties of inhaled chemicals. Sodium Persulfate (50 μ l) was mixed with a lysine-containing peptide (500 μ l) 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 $\mu\text{g}/\text{plate}$, 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 permanently 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 Dühring 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 Dühring chamber and a reaction of 0 using the Finn chamber. A 10% solution produced reactions of 3+ and 1+ using the Dühring and Finn chambers, respectively.

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

Urticarial Reactions

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

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

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

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

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

TABLE 2
Case studies of dermal reactions to Persulfates in hair bleaches

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 re-

actions 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 Doods-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/m³ for nuisance dust was employed for control purposes, no cases of occupational illness occurred. They also stated no "significant cases of dermatitis have occurred from skin contact when good personal hygiene practices were being followed."

Adverse effects are most commonly reported in the hair-dressing 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/m³, measured as persulfate

(ACGIH 1986). However, the ACGIH recommends a TLV of 2 mg/m³ for Potassium Persulfate (Sullivan 1992).

SUMMARY

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

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

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

TABLE 3
Occupational exposure to Persulfate Salts

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)

(Continued on next page)

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)

(Continued on next page)

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

(Continued on next page)

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

Reaction	Study description	Reference
Asthma	<p>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.</p> <p>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.</p>	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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2017 FDA VCRP Data**Ammonium Persulfate**

03G - Other Eye Makeup Preparations	1 L
05G - Tonics, Dressings, and Other Hair Grooming Aids	1 L
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	11 R
06F - Hair Lighteners with Color	8 R
06G - Hair Bleaches	13 R
06H - Other Hair Coloring Preparation	2 R
Total	36

Sodium Persulfate

06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	3 R
06F - Hair Lighteners with Color	4 R
06G - Hair Bleaches	37 R
06H - Other Hair Coloring Preparation	2 R
09A - Dentifrices	2 R
Total	48

Potassium Persulfate

05G - Tonics, Dressings, and Other Hair Grooming Aids	1 L
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	14 R
06F - Hair Lighteners with Color	9 R
06G - Hair Bleaches	46 R
06H - Other Hair Coloring Preparation	3 R
Total	73



Memorandum

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

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

DATE: June 1, 2016

SUBJECT: Comments on the Draft Amended Safety Assessment of Persulfates as Used in Cosmetics (prepared for the June 6-7, 2016 meeting)

Cosmetic Use, Summary - In the Cosmetic Use section and Summary, it should be made clear that the Council concentration of use survey only reported uses in various types of hair coloring preparations. In this section, it would be helpful to compare uses reported to the VCRP in 1998 to the uses reported in 2016.

Toxicological Studies - The information concerning the conclusions of the NICNAS assessment should be presented in a risk assessment section rather than the Toxicological Studies section.

Acute, Inhalation - The meaning of "S" (occurs 3 times) in this section is not clear.

Short-Term vs Subchronic - It does not make sense to discuss the 90-day study of Ammonium Persulfate in the Short-Term section and 13-week studies (91 days) in the Subchronic section as there is just a one day difference between the two durations. These studies should be presented in the same section.

Short-Term, Inhalation, Ammonium Persulfate - In the discussion from the original report, it is not clear what is meant by "Inhalation toxicity". Does this mean only respiratory tract effects were observed in rats exposed to aerosolized Ammonium Persulfate? What was the duration of this study?

Subchronic, Oral, Ammonium Persulfate - What were the durations of the rat and dog studies described in the original report?

Genotoxicity, In Vivo - Please provide a reference for the mouse micronucleus assay. It would be helpful to note that there were no changes in the ratio of polychromatic erythrocytes to total erythrocytes at 85 mg/kg Sodium Persulfate.

Irritation, Animal, Ammonium Persulfate - It is not clear what is meant by "loss of substance" - what was the "substance"?


Other Clinical Reports - It would be helpful if the studies described in this section were summarized in a table.

Reference 11 - Please correct: "hai bleach"



Memorandum

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

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

DATE: November 29, 2016

SUBJECT: Draft Amended Report: Safety Assessment of Persulfates as Used in Cosmetics
(draft prepared for the December 5-6, 2016 CIR Expert Panel Meeting)

Key Issue

The Non-Cosmetic Use section should mention that persulfates are used in denture cleansers (medical device) and cite FDA's 2008 Public Health Notification (see <http://www.fda.gov/MedicalDevices/Safety/AlertsandNotices/PublicHealthNotifications/ucm062012.htm>) concerning this use.

Additional Considerations

Acute, Oral, Sodium Persulfate - How many rats died in the 464 and 562 mg/kg dose groups?
Case Reports - Please correct: "during g time off"
Table 3 - As stated in the cosmetic use section, the FDA VCRP reported use of Ammonium Persulfate in "eye makeup preparations", yet Table 3 has "NR" in the eye area row for Ammonium Sulfate.



Memorandum

TO: COSMETIC INGREDIENT REVIEW (CIR)

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

DATE: June 7, 2017

SUBJECT: Draft Tentative Report: Amended Safety Assessment of Persulfates as Used in Cosmetics (draft prepared for the June 12-13, 2017 CIR Expert Panel Meeting)

Key Issues

Extending the conclusion to hair dressers is not appropriate as this conclusion suggests that rinsing may be sufficient protection for hair dressers. It would be better if the Discussion also noted that everyone using hair dyes, including consumers and hairdressers, should follow package directions and try to avoid skin contact by using skin protectants and gloves. For example, the FDA hair dye website at <https://www.fda.gov/cosmetics/productsingredients/products/ucm143066.htm#law> includes the following safety checklist:

- “Follow all directions on the label and in the package.
- Do a patch test on your skin every time before dyeing your hair.
- Keep hair dyes away from your eyes, and do not dye your eyebrows or eyelashes. This can hurt your eyes and may even cause blindness.
- Wear gloves when applying hair dye.
- Do not leave the product on longer than the directions say you should. Keep track of time using a clock or a timer.
- Rinse your scalp well with water after using hair dye.
- Keep hair dyes out of the reach of children.
- Do not scratch or brush your scalp three days before using hair dyes.
- Do not dye or relax your hair if your scalp is irritated, sunburned, or damaged.
- Wait at least 14 days after bleaching, relaxing, or perming your hair before using dye.
- Read the ingredient statement to make certain that ingredients that may have caused a problem for you in the past, such as p-phenylenediamine (PPD) are not present.
- If you have a problem, tell your healthcare provider. Then, please report it to FDA.”

The following paper concerning exposure of hair dressers should be added to the report (paper ordered 6/6/2017):

Nilsson PT, Marini S, Wierzbicka A, et al. 2016. Characterization of hairdresser exposure to airborne particles during hair bleaching. *Ann Occup Hyg* 60(1): 90-100.

As a comparison, the ACGIH TLV-TWA for persulfates (0.1 mg/m³) should also be added to the report (see: <https://www.cdc.gov/niosh/ipcsneng/neng0632.html>)

Additional Considerations

Cosmetic Use - It would be helpful to note that among the 73 products containing Potassium Persulfate reported to the VCRP, 72 of the products were hair coloring products.

Short-Term, Oral, Ammonium Persulfate, old report summary - What was the effect observed at the LOAEL?

Subchronic, Inhalation, Ammonium Persulfate - The summary of the subchronic inhalation study of Ammonium Persulfate (reference 12) indicates that particle size was measured. It would be helpful to state the results of these measurements. What was the mean particle size? Were the particles in the respirable range?

Irritation, Animal, Sodium Persulfate - Although the concentration of Sodium Persulfate was not stated, it would be helpful to provide the pH of the solution tested (11).

Summary - Please state the species in which hyperresponsiveness to acetylcholine was observed after persulfate inhalation exposure.



Memorandum

TO: Bart Heldreth, Ph.D., Interim Director
COSMETIC INGREDIENT REVIEW (CIR)

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

A handwritten signature in blue ink that reads "Beth A. Jonas".

DATE: June 28, 2017

SUBJECT: Comments on the Tentative Amended Safety Assessment of Persulfates as Used in Cosmetics

Tumor Promotion, original report summary - What was the initiator used in the tumor promotion study of Ammonium Persulfate?

Other Clinical Reports - Is it necessary to state that most of the clinical reports concerned Ammonium Persulfate twice in this section (which is only two sentences long)?

Summary, Discussion - It would be helpful to add information about potential inhalation exposure to both the Summary and Discussion sections.

Summary - Please correct "aquesous"

Table 4, reference 25 - "form" needs to be corrected to "from"