Safety Assessment of *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate as Used in Cosmetics

Status: Draft Amended Report for Panel Review
Release Date: May 22, 2026
Panel Meeting Date: June 15-16, 2026

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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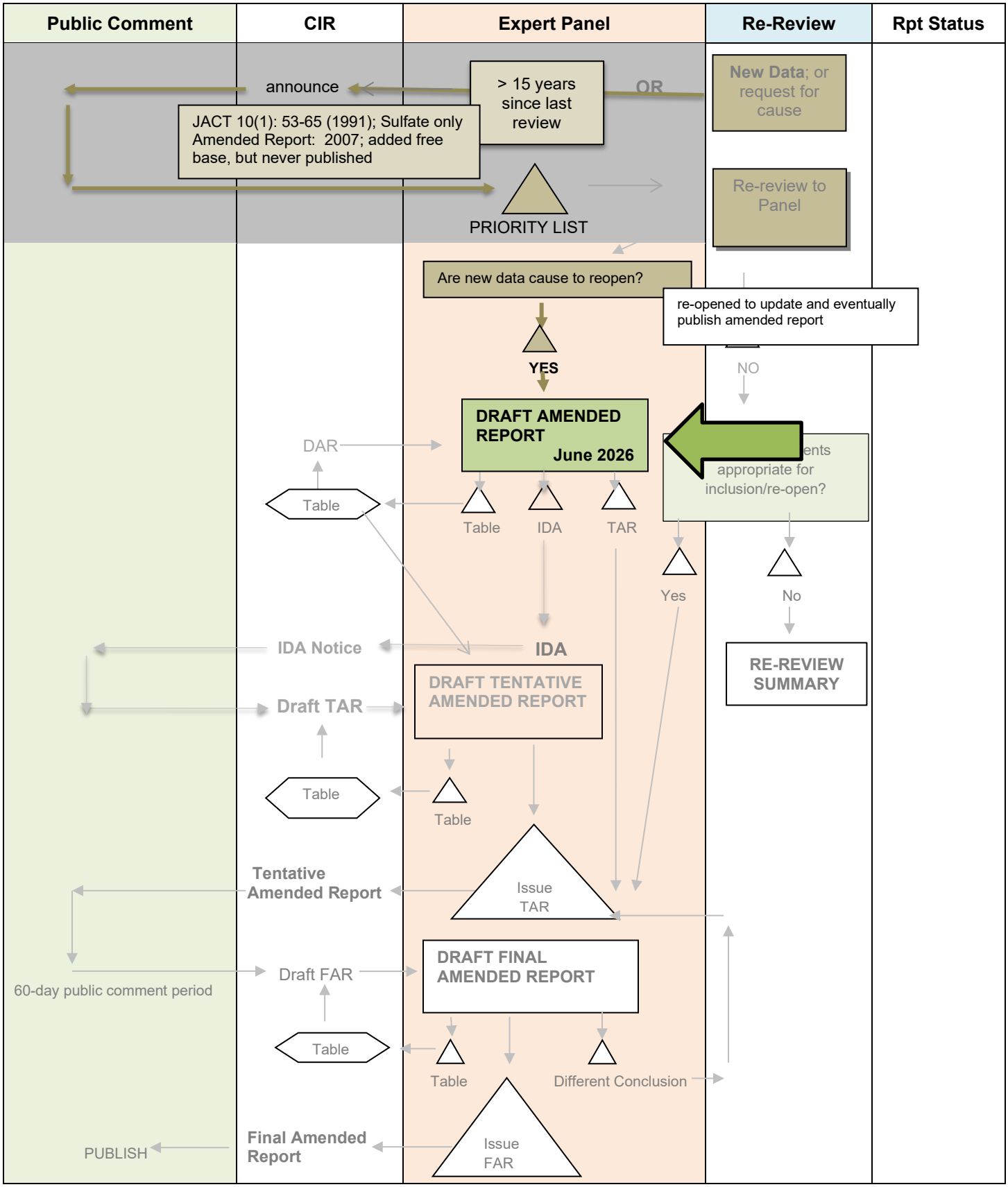
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate

MEETING June 2026



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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, M.S., Senior Scientific Analyst/Writer, CIR
Date: May 22, 2026
Subject: Safety Assessment of *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate as Used in Cosmetics

Enclosed is the Draft Amended Report on the Safety of *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate as Used in Cosmetics. (It is identified as *report_Methylaminophenol_062026* in the pdf document). In 1991, the Panel published a safety assessment on *p*-Methylaminophenol Sulfate with the conclusion that "*p*-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration" (*originalreport1991_Methylaminophenol_062026*).

In 2007, the Panel issued a Final Amended Report that included the free base (*amendedreport2007_Methylaminophenol_062026*). Because more than 15 years have passed since the Panel last reviewed this report and because the 2007 report was never published, this amended safety assessment on *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate is being presented to the Panel as a Draft Amended Report.

According to RLD that CIR received in 2025, *p*-Methylaminophenol is used in 1 hair tint. Additionally, the RLD reported *p*-Methylaminophenol Sulfate is used in 1759 cosmetic formulations, with the majority being hair dyes and colors. One use was reported for an eyelash and eyebrow dye. No concentrations of use were submitted for either ingredient in response to the survey conducted by the Council in 2025 (*data_Methylaminophenol_062026*).

In our analysis of each product reported in the RLD with a categorization of "(17) other preparations (i.e., those preparations that do not fit another category)," all 81 products were co-categorized as "(07) hair coloring preparations." Thus, all of these products have already been accounted for in the use table of this report as various hair coloring preparations. Thereby, there are effectively no reported products of unknown category in this report.

In the FDA Voluntary Cosmetic Registration Program (VCRP) survey data submitted to CIR in 2023, *p*-Methylaminophenol Sulfate was reported to be used in 3 hair dyes and colors. When comparing this data to that last reviewed by the Panel in 2007, the frequencies of use for *p*-Methylaminophenol Sulfate have greatly decreased. In the 2007 re-review, this ingredient was reported to have 112 uses in hair dyes and colors. No uses were reported in the VCRP for the free base in 2007 or 2023. In the 2007 re-review, the maximum concentration of use range for *p*-Methylaminophenol Sulfate was 0.1 - 0.7% in hair dyes and colors, and *p*-Methylaminophenol was reported to have a maximum concentration of use of 0.7% in hair dyes and colors.

CIR staff reviewed the available genotoxicity studies, in that some genotoxicity studies are now considered obsolete. Based on the equivocal relevance of certain genotoxicity study methods, CIR staff have excluded an in vivo unscheduled DNA synthesis assay in rats that was reported by the Scientific Committee on Consumer Products in 2006.

Additional supporting documents for this report package include a flow chart (*flow_Methylaminophenol_062026*), report history (*history_Methylaminophenol_062026*), a search strategy (*search_Methylaminophenol_062026*), a data profile (*dataprofile_Methylaminophenol_062026*), and the minutes from all the meetings at which *p*-Methylaminophenol and the sulfate salt were discussed during the original review (*originalminutes_Methylaminophenol_062026*).

If no further data are needed, the Panel should formulate an updated Discussion and issue a Tentative Amended Report. However, if additional data are required, the Panel should be prepared to identify those needs and issue an Insufficient Data Announcement.

***p*-Methylaminophenol & *p*-Methylaminophenol Sulfate History**

1991 – The CIR Final Report on the Safety Assessment of *p*-Methylaminophenol Sulfate was published in the *Journal of the American College of Toxicology*. The Panel concluded that *p*-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

2007 – In a re-review, the Panel reopened the *p*-Methylaminophenol Sulfate report to add *p*-Methylaminophenol. That amended report was finalized in same year with the conclusion that these ingredients are safe as hair dyes in the practices of use and concentration as described in the safety assessment, but the amended report was never published.

Late 2025 – Because it had been at least 15 years since the Panel reviewed these ingredients last and because the 2007 amended report was never published, in accordance with the CIR Procedures, it was determined that the re-review should be resumed, and revised to include all information that has become available since it was last reviewed by the Panel.

***p*-Methylaminophenol & *p*-Methylaminophenol Sulfate Data Profile* – June 2026 – Christina Burnett**																														
	Use				**Toxico-kinetics**			**Acute Tox**			**Repeated Dose Tox**			**DART**		**Genotox**		**Carci**		**Dermal Irritation**			**Dermal Sensitization**				**Ocular Irritation**		**Clinical Studies**	
	New Rpt	**Old Rpt**	**Method of Mfg**	**Impurities**	**log P/log K_{ow}**	**Dermal Penetration**	**ADME**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**Inhalation**	**Dermal**	**Oral**	**In Vitro**	**In Vivo**	**Dermal**	**Oral**	**In Vitro**	**Animal**	**Human**	**In Vitro**	**Animal**	**Human**	**Phototoxicity**	**In Vitro**	**Animal**	**Retrospective/ Multicenter**	**Case Reports**
***p*-Methylaminophenol CAS No. 150-75-4**	X	O			X											O	O				O			O				O	X	
***p*-Methaylaminophenol Sulfate CAS No. 1936-57-8; 55-55-0**	X	O	O	X	X	X	X	X	X		O	X		O	X	X	X	XO			X			X				X	X	X

* "X" indicates that new data were available in this category for the ingredient; "O" indicates that data from the original assessment were available

p-Methylaminophenol & *p*-Methylaminophenol Sulfate

Ingredient	CAS #	PubMed	FDA	CompTox	ChemPort	NIOSH	NTIS	NTP	FEMA	EU	ECHA	SIDS	SCCS	AICIS	FAO	WHO	Web
p-Methylaminophenol	150-75-4	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
p-Methylaminophenol Sulfate	1936-57-8; 55-55-0	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed

Search performed from 2005 to present
(p-Methylaminophenol) OR (150-75-4[EC/RN Number]) – 9 hits, 6 relevant
(p-Methylaminophenol Sulfate) OR (1936-57-8[EC/RN Number]) OR (55-55-0[EC/RN Number]) – 3 hits, 1 relevant

ECHA

No dossier for *p*-Methylaminophenol. In active dossier identified for *p*-Methylaminophenol Sulfate (under bis(4-hydroxy-N-methylanilinium) sulphate, CAS No. 55-55-0)

LINKS

Search Engines

- Pubmed - http://www.ncbi.nlm.nih.gov/pubmed
  - appropriate qualifiers are used as necessary
  - search results are reviewed to identify relevant documents
- CompTox: https://comptox.epa.gov/dashboard/chemical/pubmed-abstract-sifter/DTXSID3039242; https://www.epa.gov/comptox-tools/downloadable-computational-toxicology-data#LM
- eChemPortal: https://www.echemportal.org/echemportal/
- DeepDyve: https://www.deepdyve.com/
- Connected Papers - https://www.connectedpapers.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en

- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

JANUARY 1989 PANEL MEETING – FIRST OPEN REVIEW

Dr. Bergfeld brought the attention of the Panel to the memo of 12-20-88 that had requested dermal sensitization in the guinea pig and UV spectral analysis. A third item was now being added to that request, additional genotoxicity data. After re-evaluating the available mutagenicity data, the Panel recommended that a genotoxicity study be requested. Dr. Berndt cited a reference (Grasselli et al., 1975) in the text that suggested the availability of existing spectral data and asked that it be checked before an Insufficient Data Announcement was issued. Dr. Shank asked why a sensitization test is needed on an ingredient such as this, which already requires a patch test labelling. After a brief discussion, an Insufficient Data Announcement was approved by the Panel.

JULY 1989 PANEL MEETING – SECOND OPEN REVIEW

Dr. Schroeter briefly summarized the data on p-Methylaminophenol Sulfate. He stated that the ingredient is well known, a well a other oxidative hair dye ingredients, such as p-phenylenediamine and its salts. Data on these ingredients are useful in the safety assessment of p-Methylaminophenol Sulfate, and such data are used in this document. He noted that additional information on p-Methylaminophenol Sulfate requested by the Schroeter Team had been received and incorporated into the Tentative Report. The fact that data are lacking in the clinical assessment of safety section of the report, and information present is related only to occupational studies were also noted. However, the Schroeter Team was somewhat abridged to request clinical studies, due to sensitization in the occupational studies and the fact that the ingredient is included under the coal tar caption on page 5 of the Tentative Report. Dr. Schroeter then made a motion that, as recommended by the Schroeter Team, p-Methylaminophenol Sulfate is safe as used in cosmetics.

Dr. Bergfeld stated that her Team decided that the UV data were insufficient and asked Dr. Hoffmann to elaborate.

According to Dr. Hoffmann, the concentration tested in the UV absorption study was not high enough to allow for the detection of impurities, and the test concentration should have been 1.0 gram per liter of appropriate solvent.

Dr. Elder indicated that he would relay Dr. Hoffmann's concerns to Dr. McEwen.

Dr. Schroeter recommended that his motion be amended with a request for UV absorption data generated in accordance with Dr. Hoffmann's specification of a test concentration of 1.0 g per liter of appropriate solvent. He requested that if upon receipt of the data, there is no evidence that the ingredient may be phototoxic, the original motion would be accepted.

According to Dr. Bergfeld's comments, the Panel would conclude that the ingredient is safe, unless the new UV absorption data turn out to be positive. Furthermore, the Panel is under the assumption that the data will turn out to be negative.

Dr. Hoffmann reiterated his recommendation that p-Methylaminophenol Sulfate be tested in the UV absorption study at a concentration of 1.0 g per liter of solvent, and that the spectrum would include a range of wavelengths between 280 and 320 nm. Furthermore, if the data indicate no absorbance in the region between 280 and 320 nm, or above, the Panel should conclude that the ingredient is safe as used in cosmetics. If absorbance due to impurities is observed in this region, then the Pane could request phototoxicity data.

Dr. Bergfeld indicated that her Team originally had wanted either animal or human phototoxicity or photosensitization data, but requested a UV spectral analysis, provided that it was to have been done properly.

Dr. Elder requested that the Panel issue an Insufficient Data Report on p-Methylaminophenol Sulfate, indicating the lack of a UV spectrum; a 90-day comment period will follow. Furthermore, it is important to indicate to the cosmetics industry that the Panel is questioning the potential for impurities to absorb, for UV data received indicate that p-Methylaminophenol Sulfate des not absorb. It should be stated in the Insufficient Data Report that the concentration tested in the UV absorption study received was too low to allow for the detection of possible absorption by contaminants.

Dr. Hoffmann indicated that he would not delay a decision regarding the safety of this ingredient, because he does not expect absorbance due to the presence of impurities. He also expressed his concern about standard guidelines for UV spectral analyses.

Mr. Eiermann indicated that p-Methylaminophenol Sulfate, as is, never remains on the skin because it reacts immediately. In his opinion, "you may get a beautiful UV curve, but it has no bearing on impurities".

Dr. Boutwell also indicated that there is uncertainty as to whether or not impurities may undergo changes similar to that of the ingredient.

Drs. Hoffmann and Boutwell reiterated that the Panel would have to be tougher in the future with respect to making sure that the cosmetics industry adheres to the guidelines for UV spectral analyses.

Mr. Chris Kellig, with Procter and Gamble, reminded Dr. Hoffmann of his statement on the preceding day regarding the need for specifying the grade of the chemical to be tested in a UV spectral analysis.

Dr. Hoffmann agreed that the cosmetic grade of the chemical in question should be tested.

Dr. Elder confirmed the inclusion in the minutes of a statement indicating that whenever a UV absorption spectrum on an ingredient is requested, the Panel will be specific in requesting that the cosmetic grade is tested at a concentration of 1.0 gram per liter.

Dr. Schroeter restated the motion that p-Methylaminophenol Sulfate is safe as used in cosmetics. The motion was seconded and unanimously approved.

Mr. Eiermann requested that an editorial change be made on page 3 of the Tentative Report. The first sentence in the section on cosmetic use should read as follows: p-Methylaminophenol Sulfate is used as an intermediate in hair dyes/colors which usually bear warning labelling.

Dr. Schroeter requested that an editorial change be made on page 15 of the Tentative Report. The second full paragraph under the section on mutagenicity should be deleted.

APRIL 2007 PANEL MEETING – RE-REVIEW

Belsito's Team – April 16, 2007

Drs. Snyder and Belsito made editorial comments.

DR. BELSITO - How is the REACH program in Europe affecting the industry in the US?

DR. EISENMANN - We do not know yet. We will be looking into that.

Dr. Belsito summarized the REACH program.

DR. BELSITO - We will table this ingredient for the addition of p-Methylaminophenol.

Marks' Team – April 16, 2007

DR. MARKS - Do the new procedures need to be reviewed?

Dr. BERGFELD - As stated, the procedure was confusing and a flow chart needs to be developed. We will probably table this ingredient for today.

DR. MARKS - We will go to a Tentative Final Report. We will work out the glitches of what we see when we have the Report. What version goes out for public comment?

DR. BAILEY - It does not go out for public comment if there is no add on. If there is an add-on, then there is a public announcement with the add-on's identified. Then it is an Amended Final Report with new data. The Panel then issues it as an Amended Report.

Dr. Bergfeld - We need it to look like a Tentative Final Report when we see it.

Dr. Bailey - The Tentative Final Report will have a changed title.

DR. MARKS - The Panel must feel comfortable that the Tentative Final Report looks like the final issued document. All the data will be written up as in the longer report.

DR. BAILEY - That is the current standard for an Amended Report.

MS. WEINTRAUB - Do the staff not look for associated ingredients for a report?

DR. BERGFELD - That would depend on the report.

DR. BAILEY - The table and conclusion need to be added.

MS. WEINTRAUB - So an additional search is unlikely.

Dr. Marks reviewed the information on p-Methylaminophenol Sulfate.

DR. MARKS - Do we add the other ingredient and table the report? Are there any concerns.

DRS. SHANK AND SLAGA - No concerns.

DR. MARKS - Should we open to include the new ingredient, p-Methylaminophenol?

Dr. SLAGA - Reopen and add the ingredient.

DR. BERGFELD - Table and reopen the report.

DR. MARKS - The LLNA is OK with the pretest boiler plate for the sensitization issue. Do we expect much more data?

MS. BECKER - No.

DR. BAILEY - We will reopen it in September.

DR. MARKS - We will table this ingredient and reopen for September.

Full Panel – April 17, 2007

A CIR Final Report with the following conclusion was published in 1991: On the basis of the available data presented in this report, the CIR Expert Panel concludes that p-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

Drs. Belsito and Marks stated that their Teams wanted to table the re-review document so that p-Methylaminophenol could be added.

Dr. Bergfeld wanted to know, according to the new Procedures, whether the Final Report needs to be reopened. If this is the case, it would be announced for a 60-day comment period, with the intent of issuing an amended conclusion for the Final Report. She said that it is her understanding that this equals 120 days of comment.

Dr. Marks was unsure about whether the proper terminology should be to reopen or table.

The Panel voted unanimously in favor of reopening the Final Report on p-Methylaminophenol Sulfate to add p-Methylaminophenol.

Dr. Belsito wanted to know, for new hair dye ingredients that are being reviewed, whether there would routinely be a search for any new epidemiology data that may have been published since the last time a hair dye was reviewed by the Panel.

In light of Dr. Belsito's concern, the Panel had the understanding that Dr. Andersen would need to confirm how frequently the hair dye epidemiology boilerplate would need to be updated.

Dr. Belsito said that the fact that a hair dye ingredient will be reviewed by the Panel would be a signal, beyond just a periodic update of the boilerplate, to perform a literature search to identify new hair dye epidemiology data. He noted that the Helzlsouer report has been published, which means that the pre-publication reference for the report needs to be replaced with the reference for the published report. Helzlsouer is not the first author in the published reference. Dr. Belsito reiterated that the hair dye epidemiology boilerplate should be updated each time a new hair dye ingredient is being reviewed by the Panel.

Dr. Bergfeld recalled that, at yesterday's Team meetings, Dr. Andersen stated that the Helzlsoeur reference will be updated.

The Panel voted unanimously in favor of reopening the Final Report on p-Methylaminophenol Sulfate to add p-Methylaminophenol.

SEPTEMBER 2007 PANEL MEETING – TENTATIVE AMENDED REPORT

Belsito's Team – September 24, 2007

DR. BELSITO - We reviewed p-Methylaminophenol Sulfate. Do we add p-Methylaminophenol? We do not need to change the conclusion but we need to add the new hair dye epidemiology information.

DR. SNYDER - There is no sensitization data? I could not find why I wrote that down.

DR. BELSITO - Is it appropriate to add m-, o-, and p-Aminophenol?

PANEL MEMBERS - Yes.

DR. EISENMANN - Is the aquatic toxicity data appropriate?

DR. BELSITO - Is CTFA handling the European REACH group that is considering environmental data?

DR. EISENMANN - I do not know if that will change CIR's charge.

DR. BELSITO - It is safe and will advance.

Marks' Team – September 24, 2007

DR. MARKS - The Panel re-reviewed p-Methylaminophenol Sulfate and decided not to re-open. The Panel did decide that the data did support adding p-Methylaminophenol. It is safe? Any comments?

DRS. SLAGA and SHANK had no comments.

DR. MARKS - It goes to a final safety assessment. About the warning to hairdressers about sensitization, do we need it?

MS. BECKER - It is in the new data.

DR. BERGFELD - The hairdressers should wear latex gloves. We do not need the sensitization warning.

DR. SHANK made some editorial comments.

DR. ANSELL - We should remove the fish data. It is irrelevant, environmental, not human health data.

DR. MARKS - It is safe as used and will advance.

Full Panel – September 25, 2007

Dr. Belsito stated that, at the April 16-17, 2007 Panel meeting, the Panel determined that the CIR Final Report on p-Methylaminophenol Sulfate should not be reopened. However, subsequently, his Team determined that the data on p-Methylaminophenol Sulfate in the Final Report are sufficient for evaluating the safety of p-Methylaminophenol in cosmetics and, thus, that it could be concluded that the latter ingredient is also safe as used. This means that the Final Report needs to be reopened to add p-Methylaminophenol.

Dr. Marks noted that his Team agreed that the fish toxicity studies should be deleted from the report text and summary.

Referring to the study by Scheper et al. 1991 in the Metabolism section of the report, Dr. Shank noted that this study should be deleted because it actually is not a metabolism study and is not relevant. He also noted that the SCCP (2006) study, also included in the Metabolism section, is actually an absorption study. Thus, this subheading needs to be changed.

Dr. Shank also said that a methyl group needs to be added to the structure for p-Methylaminophenol Sulfate in the report text, noting that the structure for this chemical should be identical to the structure in the International Cosmetic Ingredient Dictionary and Handbook.

The Panel voted unanimously in favor of issuing a Tentative Amended Final Report with the following conclusion: On the basis of data presented in this report, the CIR Expert Panel concludes that p-Methylaminophenol Sulfate and p-Methylaminophenol are safe as cosmetic ingredients in the present practices of use and concentration as described in this safety assessment.

DECEMBER 2007 PANEL MEETING – FINAL AMENDED REPORT

Belsito's Team – December 10, 2007

DR. BELSITO - We opened to add p-Methylaminophenol. They are safe as hair dye ingredients. The summary of the Aminophenols at the end should be incorporated into the report and not at the end.

EDITORIAL COMMENTS

DR. BAILEY - Take out the lead parts and leave the nitrosamine information.

DR. SNYDER - Safe as used?

DR. BELSITO - Yes.

Marks' Team – December 10, 2007

DR. MARKS - Went over the history of the report. We are to issue a final report. The conclusion contains "hair dye". Dr. Shank, were the edits OK?

DR. SHANK - Yes.

DR. EISENMANN - You should take the heavy metals out of the discussion. The epidemiology will be reworded with the new boilerplate.

EDITORIAL COMMENTS

DR. MARKS - It is safe and moves on to final report.

Full Panel – December 11, 2007

Dr. Marks noted that a CIR Final Report with a conclusion stating that p-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration was published in 1991. He added that, in April of 2007, the Panel reopened this safety assessment to include p-Methylaminophenol and that a Tentative Amended Final Report indicating that both ingredients are safe was issued at the September 24-25, 2007 Expert Panel meeting.

Dr. Marks noted that his Team agreed that an Amended Final Report with this conclusion should be issued and also made editorial comments. Replacement of the last paragraph of the summary with the new hair dye epidemiology boilerplate was recommended.

Dr. Belsito said that his Team determined that it appears somewhat awkward for the summary from the CIR safety assessment on aminophenols to be placed before the summary on p-Methylaminophenol and p-Methylaminophenol Sulfate. Thus, it was recommended that the data on aminophenols be removed from the summary and added to appropriate sections of the report text, respectively.

The Expert Panel voted unanimously in favor of issuing an Amended Final Report with the following conclusion: The CIR Expert Panel concluded that p-Methylaminophenol Sulfate and p-Methylaminophenol are safe as hair dye ingredients in the practices of use and concentration as described in this safety assessment.

Safety Assessment of *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate as Used in Cosmetics

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Bruce A. Brod, M.D., M.H.C.I., F.A.A.D.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

ADP	adenosine 5'-diphosphate
AUC	area under the curve
CD-2	4-N,N-diethyl-2-methyl-1,4-phenylenediamine · HCl
CD-3	4-(N-ethyl-N-2-methan-sulphonamido-ethyl)-2-methyl-1,4-phenylenediamine · H_2SO_4 · H_2O
CHO	Chinese hamster ovary
CIR	Cosmetic Ingredient Review
C_{max}	peak concentration
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary*
DMSO	dimethyl sulfoxide
DPPH	α,α-diphenyl-β-picrylhydrazyl
EC_3	estimated concentrations of an stimulation index of 3
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FD&C	Food, Drug, and Cosmetic
GPMT	guinea pig maximization test
HL-60	human myeloid leukemia cells
HPLC	high-performance liquid chromatography
IC_{50}	median inhibition concentration
ICDRG	International Contact Dermatitis Research Group
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LLNA	local lymph node assay
MoCRA	Modernization of Cosmetics Regulation Act of 2022
MOE	margin of exposure
MOS	margin of safety
NACDG	North American Contact Dermatitis Group
NOAEL	no-observed-adverse-effect level
NR	not reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PBA-1	persulfate bleach accelerator
PII	primary irritation index
QSAR	quantitative structure-activity relationship
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals
RLD	Registration and Listing Data
r.o.	rinse-off
SCCNFP	Scientific Committee on Cosmetic Products and Non-Food Products intended for Consumers
SCCP	Scientific Committee on Consumer Products
SCCS	Scientific Committee on Consumer Safety
SED	systemic exposure dose
SI	stimulation index
TG	test guideline
UDS	unscheduled DNA synthesis
US	United States
VCRP	Voluntary Cosmetic Registration Program

INTRODUCTION

This assessment is a rereview of the safety of *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary* (*Dictionary*), these ingredients function as hair colorants in cosmetic products.[1]

The Expert Panel for Cosmetic Ingredient Safety (Panel) first reviewed the safety of *p*-Methylaminophenol Sulfate individually in a report published in 1991, with the conclusion "*p*-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration."[2] In a 2007 re-review, the *p*-Methylaminophenol Sulfate report was reopened to add *p*-Methylaminophenol. That amended report was finalized in same year with the conclusion that these ingredients are safe as hair dyes in the practices of use and concentration as described in the safety assessment, but the amended report was never published.[3] Accordingly, this current amended report is an updated version of the 2007 assessment, and includes all studies considered in the 2007 amended report (as presented in that document and using normal font) as well as studies published since then. Additionally, excerpts from the summaries of the 1991 report are disseminated throughout the text of this document, as appropriate, and are identified by *italicized* text.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an extensive search of the world's literature; this search was last performed in May 2026. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cirsafety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Some chemical and toxicological data on *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate included in this safety assessment were obtained from an opinion produced by the Scientific Committee on Consumer Products (SCCP) of the European Commission.[4] Additionally, data were obtained from robust summaries of data submitted to the European Chemicals Agency (ECHA) by companies as part of the Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) chemical registration process.[5] These data summaries are available on the databases for ECHA and the European Commission, respectively, and when deemed appropriate, information from the summaries has been included in this report.

CHEMISTRY

p-Methylaminophenol Sulfate is used as a primary intermediate in oxidative or permanent hair dyes.[2] *The primary intermediate undergoes a reaction with hydrogen peroxide (the oxidant) to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye. As an intermediate in combination with other intermediates, p-Methyl-aminophenol Sulfate is capable of producing browns, reds, gold blonds, blues, and grays.*

Definition and Structure

p-Methylaminophenol (CAS No. 150-75-4) is the substituted phenol that conforms to the structure in Figure 1.[1] *p*-Methylaminophenol Sulfate (CAS Nos. 1936-57-8; 55-55-0) is the substituted phenol that conforms to the structure in Figure 2.

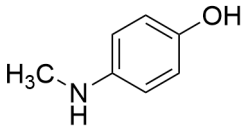

Figure 1. *p*-Methylaminophenol

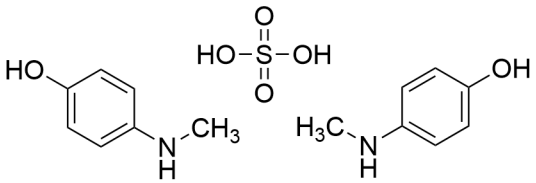

Figure 2. *p*-Methylaminophenol Sulfate

Both of these ingredients function as oxidative hair colorants in cosmetic products.

Chemical Properties

Chemical properties for *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate are summarized in Table 1. *p*-Methylaminophenol is a colorless crystalline product with a molecular weight of 123.15 g/mol.[6] The estimated log P_{ow} is

0.79. *p*-Methylaminophenol Sulfate is a colorless crystalline product or white to beige powder with a formula weight of 344.38 g/mol.[2,4,7] The estimated log P_{ow} at 25ºC is 0.79. [5]

Method of Manufacture

p-Methylaminophenol Sulfate is manufactured by the methylation of p-aminophenol and the subsequent neutralization with sulfuric acid.[2]

Composition/Impurities

p-Methylaminophenol Sulfate

The purity of 4 batches of *p*-Methylaminophenol Sulfate was reported to be 98.5 - 100% (w/w) by titer and > 97.% by high-performance liquid chromatography (HPLC).[4] The sulfate ion content was 30.0 - 30.5%. Impurities may include *p*-aminophenol (~2.5 g/100 g), *N*,*N*'-dimethylparaphenylenediamine (< 0.4 g/100 g), arsenic (< 5 mg/kg), antimony (< 5 mg/kg), mercury (< 5 mg/kg), cadmium (< 10 mg/kg), and lead (< 20 mg/kg). No residual solvents, such as methanol, ethanol, isopropanol, n-propanol, acetone, ethyl acetate, cyclohexane, methylethyl ketone, or monochlorobenzene, were detected (detection limit < 100 µg/g).

Nitrosation

p-Methylaminophenol and *p*-Methylaminophenol Sulfate are secondary amines, thus prone to nitrosation.[4] Nitrosamine content for these ingredients was not reported.

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e. RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[8] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025, *p*-Methylaminophenol is used in 1 hair tint (Table 2).[9,10] Additionally, the RLD reported *p*-Methylaminophenol Sulfate is used in 1759 cosmetic formulations, with the majority being hair dyes and colors. One use was reported for an eyelash and eyebrow dye. No concentrations of use were submitted for either ingredient in response to the survey conducted by the Council in 2025.[11]

These ingredients are considered coal tar hair dyes for which regulations require caution statements and instructions regarding patch tests in order to be exempt from certain adulteration and color additive provisions of the US Federal Food, Drug, and Cosmetic (FD&C) Act. In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution - this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

Product labels shall also bear patch test instructions for determining whether the product causes skin irritation. However, whether or not patch testing prior to use is appropriate is not universally agreed upon. The Panel recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 48 h after application of the test material and prior to the use of a hair dye formulation. Conversely, a report in Europe suggests that self-testing has severe limitations, and may even cause morbidity in consumers.[12,13] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the FD&C Act. However, according to the RLD, *p*-Methylaminophenol Sulfate is used in eyelash and eyebrow dyes. As stated above, the FD&C Act also specifies that coal tar hair dyes must not be used for dyeing the eyelashes or eyebrows.

It is possible that some products containing *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate may be marketed for use with airbrush delivery systems. With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product

categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available, in some instances. None of the reported product categories for these ingredients as listed in the RLD include a designation indicating airbrush application, so it is possible that these ingredients are used with airbrush delivery systems, but not reported as such. Additionally, concentration of use surveys are conducted based on product categories as stated in the RLD, but airbrush use was not reported in response to the survey. No consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with airbrush technology, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. If these ingredients were to be used in airbrush formulations, the data are insufficient to evaluate the exposure resulting from cosmetics applied in such a manner.

Under European regulations for cosmetic ingredients, *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate are listed in Annex III, with the restrictions that these ingredients may be used as hair dyes substances in oxidative hair dye products at a maximum concentration of 0.68% (on head, as sulfate salt).[14] Additionally, these ingredients should not be used with nitrosating agents. The maximum nitrosamine content is 50 µg/kg, and these ingredients should be kept in nitrite-free containers. The 2006 opinion by the SCCP on the sulfate salt also states these limitations.[4]

Non-Cosmetic Use

The ingredient p-Methylaminophenol Sulfate is used in spectrophotometric analyses of such compounds as dapsone, isoniazid, riboflavin, and antibiotics and in the calorimetric analyses of thiamine hydrochloride and penicillins G and V.[2] *It also is listed in various patents for pharmaceuticals as a treatment for neoplastic disease. p-Methylaminophenol Sulfate also is used in film developing.*

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

p-Methylaminophenol Sulfate

The percutaneous absorption of [benzyl-U-^{14}C]-*p*-Methylaminophenol Sulfate under oxidative and non-oxidative conditions was determined using human dermatomed skin samples (350 - 390 µm thick) mounted in flow-through diffusion cells.[4] *p*-Methylaminophenol Sulfate in a hair dye formulation at 1.35% (w/w) with the coupler *m*-aminophenol (0.86%) was mixed with the oxidative developer (1;1, w/w) to yield a final concentration of 0.68% *p*-Methylaminophenol Sulfate. Under non-oxidative conditions, *p*-Methylaminophenol Sulfate was used in the same hair dye formulation without a coupler at 1.35% before mixing with water (1:1, w/w) to yield a similar final concentration of 0.68% *p*-Methylaminophenol Sulfate. Approximately 20 mg/cm^2 of both test preparations were applied to the skin surface. After 30 min, the skin was cleaned using a standardized washing procedure. Percutaneous absorption was measured 24 h after application by liquid scintillation counting of the extractable dose, stratum corneum (isolated from tape strippings), skin (epidermis + dermis), and receptor fluid (phosphate buffered saline). Most of the *p*-Methylaminophenol Sulfate applied on the skin surface was removed at 30 min post-application (91.34 and 90.70% of the applied dose in oxidative and non-oxidative conditions, respectively). At 24 h post-application, a further 1.37 and 0.73% were removed, yielding a total extractable dose of 92.72 and 91.44% for a total recovery rate of 96.42 and 97.74% in oxidative and non-oxidative conditions, respectively. The penetrated dose (amount measured in the receptor fluid) was 0.49 ± 0.24 (0.36%) and 3.04 ± 1.10 µg equiv/cm^2 (2.21%) in oxidative and non-oxidative conditions, respectively. The amounts considered to be absorbed (dermal delivery, sum of the amounts measured in the living epidermis, dermis, and receptor fluid) were 1.35 ± 0.78 µg equiv/cm^2 (1.0%; 0.33 – 4.01 µg equiv/cm^2) and 6.19 ± 2.24 µg equiv/cm^2 (4.49%; 2.75 – 9.38 µg equiv/cm^2) in oxidative and non-oxidative conditions, respectively.

Absorption, Distribution, Metabolism, and Excretion

In Vitro

p-Methylaminophenol Sulfate

The potential for oxidative metabolism of *p*-Methylaminophenol Sulfate was evaluated in human liver microsomes at concentrations of 10 and 100 µM.[16] The test material, the positive control (100 µM 2-aminofluorence), and the negative control (100 µM *p*-phenylenediamine) were incubated with the human liver microsomes (1 mg/ml microsomal protein, final concentration) for 20 min. Cytochrome P450 activities of the human liver microsomes were determined by incubating microsomes with a mixture of several substrates (phenacetin, tolbutamide, omeprazole, bufuralol, and midazolam) for 20 min. Cytochrome P450 activities were measured by quantifying the formation of metabolites for each of these substrates by liquid chromatography-tandem mass spectrometry (LC-MS/MS; scanning *m*/*z* range = 100 - 200). Neither the test compound nor the positive or negative controls showed evidence for the formation of di-oxygenated metabolites under the conditions of the assay. As expected, 2-aminofluorence was mono-hydroxylated at multiple sites. Incubation of the negative control or *p*-Methylaminophenol Sulfate did not produce any oxidized metabolites

Animal

Oral

p-Methylaminophenol Sulfate

In an oral study, groups of 10 male and 10 female Sprague Dawley (Crl CD(SD) IGS BR) rats received 0, 3, 10, or 30 mg/kg bw/d *p*-Methylaminophenol Sulfate in a 0.5% suspension of carboxymethyl cellulose via gavage daily for 90 d (additional details are in the Subchronic Toxicity section below).[4] Blood was sampled to determine plasma levels of the test material on day 1 and in week 13 at 0.5, 1, 2, 4, 8, and 24-h post-administration. Plasma levels of *p*-Methylaminophenol Sulfate were below detectable limits at all time points in the 3 mg/kg/d group, and were only detectable at 0.5 h in week 13 in the 10 mg/kg/d group. In the high dose group, the maximum plasma level was measurable at 0.5 h at both day 1 and week 13 in both sexes. Thereafter, the levels quickly decreased and *p*-Methylaminophenol Sulfate was below detectable limits at 2 h on day 1 and 4 h after dosing in week 13. The systemic exposure (as measured by peak concentration (C_{max}) and area under the curve ($AUC_{(0-t)}$)), was difficult to analyze due to the low number of available results, but the systemic exposure seemed to increase with the dose level (no further details provided). No definitive gender or time effects to the plasma levels were observed.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The intravenous LD_{50} for p-Methylaminophenol Sulfate in NMRI mice was estimated as 85 mg/kg.[2] *No further details were provided.*

Dermal and oral acute toxicity studies on *p*-Methylaminophenol Sulfate summarized here are detailed in Table 3. In a dermal study in guinea pigs, the LD_{50} for *p*-Methylaminophenol Sulfate was determined to be greater than the test dose of 1000 mg/kg bw after no mortality was observed (no further details available).[5] For oral studies, the LD_{50} was 565 mg/kg bw in male mice that received a 10% suspension of *p*-Methylaminophenol Sulfate in 0.5% guar-gum. A preliminary acute oral toxicity study with female rats (1 rat/dose) *p*-Methylaminophenol Sulfate in 0.5% carboxymethyl cellulose resulted in no clinical signs of toxicity or mortality at 100 mg/kg and in death of the rats that received 200 and 500 mg/kg.[4] In the main experiment, *p*-Methylaminophenol Sulfate (100 mg/kg) administered orally to 4 rats resulted in hypoactivity, piloerection, and dyspnea in all animals within 3 h. All animals survived until necropsy; no abnormalities were observed. The maximum non-lethal dose of *p*-Methylaminophenol Sulfate was determined to be 100 mg/kg and the minimal lethal dose was determined to be 200 mg/kg.

Computational Analyses/Predictions

p-Methylaminophenol Sulfate

Acute toxicity of *p*-Methylaminophenol Sulfate from dermal exposure predicted using the Organisation for Economic Co-operation and Development (OECD) quantitative structure-activity relationship (QSAR) toolbox determined the LD_{50} to be 7087 mg/kg bw in rabbits.[5] The prediction averaged the value from the 5 nearest neighbors (no further details provided) and had a parametric boundary of log K_{ow} between 3.26 and 4.66.

Acute toxicity from oral exposures in rats had predicted the LD_{50} to be 1579 mg/kg bw using the OECD QSAR toolbox with log k_{ow} as the primary descriptor.[5] The predictions averaged the value from the 6 nearest neighbors (no further details provided) and had a parametric boundary of log k_{ow} between 2.52 and 4.55. The Danish QSAR predicted the LD_{50} to be 1300 mg/kg bw in rats. No further details were provided.

Subchronic Toxicity Studies

Dermal

Two hair dye formulations containing 0.05 or 1.0% p-Methylaminophenol Sulfate were tested for dermal toxicity in groups of 12 rabbits.[2] *These dye formulations were mixed with an equal volume of 6% hydrogen peroxide, and formulations were applied twice weekly for 13 wk to the clipped skin, with the skin of 3 rabbits of each group having been abraded at the beginning of each week. No significant differences were found between control and test animals with respect to body weight gain and urinalyses, and no discoloration of the urine was produced by the dyes. Statistically significant differences were found in some organ weights and in certain clinical chemistry and hematological values, but these were not considered toxicologically significant.*

Oral

p-Methylaminophenol Sulfate

In a 90-d oral toxicity study, groups of 10 male and 10 female Sprague-Dawley (Crl CD (SD) IGS BR) rats received 0, 3, 10, or 30 mg/kg bw/d *p*-Methylaminophenol Sulfate in a 0.5% suspension of carboxymethyl cellulose via gavage.[4] An additional 6 rats per sex were followed for a 4-wk recovery period in the control and high dose groups. Rats were checked daily for mortality and clinical signs of toxicity; body weights and feed consumption were recorded weekly. Ophthalmological examinations were performed at the beginning of the study before treatment and at study end.

Hematological studies, blood chemistry studies, and urinalysis were conducted at the end of the treatment period. Rats were killed for necropsy and histopathological study at the end of treatment and recovery periods.

No deaths occurred and no clinical signs of toxicity were observed during the treatment period. Body weights and feed consumption rates were unaffected. There were no ophthalmological findings and no effects on the hematology or blood biochemistry parameters. Males in the high-dose group had a higher urinary output with a lower specific gravity. A slight decrease in thymus weight was seen in a few females from the high dose group; no other treatment-related-effects on organ weights were noted at the end of the treatment and the recovery period. There were no notable observations at necropsy. Microscopic examination found tubular epithelial degeneration/single cell necrosis in the kidneys of most males and half the females in the high-dose group, but not in the rats who had the 4-wk recovery period. No other adverse effects were reported. The no-observed-adverse-effect level (NOAEL) for *p*-Methylaminophenol Sulfate in this 90-d rat study was determined to be 10 mg/kg/d.[4]

In another oral repeated-dose study, groups of 20 male and 20 female Crl: COBS, CD, SD, BR rats received 0, 30, 100, or 300 mg/kg bw (0, 0.3, 1, or 3%) *p*-Methylaminophenol Sulfate in distilled water via gavage 5 d/wk for 91 - 94 d.[5] The animals were observed for mortality, morbidity, clinical signs, body weight and organ changes, feed consumption, hematology, serum chemistry, urinalysis, and gross and histopathological parameters.

Treatment-related effects were observed primarily in the 100 and 300 mg/kg groups of both sexes and sporadically in males of the 30 mg/kg group. Major effects included degeneration of hemoglobin in circulating erythrocytes, hemolytic anemia, hemoglobinuric nephrosis, and death. Treatment-related effects in erythrocytes were slight in the 100 mg/kg group to moderate in the 300 mg/kg group, and included polychromasia, macrocytosis, anisocytosis, siderocytosis, and incidence of Howell-Jolly bodies. Treatment-related effects in urine were minimal to minor in the 100 mg/kg group and moderate in the 300 mg/kg group, and included decreased urine volume and pH, increased specific gravity, increased concentration of protein, increased incidence of red and white blood cells per high power microscopic field of urine sediment, green to brown color, and a hazy appearance. Hepatic extramedullary hematopoiesis and hypertrophy of hepatocytes; renal tubular pigmentation, hemoglobinuric nephrosis and regeneration; and splenic extramedullary hematopoiesis, hemosiderosis and congestion were observed. The NOAEL was determined to be 30 mg/kg bw.[5]

Computational Analyses/Predictions

p-Methylaminophenol Sulfate

An OECD QSAR estimation for a subchronic (3-mo) oral exposure of *p*-Methylaminophenol Sulfate in rats determined the NOAEL to be 57 mg/kg bw/d.[5] The predictions averaged the value from the 6 nearest neighbors (no further details provided) and had a parametric boundary of log k_{ow} between 2.8 and 5.92.

Chronic Toxicity Studies

Dermal

Two hair dye formulations containing 0.05 or 1.0% p-Methylaminophenol Sulfate were administered topically to groups of male and female mice (n = 50) weekly for periods of 23 and 21 mo, respectively.[2] *The dye formulations were mixed with an equal volume of 6% hydrogen peroxide, and a dose of 0.05 ml was applied to the clipped skin within 15 min of mixing. At the conclusion of the study, the survival rates and organ/body weight ratios of the test animals did not differ significantly from those of the controls, although there was considerable variation among the individual values.*

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Dermal

The dermal developmental and reproductive toxicity of two hair dye formulations containing 0.05 or 1% p-Methyl-aminophenol Sulfate was evaluated following topical application during gestation at a dose of 2 ml/kg every 3 d, for a total of 7 doses, to the shaved dorsoscapular region of groups of 20 mated female rats.[2] *The hair dyes were mixed with 6% hydrogen peroxide before application. No significant embryotoxic or teratogenic effects were observed. No further details were available.*

Oral

p-Methylaminophenol Sulfate

In an oral teratology study, groups of 24 female Sprague Dawley (Crl CD (SD) IGS BR) rats received 0, 5, 25, or 125 mg/kg bw/d *p*-Methylaminophenol Sulfate via gavage on gestation days 6 - 19.[4] The rats were observed for clinical signs of toxicity daily; feed consumption and body weight were monitored at designated intervals. On gestation day 20, the rats were killed and necropsied. The gravid uterus was weighed, and fetuses were removed and weighed, sexed, and subjected to external soft tissue or skeletal examinations. Litter parameters recorded were number of corpora lutea, implantation sites, early and late resorptions, and dead and live fetuses. There were no maternal deaths during the study and no treatment-related signs of toxicity were observed. Net body weight gain was slightly reduced in the 25 and 125 mg/kg/d groups. No treatment-related findings were reported at necropsy. There were no treatment-related effects observed in the litters, and

there were no treatment-related malformations or variations in any of the fetuses. The NOAEL for maternal toxicity was 5 mg/kg/d and the NOAEL for embryo-fetal toxicity was 125 mg/kg/d.

Computational Analyses/Predictions

p-Methylaminophenol Sulfate

Reproductive toxicity of *p*-Methylaminophenol Sulfate from oral exposure was predicted using the OECD QSAR toolbox, with log k_{ow} as the primary descriptor.[5] The analysis was based on a modeled study scenario involving groups of 12 male and 12 female Crj: CD(SD) mice administered the test material at 740 mg/kg bw/d in corn oil via gavage starting 14 d prior to mating through lactation day 3. The prediction averaged the value from the 5 nearest neighbors (no further details provided) and had a parametric boundary of log k_{ow} between 2.19 and 6.83. *p*-Methylaminophenol Sulfate was predicted to not affect reproductive function, and the NOAEL was estimated to be 740 mg/kg bw. No further details were provided.

GENOTOXICITY STUDIES

The mutagenic potential of p-Methylaminophenol (30 µg to 2 mg) was tested in the Ames assay using Salmonella typhimurium strains TA98, TA100, TA1535, TA1537, and TA1538.[2] *No mutagenicity was observed, but the test material was cytotoxic, especially to strains TA98 and TA1538, without metabolic activation. In a chromosomal aberration test with and without metabolic activation, p-Methylaminophenol (0.125, 0.25, 0.5, or 1 mg/ml) was quite toxic to Chinese hamster ovary (CHO) cells, but no clastogenic activity was observed under the conditions of the study. In an in vivo mouse micronucleus test, p-Methylaminophenol was not genotoxic when administered at doses up to 100 mg/kg.*

In vitro and in vivo genotoxicity studies on *p*-Methylaminophenol Sulfate summarized here are detailed in Table 4. In in vitro studies examining effects on gene mutation, *p*-Methylaminophenol Sulfate (up to 1000 µg/plate without metabolic activation and up to 2000 µg/plate with metabolic activation) induced gene mutations in the Ames test using *S. typhimurium* strains TA100 (with and without metabolic activation) and strains TA98 and TA1537 (with metabolic activation only).[4] In additional Ames tests, *p*-Methylaminophenol Sulfate (up to 2000 µg/plate) caused gene mutations in *S. typhimurium* strains TA97, TA100, and TA1537 with metabolic activation, but genotoxicity was not observed without metabolic activation in any of these strains nor in strains TA98 or TA1535.[17] In a mammalian cell gene mutation assay, *p*-Methylaminophenol Sulfate induced mutations in L5178Y mouse lymphoma cells at the TK +/- locus at concentrations up to 3.0 µg/ml without metabolic activation and up to 38 µg/ml with metabolic activation. In contrast, genotoxicity to *p*-Methylaminophenol Sulfate was not observed at the *hprt* locus at concentrations up to 2.0 µg/ml without metabolic activation and up to 60 µg/ml with metabolic activation. The ability to induce chromosomal damage was evaluated in vitro and in vivo. In an in vitro chromosomal aberration test using human lymphocytes, *p*-Methylaminophenol Sulfate (11.26 - 27.49 µg/ml) was clastogenic both with and without metabolic activation. In vivo, *p*-Methylaminophenol Sulfate was not genotoxic in a rat bone marrow micronucleus tested at up to 400 mg/kg via gavage.

Computational Analyses/Predictions

p-Methylaminophenol Sulfate

Computational analysis using OECD QSAR toolbox, with log k_{ow} as the primary descriptor, estimated that *p*-Methylaminophenol Sulfate is not likely to be genotoxic in mice in vivo.[5] The prediction averaged the value from the 7 nearest neighbors (no further details provided) and had a parametric boundary of log k_{ow} between 1.03 and 4.74.

CARCINOGENICITY STUDIES

Dermal

p-Methylaminophenol Sulfate

In a chronic dermal toxicity study of two hair dye formulations containing 0.05 or 1% p-Methylaminophenol Sulfate under oxidative conditions (see Chronic Toxicity Studies), mice (n = 50; 12 treatment groups; 3 negative control groups) were evaluated for neoplasms at the end of the 21- and 23-mo treatment periods.[2] *Of special interest were neoplasms of the skin, which were of low incidence. Several other types of neoplasms were found at necropsy and microscopic evaluation, but none of the incidences were statistically significant. There were no differences in liver or kidney weights. It was concluded that the hair dye formulations tested did not have any carcinogenic effects.*

In a dermal carcinogenicity test, hair dye formulations containing 0.05 or 1% *p*-Methylaminophenol Sulfate were applied on groups of 60 male and 60 female Sprague Dawley rats.[4] The rats were obtained from the first mating of a multigeneration reproduction study in rats treated with 2 different hair dye formulations containing up to 0.5% *p*-Methylaminophenol. The test materials (0.5 ml) were applied to the shaved neck and back area of the test animals twice weekly for 114 wk. There were 3 independent control groups (60 males and 60 females each) which received no treatment. The rats were observed daily for signs of toxicity and mortality. Body weights were recorded weekly for the first 14 wk, and monthly thereafter. Group feed consumption was recorded weekly. Hematological, biochemical, and urinalysis studies were conducted on 5 males and 5 females/group at 3, 12, 18, and 24 mo. After 12 mo of treatment, 5 males and 5 females/group were killed and necropsied, and all the rats of a sex group were killed when survival reached 20%. All surviving rats were killed at study end. Histopathological evaluations were performed on 18 tissues (plus tumor masses), including treated skin.

Survival to 114 wk was 16 - 24 males and 14 - 17 females/treatment group and 15 males and 9 - 18 females in the control groups. The dyes containing *p*-Methylaminophenol Sulfate did not affect survival nor produce any adverse local effects. No clinical signs of toxicity or any changes to body weights, feed consumption, or clinical pathology parameters were observed. There were no significant differences observed in the biochemical analyses or urinalysis. Females treated with the hair dye containing 1% *p*-Methylaminophenol Sulfate had a significant increase in the incidence of mammary adenomas when compared to a single control group, but not the other 2 control groups. This finding was not considered to be biologically significant. Life-table analyses found no treatment-related variations for the treated groups as compared to the 3 control groups by sex.[4]

Computational Analyses/Predictions

p-Methylaminophenol Sulfate

Carcinogenicity of *p*-Methylaminophenol Sulfate was predicted using the Danish QSAR database.[5] The prediction was based on models for mice as the target organism and incorporated two software systems (Leadscope and CASE Ultra). *p*-Methylaminophenol Sulfate was predicted to not be carcinogenic. No further details were provided.

OTHER RELEVANT STUDIES

Nephrotoxic Effects

In a nephrotoxicity study, 2 groups of 5 female hooded rats received 0.1 or 0.6 mM/kg p-Methylaminophenol Sulfate intravenously.[2] *p-Methylaminophenol Sulfate at 0.1 mM/kg caused necrosis of the distal third of all tubules of the kidneys of the rats. At 0.6 mM/kg, p-Methylaminophenol Sulfate caused necrosis of the entire proximal convoluted tubule and the rats died in anuria.*

Antioxidant Effects

p-Methylaminophenol

In a radical analysis using α,α-diphenyl-β-picrylhydrazyl (DPPH) to test the antioxidant activities of *p*-Methylaminophenol (10, 20, or 40 µM in dimethyl sulfoxide(DMSO)) along with 4-aminophenol and *p*-acetaminophen, a dose-dependent response was observed with *p*-Methylaminophenol that was similar to that of vitamin E.[18] One molecule of *p*-Methylaminophenol scavenged 2 DPPH radical molecules. Further studies with this assay compared the antioxidant properties of *p*-Methylaminophenol (20 µM in DMSO) with *p*-butylaminophenol, *p*-hexylaminophenol, *p*-octylaminophenol, and *p*-methoxybenzylaminophenol.[19] All these *p*-alkylaminophenols quenched DPPH radicals, and *p*-Methylaminophenol, along with *p*-butylaminophenol, *p*-hexylaminophenol, and *p*-octylaminophenol, exhibited the same level of antioxidant activity as vitamin E.

Antioxidant activity of *p*-Methylaminophenol in DMSO was also assessed using microsomes from Sprague-Dawley rats.[18] Microsomal lipid peroxidation was quantified through the measurement of malondialdehyde formation induced by adenosine 5'-diphosphate (ADP)-chelating ions and ascorbate. *p*-Methylaminophenol inhibited malondialdehyde formation in a dose-dependent manner by in the range of 1 to 10 µM, with an approximate median inhibition concentration (IC_{50}) of 4.5 µM. Further testing using microsomes yielded similar results with *p*-Methylaminophenol inhibiting lipid peroxidation in a dose-dependent manner in the range of 1 to 5 µM with an IC_{50} of 4.6 µM.[19]

Additional testing evaluated the superoxide scavenging activity of a series of *p*-alkylaminophenols of varying chain lengths, including *p*-Methylaminophenol.[20] Superoxide scavenging activity was assessed by measuring the formation of blue formazan from the yellow dye NBT^{2+}, which reflects residual superoxide generated by a hypoxanthine/xanthine oxidase system. At 10 µM concentration, *p*-Methylaminophenol scavenged superoxides completely (>85%), which showed no effects on xanthine oxidase activity. *p*-Methylaminophenol also eliminated superoxide in a dose-dependent manner. At 1 µM, superoxide levels decreased approximately 72%, and the IC_{50} value was approximately 0.6 µM.

Cytotoxicity

p-Methylaminophenol

The potential of *p*-Methylaminophenol (1 or 10 µM) to inhibit cell growth was studied using cultured human myeloid leukemia cells (HL-60).[18] The cells were exposed to the test material for 96 h. At 1 µM, *p*-Methylaminophenol inhibited approximately 33% of HL-60 cell growth; at 10 µM, cell growth was inhibited by 99.7%. DNA isolated from HL-60 cells exposed to 1 or 10 µM *p*-Methylaminophenol for 24 h was extracted and dried under vacuum then dissolved in sample solution for analysis by agarose gel electrophoresis. There was no DNA fragmentation observed at the lower concentration (1 µM) of *p*-Methylaminophenol; the higher concentration (10 µM) contained fragmented ladder DNA demonstrating that *p*-Methylaminophenol may potentially induce apoptosis of HL-60 cells. Further cytotoxicity testing was performed with HL-60R (resistant to retinoic acid), MCF-7 and MCF-7/AdrR (having and not having estradiol receptors, respectively), HepG2, and DU-145 cells to various concentrations of *p*-Methylaminophenol (details on concentrations not well described). HL-60R cell growth was completely inhibited by *p*-Methylaminophenol (> 99%) at 10 µM, while *p*-Methylaminophenol inhibited MCF-7 cell growth 20% at 10 µM. In MCF-7/AdrR cells, cell growth was inhibited approximately 60%. The proliferation of HepG2 and DU-145 cells was also suppressed by exposure to *p*-Methylaminophenol at 40 µM by > 80%.

Additional testing with the same cell lines described above was performed in a study of a series of *p*-alkylaminophenols of varying chain lengths, including *p*-Methylaminophenol.[20] At a concentration of 4 µM, cell growth was inhibited by *p*-Methylaminophenol by approximately 38% in HL-60 cells, 12% in HL-60R cells, 8% in MCF-7 cells, 13% in MCF-7/AdrR cells, 43% in DU-145 cells, 10% for HepG2 cells.

Neurological Effects

In a study of various chemicals on the depolarizing or hyperpolarizing effects of acetylcholine on the giant neurons of Lymnea stagnalis, p-Methylaminophenol Sulfate was inhibitory to the depolarizing action of acetylcholine in 92% of the giant neuron D cells tested.[2] *p-Methylaminophenol Sulfate did not enhance the action of acetylcholine in any test.*

Hematological Effects

The effects of p-Methylaminophenol Sulfate on hemoglobin oxidation were evaluated in vivo and in vitro.[2] *In erythrocytes from multiple species p-Methylaminophenol Sulfate reacted with hemoglobin to form methemoglobin at a much faster rate (40 x 10^{-5} equiv/l/min) than did p-aminophenol. Rates in human and rabbit erythrocytes were slightly faster than those observed in oxen. In vitro experiments further indicated that methemoglobin formation reached a plateau and was not increased by repeated additions of the compound. In intravenous studies in dogs and cats, administration of p-Methylaminophenol Sulfate at 15 mg/kg resulted in a rapid, dose-dependent increase in methemoglobin concentrations, with peak levels (approximately 7 g/100 ml blood) observed within 5 - 10 min after dosing. The authors attributed observed interspecies differences in response to structural differences in hemoglobin.*

DERMAL IRRITATION AND SENSITIZATION STUDIES

In a primary irritation study, patches containing 2% aq. p-Methylaminophenol (0.5 ml) were applied to intact and abraded skin of 6 rabbits (3/sex) for 24 h.[2] *The test sites were evaluated 30 min after patch removal and again 48 h later. The primary irritation index (PII) for p-Methylaminophenol was 0.74 out of a maximum of 8, and the ingredient was considered slightly irritating to rabbit skin.*

In a guinea pig maximization test (GPMT), guinea pigs received 0.5 g of p-Methylaminophenol under an occlusive patch to shaved skin for both the induction and challenge phases.[2] *Two of the guinea pigs died during the study; death was not related to treatment with p-Methylaminophenol. Of the 18 remaining guinea pigs, 3 had doubtful signs of erythema; biopsies were performed, and no signs of sensitization were noted. p-Methylaminophenol was not considered a dermal sensitizer.*

Dermal irritation, sensitization, and cross-sensitization studies on *p*-Methylaminophenol Sulfate summarized here are detailed in Table 5. *p*-Methylaminophenol Sulfate was not a dermal irritant when tested undiluted in guinea pigs or at 3% in rabbits.[4,5] In a GPMT with an induction of up to 25% and a challenge of 5%, *p*-Methylaminophenol Sulfate in acetone was considered an extreme sensitizer.[21] The same research group performed a local lymph node assay (LLNA) in mice testing *p*-Methylaminophenol Sulfate at 0.5, 1, or 2.5% in dimethyl formamide. The LLNA yielded positive results and *p*-Methylaminophenol Sulfate was considered a sensitizer (no further details were provided). In another LLNA, *p*-Methylaminophenol Sulfate induced delayed contact hypersensitivity when tested at 0.25, 0.5, 1, 2.5, or 5% in DMSO.[4] No cutaneous reactions were observed at any concentration. There was a dose-related increase in the stimulation index (SI); the estimated concentration of an SI of 3 (EC_3) was exceeded at concentrations of 2.5 and 5%. The calculated EC_3 value was 2.2%.

In a GPMT study of the cross-sensitizing potential of *p*-Methylaminophenol Sulfate (challenge patch 0.5%) in animals induced with 4-*N*,*N*-diethyl-2-methyl-1,4-phenylenediamine · HCl (CD-2) or 4-(*N*-ethyl-*N*-2-methan-sulphonamido-ethyl)-2-methyl-1,4-phenylenediamine · sulfuric acid · water (CD-3), neither the controls nor the animals induced with CD-2 had a positive reaction to the challenge with *p*-Methylaminophenol Sulfate.[22] In the animals induced with CD-3, both the treated and the control groups had a single reaction to the challenge with *p*-Methylaminophenol Sulfate. In another cross-sensitization study using the GPMT in 10 animals, induction and primary challenge with 5% *p*-Methylaminophenol Sulfate yielded positive reactions in 9 animals and a questionable reaction in the 10th.[23] Cross-challenges were carried out 1 and 2 wk after the primary challenge with *p*-phenylenediamine, *p*-aminophenol, *m*-aminophenol, and *p*-benzoquinone. Nearly all animals were positive to *p*-benzoquinone and *p*-aminophenol (9/10 and 8/10, respectively). Three animals each had positive reactions to *p*-phenylenediamine and *m*-aminophenol.

OCULAR IRRITATION STUDIES

Animal

A 2% solution of p-Methylaminophenol in distilled water (0.10 ml) instilled into the conjunctival sac of the right eye of 6 rabbits was considered practically non-irritating.[2] *In this study, the eyes were not rinsed and were examined 1, 2, 3, 4, and 7 d after instillation of the test substance. The eyes were also examined under UV light with fluorescein dye. Three of the rabbits had no reaction to the test material. Slight-to-severe redness of the conjunctiva was observed in the remaining rabbits that took up to 4 d to clear. The average irritation score on day 1 was 2 out of a total possible score of 110; on day 2, the group average was 1/110; on day 3, the group average was 0.33/110. The score was 0 for the rest of the study.*

p-Methylaminophenol Sulfate

In an ocular study, 3% *p*-Methylaminophenol Sulfate (0.1 ml in 0.5% aqueous carboxymethylcellulose) was instilled into the conjunctival sac of the left eyes of 3 New Zealand White rabbits.[4] The eyes were not rinsed. The eyes were examined at 1, 24, 48, and 72 h after application. One rabbit had chemosis and redness of the conjunctiva at 1 h. No other signs of ocular irritation were noted. *p*-Methylaminophenol Sulfate at 3% was considered slightly and transiently irritating in rabbit eyes.

CLINICAL STUDIES

Multicenter and Retrospective Studies

p-Methylaminophenol

In a European multicenter study, 914 patients were patch tested with 27 hair dye ingredients, including *p*-Methylaminophenol.[24] Of these patients, 20 (2.2%) tested positive to *p*-Methylaminophenol and 3 had clinical relevance. No co-reactions were observed with *p*-phenylenediamine, toluene-2,5-diamine, *p*-aminophenol, *m*-aminophenol, or resorcinol.

p-Methylaminophenol Sulfate

Allergic contact dermatitis caused by hair coloring agents was investigated in a multicenter study in Japan.[25] From 14 hospitals between October 2012 and May 2014, 203 patients with suspected allergic contact dermatitis caused by hair dyes or perming solutions were identified. Of these, 26 (13%) were hairdressers or barbers. The patients were patch tested with 15 hair dye substances (including *p*-Methylaminophenol Sulfate; 1% pet.), a bleaching agent, 2 perming solution ingredients, and Bandrowski's base using Finn Chambers for 2 d. Readings were performed on day 2, 3 and 7 after application. *p*-Methylaminophenol Sulfate elicited the second most positive responses after *p*-phenylenediamine, with 21% (41 out of 195 total) of the patients testing positive. Testing was also performed with *p*-Methylaminophenol at 0.5%, which yielded similar positivity rates. When comparing sensitization prevalence of *p*-Methylaminophenol Sulfate between *p*-phenylenediamine positive and negative patients, *p*-Methylaminophenol Sulfate had high sensitization prevalences in both groups.

Cross-Sensitization

p-Methylaminophenol Sulfate

Patients in Sweden (n = 10) with a history of positive patch test reactions to *p*-phenylenediamine (++ or +++ reactions) were patch tested for cross reactions with structurally similar chemicals, including 1% *p*-Methylaminophenol Sulfate.[23] Finn Chambers were used to apply the patches to the upper back. The patches were left in place for 2 d and the readings were performed 3 d after application. Four of the 10 patients had positive reactions to *p*-Methylaminophenol Sulfate, with one patient having a ++ reaction and one other having a +++ reaction.

Cross-sensitivity of *p*-phenylenediamine to benzene derivatives, including *p*-Methylaminophenol Sulfate, was studied in 22 patients in Italy with known *p*-phenylenediamine allergy.[26] The patients received Van der Bend square chambers on the upper back containing 1% *p*-Methylaminophenol Sulfate. The chambers were removed after 2 d and the readings were carried out on days 2 and 4 after application. Positive test reactions to *p*-Methylaminophenol Sulfate were observed in 5 of the *p*-phenylenediamine patients.

Case Reports

p-Methylaminophenol Sulfate

In a case report, a 62-yr-old man employed as a manager in photography laboratories was observed with allergic contact dermatitis.[27] The patient had a 2-yr history of hand dermatitis. Both palms were erythematous with diffuse scaling and fissuring; the fingers had confluent vesicles. Diffuse erythematous scaling plaques were present on both lower extremities and scaling was observed on the forearms. A biopsy showed superficial and mid-perivascular infiltrate of lymphocytes, histiocytes, and eosinophils. Patch testing with a standard photographic series and the solutions the patient had been exposed to resulted in positive results for *p*-Methylaminophenol Sulfate, 2-amino-5 diethylaminotoluene hydrochloride, 4-amino-*N*-ethyl-*N*-β-(methyl-sulphamidoethyl)-*m*-toludine sesquisulfate monohydrate, 4-amino-3-methyl-*N*-ethyl-*N*-(β-hydroxyethyl) aniline sulfate, and *p*-phenylenediamine.

A 38-yr-old man employed as a film developer for 16 yr without any skin problems developed eczema that spread to his arms, neck, and face a few days after grazing his hand.[28] The patient recovered after topical treatment and a few days off of work, but the eczema returned within hours of resuming employment. Patch testing for 48 h was performed with the International Contact Dermatitis Research Group (ICDRG) standard series and some photographic chemicals from the patient's workplace. Patch site readings were made 72 h after application. Positive reactions were observed to 1% *p*-Methylaminophenol Sulfate, persulfate bleach accelerator (PBA-1), diphenyl quinidine, and balsam of Peru.

In another case report, a 39-yr-old man employed as a photographer presented with severe allergic contact dermatitis on the dorsal aspect of his hands and forearms.[29] The patient had a 4-yr history of recurrent acute contact dermatitis following exposure to photochemicals, and previously had a severe allergic reaction to a black henna tattoo. Patch testing was performed with the North American Contact Dermatitis Group (NACDG) standard screening series, the Chemotechnique

photography series (including *p*-Methylaminophenol Sulfate), select textile allergens, *m*-aminophenol, and *p*-aminophenol using Finn Chamers applied for 48 h. Test sites were evaluated 48 and 120 h after application. Strong (3+) positive reactions were observed to *p*-Methylaminophenol Sulfate and *p*-phenylenediamine. Positive reactions were also observed to *p*-aminophenol, disperse orange dye nos. 1 and 3, disperse red dye no. 1, disperse yellow dye no. 3, and disperse blue dye no. 124.

RISK ASSESSMENT

Margin of exposure (MOE) is a quantitative ratio calculated for cosmetic ingredients by dividing the Point of Departure (POD) obtained for an ingredient in an animal experiment by the estimated systemic exposure dose (SED) for the ingredient in humans, generally according to US EPA and European Commission (EC) Scientific Committee on Consumer Safety (SCCS) guidelines. An MOE value greater than 100 has traditionally been considered an indication of safety. The basis for this MOE value of 100 comes from two multiplication factors: a 10-fold factor for extrapolating data from test animals to human being (interspecies extrapolation), and an additional 10-fold for differences among the human population (intraspecies extrapolation). Notably, the MOE value is sometimes referred to as the margin of safety (MOS) despite the parameters being definitionally different.

The SCCP calculated an MOE value for 0.68% *p*-Methylaminophenol Sulfate as used under oxidative conditions to be 106.[4] This calculation is based on an NOAEL of 5 mg/kg bw/d (from an oral developmental rat study) and an SED of 0.047 mg/kg bw (skin area surface of 700 cm^2 x absorption through skin of 4.01 µg/cm^2 x 0.001 (unit conversion)/typical human bw of 60 kg).

OCCUPATIONAL STUDIES

Of 23 panelists from a film laboratory known to have occupationally-related dermatoses who were patch tested with p-Methylaminophenol Sulfate, 6 had positive reactions to the ingredient at concentrations of 1 and 5%.[2] *Three of these panelists also had positive reactions to two or three of a group of four chemicals used in film laboratories. When p-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction.*

Employees of a film processing plant with reported incidences of contact dermatitis were patch tested with *p*-Methylaminophenol Sulfate (1 or 5% aq.) along with other film chemicals and protective glove materials using A1-test patches.[30] Patches were left on for 48 h and read 72 h after application and 2- to 3-wk later. Of the 23 employees exposed to *p*-Methylaminophenol Sulfate, 6 had positive reactions. In 200 non-exposed volunteers that were patch tested as controls, one volunteer tested positive (controls were tested with 1% *p*-Methylaminophenol Sulfate in pet.).

In testing for the occurrence of occupational dermatoses following modernization at the same film processing plant described above, 14 employees were tested for sensitivity to *p*-Methylaminophenol Sulfate at 0.1, 0.5, and 1% in both water (using A1-test patches) and petrolatum (using Finn Chambers).[31] The induction patches were in place for 48 h, read 72 h after exposure, and read again after 2 wk (when possible). Six employees tested positive. In control patch tests on 11 unexposed subjects, 2 tested positive to aqueous solutions of *p*-Methylaminophenol Sulfate (1%) using the Finn Chamber and 4 tested positive to the same solution using the A1-test. There were no positive results for *p*-Methylaminophenol Sulfate in petrolatum (1%) with either patch type.

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped into oxidative (permanent) and direct (temporary or semi-permanent) dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes consist of preformed colors. *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate are reported to be used in oxidative hair dye formulations. While the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. The Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. A detailed summary of the available hair dye epidemiology data is available at https://www.cir-safety.org/cir-findings.

SUMMARY

p-Methylaminophenol and *p*-Methylaminophenol Sulfate are reported to function as hair colorants in cosmetic products. The Panel first review the safety of *p*-Methylaminophenol Sulfate individually in a report published in 1991, with the conclusion that this ingredient was safe in the present practice of use and concentration. In a 2007 re-review, the *p*-Methylaminophenol Sulfate report was reopened to add *p*-Methylaminophenol. That amended report was finalized in same year with the conclusion that these ingredients are safe as hair dyes in the practices of use and concentration as described in the safety assessment. Because it had been at least 15 years since the Panel reviewed these ingredients last and because the 2007 amended report was never published, in accordance with the CIR Procedures, the Panel determined that the re-review should be resumed, and revised to include all information that has become available since it was last reviewed by the Panel.

According to RLD obtained from the FDA in 2025, *p*-Methylaminophenol is used in 1 hair tint. Additionally, the RLD reported *p*-Methylaminophenol Sulfate is used in 1759 cosmetic formulations, with the majority being hair dyes and colors. One use was reported for an eyelash and eyebrow dye. No concentrations of use were submitted for either ingredient in response to the survey conducted by the Council in 2025.

Under European regulations for cosmetic ingredients, *p*-Methylaminophenol and *p*-Methylaminophenol Sulfate are listed in Annex III with the restrictions that these ingredients may be used as hair dyes substances in oxidative hair dye products at a maximum concentration of 0.68% (on head, as sulfate salt). Additionally, these ingredients should not be used with nitrosating agents. The maximum nitrosamine content is 50 µg/kg, and these ingredients should be kept in nitrite-free containers.

In a percutaneous absorption using human dermatomed skin sample, *p*-Methylaminophenol Sulfate in a hair dye formulation at 1.35% (w/w) with the coupler *m*-aminophenol (0.86%) was mixed with the oxidative developer (1;1, w/w) to yield a final concentration of 0.68% *p*-Methylaminophenol Sulfate. Under non-oxidative conditions, *p*-Methylaminophenol Sulfate was used in the same hair dye formulation without a coupler at 1.35% before mixing with water (1:1, w/w) to yield a similar final concentration of 0.68% *p*-Methylaminophenol Sulfate. Most of the *p*-Methylaminophenol Sulfate applied on the skin surface was removed at 30 min post-application (91.34 and 90.70% of the applied dose in oxidative and non-oxidative conditions, respectively). The penetrated dose was 0.49 ± 0.24 (0.36%) and 3.04 ± 1.10 µg equiv/cm^2 (2.21%) in oxidative and non-oxidative conditions, respectively. The amounts considered to be absorbed were 1.35 ± 0.78 µg equiv/cm^2 (1.0%; 0.33 – 4.01 µg equiv/cm^2) and 6.19 ± 2.24 µg equiv/cm^2 (4.49%; 2.75 – 9.38 µg equiv/cm^2) in oxidative and non-oxidative conditions, respectively.

p-Methylaminophenol Sulfate in human liver microsomes did not produce any oxidized metabolites. In an oral rat study, *p*-Methylaminophenol Sulfate in a 0.5% suspension of carboxymethyl cellulose via gavage daily for 90 d. Plasma levels of *p*-Methylaminophenol Sulfate were below detectable limits at all time points in the 3 mg/kg/d group, and were only detectable at 0.5 h in week 13 in the 10 mg/kg/d group. In the high dose group, the maximum plasma level was measurable at 0.5 h at both day 1 and week 13 in both sexes. Thereafter, the levels quickly decreased and *p*-Methylaminophenol Sulfate was below detectable limits at 2 h on day 1 and 4 h after dosing in week 13.

In a dermal study in guinea pigs, the LD_{50} for *p*-Methylaminophenol Sulfate was determined to be greater than the test dose of 1000 mg/kg bw after no mortality was observed (no further details available). For oral studies, the LD_{50} was 565 mg/kg bw in male mice that received a10% suspension of *p*-Methylaminophenol Sulfate in 0.5% guar-gum. A preliminary acute oral toxicity study of 3 female rats *p*-Methylaminophenol Sulfate in 0.5% suspension of carboxymethylcellulose) resulted in no clinical signs of toxicity or mortality at 100 mg/kg and death of the rats that received 200 or 500 mg/kg. In the main experiment, *p*-Methylaminophenol Sulfate (100 mg/kg) administered orally to 4 more rats resulted in hypoactivity, piloerection, and dyspnea in all animals within 3 h. All animals survived until necropsy, where no abnormalities were observed. The maximum non-lethal dose of *p*-Methylaminophenol Sulfate was determined to be 100 mg/kg and the minimal lethal dose was determined to be 200 mg/kg. Acute toxicity of *p*-Methylaminophenol Sulfate from dermal exposure predicted using the OECD QSAR toolbox determined the LD_{50} to be 7087 mg/kg bw in rabbits. Predictions for oral exposures in results determined the LD_{50} to be 1300 - 1579 mg/kg bw.

In a 90-d oral toxicity study, groups of male and female rats received 0, 3, 10, or 30 mg/kg bw/d *p*-Methylaminophenol Sulfate in a 0.5% suspension of carboxymethyl cellulose via gavage. Males in the high-dose group had a higher urinary output with a lower specific gravity. A slight decrease in thymus weight was seen in a few females from the high dose group. Microscopic examination found tubular epithelial degeneration/single cell necrosis in the kidneys of most males and half the females in the high-dose group but not the rats who had the 4-week recovery period. No other adverse effects were reported. The NOAEL for *p*-Methylaminophenol Sulfate in this 90-d rat study was determined to be 10 mg/kg/d. In another oral repeated dose study, groups of male and female rats received 0, 30, 100, or 300 mg/kg bw *p*-Methylaminophenol Sulfate in distilled water via gavage. Major effects were primarily observed in the 100 and 300 mg/kg groups of both sexes included degeneration of hemoglobin in circulating erythrocytes, hemolytic anemia, hemoglobinuric nephrosis, and death. Hepatic extramedullary hematopoiesis and hypertrophy of hepatocytes; renal tubular pigmentation, hemoglobinuric nephrosis and regeneration; and splenic extramedullary hematopoiesis, hemosiderosis and congestion were observed. The NOAEL was determined to be 30 mg/kg bw. An OECD QSAR estimation for a subchronic (3 mo) oral exposure of *p*-Methylaminophenol Sulfate in rats determined the NOAEL to be 57 mg/kg bw/d.

In an oral teratology study, groups of female rats received 0, 5, 25, or 125 mg/kg bw/d *p*-Methylaminophenol Sulfate via gavage on gestation days 6 - 19. The NOAEL for maternal toxicity was 5 mg/kg/d and the NOAEL for embryo-fetal toxicity was 125 mg/kg/d. An OECD QSAR estimation for reproductive toxicity following oral exposure of *p*-Methylaminophenol Sulfate in rats starting 14 d prior to mating through lactation day 3determined the NOAEL to be 740 mg/kg bw/d.

In in vitro studies examining effects on gene mutation, *p*-Methylaminophenol Sulfate (up to 1000 µg/ plate without metabolic activation and up to 2000 µg/plate with metabolic activation) induced gene mutations in the Ames test using *S. typhimurium* strains TA100 (with and without metabolic activation) and strains TA98 and TA1537 (with metabolic activation only). In additional Ames tests, *p*-Methylaminophenol Sulfate (up to 2000 µg/plate) caused gene mutations in

S. typhimurium strains TA97, TA100, and TA1537 with metabolic activation, but genotoxicity was not observed without metabolic activation in any of these strains nor in strains TA98 or TA1535. In a mammalian cell gene mutation assay, *p*-Methylaminophenol Sulfate induced mutations in L5178Y mouse lymphoma cells at the TK +/- locus at concentrations up to 3.0 µg/ml without metabolic activation and up to 38 µg/ml with metabolic activation. In contrast, genotoxicity to *p*-Methylaminophenol Sulfate was not observed at the *hprt* locus at concentrations up to 2.0 µg/ml without metabolic activation and up to 60 µg/ml with metabolic activation. The ability to induce chromosomal damage was evaluated in vitro and in vivo. In an in vitro chromosomal aberration test using human lymphocytes, *p*-Methylaminophenol Sulfate (11.26 - 27.49 µg/ml) was clastogenic both with and without metabolic activation. In vivo, *p*-Methylaminophenol Sulfate was not genotoxic in a rat bone marrow micronucleus tested at up to 400 mg/kg via gavage.

In a dermal carcinogenicity test, hair dye formulations containing 0.05 or 1% *p*-Methylaminophenol Sulfate were applied to the shaved neck and back area in male and female rats twice weekly for 114 wk. Survival to 114 wk was 16 - 24 males and 14 - 17 females/treatment group and 15 males and 9 - 18 females in the control groups. The dyes containing *p*-Methylaminophenol Sulfate did not affect survival nor produced any adverse local effects. Females treated with the hair dye containing 1% *p*-Methylaminophenol Sulfate had a significant increase in the incidence of mammary adenomas when compared to a single control group, but not 2 other control groups. This finding was not considered to be biologically significant. Life-table analyses found no treatment-related variations for the treated groups as compared to the 3 control groups by sex. Computational analysis using the Danish QSAR database predicted that *p*-Methylaminophenol Sulfate was not carcinogenic in mice.

In a radical analysis using DPPH to test the antioxidant activities, a dose-dependent response was observed with *p*-Methylaminophenol (up to 40 µM) that was similar to that of vitamin E. One molecule of *p*-Methylaminophenol scavenged 2 DPPH radical molecules. Antioxidant activity of *p*-Methylaminophenol was also assessed using microsomes from rats. Malondialdehyde formation was inhibited in a dose-dependent manner by *p*-Methylaminophenol in the range of 1 to 10 µM. The approximate IC_{50} of *p*-Methylaminophenol was 4.5 µM. Further testing using microsomes yielded similar results with *p*-Methylaminophenol inhibiting lipid peroxidation in a dose-dependent manner in the range of 1 to 5 µM with an IC_{50} of 4.6 µM. In additional studies, *p*-Methylaminophenol at 10 µM scavenged superoxides completely (>85%), which showed no effects on xanthine oxidase activity. *p*-Methylaminophenol also eliminated superoxide in a dose-dependent manner. At 1 µM, the extent of superoxide decreased approximately 72%, and the IC_{50} value was approximately 0.6 µM.

p-Methylaminophenol inhibited cell growth in HL-60 cells at 1 µM (33% inhibition) 10 µM (99.7% inhibition). HL-60R cell growth was completely inhibited by *p*-Methylaminophenol (> 99%) at 10 µM, while *p*-Methylaminophenol inhibited MCF-7 cell growth 20% at 10 µM. In MCF-7/AdrR cells, cell growth was inhibited approximately 60%. The proliferation of HepG2 and DU-145 cells was also suppressed by exposure to *p*-Methylaminophenol at 40 µM by > 80%. At a concentration of 4 µM, cell growth was inhibited by *p*-Methylaminophenol by approximately 38% in HL-60 cells, 12% in HL-60R cells, 8% in MCF-7 cells, 13% in MCF-7/AdrR cells, 43% in DU-145 cells, 10% for HepG2 cells.

p-Methylaminophenol Sulfate was not a dermal irritant when tested undiluted in guinea pigs or at 3% in rabbits. In a GPMT with an induction of up to 25% and a challenge of 5%, *p*-Methylaminophenol Sulfate in acetone was considered an extreme sensitizer. The same research group performed a LLNA in mice testing *p*-Methylaminophenol Sulfate at 0.5, 1, or 2.5% in dimethyl formamide. The LLNA yielded positive results and *p*-Methylaminophenol Sulfate was considered a sensitizer (no further details were provided). In another LLNA, *p*-Methylaminophenol Sulfate induced delayed contact hypersensitivity when tested at 0.25, 0.5, 1, 2.5, or 5% in DMSO. No cutaneous reactions were observed at any concentration. There was a dose-related increase in the SI; the EC_3 was exceeded at concentrations of 2.5 and 5%. The calculated EC_3 value was 2.2%.

In a GPMT study of the cross-sensitizing potential of *p*-Methylaminophenol Sulfate (challenge patch 0.5%) in animals induced with CD-2 or CD-3, neither the control nor the animals induced with CD-2 had a positive reaction to the challenge with *p*-Methylaminophenol Sulfate. In the animals induced with CD-3, both the treated and the control groups had a single reaction to the challenge with *p*-Methylaminophenol Sulfate. In another cross-sensitization study using the GPMT in 10 animals, induction and primary challenge with 5% *p*-Methylaminophenol Sulfate yielded positive reactions in 9 animals and a questionable reaction in the 10^{th}. Cross-challenges were carried out 1 and 2 wk after the primary challenge with *p*-phenylenediamine, *p*-aminophenol, *m*-aminophenol, and *p*-benzoquinone. Nearly all animals were positive to *p*-benzoquinone and *p*-aminophenol (9/10 and 8/10, respectively). Three animals each had positive reactions to *p*-phenylenediamine and *m*-aminophenol. In an ocular study, *p*-Methylaminophenol Sulfate at 3% was considered slightly and transiently irritating in rabbit eyes.

In case reports, positive patch test results were observed for *p*-Methylaminophenol Sulfate in men that worked with photograph developing agents. A European multicenter study of allergic reactions to 27 hair dye ingredients found 20 out of 914 patients (2.2%) tested positive to *p*-Methylaminophenol and 3 had clinical relevance. No co-reactions were observed with *p*-phenylenediamine, toluene-2,5-diamine, *p*-aminophenol, *m*-aminophenol, or resorcinol. In a Japanese multi-center study of allergic contact dermatitis caused by hair coloring agents, *p*-Methylaminophenol Sulfate elicited the second most positive responses after *p*-phenylenediamine, with 21% (41 out of 195 total) of the patients testing positive. When comparing

sensitization prevalence of *p*-Methylaminophenol Sulfate between *p*-phenylenediamine positive and negative patients, *p*-Methylaminophenol Sulfate had high sensitization prevalences in both groups.

Patients with a history of positive patch test reactions to *p*-phenylenediamine in Sweden were patch tested for cross reactions with structurally similar chemicals, including 1% *p*-Methylaminophenol Sulfate. Four of the 10 patients had positive reactions to *p*-Methylaminophenol Sulfate, with one patient having a ++ reaction and one other having a +++ reaction. Cross-sensitivity of *p*-phenylenediamine to benzene derivatives, including *p*-Methylaminophenol Sulfate, was studied in 22 patients with known *p*-phenylenediamine allergy in Italy. Positive test reactions to *p*-Methylaminophenol Sulfate were observed in 5 of the *p*-phenylenediamine patients.

Employees of a film processing plant with reported incidences of contact dermatitis were patch tested with *p*-Methylaminophenol Sulfate (1 or 5% aq.). Of the 23 employees exposed to *p*-Methylaminophenol Sulfate, 6 had positive reactions. In testing for the occurrence of occupational dermatoses following modernization at the same film processing plant, 14 employees were tested for sensitivity to *p*-Methylaminophenol Sulfate at 0.1, 0.5, and 1%. Six employees tested positive.

The SCCP calculated an MOE value for 0.68% *p*-Methylaminophenol Sulfate as used under oxidative conditions to be 106. This calculation is based on an NOAEL of 5 mg/kg bw/d (from an oral developmental rat study) and a SED of 0.047 mg/kg.

The Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer.

PREVIOUS DISCUSSIONS

1991 Original Report Discussion

No discussion was included in the original report.[2]

2007 Amended Report Discussion

In the earlier safety assessment, only p-Methylaminophenol Sulfate was considered, even though data for p-Methylaminophenol was included.[3] *The Panel notes that p-Methylaminophenol Sulfate is the salt of p-Methylaminophenol and believe that the safety data on each ingredient may be applied to the other.*

Both ingredients have low dermal penetration and are used in rinse-off products. Therefore, there is no expectation of systemic toxicity from their use. This is confirmed with animal studies with dermal exposure. These ingredients are not irritants to eyes. They are not genotoxic, carcinogenic, nor reproductively/developmentally toxic. Data on m-, o-, and p-aminophenol from a separate assessment, which are chemically related, were also considered and found safe.

p-Methylaminophenol Sulfate and p-Methylaminophenol are known sensitizers. However, as coal tar hair dyes, they fall under the coal tar derivative exemption to the Federal Food, Drug, and Cosmetic Act which requires caution statements and instruction regarding patch tests. The Panel expects that individuals following these instructions will minimize sensitization.

The Expert Panel expressed concern about toxic metal residues that may be present in p-Methylaminophenol Sulfate and p-Methylaminophenol and advised industry that this ingredient should not contain more than: 3 mg/kg of arsenic (as As), 1 ppm mercury (as Hg), and 0.1 mg/kg of lead (as Pb). Additionally, p-Methylaminophenol Sulfate and p-Methylaminophenol should not contain N-nitroso impurities, nor should they be used in products where N-nitroso compounds may be formed.

DISCUSSION

To be developed…

CONCLUSION

To be determined…

TABLES

Table 1. Chemical properties

Property	Value	Reference
	***p*-Methylaminophenol**	
Physical Form	colorless needles or crystals	6
Molecular Weight (g/mol)	123.15	6
Vapor pressure (mmHg @ 25 ºC)	3×10^{-3}	6
Melting Point (ºC)	87	6
Boiling Point (ºC)	209 - 211	6
Water Solubility (g/l @ 25 ºC)	11.7	6
Other Solubility	soluble in alcohol and ether; slightly soluble in ethanol; insoluble in diethyl ether	6
log P_{ow}	0.79 (estimated) 0.97	6,32 6,33
	***p*-Methylaminophenol Sulfate**	
Physical Form	colorless needles or other crystalline products white to beige powder	2 4
Formula Weight (g/mol)	344.38	7
Density (g/ml @ 20 ºC)	0.60 - 0.69	5
Vapor pressure (mmHg @ 25 ºC)	2×10^{-21}	5
Melting Point (ºC)	250-260 (decomp.)	2
Boiling Point (ºC)	> 300	5
Water Solubility (% @ 20 ºC) (g/l @ 25 ºC)	soluble 4.92 81.65	2 4 5
Other Solubility (% @ 23 ºC)	slightly soluble to soluble in alcohol; insoluble in ether less than 1% in ethanol; more than 20% in DMSO	2 4
log P_{ow} (@ 24 ºC at pH 7.2 (@ 25 ºC)	0.04 0.79	4 5
UV/Visible Spectrum (λ_{max}; nm)	220.5, 271.5	4

Table 2. Frequency and concentration of use according to likely duration and exposure and by product category

	p-Methylaminophenol		*p*-Methylaminophenol Sulfate	
	# of Uses	Max Conc of Use	# of Uses	Max Conc of Use
	RLD (2025)[9,10]	% (2025)[11]	RLD (2025)[9,10]	% (2025)[11]
Totals*	**1**	**NR**	**1759**	**NR**
summarized by likely duration and exposure**				
Duration of Use				
Leave-On	*NR*	*NR*	*NR*	*NR*
Rinse-Off	*1*	*NR*	*1937*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Unknown	*NR*	*NR*	*81*	*NR*
Exposure Type				
Baby Products	NR	NR	NR	NR
Children's Makeup	NR	NR	NR	NR
Eye Area	NR	NR	1	NR
Incidental Ingestion	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	82[a]	NR
Incidental Inhalation-Airbrush	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	1	NR	1937	NR
Nail	NR	NR	NR	NR
Other Preparations (Unknown Exposure Type)	NR	NR	81	NR
as reported by product category				
Hair Coloring Preparations				
Hair Dyes and Colors (all types requiring caution statements and patch tests)	NR	NR	1736	NR
Hair Tints	1	NR	98	NR
Hair Rinses (coloring)	NR	NR	15 (r.o.)	NR
Hair Bleaches	NR	NR	5	NR
Eyelash and Eyebrow Dyes	NR	NR	1	NR
Other Hair Coloring Preparation	NR	NR	82 (r.o.)	NR
Other Preparations (i.e., those preparations that do not fit another category)	NR	NR	81	NR

NR – not reported

r.o. = rinse-off

*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.

**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

Table 3. Acute toxicity studies

Test Article	Vehicle	Animals/Group	Concentration/Dose	Protocol	LD_{50}/LC_{50}/Results	Reference
DERMAL						
p-Methylaminophenol Sulfate	not reported	guinea pigs; no further details	1000 mg/kg	Acute dermal toxicity study; no further details	LD_{50} > 1000 mg/kg bw; no mortality observed at 1000 mg/kg bw. No further details provided	[5]
ORAL						
10% suspension of *p*-Methylaminophenol Sulfate	0.5% guar-gum	male mice; no further details	565 mg/kg bw	Acute oral toxicity study; no further details	LD_{50} = 565 mg/kg bw; 50% mortality was observed at dose tested. General depressed activity, tremor, and effects on the kidney, ureter, bladder, and urine composition were observed. No further details provided	[5]
p-Methylaminophenol Sulfate	0.5% carboxymethyl cellulose	preliminary test: 3 female Sprague-Dawley RjSD rats, one for each dose main test: 4 female rats	preliminary test: 100, 200, and 500 mg/kg bw main test: 100 mg/kg bw	Acute oral toxicity study; in preliminary and main test, rats received test material as a single dose after fasting.	Minimum lethal dose = 200 mg/kg and maximum non-lethal dose = 100 mg/kg. In preliminary test, no clinical signs of toxicity or mortality were observed at 100 mg/kg. The 200 mg/kg rat died on day 3 of the observation period; prior to death, hypoactivity, piloerection, and dyspnea were observed. At 500 mg/kg, hypoactivity, sedation, piloerection, dyspnea, and tremors were observed before death on day 4. In the main experiment hypoactivity, piloerection, and dyspnea were observed in all 4 animals within 3 h. Body weights were not affected during the observation period. All animals survived until necropsy, where no abnormalities were observed.	[4]

Table 4. Genotoxicity studies

Ingredient	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Gene Mutation						
p-Methylaminophenol Sulfate, 98.7% pure	0.064 - 1000 µg/plate without metabolic activation; 0.064 - 2000 µg/plate with metabolic activation	not reported	*S. typhimurium* strains TA98, TA100, TA102, TA1535, TA1537	Bacterial reverse mutation test in accordance with OECD test guideline (TG) 471; with and without S9 metabolic activation; appropriate negative and positive controls used	Genotoxic; gene mutations were induced in strain TA100 with and without metabolic activation and in strains TA98 and TA1537 with metabolic activation only	[4]
p-Methylaminophenol Sulfate, 99% pure	up to 1667 µg/plate	DMSO	*S. typhimurium* strains TA98, TA100, TA1535, TA1537	Bacterial reverse mutation test; with and without S9 metabolic activation; appropriate negative and positive controls used	Genotoxic only in strains TA100 and TA1537 with metabolic activation, but not genotoxic without metabolic activation in these strains	[17]
p-Methylaminophenol Sulfate, 99% pure	up to 2000 µg/plate	water	*S. typhimurium* strains TA97, TA98, TA100, TA1535	Bacterial reverse mutation test; with and without S9 metabolic activation; appropriate negative and positive controls used	Genotoxic only in strains TA97 and TA100 with metabolic activation, but not genotoxic without metabolic activation in these strains	[17]
p-Methylaminophenol Sulfate, 99.6% pure	0.1 - 3.0 µg/ml without metabolic activation; 1.0 - 38 µg/ml with metabolic activation	not reported	L5178Y mouse lymphoma cells	Mammalian cell gene mutation test at the TK+/- locus in accordance with OECD TG 476; 3-h exposure with and without metabolic activation; appropriate negative and positive controls used	Genotoxic; test material induced significant increases in the mutant frequencies after 3 h treatment with metabolic activation; no further details provided	[4]
p-Methylaminophenol Sulfate, 98.7% pure	0.5 - 2.0 µg/ml without metabolic activation; 2.5 - 60 µg/ml with metabolic activation	not reported	L5178Y mouse lymphoma cells	Mammalian cell gene mutation test at the *hprt* locus in accordance with OECD TG 476; 3-h exposure with and without metabolic activation; appropriate negative and positive controls used	Not genotoxic; no statistically significant and/or reproducible increases in mutant frequency observed with or without metabolic activation	[4]
Chromosomal Damage						
p-Methylaminophenol Sulfate, 98.7% pure	11.26 - 27.49 µg/ml	not reported	human lymphocytes	Chromosome aberration test in accordance with OECD TG 473; appropriate negative and positive controls used; cultures were exposed to test material for 3 h with and without metabolic activation	Clastogenic with and without metabolic activation; no further details provided	[4]
IN VIVO						
Chromosomal Damage						
p-Methylaminophenol Sulfate, 98.7% pure	100, 200, or 400 mg/kg	not reported	groups of 5 male and 5 female Sprague-Dawley rats	Mammalian bone marrow micronucleus test in accordance with OECD TG 474; rats received a single dose of test material via gavage; rats were killed 24 h after treatment, an additional high dose group of rats were killed 48 h after treatment; appropriate positive and negative controls used	Not genotoxic; one animal in 400 mg/kg group died (sex not stated) with clinical signs of toxicity (not described); micronucleus frequencies were not significantly increased in any treated group when compared to vehicle control; no statistically significant decreases in polychromatic erythrocyte: normochromatic erythrocyte ratios observed in doses up to 400 mg/kg in either sex	[4]

Table 5. Dermal irritation and sensitization studies

Test Article	Vehicle	Concentration/Dose	Test Population/System	Protocol	Results	Reference
IRRITATION						
ANIMAL						
p-Methylaminophenol Sulfate	0.5% carboxymethyl cellulose	3%	3 New Zealand White rabbits; sex not reported	Skin irritation study; test material (0.5 ml) applied with gauze pads to a clipped area of left flank for 3 min, anterior right flank for 1 h, and posterior right flank for 4 h in 1 animal. When no irritation was observed in the 1 animal, test material was applied for 4 h to the additional 2 animals. Skin examined 1, 24, 48, and 72 h after dressing was removed. Test sites were occluded	No reactions observed	[4]
p-Methylaminophenol Sulfate	none	undiluted	guinea pigs; no further details	Skin irritation study; test material applied to depilated skin on the abdomen under occlusion. Single exposure; test site observed for up to 1 wk after application	Not irritating; slight erythema and edema were observed after 24 h; the effects were reversible within 1 wk	[5]
SENSITIZATION						
ANIMAL						
p-Methylaminophenol Sulfate	acetone	induction injection = 0.5% topical induction = 25% challenge = 5%	albino Dunkin-Hartley guinea pigs, no further details provided	GPMT; animals were treated with 6 intradermal injections followed 6-8 d later with a 48 h occluded patch on the injection site. After a 2-wk rest, animals were challenged by a 24-h occluded patch. Challenge sites were scored for erythema and edema 24 and 48 h after patch removal	90% positive response; test material classified as an extreme sensitizer; no further details provided	[21]
p-Methylaminophenol Sulfate	dimethyl formamide	0.5, 1, or 2.5%	groups of 4 CBA/Ca mice; both sexes used, but single experiments limited to 1 sex; no further details provided	LLNA; mice treated with daily topical application of 25 µl test material on dorsal surface of each ear for 3 d; control mice received vehicle alone	positive for sensitization; no further details provided	[21]
p-Methylaminophenol Sulfate	DMSO	0.25, 0.5, 1, 2.5, or 5%	groups of 4 female CBA/J mice	LLNA; mice treated with daily topical application of 25 µl test material on dorsal surface of each ear for 3 d. Negative control was vehicle, positive control was 25% (v/v) α-hexylcinnamaldehyde in DMSO	Moderate sensitizer; no cutaneous reactions were observed at any concentration. There was a dose-related increase in the SI; EC_3 was exceeded at concentrations of 2.5 and 5%. The calculated EC_3 value was 2.2%.	[4]
CROSS-SENSITIZATION						
ANIMAL						
p-Methylaminophenol Sulfate	saline	challenge = 0.5%	groups of 19-21 female outbred albino Dunkin-Hartley guinea pigs, no further details provided	GPMT; intradermal induction with Freund's complete adjuvant and 0.25% CD-2 or 0.25% CD-3 on day 0. Sodium lauryl sulfate topical treatment was performed on day 6, followed by topical induction of either test material at 20% in water on day 7. Challenge patching was performed with *p*-Methylaminophenol Sulfate and read 48 and 72 h after application.	Neither the control nor the animals induced with CD-2 had a positive reaction to the challenge with *p*-Methylaminophenol Sulfate. In the animals induced with CD-3, both the treated and the control groups had a single reaction to the challenge with *p*-Methylaminophenol Sulfate.	[22]
p-Methylaminophenol Sulfate	0.9% sodium chloride solution	intradermal and topical induction = 5% primary challenge = 5%	10 guinea pigs, no further details provided	GPMT; *p*-Methylaminophenol Sulfate administered intradermally and topically. A primary challenge was conducted with *p*-Methylaminophenol Sulfate. Cross-challenges were carried out 1 and 2 wk after the primary challenge using *p*-phenylenediamine (0.5% in 0.9% sodium chloride), *p*-aminophenol and *m*-aminophenol (each 5% in acetone/0.9% sodium chloride (50/50 v/v)), and *p*-benzoquinone (2.5% in acetone/polyethylene glycol 400 (70/30 v/v)). Four naive guinea pigs were controls.	In primary challenge, 9 animals had positive reactions and a questionable reaction was observed in the 10th. In second challenge, nearly all animals were positive to *p*-benzoquinone and *p*-aminophenol (9/10 and 8/10, respectively). Three animals each had positive reactions to *p*-phenylenediamine and *m*-aminophenol.	[23]

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JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 10, Number 1, 1991
Mary Ann Liebert, Inc., Publishers

5

Final Report on the Safety Assessment of *p*-Methylaminophenol Sulfate

_p_-Methylaminophenol Sulfate is a substituted phenol used as a dye and a photographic developer. In skin absorption studies of radioactive _p_-aminophenol, as much as 11% of the radioactivity was found in the excreta, viscera, and skin of rats.

In subchronic and chronic dermal toxicity studies of hair dyes containing _p_-Methylaminophenol Sulfate, among other active ingredients, no toxicologically significant differences were observed between the test and control animals. In an ocular irritation study, this ingredient was considered practically nonirritating to the rabbit eye and only slightly irritating to the skin and was not a sensitizer.

No significant embryotoxic or teratogenic effects were found when hair dyes containing _p_-Methylaminophenol Sulfate were administered to rats.

***p*-Methylaminophenol was not mutagenic in the Ames assay nor in the mouse micronucleus assay and in the Chinese hamster ovary chromosome aberration test. No statistically significant incidences of neoplasms, dermal and other, were found in mice after 21 and 23 months of weekly dermal exposure to hair dyes containing _p_-Methylaminophenol Sulfate.**

When _p_-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction.

On the basis of the available data presented in this report, it is concluded that _p_-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

INTRODUCTION

The following report is a literature review on the chemistry, use, and toxicology of the oxidative hair dye ingredient *p*-Methylaminophenol Sulfate. *p*-Methylaminophenol Sulfate is a substituted *p*-aminophenol, and thus data found in the reports on the aminophenols, as well as on other oxidative hair dye ingredients, such as the phenylenediamines and resorcinols, are useful in the evaluation of the safety of *p*-Methylaminophenol Sulfate. These reports, previously prepared by the Cosmetic Ingredient Review and referenced below, are only summarized here.

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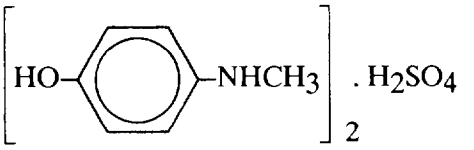
CHEMISTRY

Definition and Structure

p-Methylaminophenol Sulfate is a substituted phenol used as a dye and a photographic developer. *p*-Methylaminophenol Sulfate (CAS No. 55-55-0) is also known as 4-Methylaminophenol Sulfate,[1] N-Methyl-*para*-aminophenol Sulfate,[2] Monomethyl-*p*-aminophenol Sulfate, *p*-Hydroxymethylaniline Sulfate, and commercially as Metol, Pictol, Rhodol, and various other names.[3] It conforms to the following structure:



p-Methylaminophenol Sulfate

PROPERTIES

p-Methylaminophenol Sulfate occurs as colorless needles[2] or other crystalline products.[3] On exposure to air, *p*-Methylaminophenol Sulfate becomes discolored.[2,3] It has a molecular weight of 344.39 and a melting range between 250°C and 260°C.[4] Decomposition of *p*-Methylaminophenol Sulfate occurs upon melting.[3] It is soluble in water,[2,3,4] slightly soluble[3] to soluble[2,4] in alcohol, and insoluble in ether.[2,3]

Method of Manufacture

p-Methylaminophenol Sulfate is manufactured by the methylation of *p*-aminophenol and the subsequent neutralization with sulfuric acid.[2]

Analytical Methods

Infrared, ultraviolet, and nuclear magnetic resonance spectra have been published for *p*-Methylaminophenol Sulfate. The UV spectrum had peaks at 271 and 220 nm, with water as the solvent.[5] A UV spectrum also has been performed on *p*-Methylaminophenol at a concentration of 0.02 g/l in distilled water. The chemical absorbed at 219, 270, and 277 nm.[6] The compound may be determined by thin layer chromatography, using a method that depends on color rather than R_F values as a more reliable method for distinguishing among *o*-, *m*-, and *p*-isomers.[7] In addition, it may be analyzed by either visual or potentiometric titration with N-bromosuccinamide using the following indicators: butaperazine dimaleate, trifluoperazine dihydrochloride, or promethazine hydrochloride.[8]

Chemical Reactions

p-Methylaminophenol Sulfate is used as a primary intermediate in oxidative or permanent hair dyes.[9] The primary intermediate undergoes a reaction with hydrogen

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peroxide (the oxidant) to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye.[10] As an intermediate in combination with other intermediates, *p*-Methylaminophenol Sulfate is capable of producing browns, reds, gold blonds, blues, and grays.[9] More detailed accounts of the reactions of aminophenols and of oxidative hair coloring chemistry have been published previously.[11–14]

USE

Noncosmetic Use

p-Methylaminophenol Sulfate is used in spectrophotometric analyses of such compounds as dapsone,[15] isoniazid,[16] riboflavin,[17] and antibiotics[18] and in the colorimetric analyses of thiamine hydrochloride[19] and penicillins G and V.[16] It also is listed in various patents for pharmaceuticals as a treatment for neoplastic disease.[20,21] *p*-Methylaminophenol Sulfate also is used in film developing.[22]

Cosmetic Use

p-Methylaminophenol Sulfate is used as an intermediate in hair dyes/colors, which usually bear warning labels. According to information voluntarily supplied to the Food and Drug Administration,[23] *p*-Methylaminophenol Sulfate is used in a total of 49 hair dyes (Table 1). Its concentration of use ranges from ≤0.1% (31 products) to 0.1–1% (17 products). One product is listed at >5–10%; this is a powder concentrate that is to be diluted before use.

The FDA cosmetic product formulation computer printout[23] is compiled through voluntary filing of such data in accordance with Title 21 Part 720.4 of the Code of Federal Regulations.[24] Ingredients are listed in present concentration ranges under specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product. The actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provide the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same as one entered at the highest end of that range, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

The oxidative or permanent hair dyes containing *p*-Methylaminophenol Sulfate, as "coal tar" hair dye products,[11] are exempt from the principal adulteration provision and from the color additive provision in Sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation.[25] In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution—This product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

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Patch test instructions call for a 24-h patch on the skin of the user with the intermediates and hydrogen peroxide mixed in the same manner as in use. This test is to be performed prior to each and every application of the hair dye.[26]

Reports containing a more in-depth review of the labeling requirements for "coal tar" hair dyes have been published. Hair dyes containing *p*-Methylaminophenol Sulfate may come into contact with the hair, skin, eyes, and nails, and may be applied every few weeks, or in the case of hairdressers, exposure may be several times daily.[11,12]

GENERAL BIOLOGY

Biochemical Effects

In a study of the effects of various chemicals on the depolarizing or hyperpolarizing effects of acetylcholine on the giant neurons of *Lymnea stagnalis*, *p*-Methylaminophenol Sulfate was inhibitory to the depolarizing action of acetylcholine in 92% of the giant neuron D cells tested. *p*-Methylaminophenol Sulfate did not enhance the action of acetylcholine in any test.[27]

The effects of aminophenols on hemoglobin and methemoglobin in the blood of various species were studied *in vivo* and *in vitro*.[28] In ox erythrocytes in Krebs-Ringer phosphate solution, *p*-Methylaminophenol Sulfate reacted with hemoglobin to form methemoglobin at a much faster rate (40×10^{-5} equiv/L/min) than did *p*-aminophenol. The reaction in dog erythrocytes was considerably faster than that in ox erythrocytes, with all of the *p*-Methylaminophenol Sulfate having disappeared from the solution within 10 min and with the methemoglobin concentration reaching its peak at 5 min. In the erythrocytes of both humans and rabbits, the rate of methemoglobin formation was a little faster than that of ox erythrocytes. When the *p*-Methylaminophenol Sulfate was added to a cell suspension already containing a high concentration of methemoglobin, the methemoglobin concentration decreased initially and then remained unchanged, whereas the aminophenol concentration remained high. Repeated additions of the *p*-Methylaminophenol Sulfate to the same erythrocyte solution had no greater effect on the methemoglobin concentration.

In a second part of the same study, *p*-Methylaminophenol Sulfate was injected intravenously into dogs and cats. The *p*-Methylaminophenol Sulfate was administered at a dose of 15 mg/kg, and after 2 min, the concentration in the blood was 3 μg/ml. The methemoglobin reached its maximum concentration (approximately 7 g/100 ml blood) in both species in 5 to 10 min. In cats, the effect of the dose of *p*-Methylaminophenol Sulfate "increased in proportion to the logarithm of the dose over a wide range of doses." The slopes of the lines characterizing the increase of effect of a particular

TABLE 1. PRODUCT FORMULATION DATA FOR *p*-METHYLAMINOPHENOLSULFATE[23]

Product Category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*		
			>5–10	*>0.1–1*	*≤0.1*
Hair dyes and colors	1073	49	1	17	31
1989 Totals		49	1	17	31

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aminophenol with the log dose were similar for all of the aminophenols tested, but it was noted that the activities of the individual aminophenols varied independently of these slopes.

The authors concluded that the differences between species with regard to the rates of reaction of the aminophenols with hemoglobin were due to the differences in structure of the various hemoglobins. Because both *p*-Methylaminophenol Sulfate (and similar *p*-alkylaminophenols) and *o*-aminophenol cause a rapid increase in methemoglobin concentration and because there is a dose–response relationship, the authors suggested that these aminophenols may be useful for rapid alleviation of the effects of cyanide poisoning.[28]

Absorption, Distribution, Metabolism, and Excretion

p-Methylaminophenol Sulfate is structurally similar to other aminophenols, and the data available on these[11–14] may be useful for assessment of the absorption, distribution, metabolism, and excretion of *p*-Methylaminophenol Sulfate. In addition, because of the similar chemical behavior of the hair dye intermediates previously mentioned, an understanding of the data presented in the completed hair dye reports may provide a better understanding of the potential pathway of *p*-Methylaminophenol Sulfate in the body. Because *p*-Methylaminophenol Sulfate is a substituted aminophenol, the summary of the metabolism data from the Cosmetic Ingredient Review safety assessment of the aminophenols, specifically *p*-aminophenol (PAP), is presented here.[14]

> *In vivo* and *in vitro* studies of skin absorption have been performed using radioactive PAP, MAP [m-aminophenol], phenols and other hair dye intermediates. As much as 11 percent of the radioactivity introduced as ^{14}C-PAP in a simple vehicle was detected in the excreta, viscera and skin of rats after topical application. Hepatic metabolism of aminophenols includes such reactions as glucuronidation, sulfation and acetylation to form aminophenol-conjugates excreted in the urine.[14]

Because the amino group of *p*-Methylaminophenol Sulfate is methylated, this ingredient would not be expected to be acetylated.

In addition, data in the aminophenols report indicated that PAP was not metabolized by tissue preparations of pulmonary and renal microsomes from the rabbit, rat, and mouse.[14]

ANIMAL TOXICOLOGY

Acute Toxicity

Intravenous

In a study to determine the varying effects of aminophenols on hemoglobin and oxygen *in vitro* and *in vivo*, the i.v. LD_{50} for *p*-Methylaminophenol Sulfate in NMRI mice was estimated as 85 mg/kg.[28]

Groups of 5 female hooded rats were used in a comparative study of the nephrotoxicity of aspirin and its derivatives and of phenacetin derivatives (which are structurally similar to *p*-Methylaminophenol).[29] *p*-Methylaminophenol Sulfate was

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administered intravenously to two groups of rats at doses of 0.1 mM/kg and 0.6 mM/kg. Renal proximal tubular necrosis was observed and was graded 1 to 4 to indicate the degree of severity. Necrosis of individual cells or groups of cells but not of all of the cells in adjoining tubules was defined as grade 1, and grade 4 was defined as necrosis of the entire proximal convoluted tubule. Those rats with grade 4 renal damage died in anuria, but the other test rats remained in good condition throughout the study. Those rats receiving the lower dose of *p*-Methylaminophenol Sulfate had grade 3 lesions of the tubules (necrosis of the distal third of all tubules as indicated by a band of necrosis in the inner cortex), whereas those rats receiving the higher dose had grade 4 lesions. The phenacetin derivatives were more nephrotoxic than aspirin and its derivatives, and the renal damage induced by the phenacetin derivatives was more clearly dose dependent than that caused by the aspirin derivatives. The authors concluded that a *para* arrangement of the amino and hydroxyl groups on the benzene ring was the basis for the nephrotoxicity of the phenacetin derivatives. In addition, substitutions on the amino group could also affect the nephrotoxicity of a particular compound, as in the case of *p*-Methylaminophenol Sulfate. The dose of *p*-aminophenol required to cause renal toxicity of grade 3 was approximately 20 times greater than that of *p*-Methylaminophenol Sulfate (2.1 mM/kg and 0.1 mM/kg, respectively).

Subchronic Dermal Toxicity

Two hair dye formulations containing 0.05% and 1.0% *p*-Methylaminophenol Sulfate were tested for dermal toxicity in groups of 12 adult New Zealand white rabbits.[30] These dye formulations contained other active ingredients in an aqueous solution and were mixed with an equal volume of 6% H_2O_2 prior to application. The formulations were applied twice weekly for 13 weeks to the clipped skin, with the skin of 3 rabbits of each group having been abraded at the beginning of each week. No significant differences were found between control and test animals with respect to body weight gain and urinalyses, and no discoloration of the urine was produced by the dyes. Statistically significant differences were found in some organ weights and in certain clinical chemistry and hematological values, but these were not considered toxicologically significant.

Chronic Dermal Toxicity

Two hair dye formulations containing 0.05% and 1.0% *p*-Methylaminophenol Sulfate were administered topically to groups of male and female Eppley Swiss Colony mice weekly for periods of 23 and 21 months, respectively.[31] The dye formulations were mixed with an equal volume of 6% H_2O_2, and a dose of 0.05 ml was applied to the clipped skin within 15 min. At the conclusion of the study, the survival rates and organ/body weight ratios of the test animals did not differ significantly from those of the controls, although there was considerable variation among the individual values.

Ocular Irritation

A 2% solution of *p*-Methylaminophenol in distilled water, 0.10 ml, was instilled into the conjunctival sac of the right eye of 6 albino rabbits, the eyes were not rinsed, and the untreated left eye served as a control.[32] The eyes were examined 1, 2, 3, 4, and

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7 days after instillation of the test substance. The eyes were also examined under UV light with fluorescein dye. Three of the rabbits had no reaction to the *p*-Methylaminophenol. Of the remaining 3 rabbits, 1 rabbit had slight redness of the conjunctiva on days 1 and 2, clearing by day 3; 1 rabbit had slight redness of the conjunctiva on day 1 that had cleared by day 2; and the third rabbit had severe redness of the conjunctiva that moderated through days 2 and 3 and cleared by day 4. This rabbit also had a slight discharge on day 1 that did not continue through day 2. The test group average irritation score on day 1 was 2 out of a total possible score of 110; on day 2, the group average was 1/110; on day 3, the group average was 0.33/110. The score was 0 for the rest of the study. *p*-Methylaminophenol was considered practically nonirritating to the rabbit eye.

Dermal Irritation and Sensitization

Dermal Irritation

The primary irritation potential of *p*-Methylaminophenol was assessed using 6 albino Bouscat rabbits, equally divided by sex.[33] *p*-Methylaminophenol, 0.5 ml of a 2% solution in distilled water, was applied under a patch to abraded and intact skin on the flanks of each rabbit. The patches remained in place for 24 h. The test sites were evaluated 1/2 h after patch removal and again 48 h later. Two rabbits had slight erythema at both the intact and the abraded sites at both readings. One rabbit had slight erythema at both sites at the first reading, and 1 rabbit had slight erythema at the abraded site at the first reading. These reactions had subsided by the 48 h reading. The remaining 2 rabbits had no reactions. The primary irritation index (PII) for *p*-Methylaminophenol was 0.74 out of a maximum of 8, and the ingredient was considered slightly irritating to rabbit skin.

Dermal Sensitization

The skin sensitization potential of *p*-Methylaminophenol was evaluated using 20 albino Hartley guinea pigs, 10 of each sex.[34] A preliminary study to determine the dose of *p*-Methylaminophenol to be used in the challenge phase of the definitive study had been previously done using 4 Hartley guinea pigs and doses of 0.25 g and 0.5 g of undiluted *p*-Methylaminophenol per animal. Patch sites were evaluated 1, 6, 24, and 48 h after patch removal. Because the test substance caused a slight discoloration of the skin, erythema scores made at 1 h were not accurate. None of the guinea pigs had any sign of erythema or edema at any of the scorings. No evidence of sensitization was noted during the study. The dose of *p*-Methylaminophenol to be used during the challenge phase of the definitive sensitization study was determined to be 0.5 g. At the start of the definitive study, 6 h after the area behind the left shoulder blade of each guinea pig had been shaved, 0.5 g of *p*-Methylaminophenol was applied under an occlusive patch to the shaved area, where it remained for 48 h. Evaluations of the site were made 1, 6, 24, and 48 h after patch removal. Any of the animals that had signs of orthoergic reactions were eliminated from the study. During the induction phase of the study, 0.5 g of *p*-Methylaminophenol was applied under an occlusive patch to the shaved area behind the right shoulder blade every Monday, Wednesday, and Friday for 3 weeks and on the Monday of week 4. Patches remained in place for 48 h. Twice during the induction phase, at the first and fifth patch applications, the test site was injected with 0.1 ml of Freund's complete adjuvant at a concentration of 50% in sterile

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isotonic saline. After removal of the final (tenth) patch, there was a 12-day nontreatment period. At the end of this period (day 36 of the study), an area on the left flank of each guinea pig was shaved, and 0.5 g of the test substance was applied under an occlusive patch, remaining in place for 48 h. Evaluations of the challenge site were made 1, 6, 24, and 48 h after patch removal, and erythema and edema were scored on a scale of 1 to 4. Histological examinations were performed on any animal that had lesions or in which a doubtful reaction was noted. Two of the guinea pigs died during the study; death was not related to treatment with *p*-Methylaminophenol. Of the 18 remaining guinea pigs, 3 had doubtful signs of erythema, 2 at the 6 h evaluation, and 1 at the 24 h evaluation. No reactions were noted in the other 15 guinea pigs. Biopsies were performed on the 3 animals that had doubtful reactions. The stratum corneum, cuticle, dermis, and appendages were examined, and no signs of sensitization were noted. *p*-Methylaminophenol was not considered a dermal sensitizer under the conditions of the study.

Teratogenicity

Two hair dye formulations containing *p*-Methylaminophenol Sulfate at concentrations of 0.05% and 1% were tested by topical application at a dose of 2 ml/kg every 3 days for a total of seven doses during gestation to the shaved dorsoscapular region of groups of 20 mated Charles River CD female rats.[30] The hair dye ingredients were in aqueous solution, and there were other active ingredients, such as phenylenediamines and aminophenols, present in the solutions. The hair dyes also were mixed with 6% H_2O_2 before application. No significant embryotoxic or teratogenic effects were observed.

MUTAGENICITY AND CARCINOGENICITY

Mutagenicity

p-Methylaminophenol was tested for mutagenic potential in the Ames assay using *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538.[35] The positive control was 2-aminoanthracene. *p*-Methylaminophenol was tested at concentrations ranging from 30 μg to 2.0 mg. Though *p*-Methylaminophenol did not appear to be mutagenic, it was toxic to the bacterial cells, especially to strains TA98 and TA1538, in the absence of S-9 mix. *p*-Methylaminophenol, at concentrations ranging from 8 to 500 μg/plate, was retested in strains TA98 and TA1538 with metabolic activation to determine whether possible mutagenic activity was masked by the toxicity of the compound when not detoxified by the S-9 mix. No mutagenic activity was noted in the repeat test, and *p*-Methylaminophenol was considered nonmutagenic in the Ames assay.

The micronucleus test also was used to determine the mutagenic potential of *p*-Methylaminophenol.[36] Groups of 10 male Swiss mice were administered two i.p. injections 24 h apart of 50, 75, or 100 mg/kg *p*-Methylaminophenol. A vehicle control (Baker water) group also was included. The mice were killed, and bone marrow was extracted from the femurs of each mouse 30 h after the first injection. Two smears were made from each mouse. When the smears were dry, they were colored with May Grundwald Giemsa. The number of micronuclei-containing polychromatophile eryth-

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rocytes were recorded out of a sample of 2000 polychromatophile erythrocytes per mouse. An increase in the number of micronuclei was considered evidence of mutagenic action. Under the conditions of the study, *p*-Methylaminophenol was considered nonmutagenic in the mouse micronucleus assay.

p-Methylaminophenol was tested for mutagenic potential in the chromosome aberration test using Chinese hamster ovary (CHO) cells.[37] CHO cells were treated for 1 h, with and without metabolic activation, with 0.125, 0.25, 0.5, or 1 mg/ml *p*-Methylaminophenol. Usually, the cells that are exposed to the test chemical without metabolic activation remain in contact with the test chemical until fixation at 6, 12, or 16 h, but because of the toxicity of the *p*-Methylaminophenol, treatments were administered for 1 h only for assays with or without metabolic activation, and fixation times remained at 6, 12, and 16 h. Methyl methanesulfonate (MMS) and cyclophosphamide were the positive controls. Chromosomal aberrations were scored per 100 metaphasic cells. A positive response was indicated when the frequency of aberrations increased in a dose-dependent manner. The 1 mg/ml dose resulted in few, if any, metaphases, and only doses of 0.5 mg/ml and below were scored. Though *p*-Methylaminophenol was quite toxic to CHO cells, no evidence of mutagenic potential was observed under the conditions of the study.

Carcinogenicity

In the chronic dermal toxicity study previously described,[31] the mice also were evaluated for neoplasms at the end of the 21 and 23-month treatment periods. Of special interest were neoplasms of the skin, which were of low incidence. Several other types of neoplasms were found at necropsy and microscopic evaluation, but none of the incidences were statistically significant. The authors concluded that the hair dye formulations tested did not have any carcinogenic effects.

CLINICAL ASSESSMENT OF SAFETY

Occupational Studies

Because certain chemicals used in photographic developing were known to cause skin diseases, an evaluation of the skin diseases reported by employees at a film developing plant was undertaken.[22] The study was an attempt to determine the frequency and types of occupational and nonoccupational dermatoses among the plant employees. The study consisted of five parts. In the first part, the employees responded to a questionnaire detailing their previous and current tasks at the plant and any previous or current skin diseases. In the second part of the study, all of the questionnaire respondents who had indicated previous or current skin diseases were invited to be examined by a doctor. At the examination, the patients were questioned about any skin problems (past or present) and about their tasks at the plant. If any skin lesions were present, these were examined, noted, and treated. A preliminary assessment of any correlation between skin disease and job was made at this time. In the third stage of the study, those patients who were thought to have occupationally related dermatoses were offered the chance to be patch tested with 11 standard series substances and with 20 film laboratory chemicals. The patches remained in place for 48 h and were scored 24 h and 2 to 3 weeks after patch removal. At this stage in the study, 23 patients were tested

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with Metol (*p*-Methylaminophenol Sulfate). Of the 23 test subjects, 6 had positive reactions to Metol at concentrations of 5% and 1%. Of these 6 subjects, 3 were also positive for either two or three of the following chemicals: CD-2, CD-3 (chemical name not specified), *p*-phenylenediamine (PPDA), and PBA-1 (persulfate bleach accelerator-1, found to be a potent sensitizer). Metol, at a concentration of 1%, was then tested on a group of 200 control subjects (eczema patients without known previous contact with the chemical), and 1 subject had a positive reaction. The fourth and fifth stages of the study involved testing five different glove materials for protection against Metol and chemical CD-2 and a guinea pig allergy test on another chemical, PBA-1. Forty-nine percent of the film laboratory employees had been afflicted with occupational dermatoses directly related to their work with film laboratory chemicals. Contact allergies to the chemicals Metol, CD-2, CD-3, and PBA-1 were found in 28% of the employees working with the chemicals. In many of these contact allergy cases, the reactions had been so severe that the employees had either seen a doctor, changed jobs, or taken sick leave.

EPIDEMIOLOGY

There have been a number of studies published attempting to determine a possible correlation between the use of hair dyes and an increased risk of cancer.[11] Clemmesen[38] has reviewed many of these reports, pointing out the difficulties involved in epidemiological studies, such as small sample sizes, varying intensities and durations of exposure, lag times, and lack of consideration of such lifestyle factors as tobacco consumption. Because of these deficiencies, he concluded that there was not a positive correlation between hair dye use and an increased risk of cancer. His conclusion was supported by a later study of 401 breast cancer patients and 625 age-matched controls without breast cancer in whom no significant differences were found between the two populations with regard to the frequency, duration, type, shade, and application times of hair dyes.[39]

SUMMARY

p-Methylaminophenol Sulfate is a substituted phenol used as a dye and a photographic developer. It is manufactured by the methylation of *p*-aminophenol followed by neutralization with sulfuric acid. *p*-Methylaminophenol Sulfate may be determined analytically by infrared, ultraviolet, and nuclear magnetic resonance spectra, by thin layer chromatography, and by visual or potentiometric titration. *p*-Methylaminophenol Sulfate absorbed in the UV range at 220 and 271 nm, whereas *p*-Methylaminophenol absorbed at 219, 270, and 277 nm.

In oxidative hair dyes, *p*-Methylaminophenol Sulfate is used as a primary intermediate. It reacts with an oxidant to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye. It is listed as an ingredient in 38 hair dye formulations, its concentration ranging from $\leq$0.1% to 0.1–1%. In addition, it is listed at concentrations of $>$ 1–5% and $>$5–10%, respectively, in two powder dye formulations that are to be diluted before use.

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p-Methylaminophenol Sulfate was an inhibitor of the depolarizing action of acetylcholine on the giant neurons of *Lymnea stagnalis*. In the erythrocytes of oxen, dogs, rabbits, and humans, *p*-Methylaminophenol Sulfate caused the formation of methemoglobin at a much greater rate than did *p*-aminophenol.

In skin absorption studies of radioactive *p*-aminophenol, as much as 11% of the radioactivity was found in the excreta, viscera, and skin of rats. Aminophenols undergo glucuronidation, sulfation, and acetylation reactions in the liver. The aminophenol conjugates formed in these reactions are excreted in the urine. *p*-Aminophenol was not metabolized by tissue preparations of pulmonary and renal microsomes from several species.

The intravenous LD_{50} of *p*-Methylaminophenol Sulfate in NMRI mice was 85 mg/kg. The dose of *p*-Methylaminophenol Sulfate causing necrosis of the distal third of all tubules of the kidneys of hooded rats was 0.1 mM/kg, 20 times greater than the dose of *p*-aminophenol required to produce the same effect.

In subchronic and chronic dermal toxicity studies of hair dyes containing *p*-Methylaminophenol Sulfate, among other active ingredients, no toxicologically significant differences were observed between the test and control animals (rabbits and mice, respectively).

In an ocular irritation study, *p*-Methylaminophenol was considered practically nonirritating to the rabbit eye.

p-Methylaminophenol was slightly irritating to rabbit skin in a primary irritation study and was not considered a dermal sensitizer in a guinea pig skin sensitization study.

No significant embryotoxic or teratogenic effects were found when hair dyes containing *p*-Methylaminophenol Sulfate and other active ingredients were administered topically to Charles River CD rats once every 3 days for a total of 21 days during gestation.

p-Methylaminophenol was not mutagenic in the Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The *p*-Methylaminophenol was toxic to the bacterial cells, especially to those of strains TA98 and TA1538, in the absence of metabolic activation. Additional testing in strains TA98 and TA1538 with metabolic activation indicated that the toxic effect of the *p*-Methylaminophenol did not mask any possible mutagenic effect. *p*-Methylaminophenol was nonmutagenic in the mouse micronucleus assay and in the Chinese hamster ovary chromosome aberration test.

No statistically significant incidences of neoplasms, dermal and other, were found in mice after 21 and 23 months of weekly dermal exposure to hair dyes containing *p*-Methylaminophenol Sulfate in addition to other active ingredients.

Of 23 panelists known to have occupationally related dermatoses who were patch tested with *p*-Methylaminophenol Sulfate, 6 had positive reactions to the ingredient at concentrations of 1 and 5%. Three of these panelists also had positive reactions to two or three of a group of four chemicals used in film laboratories. When *p*-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction.

A number of studies have been performed in order to determine the possibility of a correlation between the use of hair dyes and an increased risk for cancer. No positive correlation has been found.

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CONCLUSION

On the basis of the available data presented in this report, the CIR Expert Panel concludes that *p*-Methylaminophenol Sulfate is safe as a cosmetic ingredient in the present practices of use and concentration.

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*Available for review: Director, Cosmetic Ingredient Review, 1101 17th Street, N.W., Suite 310, Washington, DC 20036.

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Amended Report of the Cosmetic Ingredient Review Expert Panel

Amended Safety Assessment of p-Methylaminophenol Sulfate and p-Methylaminophenol

December 10, 2007

All interested persons are provided 60 days from the above date to comment on this Tentative Safety Assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings , will be available at the CIR office for review by any interested party, and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. F. Alan Andersen.

The 2007 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Lillian Becker, Scientific Analyst/Writer.

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INTRODUCTION

The following report is an Amended Tentative Report on the chemistry, use, and toxicology of the oxidative hair dye ingredients p-Methylaminophenol Sulfate and p-Methylaminophenol (p-MAP). The ingredient p-Methylaminophenol Sulfate was previously reviewed by the Cosmetic Ingredient Review (CIR) Expert Panel and was found to be "...safe as a cosmetic ingredient in the present practices of use and concentration". The original safety assessment considered data on the safety of p-MAP but did not include the ingredient in the conclusion (Elder 1991). Upon re-review, the Expert Panel felt that there was enough data to include p-MAP in the safety assessment. Therefore, this Tentative Amended Report adds the ingredient p-MAP.

In further support of the addition of p-MAP, the data in the original safety assessment of p-Aminophenol, m-Aminophenol, and o-Aminophenol are relevant (Elder 1988); this safety assessment has been re-reviewed by the Expert Panel and that data is also relevant. Both of these documents are summarized in this report.

CHEMISTRY

DEFINITION AND STRUCTURE

p-Methylaminophenol Sulfate (CAS Nos. 55-55-0 and 1936-57-8) and p-MAP (CAS No. 150-75-4) are substituted phenols. The are chemically classified as amines, color additives - hair, and phenols (Gottschalck and McEwen 2006).

p-Methylaminophenol Sulfate is also known as 4-(Methylamino)Phenol Sulfate (Estrin et al. 1982; Gottschalck and McEwen 2006); N-Methyl-para-Aminophenol Sulfate (Hawley 1971); Monomethyl-p-Aminophenol Sulfate; p-Hydroxymethylaniline Sulfate (Windholz 1983); Metol; Paramethylaminophenol Sulfate; and Phenol, 4-(Methylamino)-Sulfate Salt (2:1) (Gottschalck and McEwen 2006). It is also known as: 1-Hydroxy-4-Methylamino-Benzine Hemisulphate, 4-(Methylammonio)-Phenol Sulphate, N-(Methyl-4-Ammoniophenol) Sulphate, 4-Hydroxy-N-Methylanilinium Sulphate, p-Hydroxy-N-Methylaniline Sulphate, N-Methyl-4-Hydroxyanilinium Sulphate, N-Methyl-p-Hydroxyaniline Sulphate, and N-Methyl-N-(4-Hydroxy)Phenylammonium Sulphate (Scientific Committee on Consumer Products [SCCP] 2006). It is known commercially as Metol, Pictol, Rhodol,

and various other names (Windholz 1983) as well as Colorex PM and Rodol PM (Gottschalck and McEwen 2006). It conforms to the structure in Figure 1A.

p-MAP is also known as the following technical names: 4-Hydroxy-N-Methylaniline; 4-(Methylamino)Phenol; N–Methyl-p-Hydroxyaniline; Paramethylaminophenol; and Phenol, 4-(Methylamino)- (Gottschalck and McEwen 2006). It conforms to the structure in Figure 1B.

In many instances in the literature, the common name Metol, used for photographic developing, refers to both p-MAP and p-Methylaminophenol Sulfate interchangeably. In several publications on Metol, it is not clear which ingredient is being tested. In this paper, where the identification of the ingredient is clear it is identified; where the identification is not clear, the term Metol is used.

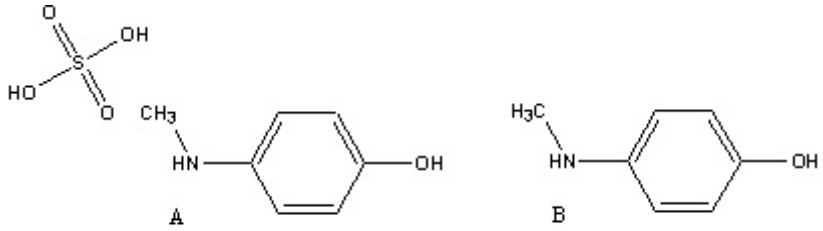

Figure 1. The structures of A) p-Methylaminophenol Sulfate and B) p-Methylaminophenol.

PROPERTIES

p-METHYLAMINOPHENOL SULFATE

p-Methylaminophenol Sulfate occurs as colorless needles (Hawley 1971) or other crystalline products (Windholz 1983). On exposure to air, p-Methylaminophenol Sulfate becomes discolored (Hawley 1971; Windholz 1983). It has a molecular weight of 344.39 and a melting range between 250°C and 260°C (Weast 1983). Decomposition of p-Methylaminophenol Sulfate occurs upon melting (Windholz 1983). It is soluble in water (Hawley 1971; Windholz 1983; Weast 1983), slightly soluble (Windholz 1983) to soluble (Hawley 1971; Weast 1983) in alcohol, and insoluble in ether (Hawley 1971; Windholz 1983).

p-METHYLAMINOPHENOL

p-MAP at 5 x 10^{-3} M is stable in the dark, at room temperature and pH values lower than ~7 for at least 1 week. The concentration decreases slowly over time at basic pH values (pH 9 decreases the concentration to ~86% after 24 h). Stability can be maintained by storage in nitrogen saturated solutions; oxidation with dissolved oxygen causes instability (Aceituno et al. 2002).

METHOD OF MANUFACTURE

p-Methylaminophenol Sulfate is manufactured by the methylation of p-aminophenol and the subsequent neutralization with sulfuric acid (Hawley 1971).

ANALYTICAL METHODS

Infrared, ultraviolet (UV), and nuclear magnetic resonance spectra have been published for p-Methylaminophenol Sulfate. The UV spectrum had peaks at 271 and 220 nm, with water as the solvent (Grasselli 1975). A UV spectrum also has been performed on p-Methylaminophenol at a concentration of 0.02 g/l in distilled water. The chemical absorbed at 219, 270, and 277 nm (L'Oreal 1989). The compound may be determined by thin layer chromatography (TLC), using a method that depends on color rather than R_F values as a more reliable method for distinguishing among o-, m-, and p-isomers (Mitchell and Waring 1978). In addition, it may be analyzed by either visual or potentiometric titration with N-bromosuccinamide using the following indicators: butaperazine dimaleate, trifluoperazine dihydrochloride, or promethazine hydrochloride (Gowda and Ahmed 1978).

IMPURITIES

The SCCP (2006) reported on the test of 3 batches of p-Methylaminophenol Sulfate and report the purity to be ≥97.0% (w/w) by titre and >97.5% by high-performance liquid chromatography (HPLC). The sulphate ion content was 30.0% to 30.5%. Water and ash content were < 0.1%. Other impurities include p-Aminophenol (~2.5g/100g) and N,N'-dimethylparaphenylenediamine (<0.4 g/100 g). Heavy metal impurities included: arsenic, antimony, and mercury (< 5 mg/kg); cadmium(< 10 mg/kg); and lead (< 20 mg/kg). There were no residual solvents detected.

CHEMICAL REACTIONS

p-Methylaminophenol Sulfate is used as a primary intermediate in oxidative or permanent hair dyes (Balsam and Sagarin 1972). The primary intermediate undergoes a reaction with hydrogen peroxide (the oxidant) to produce the corresponding imine, which then reacts with a coupler to form an indophenol

dye (Frost and Horowitz 1982). As an intermediate in combination with other intermediates, p-Methylaminophenol Sulfate is capable of producing browns, reds, gold blonds, blues, and grays (Balsam and Sagarin 1972).

NITROSATION

The SCCP (2006) stated that p-Methylaminophenol Sulfate is a secondary amine, thus prone to nitrosation. They have no information on the nitrosamine content of this ingredient.

USE

COSMETIC USE

The ingredients p-Methylaminophenol Sulfate and p-MAP are used as an intermediate in hair dyes/colors, which usually bear warning labels. According to information voluntarily supplied to the Food and Drug Administration (FDA 1989), p-Methylaminophenol Sulfate was used in a total of 49 hair dyes at the time of the first safety assessment (Table 1). Its concentration of use ranged from < 0.1% (31 products) to 10% (17 products). One product is listed at X-1 0%; this is a powder concentrate that was to be diluted before use. p-Methylaminophenol Sulfate is currently used in 112 hair coloring products (FDA 2006) with a concentration range of 0.1% to 0.7% (Cosmetic, Toiletry, and Fragrance Association [CTFA] 2007).

FDA (2006) has no reported uses for p-MAP. CTFA (2007) reports that p-MAP is used at the concentration of 0.7% in hair coloring products (Table 1).

Table 1. Historical and current cosmetic product uses and concentrations for p-Methylaminophenol Sulfate and p-MAP.

Product Category	1989 uses (Elder 1991)	2006 uses (FDA 2006)	1981 concentrations (Elder 1991) (%)	2007 concentrations (CTFA 2007) (%)
		p-Methylaminophenol Sulfate		
Hair coloring products				
Dyes and colors	49	112	<0.1-10	0.1-0.7
Total uses/ranges for p-Methylaminophenol Sulfate	**49**	**112**	**<0.1-10**	**0.1-0.7**
		p-Methylaminophenol		
Hair coloring products				
Dyes and colors	n/a	-	n/a	0.7
Total uses/ranges for p-Methylaminophenol	**n/a**	**-**	**n/a**	**0.7**

Both p-Methylaminophenol Sulfate and p-MAP are considered coal tar hair dyes for which regulations require caution statements and instructions regarding patch tests in order to be exempt from the principal adulteration provision and from the color additive provision in sections 601 and 706 of the Federal Food, Drug, and Cosmetic Act of 1938 (FDA 1979).

Product labels shall bear a caution statement and patch test instructions for determining whether the product causes skin irritation. In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

> Caution - this product contains ingredients which may cause skin irritation on certain individuals and a preliminary test according to accompanying directions should be made. This product must not be used for dyeing the eyelashes or eyebrows; to do so may cause blindness.

At its February 11, 1992 meeting, the Cosmetic Ingredient Review (CIR) Expert Panel issued the following policy statement on coal tar hair dye product labeling:

> The Cosmetic Ingredient Review (CIR) Expert Panel has reviewed the cosmetic industry's current coal tar hair dye product labeling, which recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 24 hours after application of the test material and prior to the use of a hair dye formulation.
>
> Since the recommendation on the industry's adopted labeling establishes a procedure for individual user safety testing, it is most important that the recommended procedure be consistent with current medical practice.
>
> There is a general consensus among dermatologists that screening of patients for sensitization (allergic contact dermatitis) should be conducted by the procedures used by the North American Contact Dermatitis Group and the International Contact Dermatitis Group (North American Contact Dermatitis Group, 1980; Eiermann et al., 1982; Adams et al., 1985). Basically, these procedures state that the test material should be applied at an acceptable concentration to the patient, covered with an appropriate occlusive patch, and evaluated for sensitization at 48 and 72 hours after application. The CIR Expert Panel has cited the results of studies conducted by both the North American Contact Dermatitis Group and the International Contact Dermatitis Group in its safety evaluation reports on cosmetic ingredients (Elder, 1985).
>
> During the August 26-27, 1991 public meeting of the CIR Expert Panel, all members agreed that the cosmetics industry should change its recommendation for the evaluation of the open patch test from 24 hours to 48 hours after application of the test material.
>
> The industry was advised of this recommendation and asked to provide any compelling reasons why this recommendation should not be made by the Expert Panel and adopted by the cosmetics industry. No opposition to this recommendation was received. At the February 11, 1992 public meeting of the CIR Expert Panel, this policy statement was adopted.

NON-COSMETIC USE

The ingredient p-Methylaminophenol Sulfate is used in spectrophotometric analyses of such compounds as dapsone (Siraj et al. 1981), isoniazid (Siraj et al. 1982), riboflavin (Sastry et al. 1986a), and antibiotics (Sastry et al 1986b) and in the calorimetric analyses of thiamine hydrochloride (Sane et al. 1985) and penicillins G and V (Siraj et al. 1982). It also is listed in various patents for pharmaceuticals as

a treatment for neoplastic disease (Danila 1984; Leontopol and Andronescu 1984). p-Methylaminophenol Sulfate also is used in film developing (Liden 1984a,b).

Both p-Methylaminophenol Sulfate and p-MAP are used to in the film developing process (Brancaccio et al. 1993; Aceituno et al. 2002).

The ingredient p-Methylaminophenol Sulfate is used to react with Nicorandil ((*N*-92-nitroxy)ethyl]3-pyridine carboxamide), a potassium channel activator, for its detection in drug formulation and biological fluids by color recognition (Rahman et al. 2004).

INTERNATIONAL

The European Commission (2002) restricts the concentration of p-Methylaminophenol and its salts to 1.5% in combination with hydrogen peroxide.

p-Methylaminophenol and its sulfates are listed as quasi-drugs by the Minister of Health and Welfare of Japan (Ministry of Health, Labor and Welfare [MHLW] 2001).

GENERAL BIOLOGY

ABSORPTION

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported on an in vitro absorption study using 8 female human skin donors (5 breast and 3 abdomen donors; n = 12 samples). The skin was frozen until use. Skin samples were dermatomed and mounted in flow-through diffusion cells with calcium and magnesium-free phosphate buffered saline in the receptors. [^{14}C]p-Methylaminophenol Sulfate was applied under oxidative (use) and non-oxidative conditions. In the former, the test substance was incorporated into a hair coloring formulation at 1.35% (w/w) associated to the coupler m-Aminophenol at 0.86% (w/w) before mixing with oxidative developer (1:1, w/w) giving a final concentration of 0.68% p-Methylaminophenol Sulfate. In the latter, the test substance was incorporated into the same formulation (without a coupler) at 1.35% (w/w) before mixing with water (1:1, w/w), also at a concentration of 0.68%. The test preparations (~20 mg/cm^2) were applied to the skin surface for 30 min. The skin surfaces were then washed. Twenty-four h after application, the percutaneous absorptions of [^{14}C]p-Methylaminophenol Sulfate was measured.

One oxidative cell did not yield usable results. Most of the p-Methylaminophenol Sulfate, oxidative and non-oxidative, was removed at washing (91.34% and 90.70%, respectively). At 24 h, an

additional 1.37% and 0.73% was recovered, for total recoveries of 96.42% and 97.74%, respectively. The receptors held 0.49 ± 0.24 (0.36%) and 3.04 ± 1.10 µg equiv/cm^2 (2.21%), respectively (Table 2).

Table 2. Recovery of p-Methylaminophenol Sulfate after application to human skin (SCCP 2006).

	Oxidative conditions in hair dye formulation		Non-oxidative conditions	
Cutaneous distribution	µg equiv/cm^2	% applied dose	µg equiv/cm^2	% applied dose
Extractable dose	125.60 ± 3.80	92.72 ± 3.17	126.03 ± 6.14	91.44 ± 4.73
Receptor fluid	0.49 ± 0.24	0.36 ± 0.18	3.04 ± 1.10	2.21 ± 0.80
Dermal delivery (receptor fluid + epidermis/dermis)	1.35 ± 0.78	1.00 ± 0.59	6.19 ± 2.24	4.49 ± 1.62

DISTRIBUTION

The SCCP (2006) reported on the oral administration of p-Methylaminophenol Sulfate to Sprague Dawley (Crl CD(SD) IGS BR) rats (n = 10 of each sex). The test substance (0, 3, 10, or 30 mg/kg/d) was administered daily for 13 weeks (additional details are in the SUBCHRONIC TOXICITY section). Blood was sampled on day 1 and in week 13 at 0.5, 1, 2, 4, 8, and 24 h after dosing. Plasma levels of p-Methylaminophenol Sulfate were below detectable limits at all time points in the 3 mg/kg/d group and only detectable at 0.5 h in week 13 in the 10 mg/kg/d group. In the high dose group, the maximum plasma level was at 0.5 h at both day 1 and week 13. The levels quickly decreased and p-Methylaminophenol was below detectable limits at 2 h on day 1 and 4 h at week 13. No definitive gender or time effects to the plasma levels were observed.

NEPHROTOXIC EFFECTS

p-METHYLAMINOPHENOL SULFATE

Groups of 5 female hooded rats were used in a comparative study of the nephrotoxicity of aspirin and its derivatives and of phenacetin derivatives (which are structurally similar to p-MAP) (Calder et al. 1971). p-Methylaminophenol Sulfate was administered intravenously to 2 groups of rats at doses of 0.1 mM/kg and 0.6 mM/kg. Renal proximal tubular necrosis was observed and was graded 1 to 4 to indicate the degree of severity. Grade 1 was defined as necrosis of individual cells or groups of cells but not of all of the cells in adjoining tubules, and grade 4 was defined as necrosis of the entire proximal convoluted tubule. Those rats with grade 4 renal damage died in anuria, but the other test rats remained

in good condition throughout the study.

Those rats receiving the lower dose of p-Methylaminophenol Sulfate had grade 3 lesions of the tubules (necrosis of the distal third of all tubules as indicated by a band of necrosis in the inner cortex), whereas those rats receiving the higher dose had grade 4 lesions. The phenacetin derivatives were more nephrotoxic than aspirin and its derivatives, and the renal damage induced by the phenacetin derivatives was more clearly dose dependent than that caused by the aspirin derivatives. The authors concluded that a *para* arrangement of the amino and hydroxyl groups on the benzene ring was the basis for the nephrotoxicity of the phenacetin derivatives. In addition, substitutions on the amino group could also affect the nephrotoxicity of a particular compound, as in the case of p-Methylaminophenol Sulfate. The dose of p-aminophenol required to cause renal toxicity of grade 3 was approximately 20 times greater than that of p-Methylaminophenol Sulfate (2.1 mM/kg and 0.1 mM/kg, respectively).

BIOCHEMICAL EFFECTS

p-METHYLAMINOPHENOL SULFATE

In a study of the effects of various chemicals on the depolarizing or hyperpolarizing effects of acetylcholine on the giant neurons of *Lymnea stagnalis*, p-Methylaminophenol Sulfate was inhibitory to the depolarizing action of acetylcholine in 92% of the giant neuron D cells tested. p-Methylaminophenol Sulfate did not enhance the action of acetylcholine in any test (Puppi and Kiss 1973).

The effects of aminophenols on hemoglobin and methemoglobin in the blood of various species were studied in vivo and in vitro (Kiese and Rachor 1964). In ox erythrocytes in Krebs-Ringer phosphate solution, p-Methylaminophenol Sulfate reacted with hemoglobin to form methemoglobin at a much faster rate (40 x 10-5 equiv/l/min) than did p-aminophenol. The reaction in dog erythrocytes was considerably faster than that in ox erythrocytes, with all of the p-Methylaminophenol Sulfate having disappeared from the solution within 10 min and with the methemoglobin concentration reaching its peak at 5 min. In the erythrocytes of both humans and rabbits, the rate of methemoglobin formation was a little faster than that of ox erythrocytes. When the p-Methylaminophenol Sulfate was added to a cell suspension already containing a high concentration of methemoglobin, the methemoglobin concentration decreased initially and then remained unchanged, whereas the aminophenol concentration remained high. Repeated additions of the p-Methylaminophenol Sulfate to the same erythrocyte solution had no greater effect on

the methemoglobin concentration.

In a second part of the same study, p-Methylaminophenol Sulfate was injected intravenously into dogs and cats. The p-Methylaminophenol Sulfate was administered at a dose of 15 mg/kg, and after 2 min, the concentration in the blood was 3 pg/ml. The methemoglobin reached its maximum concentration (approximately 7 g/100 ml blood) in both species in 5 to 10 min. In cats, the effect of the dose of p-Methylaminophenol Sulfate "...increased in proportion to the logarithm of the dose over a wide range of doses." The slopes of the lines characterizing the increase of effect of a particular aminophenol with the log dose were similar for all of the aminophenols tested, but it was noted that the activities of the individual aminophenols varied independently of these slopes.

The authors concluded that the differences between species with regard to the rates of reaction of the aminophenols with hemoglobin were due to the differences in structure of the various hemoglobins. Because both p-Methylaminophenol Sulfate (and similar p-alkylaminophenols) and o-aminophenol cause a rapid increase in methemoglobin concentration and because there is a dose-response relationship, the authors suggested that these aminophenols may be useful for rapid alleviation of the effects of cyanide poisoning (Kiese and Rachor 1964).

ANTIOXIDATIVE ACTIVITY

p-METHYLAMINOPHENOL

Takahashi et al. (2002) used an α,α-diphenyl-β-picrylhydrazyl (DPPH) radical analysis to test the antioxidant activities of p-MAP. Ethanol (2 ml) and DPPH (500μM) were added to an acetic acid buffer (pH 5.5, 2 ml). To 5 ml of this mixture 100 μl of 1mM solution of p-MAP dissolved in dimethylsulfoxide (DMSO) and cysteine in acetic acid buffer were added. The final concentrations were 10, 20, and 40 μM. The mixture was incubated for 30 min at room temperature and absorbance measured at 517 nm. Acetic acid buffer or DMSO in place of p-MAP served as the blank.

The control absorbance was ~0.99; the absorbance of 20 μM p-MAP was 0.60, a 40% decrease from DPPH radicals relative to the control. p-MAP exhibited a dose-dependent antioxidant activity in the range of 0 to 40 μM to the same extent as vitamin E. One molecule of p-MAP scavenged 2 DPPH

radical molecules.

These authors also used microsomes (0.5 mg protein/ml) from Sprague-Dawley rats (Slc. SD) to measure microsomal lipid peroxidation by measurement of malondialdehyde using adenosine 5'-diphosphate (ADP)-chelating ions and ascorbate. p-MAP dissolved in DMSO in 100 mM Tris-HCl (pH 7.5) containing 15 μM $FeCl_3$ and 4 mM ADP were preincubated at 37°C for 1 min. Reaction mixtures with ascorbic acid (1 mM) were incubated at 37°C for 20 min. An equal volume of tert-butyl alcohol (TBA) reagent was added, the mixtures heated in boiling water for 15 min, and centrifuged. Absorbance was measured at 535 nm.

Malondialdehyde formation, resulting from the breakdown of polyunsaturated fatty acids, was inhibited in a dose-dependent manner by p-MAP in the range of 1 to 10 μM. The approximate median inhibition concentration (IC_{50}) was 4.5 μM (Takahashi et al. 2002).

Takahashi et al. (2003) used a DPPH radical assay, as above, to measure the antioxidant properties of p-MAP and to compare them to similar compounds. p-MAP exhibited the same level of antioxidant activity relative to vitamin E as *p*-hexylaminophenol, *p*-octylaminophenol, and *p*-methoxybezylaminophenol in a dose-dependent manner in the range of 0 to 20 μM.

These authors used a lipid-derived malondialdehyde production test, as above, to measure lipid peroxidation in vitro. p-MAP inhibited lipid peroxidation in a dose-dependent manner in the range of 1 to 5 μM with an IC_{50} of ~4.6 μM (Takahashi et al. 2003).

CYTOTOXICITY

p-METHYLAMINOPHENOL

Richard et al. (1991), after growing the cells in a medium including [^{14}C]thymidine (TdR) (0.01 μCi/ml) for 24 h, exposed V79 Chinese hamster cells to p-MAP at various concentrations (up to 0.5% for 30 min; n = 2). [^{3}H]TdR (4 μCi/ml) was then incorporated into the medium for a 10-min pulse-labeling period. The incorporation of [^{14}C]TdR and [^{3}H]TdR into the DNA was determined by liquid scintillation counting. The IC_{50} for p-MAP was 0.022 mM and it was classified as having a high inhibition of DNA synthesis.

Takahashi et al. (2002) used cultured human myeloid leukemia cells (HL-60) in medium containing p-MAP (1 or 10 μM) for 94 h to measure growth inhibition. At 1 μM p-MAP inhibited

approximately 33% of HL-60 cell growth and ~99.7% at 10 µM.

DNA isolated from HL-60 cells exposed to 1 or 10 µM p-MAP for 24 h was extracted and dried under vacuum then dissolved in sample solution for analysis by agarose gel electrophoresis. Ethidium bromide was used to visualize the presence of DNA in the gels. There was no DNA fragmentation due to exposure to the lower concentration (1 µM) of p-MAP; the higher concentration (10 µM) contained fragmented ladder DNA demonstrating that p-MAP may potentially induce apoptosis of HL-60 cells.

These authors exposed HL-60R cells (resistant to retinoic acid; 1 and 2 x 10^5/ml, respectively) to various concentrations of p-MAP. Cell count was determined by electric particle counter and viability by trypan blue dye exclusion. This experiment was repeated with MCF-7 and MCF-7/AdrR cells (having and not having estradiol receptors, respectively).

HL-60R cell growth was completely inhibited by p-MAP (>99%) at 10 µM while retinoic acid was inactive (no other results were provided). p-MAP inhibited MCF-7 cell growth in a dose-dependent manner; at 10 µM cell growth was inhibited ~20% for MCF-7 cells. At 10 µM cell growth was inhibited ~60% for MCF-7/AdrR cells. The proliferation of HepG2 and DU-145 cells was also suppressed by exposure to p-MAP at 40 µM by >80% (Takahashi et al. 2002).

ANIMAL TOXICOLOGY

ACUTE TOXICITY

ORAL

P-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported a study where 3 female Sprague Dawley Rj:SD rats were orally administered a single dose of 100, 200, or 500 mg/kg p-Methylaminophenol Sulfate (in 0.5% suspension of carboxymethylcellulose) after fasting. At 500 mg/kg, hypoactivity, sedation, piloerection, dyspnea, and tremors were observed before death on day 4. At 200 mg/kg, hypoactivity, piloerection, and dyspnea were observed before death on day 3. There were no clinical signs and the rat lived until the end of the 14-d observation period at 100 mg/kg.

A single dose of p-Methylaminophenol Sulfate (100 mg/kg) was administered orally to 4 more rats. No deaths occurred. Hypoactivity, piloerection, and dyspnea were observed in all 4 animals within

3 h. Body weight was not affected during the observation period. There were no abnormalities observed at necropsy. The authors conclude that the maximum non-lethal dose of p-Methylaminophenol Sulfate was 100 mg/kg and the minimal lethal dose was 200 mg/kg (SCCP 2006).

INTRAVENOUS

P-METHYLAMINOPHENOL SULFATE

The i.v. LD_{50} for p-Methylaminophenol Sulfate in NMRI mice was estimated as 85 mg/kg (Kiese and Rachor 1964).

SUBCHRONIC TOXICITY

DERMAL

p-METHYLAMINOPHENOL SULFATE

Two hair dye formulations containing 0.05% and 1.0% p-Methylaminophenol Sulfate were tested for dermal toxicity in groups of 12 adult New Zealand white rabbits (Burnett et al. 1976). These dye formulations contained other active ingredients in an aqueous solution and were mixed with an equal volume of 6% hydrogen peroxide (H_2O_2) prior to application. The formulations were applied twice weekly for 13 weeks to the clipped skin, with the skin of 3 rabbits of each group having been abraded at the beginning of each week. No significant differences were found between control and test animals with respect to body weight gain and urinalyses, and no discoloration of the urine was produced by the dyes. Statistically significant differences were found in some organ weights and in certain clinical chemistry and hematological values, but these were not considered toxicologically significant.

ORAL

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported on the daily oral administration of p-Methylaminophenol Sulfate to Sprague Dawley (Crl CD (SD) IGS BR) rats for 92 d. Six additional rats were followed for a 4-week recovery period in the control and high-dose groups. The rats (n = 10 of each sex) were administered 0 (vehicle only), 3, 10 or 30 mg/kg/d in a 0.5% suspension of carboxymethylcellulose. The rats were weighed and observed for clinical signs. The rats were killed and necropsied.

No deaths occurred. No clinical signs were observed nor any changes were seen in function observation battery parameters or motor activity. Body weights and food consumption rates were

unaffected. There were no ophthalmological findings. There were no effects on the hematology or blood biochemistry parameters. The males in the high-dose group had a higher urinary output with a lower specific gravity. There were no notable observations at necropsy. Microscopic examination found tubular epithelial degeneration/single cell necrosis in the kidneys of most males and half the females in the high-dose group but not the rats who had the 4-week recovery period. The authors conclude that the no observed adverse effect level (NOAEL) was 10 mg/kg/d.

CHRONIC TOXICITY

DERMAL

p-METHYLAMINOPHENOL SULFATE

Two hair dye formulations containing 0.05% and 1.0% p-Methylaminophenol Sulfate were administered topically to groups of male and female Eppley Swiss Colony mice (n = 50) weekly for periods of 23 and 21 months, respectively (Burnett et al. 1980). The dye formulations were mixed with an equal volume of 6% H_2O_2, and a dose of 0.05 ml was applied to the clipped skin within 15 min. At the conclusion of the study, the survival rates and organ/body weight ratios of the test animals did not differ significantly from those of the controls, although there was considerable variation among the individual values.

OCULAR IRRITATION

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported on the administration of p-Methylaminophenol Sulfate (0.1 ml at 3% in 0.5% aqueous carboxymethylcellulose) into the conjunctival sac of the left eyes of New Zealand White rabbits (n = 3). The eyes were examined at 1, 24, 48, and 72 h after application. One rabbit had chemosis and redness of the conjunctiva at 1 h. No other signs of ocular irritation were noted.

p-METHYLAMINOPHENOL

A 2% solution of p-MAP in distilled water, 0.10 ml, was instilled into the conjunctival sac of the right eye of 6 albino rabbits, the eyes were not rinsed, and the untreated left eye served as a control (L'Oreal 1977a). The eyes were examined 1, 2, 3, 4, and 7 d after instillation of the test substance. The eyes were also examined under UV light with fluorescein dye. Three of the rabbits had no reaction to the p-MAP. Of the remaining 3 rabbits, 1 rabbit had slight redness of the conjunctiva on days 1 and 2,

clearing by day 3; 1 rabbit had slight redness of the conjunctiva on day 1 that had cleared by day 2; and the third rabbit had severe redness of the conjunctiva that moderated through days 2 and 3 and cleared by day 4. This rabbit also had a slight discharge on day 1 that did not continue through day 2. The test group average irritation score on day 1 was 2 out of a total possible score of 110; on day 2, the group average was 1/110; on day 3, the group average was 0.33/110. The score was 0 for the rest of the study. p-MAP was considered practically nonirritating to the rabbit eye.

DERMAL IRRITATION

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported a dermal irritation test of p-Methylaminophenol Sulfate (0.5 ml at 3% in 0.5% aqueous carboxymethylcellulose) on New Zealand White rabbits (n = 3). The test substance was placed on gauze pads and applied to a clipped area of the left flank for 3 min, anterior right flank for 1 h, and the posterior right flank for 4 h. The gauze was held in place under a semi-occlusive dressing. The skin was examined 1, 24, 48, and 72 h after removal of the dressing. No reactions were observed.

p-METHYLAMINOPHENOL

The primary irritation potential of p-Methylaminophenol was assessed using 6 albino Bouscat rabbits, equally divided by sex (L'Oreal 1977b). p-MAP, 0.5 ml of a 2% solution in distilled water, was applied under a patch to abraded and intact skin on the flanks of each rabbit. The patches remained in place for 24 h. The test sites were evaluated 0.5 h after patch removal and again 48 h later. Two rabbits had slight erythema at both the intact and the abraded sites at both readings. One rabbit had slight erythema at both sites at the first reading, and 1 rabbit had slight erythema at the abraded site at the first reading. These reactions had subsided by the 48-h reading. The remaining 2 rabbits had no reactions. The primary irritation index (PII) for p-MAP was 0.74 out of a maximum of 8, and the ingredient was considered slightly irritating to rabbit skin.

DERMAL SENSITIZATION

p-METHYLAMINOPHENOL SULFATE

Lidén and Boman (1988) performed the guinea pig maximization test (GPMT) to test for cross-reactivity between 4-N,N-diethyl-2-methyl-1,4-phenylenediamine · HCl (CD-2) or 4-(N-ethyl-N-2-methansulphonamido- ethyl)-2-methyl-1,4-phenylenediamine · H_2SO_4 · H_2O (CD-3) and p-

Methylaminophenol Sulfate. Induction was carried out at 0.25% (11.64 mmo/l for CD-2 and 5.73% for CD-3 in saline) intradermally. The challenge with p-Methylaminophenol Sulfate was carried out at 0.5% in saline and read 48 h after application. Neither the control (n = 19) nor treated (n = 20) animals had a positive reaction for CD-2. Both the treated (n = 21) and the control (n = 21) groups had a single reaction to p-Methylaminophenol Sulfate for CD-3.

Basketter and Lidén (1992) performed the GPMT using p-Methylaminophenol Sulfate (5.0%) administered intradermally in 0.9% sodium chloride (NaCl) solution and applied topically in 0.9% NaCl (n = 10). Cross-challenges were carried out 1 and 2 weeks after the primary challenge using: paraphenylenediamine (PPDA; 0.5%) in 0.9% NaCl, p-aminophenol and m-aminophenol (5.0%) in acetone/0.9% NaCl (50/50 v/v), and p-benzoquinone (2.5%) in acetone/polyethylene glycol 400 (70/30 v/v). Four naive guinea pigs were controls. There was sensitization to all test chemicals due to exposure to p-Methylaminophenol Sulfate (Table 3).

Table 3. Results of cross-challenges in a GPMT of p-Methylaminophenol Sulfate (Basketter and Lidén 1992).

Challenge Material (concentration)	Number of positive reactions	Mean erythema score, scale 0 - 3
p-Methylaminophenol Sulfate (5.0%)	9 + ?1/10	1.5
p-Phenylenediamine (0.5%)	3 + ?3/10	0.9
p-Benzoquinone (2.5%)	9/10	1.6
p-Aminophenol	8/10	1.3
m-Aminophenol	3/10	0.9
Control	0/4	0

The SCCP (2006) reported a local lymph node assay (LLNA) of p-Methylaminophenol Sulfate (25 µl at 0.25%, 0.5%, 1%, 2.5%, and 5% in DMSO) on female CBA/J mice (n = 4). The test substance was administered to the dorsal surface of both ears daily for 3 d. The negative control received the vehicle; the positive control received 25% (v/v) α-hexylcinnamaldehyde in DMSO. The animals were observed daily. Ear thickness was measured on days 1, 2, 3, and 6. On day 6, all mice were administered 250 µl 0.9% sodium chloride containing 20 µCi tritiated thymidine. The mice were killed 5 h later and the auricular lymph nodes excised, pooled, suspended, and proliferation of these cells measured by scintillation counting. No cutaneous reactions were observed at any concentration. There was a dose-related increase in the stimulation index; the threshold positive value of 3 (EC_3) was

exceeded at concentrations of 2.5% and 5%. The calculated EC_3 value was 2.23%. The authors conclude that p-Methylaminophenol Sulfate induced delayed contact hypersensitivity and should be considered a moderate sensitizer.

p-METHYLAMINOPHENOL

The skin sensitization potential of p-MAP was evaluated using 20 albino Hartley guinea pigs, 10 of each sex (Institut de Formation en Région Bretagne [IFREB] 1978). A preliminary study to determine the dose of p-MAP to be used in the challenge phase of the definitive study had been previously done using 4 Hartley guinea pigs and doses of 0.25 g and 0.5 g of undiluted p-MAP per animal. Patch sites were evaluated 1, 6, 24, and 48 h after patch removal. Because the test substance caused a slight discoloration of the skin, erythema scores made at 1 h were not accurate.

In the preliminary study, none of the guinea pigs had any sign of erythema or edema at any of the scorings. No evidence of sensitization was noted during the study. The dose of p-MAP to be used during the challenge phase of the definitive sensitization study was determined to be 0.5 g. At the start of the definitive study, 6 h after the area behind the left shoulder blade of each guinea pig had been shaved, 0.5 g of p-MAP was applied under an occlusive patch to the shaved area, where it remained for 48 h. Evaluations of the site were made 1, 6, 24, and 48 h after patch removal. Any of the animals that had signs of orthoergic reactions were eliminated from the study. During the induction phase of the study, 0.5 g of p-MAP was applied under an occlusive patch to the shaved area behind the right shoulder blade every Monday, Wednesday, and Friday for 3 weeks and on the Monday of week 4. Patches remained in place for 48 h. Twice during the induction phase, at the first and fifth patch applications, the test site was injected with 0.1 ml of Freund's complete adjuvant at a concentration of 50% in sterile isotonic saline. After removal of the final (tenth) patch, there was a 12-day non-treatment period. At the end of this period (day 36 of the study), an area on the left flank of each guinea pig was shaved, and 0.5 g of the test substance was applied under an occlusive patch, remaining in place for 48 h. Evaluations of the challenge site were made 1, 6, 24, and 48 h after patch removal, and erythema and edema were scored on a scale of 1 to 4. Histological examinations were performed on any animal that had lesions or in which a doubtful reaction was noted.

Two of the guinea pigs died during the study; death was not related to treatment with p-MAP. Of

the 18 remaining guinea pigs, 3 had doubtful signs of erythema, 2 at the 6 h evaluation, and 1 at the 24 h evaluation. No reactions were noted in the other 15 guinea pigs. Biopsies were performed on the 3 animals that had doubtful reactions. The stratum corneum, cuticle, dermis, and appendages were examined, and no signs of sensitization were noted. p-MAP was not considered a dermal sensitizer under the conditions of the study (IFREB 1978).

METOL

Basketter and Scholes (1992) tested Metol using both the GPMT and the LLNA. In the GPMT, induction was 6 injections (0.5%) in the shoulder region followed 6 to 8 d later by an occluded induction patch (25%) applied for 48 h. The challenge patch was 5.0%. After 24 and/or 48 h, 90% of the animals were judged to be positive for a reaction to Metol giving a rating of extreme for sensitization. In the LLNA, Metol was tested at 0.5%, 1.0%, and 2.5% with an exposure of 5 d with dimethyl formamide as the vehicle. The ratios of test to control lymphocyte proliferation were 2.5, 3.4, and 6.7, respectively. The authors classified the 90% reaction as extreme. The authors gave Metol a positive rating for sensitization.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

p-METHYLAMINOPHENOL SULFATE

Two hair dye formulations containing p-Methylaminophenol Sulfate at concentrations of 0.05% and 1% were tested by topical application at a dose of 2 ml/kg every 3 days for a total of 7 doses during gestation to the shaved dorsoscapular region of groups of 20 mated Charles River CD female rats (Burnett et al. 1976). The hair dye ingredients were in aqueous solution, and there were other active ingredients, such as phenylenediamines and aminophenols, present in the solutions. The hair dyes also were mixed with 6% H_2O_2 before application. No significant embryotoxic or teratogenic effects were observed.

The SCCP (2006) reported a teratogenicity study on Sprague Dawley (Crl CD (SD) IGS BR) rats. The rats (n = 24) were orally administered p-Methylaminophenol Sulfate (0, 5, 25, or 125 mg/kg/d) on days 6 to 19 post coitum. The rats were observed for clinical signs; food consumption and body weight were monitored. On day 20, the rats were killed and necropsied. The uterus was weighed and

fetuses weighed and examined. There were no deaths during the study and no treatment related signs were observed. Net body weight gain was slightly reduced in the 25 and 125 mg/kg/d groups. No treatment-related findings were reported at necropsy. There were no effects observed in the litters. There were no treatment-related malformations or variations in any of the fetuses.

METOL

Balaji and Kannan (1988) exposed the egg masses of the nematode *Meliodogyne incognita* to various concentration of Metol. The eggs were withdrawn at 24 h intervals and counted (n = 5). Controls were exposed to distilled water. At 1000 ppm, the hatchability of the egg masses was 644 ± 2.35, 48.48% of the control at 1250 ± 0.71 (Table 4).

Table 4. The hatchability of *M. incognita* eggs exposed to Metol (Balaji and Kannan 1988).

Concentration (ppm)				
Control	1000	500	250	125
1250 ± 0.71	644 ± 2.35 (48.48%)	700 ± 2.45 (44.00%)	758 ± 1.41 (39.36%)	813 ± 3.08 (34.96%)

GENOTOXICITY

p-METHYLAMINOPHENOL SULFATE

The SCCP (2006) reported a mutagenicity test of p-Methylaminophenol Sulfate (0.064 to 1000 µg/ plate without S9 mix and 0.064 to 2000 µg/plate with S9 mix) using *Salmonella typhimurium* TA98, TA100, TA1535, TA1537, and TA102. The test was run in duplicate. p-Methylaminophenol Sulfate induced gene mutations in TA100 (with and without S9), and TA1537 (with S9). The authors concluded that the test substance is mutagenic in the bacterial gene mutation assay.

The SCCP (2006) reported on an in vitro chromosome aberration test using human lymphocytes with and without S9 at 11.26 to 27.49 µg/ml p-Methylaminophenol Sulfate. The lymphocytes were exposed for 3 h and harvested at 20 h. There was an increase in frequency of chromosome aberration with and without S9. The authors conclude that p-Methylaminophenol Sulfate was clastogenic in mammalian cells in vitro.

The SCCP (2006) reported on a mammalian cell gene mutation test on p-Methylaminophenol Sulfate using L5178Y mouse lymphoma cells (TK+/-). The test was run in triplicate with (1.0 to 38 µg/ml) and without S9 (0.1 to 3.0 µg/ml) for 3 h. p-Methylaminophenol Sulfate induced increases in the mutant

frequencies in the presence of S9.

The SCCP (2006) reported on a mammalian cell gene mutation test on p-Methylaminophenol Sulfate using L5178Y mouse lymphoma cells (HPRT). The test was run in duplicate with (2.5 to 60 µg/ml) and without S9 (0.5 to 2.0 µg/ml) for 3 h. p-Methylaminophenol Sulfate did not induce increases in the mutant frequencies in the presence or absence of S9.

The SCCP (2006) reported a rat bone marrow micronucleus test using Sprague-Dawley rats (5 male, 5 female) to evaluate the mutagenicity of p-Methylaminophenol Sulfate (100, 200, and 400 mg/kg by gavage). One rat died in the 400 mg/kg group. There was no observed bone marrow toxicity. There were no increase in chromosome aberrations or damage to the mitotic apparatus in the bone marrow cells of the rats.

The SCCP (2006) reported on an unscheduled DNA synthesis (UDS) assay on p-Methylaminophenol Sulfate using Wistar Han rats (n = 3). The test substance was administered by gavage at 50 and 500 mg/kg; the rats were killed 16 h later. An additional high-dose group was killed at 2 h. One rat in the high-dose group died. There was no induction of UDS in any group; there was no difference in viability of hepatocytes in any group.

p-METHYLAMINOPHENOL

Yoshikawa et al. (1976) performed an Ames test of p-MAP (15 to 150 µg/plate) using *S. typhimurium* TA98 with and without S9. It was found to be non-mutagenic (Table 5).

The mutagenic potential of p-MAP was tested in the Ames assay using *S. typhimurium* strains TA98, TA100,T A1535, TA1537, and TA1538 (Inveresk Research International 1979). The positive control was 2-aminoanthracene. The concentrations of p-MAP tested ranged from 30 pg to 2.0 mg. Though p-MAP did not appear to be mutagenic, it was toxic to the bacterial cells, especially to strains TA98 and TA1538, in the absence of S-9 mix. At concentrations ranging from 8 to 500 pg/plate, p-MAP was retested in strains TA98 and TA1538 with metabolic activation to determine whether possible mutagenic activity was masked by the toxicity of the compound when not detoxified by the S-9 mix. No mutagenic activity was noted in the repeat test, and p-MAP was considered nonmutagenic in the Ames assay.

The micronucleus test also was used to determine the mutagenic potential of p-MAP (L'Oreal

1982). Groups of 10 male Swiss mice were administered 2 intraperitoneal (i.p.) injections 24 h apart of 50, 75, or 100 mg/kg p-MAP. A vehicle control (Baker water) group also was included. Under the conditions of the study, p-MAP was considered nonmutagenic in the mouse micronucleus assay.

The uterotrophic potential of p-MAP was evaluated in the chromosome aberration test using Chinese hamster ovary (CHO) cells (L'Oreal 1983). CHO cells were treated for 1 h, with and without metabolic activation, with 0.125, 0.25, 0.5, or 1 mg/ml p-MAP. Usually, the cells that are exposed to the test chemical without metabolic activation remain in contact with the test chemical until fixation at 6, 12, or 16 h, but because of the toxicity of the p-MAP, treatments were administered for 1 h only for assays with or without metabolic activation, and fixation times remained at 6, 12, and 16 h. Methyl methanesulfonate (MMS) and cyclophosphamide were the positive controls. Chromosomal aberrations were scored per 100 metaphasic cells. A positive response was indicated when the frequency of aberrations increased in a dose-dependent manner. The 1 mg/ml dose resulted in few, if any, metaphases, and only doses of 0.5 mg/ml and below were scored. Though p-MAP was quite toxic to CHO cells, no evidence of mutagenic potential was observed under the conditions of the study.

CARCINOGENICITY

p-METHYLAMINOPHENOL SULFATE

In the chronic dermal toxicity study previously described (Burnett et al. 1980) of two hair dye formulations, one with 1.0% and the other with 0.05% p-Methylaminophenol Sulfate. The mice (8 to 10 weeks old; n = 50; 12 treatment groups; 3 negative control groups) also were evaluated for neoplasms at the end of the 21- and 23-month treatment periods. Of special interest were neoplasms of the skin, which were of low incidence. Several other types of neoplasms were found at necropsy and microscopic evaluation, but none of the incidences were statistically significant. There was no differences in liver or kidney weights. The authors concluded that the hair dye formulations tested did not have any carcinogenic effects.

The SCCP (2006) reported on a carcinogenicity test of topically applied p-Methylaminophenol Sulfate on male and female Sprague Dawley rats (n = 60). The same hair dyes (0.5 ml) as in the previous study were applied to the shaved neck and back area of the rats twice weekly for 114 weeks.

There were 3 control groups containing 60 males and 60 females. The rats were observed for signs of toxicity and mortality daily. Hematological, biochemical, and urinalysis studies were conducted on 5 males and 5 females/group at 3, 12, 18, and 24 months. At 12 months, 5 males and 5 females/group were killed and necropsied. All the rats were killed when survival of a group reached 20% or at 114 weeks.

Survival to 114 weeks was 16 to 24 males and 14 to 17 females/treatment group and 15 males and 9 to 18 females in the control groups. Body weights in the treatment groups for males was 713 to 719 g and 443 to 513 g for females; in the control groups the body weights were 682 to 759 g for males and 477 to 513 g for females. The dyes containing p-Methylaminophenol Sulfate did not affect survival nor produced any adverse effects. There were no differences observed in the biochemical analyses. Females treated with the hair dye containing 0.5% p-Methylaminophenol Sulfate had an increase in incidence of mammary adenomas when compared to a single control group, but not the other 2 control groups. Life-table analyses found no treatment-related variations (SCCP 2006).

CLINICAL ASSESSMENT OF SAFETY

P-METHYLAMINOPHENOL SULFATE

Basketter and Lidén (1992) patch tested p-Methylaminophenol Sulfate on patients (n = 10, 9 women, 1 man) with a history of a positive patch test reaction to p-phenylenediamine (scored ++ or +++). Finn Chambers and Scanpor tape were used to apply the patches to the upper back. The patches were left in place for 2 d and the readings were performed 3 d after application. The minimum criteria for a positive reaction was erythema and infiltration. Four of the 10 patients had positive reactions to the p-Methylaminophenol Sulfate (2 +, 1 ++, and 1 +++).

METOL

Lisi and Hansel (1998) employed patch tests to the upper back with Van der Bend square chambers to test 22 patients (9 male, 13 female; 19 to 72 years old) sensitized to p-phenylenediamine for sensitivity to Metol (4 of these patients also had benzoquinone-positive tests). Patches were read on days 2 and 4 after 2 d of exposure. Five patients had positive reactions to Metol, 2 of them were among the 4 sensitive to benzoquinone.

OCCUPATIONAL STUDIES

p-METHYLAMINOPHENOL SULFATE

Because certain chemicals used in photographic developing were known to cause skin diseases, an evaluation of the skin diseases reported by employees at a film developing plant was undertaken (Lidén 1984a). The study was an attempt to determine the frequency and types of occupational and nonoccupational dermatoses among the plant employees. The study consisted of multiple parts. In the first part, the employees responded to a questionnaire detailing their previous and current tasks at the plant and any previous or current skin diseases. In the second part of the study, all of the questionnaire respondents who had indicated previous or current skin diseases were invited to be examined by a doctor. At the examination, the patients were questioned about any skin problems (past or present) and about their tasks at the plant. If any skin lesions were present, these were examined, noted, and treated. A preliminary assessment of any correlation between skin disease and job was made at this time.

In the third stage of the study, those patients who were thought to have occupationally-related dermatoses were offered the chance to be patch tested with 11 standard series substances and with 20 film laboratory chemicals. The patches remained in place for 48 h and were scored 24 h and 2 to 3 weeks after patch removal. At this stage in the study, 23 patients were tested with p-Methylaminophenol Sulfate. Of the 23 test subjects, 6 had positive reactions to p-Methylaminophenol Sulfate at concentrations of 5% and 1%. Of these 6 subjects, 3 were also positive for either 2 or 3 of the following chemicals: CD-2, CD-3, PPDA, and persulfate bleach accelerator-1 (PBA-1; found to be a potent sensitizer). p-Methylaminophenol Sulfate, at a concentration of 1%, was then tested on a group of 200 control subjects (eczema patients without known previous contact with the chemical); 1 subject had a positive reaction.

Forty-nine percent of the film laboratory employees had been afflicted with occupational dermatoses directly related to their work with film laboratory chemicals. Contact allergies to the chemicals p-Methylaminophenol Sulfate, CD-2, CD-3, and PBA-1 were found in 28% of the employees working with the chemicals. In many of these contact allergy cases, the reactions had been so severe that the employees had either seen a doctor, changed jobs, or taken sick leave (Lidén 1984a).

Lidén (1988) patch tested 23 volunteers with dermatoses who worked in film developing plants for sensitization to p-Methylaminophenol Sulfate (1% and 5% in water). Induction was for 48 h and read at 72 h after application. Minimum criteria for a positive reading was erythema and infiltration. Six of 23 patients who work with p-Methylaminophenol Sulfate and other film developing chemicals had positive patch test for this ingredient at 1% or 5%.

In testing for the occurrence of occupational dermatoses at a film laboratory following plant-wide modernization to minimize exposure to chemicals, Lidén (1989) patch tested the employees for sensitivity to p-Methylaminophenol Sulfate at 0.1%, 0.5%, and 1% in both water and petrolatum. The induction patches were in place for 48 h, read 72 h after exposure, and read again after 2 weeks (when possible). Six of 14 employees tested positive. No new reactions were noted after 2 weeks. Of 39 subjects, one had recurring hand eczema who patch tested positive for colophone, Venice turpentine, hydroquinone, and p-Methylaminophenol Sulfate.

In control patch tests on unexposed subjects, 2 of 11 tested positive to aqueous solutions of p-Methylaminophenol Sulfate (1%) using the Finn Chamber and 4 of 11 tested positive to the same solution using the A1-test. There were no positive results for p-Methylaminophenol Sulfate in petrolatum (1%) (Lidén 1989).

p-Methylaminophenol Sulfate is listed as an allergen in Kodak photographic developing systems material safety data sheets (Scheman and Katta 1997).

METOL

Lidén (1984b) patch tested 23 employees of a film processing plant with contact dermatitis after exposure to Metol, CD-2, CD-3, and PBA-1 for sensitivity to Metol (5% and 1% aqueous). Patches were left on for 48 h and read 72 h after application and 2 to 3 weeks later. Two hundred non-exposed volunteers were also patch tested. Six of the 23 Metol exposed employees tested positive. One in 200 non-exposed volunteers tested positive.

Lidén and Brehmer-Andersson (1988) patch tested 24 people (23 men, 1 woman) who had developed dermatoses caused by color developing agents (including CD-2 and CD-3) for an allergic reaction to Metol at 1% in petrolatum. Induction patches were removed after 48 h and read 72 h after application. A second reading was taken at 2 to 3 weeks for 18 cases. Four of the volunteers had a

positive result at 72 h. There were no positive reactions at 2 to 3 weeks.

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semipermanent) hair dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes are a preformed color.

While the safety of individual hair dye ingredients are not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information and have been considered by the CIR Expert Panel.

In 1993, an International Agency for Research on Cancer (IARC) working group evaluated 78 epidemiology literature citations and concluded that "...personal use of hair colourants cannot be evaluated as to its carcinogenicity..." and that "...occupation as a hairdresser or barber entails exposures that are probably carcinogenic" (IARC 1993). The IARC report did not distinguish between personal use of oxidative/permanent versus direct hair dyes, or distinguish among the multiple chemical exposures in addition to hair dyes to which a hairdresser or barber might be exposed.

Rollison et al. (2006) reviewed the available epidemiology literature published since 1992. The authors found that hair dye exposure assessment ranged from ever/never use to information on type, color, duration and frequency of use. The authors found insufficient evidence to support a causal association between personal hair dye use and a variety of tumors and cancers. The review highlighted well-designed studies with an exposure assessment that included hair dye type, color, and frequency or duration of use, which found associations between personal hair dye use and development of acute leukemia, bladder cancer, multiple myeloma, and non-Hodgkin's lymphoma. These findings, however, were not consistently observed across studies.

The CIR Expert Panel did specifically note reports from a case-control study (Gago-Dominguez et al. 2001, 2003), which did suggest a possible genetically susceptible subgroup, which detoxify arylamines to a lower degree than the general population. The study authors hypothesized that this subgroup may be at greater risk of bladder cancer from hair dye exposure. Rollison et al. (2006) noted that these results were based on small sample sizes.

Several studies published since 2003 also have been considered. Discussion of the available hair dye epidemiology data is also available at http://www.cir-safety.org/findings.shtml.

Bladder Cancer - Andrew et al. (2004) reported a case-control study of New Hampshire residents whose bladder cancers were entered into a state registry from 1994 to 1998. A follow-up study by Kelsey et al. (2005) examined the links between those bladder cancer cases with an inactivated tumor suppressor gene (TP53) and various exposures. Huncharek and Kupelnick (2005) performed a meta-analysis of 6 case-control and 1 cohort study. Takkouche et al. (2005) performed a meta-analysis of the Andrew et al. (2004) study and 9 other personal use case-control or cohort studies. Ji et al. (2005) reported a cohort occupational study not included in the above meta-analyses. Kogevinas et al. (2006) presented evidence from a case-control study in Spain. Lin et al. (2006) presented a case-control study of personal permanent hair dye use. Serretta et al. (2006) reported preliminary results from a multicentric study.

Lymphoma and Leukemia - Rauscher et al. (2004) reported a U.S./Canadian case-control study of adult acute leukemia. Zhang et al. (2004) and Zheng et al. (2004) examined the relationship of hair dye use or diet with non-Hodgkin's lymphoma in a case-control study in Connecticut. Takkouche et al. (2005) reported a meta-analysis of reports of hematopoietic cancers, including that by Rauscher et al. (2004) and Zhang et al. (2004) and 17 other studies. Mester et al. (2005) reviewed 10 epidemiology studies regarding the relationship between occupational exposure in hairdressing and diseases of the malignant lymphoma group. A case-control study in Spain by Benavente et al. (2005) examined the association between lifetime hair dye exposure with various lymphomas, including chronic lymphocytic leukemia. de Sanjosé et al. (2006) reported on the association between personal use of hair dyes and lymphoid neoplasm using data from a European multicenter case-control study.

Other Cancers - Takkouche et al. (2005) included breast cancer and childhood cancers in their meta-analysis. Efird et al. (2005) studied the association between the use of hair-coloring agents the month before or during pregnancy with childhood brain tumors in 1218 cases between 1976 and 1994.

Heineman et al. (2005) studied 112 women in Nebraska newly diagnosed with brain cancer (glioma). McCall et al. (2005) reported on the relationship between childhood neuroblastomas and maternal hair dye use in 538 children born between 1992 and 1994 in the U.S. and Canada.

Other Diseases - Park et al. (2005) reported an occupational case-control study of neurodegenerative diseases, including Alzheimer's disease, presenile dementia and motor neuron disease.

In considering all these data, the CIR Expert Panel concluded that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other endpoints.

The Panel stated that use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of an association with adverse events as reported in epidemiology studies. However, direct hair dyes are a diverse group of chemicals and the determination of safety may hinge on other safety test data.

The Panel recognizes that hair dye epidemiology studies do not address the safety of individual hair dyes, but is concerned that studies have demonstrated an association between use of oxidative/permanent hair dyes and some cancer endpoints. The Panel, therefore, strongly supports the need to continue these studies, along with further studies to examine the possibility of susceptible subpopulations.

OTHER EVALUATION

The SCCP (2006) reported their opinion that the use of p-Methylaminophenol Sulfate should be at a maximum of 0.68% in the finished cosmetic product. The nitrosamine content should be < 50 ppb.

CASE REPORTS

Lidén (1984b) reported on a man who had been mixing photographic chemicals for 16 years without skin problems. A few days after grazing his hand he developed eczema which quickly spread to his arms, neck, and face. He recovered after a few days off and topical treatment. The eczema

returned within hours of returning to work. He was patch tested for individual chemicals, including Metol, and chemical mixes to which he was exposed. He tested positive for Metol at 1% aqueous.

Brancaccio et al. (1993) reported on 2 men who work with photographic chemicals with contact dermatitis. The first man, 33 years old, with no history of dermatitis placed his right hand and arm into film developing solution. Two weeks later a pruritic dermatitis of the right forearm developed with patchy involvement of the face, upper chest, and left arm. He was diagnosed with acute allergic contact dermatitis and treated with topical corticosteroid ointment and an oral antihistamine. His second eruption had a distinct lichenoid appearance with violaceous flat-topped papules with polygonal borders. Biopsy showed focal vaculolar alteration and absence of hypergranulosis with patchy superficial infiltrate.

The second man was a 62-year-old man who managed a photographic laboratory with a 2-year history of hand dermatitis. Both palms were erythematous with diffuse scaling and fissuring; the fingers had confluent vesicles. Diffuse erythematous scaling plaques were present on both lower extremities and scaling was observed on the forearms. Biopsy showed superficial and mid perivascular infiltrate of lymphocytes, histiocytes, and eosinophils. He was also diagnosed with allergic contact dermatitis. Patch tests on both men resulted in positive results for CD-2, CD-3, and 4-amino-3-methyl-N-ethyl-N(betahydroxy-ethyl) aniline sulfate (CD-4). The former tested negative for p-Methylaminophenol Sulfate and the latter positive (Brancaccio et al. 1993).

Śpiewak et al. (1995) reports on 2 women working in the same photographic processing plant. The first woman's work required constant contact with photographic chemicals, including Metol. Two months after a new processing technology was introduced, the first skin lesions appeared on the wrist with itching and reddish macula. Subsequently, furfuraceous desquamation and exudating papules formed. The changes gradually extended over the upper half of the body (upper extremities, chest, and abdomen). Erythema and edema appeared on the face and neck. After hospitalization, allergic and seborrheic dermatitis was diagnosed. Skin prick tests were positive for paraaminoazobenzene, mercury chloride, N-isopropyl-N'-phenyl-paraphenylenediamine (IPPD), and 3 developing solutions but not for Metol. The second woman had the same job as the first woman, thus exposure was identical. She presented with reddish, dry macules on the hands. After contact with water, burning clusters of

exudating papules developed on the skin lesions, mostly in the palmar region. She had erythematosquamous reddish-brown lesions with tiny papules on the upper half of her body, except the back. Skin prick tests were positive for Metol, mercury chloride, and IPPD.

m-, o- and p-AMINOPHENOL SUMMARIES

SUMMARY OF SAFETY ASSESSMENT

Elder (1988) states that para-, meta-, and ortho-aminophenols are the 3 possible isomers of a disubstituted aminohydroxybenzene. The aminophenols are manufactured by nitrophenol reduction and occur as products and by-products of chemical and biological degradation or derivatization. Analytical methods for their determination include TLC and reversed-phase HPLC.

p-Aminophenol (PAP), m-Aminophenol (MAP), and o-Aminophenol (OAP) are used in permanent (oxidative) hair dyes. The FDA product formulation data lists PAP in 402, MAP in 278, and OAP in 75 hair coloring formulations in the “hair dye and colors” and “hair tints” product categories in 2002. Concentrations of the Aminophenols in these formulations range from 0.1 to 5%. The oxidative hair dyeing process involves combination of 3 types of colorless components to produce a permanent, colored, covalently bound product within the hair fiber. PAP and OAP are used as “primary intermediates,” which are oxidized by an “oxidant,” such as hydrogen peroxide. The oxidized primary intermediate then reacts with a “coupler,” such as MAP, producing a conjugated polynuclear dye.

In vivo and in vitro studies of skin absorption have been performed using radioactive PAP, MAP, phenols, and other hair dye intermediates. As much as 11% of the radioactivity introduced as ^{14}C-PAP in a simple vehicle was detected in the excreta, viscera, and skin of rats after topical application. Hepatic metabolism of aminophenols includes such reactions as glucuronidation, sulfation, and acetylation to form aminophenol conjugates excreted in the urine.

Intravenous and subcutaneous administration of PAP were melanocytotoxic to neonatal mice and nephrotoxic to rats. Varying degrees of methemoglobinemia have been induced by i.v. and i.p. administration of the aminophenols in several species, although oral administration of PAP and MAP did not affect methemoglobin concentrations in rats. The oral toxicities of PAP and MAP were studied using rats. Oral LD_{50}s for PAP in rats were 671 and 1270 mg/kg. Those for MAP ranged from 812 to 1000

mg/kg. The oral LD_{50} for OAP in rats was 1300 mg/kg. Oral administration of up to 0.70% PAP in the diet to rats for a period of 3 to 6 months resulted in decreased body weights and feed consumption as well as increased relative liver and kidney weights at the high dose and nephrosis at all doses. Oral consumption of up to 1% MAP in the diet by rats for 90 days resulted in decreased body weights and feed consumption, deposition of iron-positive pigment in the spleen, liver, and kidneys, and increased thyroid gland activity.

Topical application of PAP at doses up to 8.0 g/kg in aqueous gum tragacanth to the skin of NZW rabbits produced no mortality and no irritation.

Subcutaneous administration to rats of PAP as the hydrochloride in doses as low as 100 mg/kg produced morphological and functional nephrotoxic effects. No nephrotoxic effects were observed in similar studies with OAP and MAP.

Concentrations of 2.5% to 50% PAP and approximately 3% MAP (in an aqueous vehicle) applied to the skin of NZW rabbits produced minimal or no skin irritation. The 50% PAP preparation stained the skin at treatment sites green-brown, obscuring observations. One-half gram OAP and 5% OAP in ethanol produced no skin irritation.

MAP, 0.1 ml or at 3% in an aqueous vehicle, was nonsensitizing in guinea pigs. PAP, in petrolatum, sensitized 9 of 10 guinea pigs challenged with a 2% preparation and 3 of 10 guinea pigs challenged with a 0.1% preparation after the animals had been treated with four 24-h occlusive patches containing 2% PAP. PAP did not sensitize guinea pigs that had been treated with 18 patches containing 3% PAP in an aqueous vehicle and challenged with the same dose of PAP. Staining of the skin was noted at the site of administration. Cross sensitization between OAP and p-phenylenediamine was noted in guinea pigs. No photosensitization was produced by topical administration of PAP or MAP to the guinea pigs, although some contact hypersensitivity was noted.

Oxidative hair dye formulations containing the Aminophenols at low concentrations (0.04-1%) were tested for chronic toxicity after topical administration twice weekly for 13 weeks to rabbits and weekly for 21 to 23 months to mice under conditions designed to mimic human use of hair dyes. No gross alterations were observed. A 4-generation chronic dermal toxicity and reproduction study of 3 oxidative hair dye formulations containing the Aminophenols were performed with rats. A few skin

reactions were observed. However, no treatment-related toxicity was found.

Neither 100 mg powdered PAP nor 2.5% PAP in aqueous gum tragacanth was irritating to eyes of NZW rabbits. OAP and a 2.5% solution of MAP in aqueous gum tragacanth caused minimal or no eye irritation.

A range of results were obtained from studies assessing the mutagenic activity of the Aminophenols. PAP tested positive in 6 of 8 mutagenicity tests (not including a dominant lethal study in which the investigators suggested the study should be repeated). MAP and OAP gave positive results in 2 of 8 and 5 of 7 mutagenicity tests, respectively.

Oxidative hair dye formulations containing PAP, MAP, and OAP did not produce gross or microscopic alterations or have carcinogenic effects after chronic topical application to mice under conditions designed to mimic hair dye use. Feeding of OAP-HCI and PAP to albino rats at a dose of 8.01 mmo/kg produced no hepatic cirrhosis and no neoplasms.

Oxidative hair dye formulations containing low concentrations of PAP, MAP, and OAP were tested for teratogenic activity after topical application to mice, rats, and rabbits under typical hair dyeing conditions. No embryotoxic or teratogenic effects were observed in mice and rats, although a retardation of ossification in mice was indicated. No teratogenic effects were noted in treated rabbits; however, embryotoxicity was indicated.

Oral administration by gavage of 250 mg PAP/kg produced maternal toxicity and teratogenicity in rats. Chronic feeding of PAP in the diet of rats at a concentration of 0.70% produced embryotoxicity mediated by maternal toxicity. Chronic feeding of MAP in the diet of rats at concentrations of up to 1% resulted in maternal toxicity during gestation but produced no teratogenic effects. Oral administration of 100 to 200 mg/kg PAP to pregnant hamsters was not teratogenic, but i.p. and i.v. administration of PAP within the same dose range induced fetal malformations. Intraperitoneal administration of OAP (in hamsters) resulted in teratogenic effects, whereas no conclusive evidence was found for MAP teratogenicity by this route.

A 3% solution of MAP in an aqueous vehicle was tested for irritation and sensitization in 2 clinical studies using semiocclusive (open) repeated insult patch tests. Slight irritation during induction and no sensitization to the challenge patch were observed in one study. Some irritation and a low

degree of sensitization were observed in 2 of the 99 subjects in another study. No skin depigmentation in any subject and slight skin irritation and staining in a few subjects were observed after repeated topical applications of aqueous solutions of 1.0% MAP and 0.5% PAP. Dose-related responses to applications of PAP in petrolatum were observed on the skin of 10 of 31 workers from a chemical factory.

A variety of epidemiological studies have assessed whether and to what degree occupational exposure to and personal use of hair dyes (not chemically defined) increase the risk of cancer. Based on these studies, no definitive carcinogenic effect from hair dyes has been proven.

In a clinical study, 1 of 7 p-phenylenediamine-sensitized hairdressers cross reacted to challenge patches containing OAP and PAP.

On the basis of the available animal and clinical data presented in this report, the CIR Expert Panel concludes that p-, m-, and o-Aminophenols are safe as cosmetic ingredients in the present practices of use and concentrations (Elder 1988).

SUMMARY OF RE-REVIEW

The CIR Expert Panel (CIR 2005) reviewed the safety of m-, o- and p- aminophenol (MAP, OAP, PAP) in 1988. Based on that review, the Panel concluded that these Aminophenols "...are safe as cosmetic ingredients in the present practices of use and concentration". There have been additional studies since then including studies on irritation and sensitization that were not present in the first review. In addition, a large body of hair dye epidemiology data are now available. All studies, along with updated information regarding uses and use concentrations, were considered by the CIR Expert Panel. Based on its consideration of the data discussed below, the Panel did not reopen this safety assessment and confirmed the original conclusion.

MAP has increased in usage from 278 products in 1981 to 855 products in 2002. OAP has increased in usage from 75 products in 1981 to 89 products in 2002. PAP has increased in usage from 402 products in 1988 to 1024 products in 2002. The product categories are similar for all 3 ingredients for 1981 and 2002. The concentrations at which these ingredients are used are similar between 1981 and 2005.

The Panel noted that the discussion in the original review explained that there were likely

sufficient endogenous stores of glutathione to inactivate potentially genotoxic aminophenol metabolites. Among the additional studies reviewed by the Panel, however, were several in which glutathione conjugates produced by the reaction with aminophenols were nephrotoxic at high doses. Because of the short duration of contact with these oxidative hair dyes and the time needed for diffusion across the stratum corneum, the actual concentration of aminophenol in the skin is low relative to the amount in the hair dye product. Since the level in the hair dye product is already low, the Panel does not consider it likely that glutathione conjugates could reach nephrotoxic levels (CIR 2005).

SUMMARY

p-Methylaminophenol Sulfate and p-Methylaminophenol (p-MAP) are substituted phenols used as dyes and for photographic developing. p-Methylaminophenol Sulfate is manufactured by the methylation of p-aminophenol followed by neutralization with sulfuric acid. They may be determined analytically by infrared, UV, and nuclear magnetic resonance spectra, by TLC, and by visual or potentiometric titration. p-Methylaminophenol Sulfate absorbed in the UV range at 220 and 271 nm, whereas p-Methylaminophenol absorbed at 219, 270, and 277 nm. The term Metol may refer to either compound and is often used without distinguishing.

p-Methylaminophenol Sulfate is a secondary amine, thus prone to nitrosation.

In oxidative hair dyes, p-Methylaminophenol Sulfate and p-Methylaminophenol are used as primary intermediates. They react with an oxidant to produce the corresponding imine, which then reacts with a coupler to form an indophenol dye. p-Methylaminophenol Sulfate is listed as an ingredient in 112 hair dye formulations, its concentration ranging from 0.1% to 0. 7%. p-Methylaminophenol is not listed by FDA as an ingredient in any cosmetic products but is reported to be used by CTFA in hair dye formulations at 0.7%.

p-Methylaminophenol Sulfate was an inhibitor of the depolarizing action of acetylcholine on the giant neurons of *Lymnea stagnalis*. In the erythrocytes of oxen, dogs, rabbits, and humans, p-Methylaminophenol Sulfate caused the formation of methemoglobin at a much greater rate than did p-aminophenol.

p-Methylanimophenol Sulfate had low dermal penetration on human skin.

Oral administration of p-Methylaminophenol Sulfate to rats resulted in undetectable or very low levels of p-Methylaminophenol Sulfate over 13 weeks.

The intravenous LD_{50} of p-Methylaminophenol Sulfate in NMRI mice was 85 mg/kg. The maximum non-lethal oral dose of p-Methylaminophenol Sulfate for rats was 100 mg/kg and the minimal lethal dose was 200 mg/kg. The dose of p-Methylaminophenol Sulfate causing necrosis of the distal third of all tubules of the kidneys of hooded rats was 0.1 mM/kg, 20 times greater than the dose of p-aminophenol required to produce the same effect. In subchronic and chronic dermal toxicity studies of hair dyes containing p-Methylaminophenol Sulfate, among other active ingredients, no toxicologically significant differences were observed between the test and control animals (rabbits and mice, respectively). The subchronic oral NOAEL for rats for p-Methylaminophenol is 10 mg/kg/d.

In an ocular irritation study, p-Methylaminophenol was considered practically nonirritating to the rabbit eye. p-Methylaminophenol was slightly irritating to rabbit skin in a primary irritation study and was not considered a dermal sensitizer in a guinea pig skin sensitization study. p-Methylaminophenol Sulfate was a sensitizer in the GPMT and LLNA. In both the GPMT and LLNA, Metol received a positive rating for sensitization at 25% and 2.5%, respectively.

No significant embryotoxic or teratogenic effects were found when hair dyes containing p-Methylaminophenol Sulfate and other active ingredients were administered topically to Charles River CD rats once every 3 days for a total of 21 days during gestation or orally to Sprague Dawley rats at doses up to 125 mg/kg/d. Metol at 1,000 ppm reduced nematode hatchability by 48.48%).

p-Methylaminophenol Sulfate was mutagenic to *S. typhimurium* TA98 and TA 1537 with metabolic activation and TA100 without. It was clastogenic in mammalian cells (human lymphocytes) in an in vitro chromosome aberration test. Mixed results were reported for the mutagenicity of p-Methylaminophenol Sulfate to mouse lymphoma cells. There was no toxicity nor mutagenicity observed in the rat bone marrow micronucleus test or unscheduled DNA synthesis assay.

p-Methylaminophenol was not mutagenic in the Ames assay using *S. typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538. The p-Methylaminophenol was toxic to the bacterial cells, especially to those of strains TA98 and TA1538, in the absence of metabolic activation. Additional testing in strains TA98 and TA1538 with metabolic activation indicated that the toxic effect of the p-

Methylaminophenol did not mask any possible mutagenic effect. p-Methylaminophenol was nonmutagenic in the mouse micronucleus assay and in the Chinese hamster ovary chromosome aberration test.

No statistically significant incidences of neoplasms, dermal and other, were found in mice and rats after 21 to 28 months of weekly dermal exposure to hair dyes containing p-Methylaminophenol Sulfate in addition to other active ingredients.

Of 23 panelists known to have occupationally related dermatoses who were patch tested with p-Methylaminophenol Sulfate, 6 had positive reactions to the ingredient at concentrations of 1% and 5%. Three of these panelists also had positive reactions to 2 or 3 of a group of 4 chemicals used in film laboratories. When p-Methylaminophenol Sulfate was tested in 200 eczema patients without known previous contact with the chemical, 1 patient had a positive reaction. Four of 10 patients who had positive reactions to p-phenylenediamine had positive reactions to the p-Methylaminophenol Sulfate.

Twenty-four people who had developed dermatoses caused by color developing agents (including CD-2 and CD-3) were patch tested for an allergic reaction to Metol at 1% in petrolatum. Four of the volunteers had a positive result at 72 h. There were no positive reactions at 2 to 3 weeks. Five of 22 patients sensitized to p-phenylenediamine had positive reactions to Metol.

A number of studies have been performed in order to determine the possibility of a correlation between the use of hair dyes and an increased risk for cancer. No positive correlation has been found.

DISCUSSION

In the earlier safety assessment, only p-Methylaminophenol Sulfate was considered, even though data for p-Methylaminophenol was included. The Panel notes that p-Methylaminophenol Sulfate is the salt of p-Methylaminophenol and believe that the safety data on each ingredient may be applied to the other.

Both ingredients have low dermal penetration and are used in rinse-off products. Therefore, there is no expectation of systemic toxicity from their use. This is confirmed with animal studies with dermal exposure. These ingredients are not irritants to eyes. They are not genotoxic, carcinogenic, nor reproductively/developmentally toxic. Data on m-, o-, and p-Aminophenol from a separate assessment,

which are chemically related, were also considered and found safe.

p-Methylaminophenol Sulfate and p-Methylaminophenol are known sensitizers. However, as coal tar hair dyes, they fall under the coal tar derivative exemption to the Federal Food, Drug, and Cosmetic Act which requires caution statements and instruction regarding patch tests. The Panel expects that individuals following these instructions will minimize sensitization.

The CIR Expert Panel expressed concern about toxic metal residues that may be present in p-Methylanimophenol Sulfate and p-Methylaminophenol and advised industry that this ingredient should not contain more than: 3 mg/kg of arsenic (as As), 1 ppm mercury (as Hg), and 0.1 mg/kg of lead (as Pb). Additionally, p-Methylaminophenol Sulfate and p-Methylaminophenol should not contain N-nitroso impurities, nor should they be used in products where N-nitroso compounds may be formed.

CONCLUSION

The CIR Expert Panel concluded that p-Methylaminophenol Sulfate and p-Methylaminophenol are safe as hair dye ingredients in the practices of use and concentration as described in this safety assessment.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council (PCPC)

DATE: October 21, 2025

SUBJECT: Concentration of Use by FDA Product Category: p-Methylaminophenol and p-Methylaminophenol Sulfate

p-Methylaminophenol and p-Methylaminophenol Sulfate were included in the July 2025 PCPC concentration of use survey. No uses of p-Methylaminophenol and p-Methylaminophenol Sulfate were reported.