Amended Safety Assessment of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	November 9, 2023
Panel Meeting Date:	December 4-5, 2023

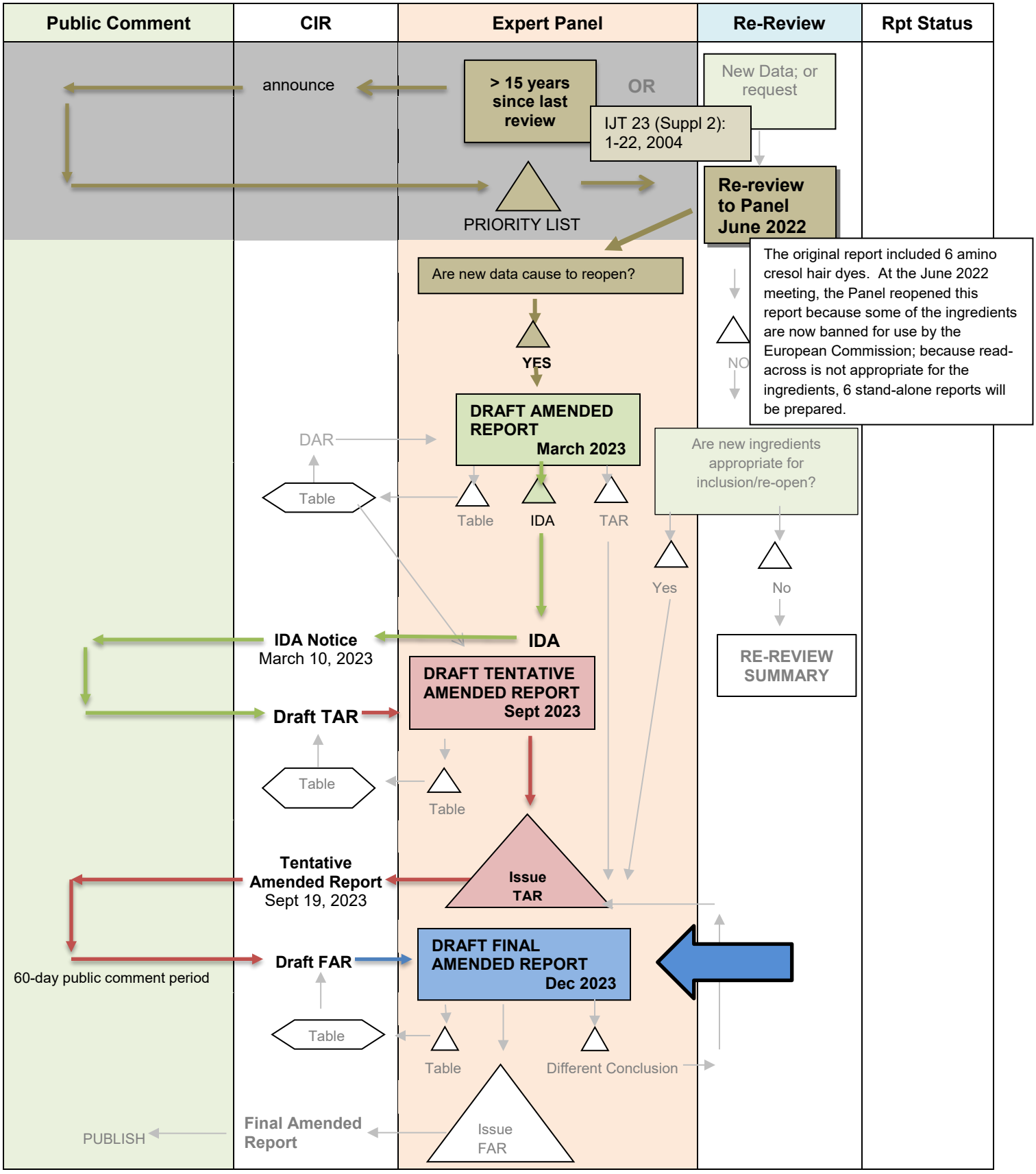
The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D.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

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651
cirinfo@cir-safety.org

RE-REVIEW FLOW CHART

INGREDIENT/FAMILY 5-Amino-4-Chloro-*o*-Cresol

MEETING December 2023



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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: November 9, 2023
Subject: Safety Assessment of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl as Used in Cosmetics

Enclosed is the Draft Final Amended Report on the Safety of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-o-Cresol HCl as Used in Cosmetics. (It is identified as *report_5-Amino-4-Chloro-o-Cresol_122023* in the pdf document). At the September 2023 meeting, the Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for these hair dye ingredients, the Panel was to conduct a margin of safety (MOS) calculation based on the available data in this safety assessment, which has been completed. Herein, the SCCP MOS and a very conservative MOS performed by the Panel at the maximum reported use concentration are included in the report; both are considered protective.

No comments were submitted by the Council on the Tentative Amended Report, and no additional data have been received. Additional supporting documents for this report package include the original report (*orginalreport_5-Amino-4-Chloro-o-Cresol_122023)*, a flow chart (*flow_5-Amino-4-Chloro-o-Cresol_122023*), report history (*history_5-Amino-4-Chloro-o-Cresol_122023*), a search strategy (*search_5-Amino-4-Chloro-o-Cresol_122023*), a data profile (*dataprofile_5-Amino-4-Chloro-o-Cresol_122023*), transcripts from the meeting at which this amended report was discussed (*transcripts_5-Amino-4-Chloro-o-Cresol_122023*), and the minutes from all the meetings at which 5-Amino-4-Chloro-*o*-Cresol was discussed during the original review (*originalminutes_5-Amino-4-Chloro-o-Cresol_122023*).

The Panel should carefully review the new margin of safety calculation, the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

5-Amino-4-Chloro-*o*-Cresol History

2004– The CIR's Final Report on the Safety Assessment of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol was published in the *IJT* after the report was finalized by the Panel in 2000. Based on the available animal and clinical data available at that time, the Panel concluded that 5-Amino-4-Chloro-*o*-Cresol is safe as used in oxidative and non-oxidative (semi-permanent) hair dyes.

June 2022 – Review of the available published literature since 2000 was conducted in accordance to CIR Procedures regarding re-review of ingredients after ~15 years. The Panel re-opened the safety assessment for this ingredient, due to it being banned for use in cosmetics by the European Commission.

March 2023 - The Panel issued an Insufficient Data Announcement (IDA) for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl. The additional data needed to determine safety for these hair dyes are:

- Method of manufacturing
- Concentration of use

September 2023 - The Panel issued a Tentative Amended Report with the conclusion that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as a hair dye ingredient. In order to come to a conclusion of safety for these hair dye ingredients, the Panel would be conducting a margin of safety calculation based on the available data in this safety assessment. Upon completion of this calculation and review by the Panel at the following meeting, a final determination of safety is to be made. No further data was requested at this time.

5-Amino-4-Chloro-*o*-Cresol Data Profile* – December 2023 – Christina Burnett																															
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	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
5-Amino-4-Chloro-*o*-Cresol	O		O												O								O						
5-Amino-4-Chloro-*o*-Cresol HCl			X	X	XO	O		O			O			O	XO	XO				XO			XO				XO		

* "X" indicates that new data were available in a category for the ingredient. "O" indicates data were reported in the original safety assessment.

5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
5-Amino-4-Chloro-o-Cresol	110102-86-8	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
5-Amino-4-Chloro-o-Cresol HCl	110102-85-7	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy (from 2002 on)

PubMed

((“5-Amino-4-Chloro-o-Cresol”) OR (110102-85-7[EC/RN Number]) OR (110102-86-8[EC/RN Number) – 0 hits

ECHA

No dossiers listed.

Internet searches using trade names and other technical names. No relevant hits.

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

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org
- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- 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/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- 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
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- 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) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

JUNE 2022 PANEL MEETING – RE-REVIEW CONSIDERATION (WITH SEVERAL OTHER HAIR DYES)

Belsito's Team Meeting – June 16, 2022

Dr. Belsito - So hair dyes, this is going to take a…. there is more than one hair dye here. I thought we were only going to look at one at a time. What's going on here? Reviewed as a group before.

Monice Fiume (CIR) - They were not, but being that this is the first time groups of reviews have been brought to you are the rereview documents. We were trying to figure out if there were ways to group hair dyes or preservatives or something like that together because they were similar types of functions. But I don't think this was the best example in retrospect.

Dr. Belsito - Yeah. So then let's go through this. So Orange 3 is now been banned in Europe, Acid Orange 3. I think we need to reopen it not only because of that, but in the use section, it says it's used and it's a new product now, which is a nail enamel.

And then the cresols are also, I think, problematic and need to be reopened. Some of them clearly seem to have carcinogenicity activity and I have a note here that seek Council comments and wave 3 of the cresols.

Will this be addressed in the rereview before publication? Let me get to wave 3.

Dr. Snyder - PCPC comments.

Dr. Belsito - Yeah, I'm just. So yeah.

Christina Burnett (CIR) - There was a typo in my memo that they pointed out at the very end. Two of the ingredients. Uh yeah, I think it's two or three of the ingredients that I said were on Annex Two are actually on Annex 3.

Dr. Belsito - Yeah. So this is starts on PDF page 8. I mean I think we need to open up the cresols as well.

Dr. Liebler - I agree.

Dr. Belsito - Because I think the amino position has significant effects on the toxicity. Then back to the next set of hair dyes. It was so it was just cresols and Acid Orange 3, right?

Dr. Liebler - There's one more.

Dr. Belsito - Oh yeah, the N,N Bis 2-Hydroxyethyl p-Phenylenediamine Sulfate. I didn't make any comment on that, so I don't think that I felt it needed to be reopened.

Dr. Liebler - Yeah, I thought it was a do not reopen unless Don identifies a rational rationale having to do with the EU, perhaps. Doesn't look like it, so do not reopen.

Dr. Snyder - Was the nitrosating issue in the original?

Dr. Belsito - It's. Yeah, the so the European Commission further advises this hair dye ingredient is a tertiary, meaning that is prone to nitrosation and should not be used in combination with nitrosating *(inaudible) substances. I guess that is usually read in our discussion, not a conclusion. So you know in the rereview summary where we say we've decided not to reopen it, we can just point that out.

Dr. Liebler - Yeah.

Dr. Belsito - Yeah, I mean the you didn't ban at, they just issued caution when he you know with use.

Dr. Liebler - Right.

Dr. Belsito - And they limited the nitrosamine content should be less than 50 parts per billion.

When?

Dr. Snyder - They asked, well, they also said it was safe up to 2.5%, my notes say.

Dr. Belsito - Yeah. And what is the current use?

Dr. Snyder - I don't know.

Christina Burnett (CIR) - 1.3 is the maximum.

Dr. Belsito - To 1.3 right.

Christina Burnett (CIR) - Yes.

Dr. Belsito - Yeah. So it's well below what the EU restricted. So I don't think we need to reopen it. And then just in the discussion or in some point the document put about the *(inaudible). But the cresols and the Acid Orange 3 I think unfortunately need to be reopened.

Dr. Carol Eisenmann (PCPC) - Hi I have one request for the cresols that they could be in the same report but all the data on each cresols be kept together because I think read across as we've said before on these materials is not appropriate. This was done before you started looking at each hair dye individually.

Dr. Belsito - Yeah. I agree, Carol.

Monice Fiume (CIR) - I'm sorry. Carol, can you please repeat what you are, clarify what you said?

Dr. Carol Eisenmann (PCPC) - That'd be nice. For all the so you, you can have them in the same report, but like all the data be in for one ingredient be together. So you can see what's the data on that ingredient rather than you know sometimes you're having a paragraph that has all the you summarize all the data, the acute tox data on all of the ingredients in one paragraph make it, you know, separate out. In other words, you the acute chronic reproductive development for one ingredient and then go to the next one and go through the order. In other words, it's going to be like several separate reports. In one report, rather than or make them separate reports because they should not read across isn't appropriate for them.

Dr. Liebler - So.

Yeah, it might be tricky to do that. I mean, one thing that could be done is the endpoint data summary tables could be organized by ingredient.

Dr. Belsito - Right.

Christina Burnett (CIR) - We can do that.

Dr. Liebler - And you could, like I don't mean to dismiss your suggestion, Carol entirely. But the, best way to get an eagle eye view of the data would be those summary tables and that should be, I agree that should be organized by ingredient.

Dr. Belsito - Exactly.

Dr. Liebler - And then you know, whatever Christina. Uh, you know, can come up with in terms of sort of organizing the various tox endpoints in the report text by ingredients to the maximum extent that's possible. I agree that's desirable.

Dr. Belsito - OK. Any other comments on this? Cresols are going to be fun.

Christina Burnett (CIR) - Wait until you see the other two I'm working on.

Dr. Belsito – Oh Lord.

Christina Burnett (CIR) - Sorry.

Cohen's Team Meeting – June 16, 2022

Minutes not captured.

Full Panel Meeting – June 17, 2022

Dr. Bergfeld - OK, we're off to the next set of items, which is other items called Hair Dyes. Doctor Belsito.

Dr. Belsito - OK, so this is not a rereview of one hair dye, that's it's a rereview of several. So we have Acid Orange 3, we have NN, Bis 2 hydroxyethyl paraphenylenediamine sulfate. And then we have the cresols and the amino phenols. And we felt that among this group. We need to reopen Acid Orange 3. We need to reopen the cresol aminophenol group, but we did not need to reopen the NN, Bis 2 hydroxyethyl paraphenylenediamine sulfate.

Dr. Bergfeld - Is there a second on the?

Dr. Cohen - 2nd.

Dr. Bergfeld - Any further discussion regarding which ones will be reopening?

Dr. Belsito - Uh, yeah. So the only discussion really is whether we do the cresol aminophenol group as a whole group, because the actually the positioning of the amino group on the cresol may have significant result in significant differences in the toxicology of the material. It was suggested that by our panel that they all be included in the same report. But that particularly would be presenting the data on toxicity etcetera that instead of as we typically would do like acute oral, you know subchronic chronic that we do that for each. So we do 6-amino-m-cresol and then we go through the various oral studies for that. Then we do 4 amino cresol and do all the tox studies for that so. It will be much clearer in our minds what we have for each of the different materials in this group, because I suspect that we may find that some are safe and some are insufficient. Maybe some should be banned, I don't know, but.

Dr. Bergfeld - I mean. I want to ask Bart about your recommendation.

Dr. Bart Heldreth (CIR)- I think that sounds perfect. I think that sounds perfectly fine. You know we need to look at all of these one way or another, and it certainly makes complete sense to me to pull these out and make it very clear that they're

separate and that there's really no chance for read across between them and that they're individuals. I think that makes perfect sense.

Dr. Bergfeld - OK, how about the orange dye? Anyone want to make a comment on that one? That one is going to be reopened at least this.

Dr. Belsito - Yeah. There's new data and it's just been banned by the EU. So I think we need to look at it.

Dr. Bergfeld - OK.

Dr. Cohen - Yeah, done. We had a lot of deliberation over this and it seems like there's also a paucity of data that may result in from the ban that results in the ban and we had gone back and forth whether this might not be reopened and put into a rereview summary, but I think we came around several times to your team's conclusion.

Dr. Bergfeld - Well, we are then voting on the reopening of the acid orange and we're not reopening the Bis, but also reopen the creosol. Is that right?

Dr. Belsito - Correct.

Dr. Klaassen - Correct.

Dr. Bergfeld - OK, I'm going to call the question then all those opposing. Abstaining. I assume it's unanimous that we're moving forward with reopening of two groups here.

MARCH 2023 PANEL MEETING - INITIAL REVIEW OF DRAFT AMENDED REPORT

Belsito's Team Meeting – March 6, 2023

DR. BELSITO: The drilling's coming back, Paul, so I'm going to turn this over to you.

DR. SNYDER: Okay. In June of 2022, we reopened this document due to this being a banned hair dye ingredient by the European Commission. Original report was comprised of six ingredients and one report, and now we're splitting them out into individual reports. This is the first of two we're going to look at this time, the 5-Amino-4-Chloro-*o*-Cresol. So this is a draft amended report. There's no new data. So Christine has developed a discussion section and everything here for this document.

There was a margin of safety calculation using a 90-day rat oral study with an NOAEL of 180 milligrams per kilogram. And there was PCPC comments on Wave 3, Page 6 related to this ingredient. I just had a couple of comments on this. Oh, you didn't -- I thought you did have discussion in here.

MS. BURNETT: No.

DR. SNYDER: Oh, I'm sorry.

MS. BURNETT: This is a draft.

DR. SNYDER: Yeah.

MS. BURNETT: And this one wasn't one of the ones that was banned.

DR. SNYDER: Right.

MS. BURNETT: It was in the report where there were six cresols, and a few of them had been banned.

DR. SNYDER: Okay.

MS. BURNETT: This one and the next one, I don't believe, were.

DR. BELSITO: The problem I have with this, is there's no reported concentrations of use, right? It doesn't appear to be used.

DR. RETTIE: That's right, no use for the concentration.

DR. BELSITO: So our usual conclusion, safe as used, we can't use because there's no apparent use. So, if we're going to make any conclusion on this, we're going to have to either say we accept the SCCS's margin of safety calculation, that it could be safely used up to this concentration; or we need to do our own, I suppose, but it creates a quandary.

MR. GREMILLION: That was going to be my question. What do you do when there's no reported use?

DR. HELDRETH: One option is you can certainly conclude that the data are insufficient to conclude on safety about that.

DR. RETTIE: Yeah. That's what I came down on, but I was just alerted by the mixed genotox signals. And I just wondered what others thought about how we would discuss those. I think we had two and two in terms of a positive and a negative genotox signal.

DR. KLAASSEN: Well, in regard to genotox, by my evaluation, there were like seven or eight tests that were done and only one was positive. That was the Ames tester strain 98. The strain 100, 102, 1535, 1537 were clean, the mouse lymphoma is clean. So, I guess, I'm satisfied with this. We can wait until tomorrow. Thanks.

DR. RETTIE: They did say there was a dose-dependent increase in micronuclei.

DR. KLAASSEN: Yeah. (Audio skip) lung cells.

DR. RETTIE: Yeah.

DR. KLAASSEN: Yeah. It's not 100 percent clean. I will agree with that. But, I guess, it's clean enough for me. Let's see what Slaga thinks. He's kind of our genotox expert.

MS. BURNETT: I was curious about the Panel's feelings about the dermal absorption data.

DR. BELSITO: While we're on the carcinogenicity, though, Christina, on PDF Page 19, the second to the last sentence, the test material did not "induce," right -- not "include" -- an increase in the number of revertant colonies?

MS. BURNETT: I'm sorry. Under genotox -- what?

DR. BELSITO: Yeah. It's genotox PDF 19, the second to the last line. The test material did not induce -- not "include," right?

MS. BURNETT: I'm not seeing what you're saying, but I assume --

DR. BELSITO: Oh, I'm so sorry, it's PDF Page 18, second to the last line.

MS. BURNETT: Yes, that's exactly what it's supposed to be.

DR. BELSITO: Okay. Then percutaneous absorption, what page was that, Christina?

MS. BURNETT: Starting on PDF Page 17.

DR. RETTIE: Yeah. This is a compound with all the physical chemical parameters for extensive percutaneous absorption, and I guess that was confirmed. Does that make it --

DR. BELSITO: So it was mixed with the developer, so we have that. It was applied for 30 minutes, which is appropriate. It was terminated by washing, which is appropriate. It's a good study.

SCCS, not P, right? Noted the number of chambers used was too few and the absorbance maximum. It's beyond my ability to understand their comment. Does anyone who have greater knowledge of these absorption studies understand what they're saying, why the number of chambers were too small or too few? And the absorbent maximum of 16.47 ug/cm squared is used for calculation of margin of safety?

So they just used the higher range because they thought the number of chambers was too small. Is that correct?

MS. BURNETT: I believe that's my understanding.

DR. SNYDER: Yeah. It's beyond my scope of understanding how these are set up. I mean, I would think, if it was under the OECD guidelines, that it would be appropriate. Everything would be appropriate.

DR. BELSITO: Yeah.

MS. BURNETT: I don't know if the SCCS has different standards for when they accept a test or not. It's the only thing I can question there.

DR. BELSITO: While we're on the absorption, Christina, again PDF Page 18, I guess, yeah, the animal studies that were sort of taken from the prior report --

MS. BURNETT: Yeah.

DR. BELSITO: -- there's no mention about how long the material was left on the skin before it was washed off and whether it was under occlusion. Was that not given in the prior report?

MS. BURNETT: Possibly. I'd have to go back and look --

DR. BELSITO: Okay.

MS. BURNETT: -- and try to include all that information if it was available. I'm going to go skim it real quickly to see if I can find it.

DR. BELSITO: Yeah. If it wasn't available, I would mention it. And if it was available, I would put that data in.

MS. BURNETT: All right.

DR. BELSITO: Any other comments on this?

DR. KLAASSEN: Okay. Under the cosmetic use, in the second paragraph it says a survey is currently underway for the hydrochloride salt.

MS. BURNETT: Correct.

DR. BELSITO: What does that really mean?

MS. BURNETT: So, when the rereview was initiated last year, the Council only surveyed the original ingredient, which was not the salt. But, as I was developing this new draft report, I realized that most of the data was on the salt, which is also in the INCI dictionary. So I asked the Council to see if they could survey the salt ingredient, too, and that survey hasn't come back yet.

DR. KLAASSEN: Okay.

MS. BURNETT: When we did the rereview back in June last year, they had only surveyed the free base --

DR. KLAASSEN: The salt. Oh, okay.

MS. BURNETT: Not the salt, the other. So we're just trying to cover all the bases for two ingredients.

DR. KLAASSEN: Okay. So you will be doing that?

MS. BURNETT: It's already underway. They were just still waiting for a member company to respond to the survey. So, hopefully, as soon as --

DR. KLAASSEN: Okay.

MS. BURNETT: The next version should hopefully have the results.

MR. GREMILLION: The dynamic of all that's going to be changed with the MoCRA or not?

MS. BURNETT: Well, what is the number of uses, the VCRP, that is going to be mandatory. So the number of uses will change, and all companies will have to report. Now, the concentration of use, I don't know if that really changes. Bart, I think you understand that better than I do.

DR. HELDRETH: Right. Yeah, unfortunately, the VCRP, or if it becomes the MCRP for mandatory, it hasn't included concentrations of use for a long time. There was a point in time where it did. But the FDA ceased including that information and it just became frequency of use. And that's when the Council started doing a survey of their members to find out maximum concentrations of use.

So the changes in MoCRA won't really change that setting because it just makes the frequency of use reporting mandatory. It doesn't make the concentration of use change at all.

DR. BELSITO: Bart, are you certain that MoCRA makes reporting of the frequency of use mandatory? I thought it just made reporting of adverse events mandatory.

DR. HELDRETH: My understanding is both.

DR. KLAASSEN: Yeah. It would --

MR. GREMILLION: Yeah. I heard both. That's why I said reports previously were all voluntary information, and now it's mandatory.

DR. ANSELL: It will include both --

DR. HELDRETH: Right. It's starting next year, basically.

DR. ANSELL: -- facility registration and formulation notification, so those are separate parts. Let me point out that, while the absolute number may change, I wouldn't expect that products which are important will become unimportant. So the absolute number will probably increase. But I would guess that, in terms of the CIR, we wouldn't see a big change in the order of the ingredients.

DR. BELSITO: (Audio skip) come in that we weren't aware of before.

DR. ANSELL: I'm sorry. Say again?

DR. BELSITO: Product categories. Since there's now mandatory reporting, there could be new product categories that we didn't consider before. Is that not correct?

DR. ANSELL: Not as I understand it today. The product categories are part of the software, and so no new product categories would be added.

DR. BELSITO: (Audio skip) companies may be using it in a product category and not reporting it under the voluntary system, right?

DR. ANSELL: Right.

DR. SNYDER: Well, case in point here. Will this ingredient likely go from not used to now being used because -- if there's mandatory reporting?

MS. BURNETT: Possible.

DR. HELDRETH: It's possible.

DR. ANSELL: It's possible.

DR. BELSITO: But I mean, if we're talking about either doing a margin of safety to come up with a safe level, as SCCS did, if we're not going to do that, then we would go insufficient for concentration of use. And then, if there's a report with a concentration of use that comes out of the salt, maybe that's it, that people are using the salt. And, when Carol goes out and surveys that, we'll end up with some concentration. So maybe the reasonable thing to do at this point, since it's just coming to us -- this is a first, right?

MS. BURNETT: Yes.

DR. HELDRETH: Yes.

DR. BELSITO: So just say insufficient for concentration of use, and we're going to see it again anyway.

DR. HELDRETH: Right. So this could go out as an IDA. And, if you wanted to include things like maybe the equivocal nature of the genotox, or something like that in there as well, I mean, you're already doing an IDA anyway.

DR. BELSITO: Well, I think we'll wait to see what Tom says about the genotox.

DR. HELDRETH: Okay.

DR. BELSITO: No. Is that what we are going to do?

DR. RETTIE: So if we're going out with an IDA, which sounds likely, insufficient for concentration of use. Looking at the table and the blanks in there, would we ask for normal things that we're not likely to get? Like method of manufacturing is not there.

MS. BURNETT: You could ask for that.

DR. RETTIE: (Audio skip) data. Are there others to ask for?

DR. BELSITO: Do we have impurities data?

DR. RETTIE: Yes.

MS. BURNETT: Yes.

DR. BELSITO: So do you really care how it's manufactured if you have the impurities?

DR. RETTIE: Probably not, just channeling Liebler there for the group, but you're right, Don. (Audio skip) impurities are there -- you won't get it anyway.

DR. BELSITO: So it's really insufficient concentration of use. Is that correct?

DR. SNYDER: Yes.

DR. BELSITO: Okay.

DR. SNYDER: I had a question, kind of, on this report and then kind of related to this new mandatory reporting. On Table 2, when we reissue these, Bart, these re-reviews and things, is it essential that we have the old voluntary reporting data like 1998? Because it's really irrelevant, we're basing it on the current data, right? Because our safety assessment is based upon the current.

DR. HELDRETH: Yes, everything is the concentration.

DR. BELSITO: It becomes relevant, Paul, when we decide to reopen a rereview because the number of uses have gone up or the concentrations of uses have gone up.

DR. SNYDER: That's true. Okay. And it's also a basis for the priorities list. I just didn't know if it was relevant to have it in the final version because it just ends up being a lot of data to look through. This one doesn't have it, but some do.

DR. BELSITO: Yeah.

DR. SNYDER: That's okay. And I had just kind of a comment on this previous discussion. There's three paragraphs. The first paragraph deals with irritation, sensitization. The second paragraph deals with the tox data and the absorption -- or the ADME data. And the third paragraph deals with sensitization data.

So I thought that probably those two paragraphs should be rearranged. Because we talk about sensitization, we talk about tox and absorption, then we talk about sensitization again. I think it would read better if it was all together.

MS. BURNETT: Sorry, what page are you on?

DR. SNYDER: Page 21 --

MS. BURNETT: Okay.

DR. SNYDER: -- where you had the previous discussion.

MS. BURNETT: That's the original discussion?

DR. SNYDER: Yeah, the original discussion.

MS. BURNETT: The order it showed --

DR. SNYDER: Yeah.

MS. BURNETT: So, when you get the next version, when I write the new discussion --

DR. SNYDER: Yeah.

MS. BURNETT: -- that won't be there anymore.

DR. SNYDER: Okay, good. All right. Insufficient for concentration and use data, previous use.

DR. BELSITO: All right. Insufficient use. Okay.

Cohen's Team Meeting – March 6, 2023

DR. COHEN: Let's move onto 5 a-mino-4-chloro-*o*-cresol and 5-amino-4-chloro-*o*-cresol hydrochloride. So, the panel previously reviewed the safety of 6-amino-*m*-cresol and *o*-cresol and 4-amino-*m*-and *o*-cresol and 5-amino-6-chloro-*o*-cresol and 4-amnio-2-aminophenol. And in June, we reopened that safety assessment primarily because some of these hair dyes have been banned in the European Union and we felt that the amino cresol hair dyes could not read across.

So, we've broken them out. Much of the 5-amino-4-*o*-cresol in the original report came from the hydrochloride. We have 2022 VCRP data of no reported uses, which created a dilemma in my mind. And since June, there is no new data that has been submitted. We have composition and impurities. And of note -- in the European Union we have note that 5-amino-4-chloro-*o*-cresol is not restricted from use in cosmetic products.

So, what does the team want to do with this? We have no concentration and no use. Tom, what do we do with this?

DR. SLAGA: First of all, I'd like to emphasize to the genotoxicity data is kind of mixed and I just want to make sure everybody knows that. There's two kind of positive ones. One of the two of the positive is at very high concentrations, so kind of rule that out. And there's two negative ones. And this is a combination of both in vitro and in vivo type of studies.

Like the European Union, I still think you have to go with the weight of evidence. And it still leans towards non-genotoxic even though there are some outliers. That happens. You know, if you do any compound a dozen times, even with the Ames assay, maybe with different doses, different people doing it, the majority of -- if it's negative, the majority will come out negative. But there's usually a outlier, one or two out of that many that would be positive or slightly positive for different reasons.

That can be taken care of in a discussion so that's not a real problem. This can be discussed. I don't know if there's no use or no concentrate- -- I don't know how you'd ask if you even wanted any data. You know, what concentration are you going to use it at?

I'm like you, David. I don't know what to do there.

DR. ROSS: Ninety-four was 1 percent.

DR. COHEN: SCCP concluded a max concentration of 1.5 percent.

DR. ROSS: Yeah.

MS. BURNETT: I will note the council is doing a survey on the salt currently, so that data hopefully will be coming in soon.

DR. ROSS: So just getting at Tom's point there, I agree with Tom. I mean, the tox looked okay, the acute tox. The 90-day looked okay. The DART looked okay. The genotox, when you get down right into it, the Ames was sort of weak (inaudible).

DR. SLAGA: I mean, if you did it a couple more times you would've probably end up with a greater weight of evidence. But it's not worthwhile here, I don't think that's needed.

DR. ROSS: The 5178Y's were negative. The B79 HGRPT was negative up to a certain dose. The V79 micronuclei was positive. But the in vivo micronuclei in mice was negative. So that's usually where I come down. I thought that was okay. Dermal was non-irritating at 10 percent, non-sensitizing at 5 and 2 percent. And the EU margin of safety was 947 at 1.5 percent. And so, I didn't really have a problem with going with as safe as used at 1 percent. And, I mean, you could even stretch to 1.5 percent to match the EU conclusion, but let's not get carried away here.

DR. SLAGA: Yeah.

DR. TILTON: So, I had very similar conclusions. I didn't have concerns about the other toxicity data. I noted the genotox, the in vitro. But the in vivo for the hydrochloride salt was negative.

I did note that there was no in vivo for the cresol, but it seems like the salt is the form that's the precursor in the oxidative hair dye systems and so I feel that we can rely on the in vivo data for the salt, which was negative.

And so, I had felt that we could also recommend it as safe for use in oxidative formulations as reported, which I had said in 1994 was one percent.

DR. ROSS: Oh, and just a caveat, there is no method of manufacture.

DR. COHEN: Yeah, I have that.

DR. TILTON: And then I did note, I guess, because it's a moderate sensitizer, non-oxidative formulations seems like it's been standard to require inclusion of a patch test.

DR. COHEN: Well, that's in the discussion. Is that where you got that from?

DR. ROSS: Coal tar isn't it?

DR. SLAGA: Yeah.

DR. TILTON: Yeah, it must've been.

DR. COHEN: Right, because available -- the paucity but available data doesn't suggest it is.

DR. TILTON: Yeah. I made note of that, that did not -- well, so I noted it was a moderate sensitizer in non-oxidative formulations.

DR. COHEN: It's just in this report --

DR. TILTON: For just this chemical.

DR. COHEN: -- for just this chemical. I don't think we had data that said it's a sensitizer, but we've come across this before a lot. So how do we reconcile the fact that the data in that report doesn't suggest it's a moderate sensitizer, but then in the discussion we put that as a moderate sensitizer? Can we put that?

MS. BURNETT: I think in the discussion we're talking about hair dye formulations as a whole or sensitizers and it's part of our boilerplate.

DR. COHEN: That's how I hoped to interpret it.

DR. TILTON: But we have separated these out now.

DR. COHEN: Right.

MS. BURNETT: Correct.

DR. TILTON: I think I noted that with the next one, actually.

MS. FIUME: In PDF Page 19.

DR. COHEN: PDF Page 19.

MS. FIUME: In the original data at higher concentrations, the hydrochloride salt was a moderate sensitizer in a guinea pig maximization test.

DR. COHEN: Where is it again?

MS. FIUME: PDF Page 19.

DR. COHEN: Where are we, at the top or the bottom?

MS. FIUME: The sensitization. So mid page.

MS. BURNETT: It's the italicized animal study.

DR. COHEN: Oh. Hold on a second. I have to convert this to a PDF, hold on. I'm sorry, can you repeat the PDF page?

MS. FIUME: Nineteen. It's the sensitization study under animal, is where it states that it was a moderate sensitizer in a guinea pig maximization test. Induced at 5 percent and challenged at 2 percent.

DR. COHEN: Okay. Got it.

MS. FIUME: And in others it was non-sensitizing.

DR. COHEN: I'm looking at my notes for one or two other things. Can someone comment on PDF 18 under dermal, under toxicokinetic studies. Where it starts as animal. It says, "A formulation containing the radiolabeled ingredient diluted 1:1 with water to make a final concentration of 1.85. The mean skin absorption was 32.7 percent." I had a note to myself that it seemed pretty high and all the risk assessments were based on much lower absorptions. But you guys see that?

DR. ROSS: It's in a rat's skin?

DR. COHEN: Huh? Yeah, the rat.

DR. ROSS: 33 percent of those, however when mixed with peroxide the absorption decreased to 1 percent. (Inaudible) 32.7 percent. Yeah, I got that.

DR. COHEN: What do you make of it?

DR. BERGFELD: Absorbed.

DR. COHEN: No. But that's a lot, right? That's a lot.

DR. ROSS: It's a pretty low molecular weight.

DR. COHEN: What's that, again?

DR. ROSS: It's a pretty low molecular weight, generally, so you expect it to be absorbed. The question is how much? The in vitro study in the pig skin was a lot less. That was with hydrogen peroxide, I guess. But, yeah, it's consistent with that one, actually.

DR. TILTON: Well, then, it notes, later in that same paragraph, that when it's combined with hydrogen peroxide that the absorption is only just over 1 percent in that case.

DR. COHEN: Yeah. That's how I kind of reconciled it. But is it notable enough that we should put in the discussion that they're in separate bottles when they come. And so, it's very important that they mix it because putting this on straight without the peroxide developer, you can really absorb a lot of this stuff.

DR. BERGFELD: Clinically or in the actual setting you would never do that, because peroxide is very interesting in how it binds and activates it.

DR. COHEN: Right. And I certainly believe in the setting of the hair salon that wouldn't happen. But in the setting of a home kit, is it possible? I mean, it just -- I don't know.

If no one's really bothered by it I can move on. I just, when I read through it I had to read that twice just to make sure I was getting it correct. It seemed like a lot.

DR. ROSS: I would just say that the margin of safety done by the European had a skin absorption number in there, and they came up with a pretty high margin of safety.

DR. COHEN: But that was with oxidized material that had a 30th less absorption, right?

DR. TILTON: Yeah. So I think we have some evidence of pretty good absorption, and then potentially some moderate sensitization or non-oxidized formulation.

DR. COHEN: So do we include that in the discussion?

DR. ROSS: Yeah. Let's discuss it. It's the best time to do it.

DR. BERGFELD: I think you have to.

DR. COHEN: Yeah. Okay. And the other thing we're faced with is, it sounds like the group's going to safe as used in a hair dye. Is that correct? Is that where we're going on this?

DR. SLAGA: Yeah.

DR. COHEN: The problem is the report has no concentration to anchor to. So, we can anchor back to the one percent when it was combined or we can anchor to the SCCP of 1.5 percent. But we probably, in the rare form, need to put a concentration in the conclusion unless the survey comes back, and we have material for the survey and that we anchor to the survey data.

DR. ROSS: Well, the number that we have in our documents right now is from '94 which is 1 percent. So I guess I would propose we anchor to that. As I said, we could equate with the Europeans with 1.5 percent but the data in our records shows 1 percent.

DR. COHEN: Okay.

DR. BERGFELD: The industry can always come back if they don't like it and present the data.

DR. COHEN: Well, I mean it --

DR. BERGFELD: If they want (inaudible).

DR. COHEN: -- one percent. So, Christina and Monice, this has got to be a situation where we would put a concentration in the conclusion, because unless we get data on use and concentration it's nowhere in the report, right?

DR. BERGFELD: Why would you have to put it in the conclusion, you could put it in the discussion.

DR. COHEN: Yeah, what would you say?

MS. BURNETT: You could say the panel noted that there's no current concentration of use or reported uses with the VCRP. But based on the (inaudible), you're gonna refer back to --

DR. SLAGA: Yeah, in the discussion you can compare it to EU.

MS. BURNETT: Yeah, you can refer it back to the original report, noting that this was a reopened re-review.

DR. COHEN: But it's not a classic reopen/re-review because we kind of split them all out like a cluster bomb. Right?

MS. BURNETT: Right.

DR. COHEN: They came in as one warhead and then we got a number of them. Sorry for that graphic.

DR. ROSS: Yeah.

MS. BURNETT: That's how I feel some days, yeah.

DR. COHEN: Yeah. But because these are tough reports to go through, and we have a lot of responsibility on these, and we just want to do it right. Okay, so we'll conclude that this is safe as used as a hair dye and we're going to reference an anchor concentration of 1 percent from the old report.

DR. TILTON: Are we going to explicitly say as a hair dye in oxidative formulations?

DR. COHEN: Well, I think it's probably a good idea, right? You're talking about the absorption, Susan, just to mitigate that?

DR. TILTON: Right. Or I can't remember how the statement about -- I mean, there's absorption but it seems like the primary issue is sensitization. So if that's something that can be covered by an individual patch test, but there should be note that there's a difference in the recommendation, I guess, between oxidative and non-oxidative formulations.

DR. COHEN: Are you basing that on the sensitization, or are you basing that on the absorption?

DR. TILTON: Both.

DR. COHEN: I would worry less about the sensitization at that point because of patch test warning.

DR. TILTON: So that's standard?

DR. BERGFELD: That's a discussion point.

DR. COHEN: Yeah, a lot of these have a capacity to sensitize people and that's why that patch test is in there.

DR. BERGFELD: But we usually discuss that in the discussion. So, all that could be clarified in the discussion, oxidative versus non-oxidative, and then the hair dye recommendations. We've done that before.

DR. COHEN: Okay.

DR. ROSS: So just to clarify the EU -- I'm just pulling it here. After mixing under oxidative conditions the maximum concentration to hair must not exceed 1.5 percent as calculated as hydrochloride. I think I have that right.

DR. COHEN: You do.

DR. TILTON: Yes, that's right.

DR. ROSS: EU conclusion. So, we're, again, with safe as used at 1 percent, (inaudible) at '94. But are we or are we not clarifying to oxidative or non-oxidative?

DR. COHEN: That's the discussion now. I think we can have the discussion as an oxidative hair dye in the discussion and relate it back to the absorption if -- it looks like the peroxide really does change the product enough that it changes the absorption markedly.

DR. BERGFELD: It binds it and activates it. Yeah.

DR. ROSS: That's a study with peroxide at 6 percent. Is that about the right concentration you would see?

DR. BERGFELD: I think that's a common solution or percentage, yeah.

DR. ROSS: Yeah.

DR. COHEN: Okay. David, do we need method of manufacturing, because I don't know if we often see that in these hair dyes?

DR. ROSS: No. I don't think you do. I mean, the impurity on this one I've got a note that it was 97 percent.

DR. COHEN: Yes.

DR. ROSS: Downside, better than some of the others in our group here but -- so, yeah.

DR. COHEN: That's right.

DR. ROSS: I mean, it's not there, but do we need it, probably not.

DR. BERGFELD: It could be in the discussion.

DR. COHEN: That we don't have it?

DR. BERGFELD: Yeah. And why you don't need it.

DR. COHEN: Wilma, why don't we need it? Because the purity is pretty good?

DR. BERGFELD: Yeah.

DR. ROSS: Susan, did you have anything to add on that one?

DR. TILTON: No, I would agree with that. I mean, method of manufacturing is very helpful if there's some variability or higher levels of impurities in order to determine if there's consistency in the manufacturing.

So, I noted it wasn't there. I noted that we didn't have it. But it didn't prevent me from making a recommendation as safe in current practice.

DR. COHEN: Okay.

DR. BERGFELD: So, what is going to go in your discussion? Can you summarize that. What have you decided, David?

DR. COHEN: In the discussion, a few things. When not mixed with peroxide the absorption was high in rats. It markedly reduced with peroxide, that absorption. And so, our safe as used is more in the context of an oxidative hair dye.

Also in the discussion is that -- unless things change and we get something back from the Council on use, that we're anchoring to our concentration from one percent from our prior report.

And we could also put in the discussion that the SCCP -- we could put in the discussion about the European Union and their use of 1.5 percent.

DR. BERGFELD: What are you going to do about the non-oxidative?

DR. COHEN: Well, what do I need to do about that?

DR. BERGFELD: Well, I guess the potential for sensitization is there, so you might have to mention that. Or you should mention it.

DR. COHEN: Yeah.

DR. BERGFELD: And then you're going to put in about the current -- you don't need the method of manufacturing because of, blah, blah, blah. So, you have method of manufacturing --

DR. COHEN: Yes, in the --

DR. BERGFELD: -- then you have oxidative dye, then you have non-oxidative dyes. I'm just trying to give the categories there that you're going to be covering.

DR. COHEN: Yeah. No, no. It's helpful.

DR. BERGFELD: And then the anchoring. Yeah.

DR. COHEN: Okay. Okay. I'm just looking back at the sensitization stuff. All right, I'll codify all this later, but I think we got all the discussion points, right? Okay.

Full Panel Meeting – March 7, 2023

DR. BERGFELD: And the first one in the category is the 5-amino-4-chloro-*o*-cresol.

DR. COHEN: Okay. So, 5-amino-4-chloro-*o*-cresol and the hydrochloride. The Panel previously reviewed the safety of 6-amino-*m*-cresol, 6-amino-*o*-cresol, 4-aminio-*m*-cresol, 5-amino-4-chloro-*o*-cresol, 5-amino-6-chloro-*o*-cresol, and 4-chloro-2-aminophenol in an assessment that was published in 2004.

In the original report, 5-amino-4-*o*-cresol was deemed safe as used in oxidative and non-oxidative hair dyes. In June, we reopened the safety assessment for these ingredients in part because some of these dyes have been banned for use in cosmetics by the European Commission. We also felt the amino cresol hair dye ingredients could not read-across.

Much of the data on 5-amino-4-chloro-*o*-cresol in the original report was actually on the salt ingredient, the HCl. This hair dye ingredient has been added to the amended report because it's a formulation of the salt and free base are identical when it's in situ.

We have 2022 VCRP survey data, and we have no reported uses. The results of the concentration of use survey conducted for the free amino base also had no additional data. Survey's currently under way for the HCl salt.

In 1994, 5-amino-4-chloro-*o*-cresol was reported to be used in up to one percent in hair dyes and colors in combination with hydrogen peroxide. Since our prior meeting, there's been no new data. Parenthetically, in the European Union, 5-amino-4-chloro-*o*-cresol is used in cosmetic products and is currently categorized in Annex 3. After consideration of the available data, our motion is safe for use as a hair dye ingredient in the use and concentration described in the safety assessment. That's my motion.

DR. BELSITO: (Audio skip) of use or concentration in the safety assessment.

DR. COHEN: Right. Don, I left the words off present practices. And after the motion I wanted to have a discussion with you and the teams about anchoring a concentration.

DR. BELSITO: Well, we'd have to say that as reported in 1998, or we'd have to do a margin of safety as the EU did and say it could be safely used up to this percent.

DR. COHEN: Yeah. So the motion was safe in hair dye. And then I have some post motion discussion, to have with you that we can put in the discussion, to anchor a concentration for the report.

DR. BELSITO: But I think if you come up with a conclusion just safe in a hair dye and someone's looking at a conclusion, they would come to their own conclusion that it could be used at any concentration.

DR. COHEN: Well, normally they're in the present practice as described in the safety assessment. We are going to describe the tox in the safety assessment, and in the discussion we're going to specifically call out that the prior concentration, which is in this safety assessment, is 1 percent. And the conversation we wanted to have across the teams was, do we use 1.5 percent that's being described by SCCP?

One way or the other, the question is, are you willing to carry the motion that it's safe as used in a hair dye ingredient and then we could discuss the concentration in the report.

DR. BELSITO: Again, I just think that's too liberal a conclusion, number one. Number two, if we're going to just simply rubberstamp what the SCCS does, why are we in existence? If we're going to come up with a 1.5 percent, then we should agree that their calculations -- their decision that it was a LOAEL and not a NOAEL in their calculations for the margin of safety, we agree with those, rather than just reporting what they found.

DR. COHEN: No. We had an option -- our base option was one percent from the prior reports.

DR. BELSITO: Right. So then, I think you can put in your -- can't you put in your conclusion that it's safe as used as reported in 1998, or whatever? You know, and then that anchors it back to the 1998 report on this and it was used at 1 percent.

I mean, I agree that that 1 percent was in the table that a reader is going to see. But I just -- you know, we actually went insufficient for concentration of use, hoping that when they come out with the VCR- -- or the PCPC survey for the hydrochloride salt, that they'll find a concentration of use.

DR. COHEN: Well, just to -- as devil's advocate -- what if the concentration of use survey has 1.75 in it?

DR. BELSITO: Then we need to look at that and see if that's the concentration. What if it does? We haven't seen those results yet. I mean, it was just decided to do the hydrochloride salt.

DR. COHEN: Yeah. I think --

DR. BERGFELD: Can I interfere a minute? Can I interfere a minute? So, it sounds to me, like Don, you're not supporting the motion. Are you willing to put forth another motion to be considered?

DR. BELSITO: Yes. Insufficient for concentration of use.

DR. BERGFELD: David? After this conversation what do you think you would do? Going to rescind or agree or what?

DR. COHEN: Well, it's clearly a more conservative approach. It's hard to disagree with it. The question is, what if we don't get it?

DR. BELSITO: Well, we don't know until we ask.

DR. COHEN: No, no, no. But, Don, I'm just being practical. Let's just go fast-forward, we get no concentration of use. Are you going to not vote for use in hair dye after that?

DR. BELSITO: I'll vote for its use in hair dye. Then we'll have the discussion again as to how we make that conclusion. But all of our data's on the hydrochloride salt. Which I think, and I'm hopeful that when council goes out and does a survey they're going to find a use for that hydrochloride salt. But we'll see. You know, I mean, we haven't asked for it yet.

DR. BERGFELD: Can I interfere and ask Alex where does PCPC stand on this or Carol? Are you there?

DR. EISENMANN: Yeah. I'm here. Concentration survey will go out soon, probably later this week. I'm waiting for the results on the priority list. I'm fine with you waiting until it's done, but it's not underway. It'll go out hopefully this week. It'll take a month or two to get the results.

DR. COHEN: Don, it's early in the report. It's really a draft report, so we can wait. I think the reason for this --

DR. BERGFELD: Should we table it or go insufficient?

DR. COHEN: No. We can go insufficient because at that point we want to light a fire for the data. But recall, though, Don, when we do re-reviews, they anchor back to the original report, right, that concentration. But I'll reamend --

DR. BELSITO: We mentioned that the concentration hasn't changed or there's been a significant increase in the concentration. I mean, this is the first time we're seeing some re-reviews where we don't have a current concentration of use.

And perhaps we'll deal with that when we have data that shows that it's safe. But, I mean, at this point for this particular ingredient, there's a second ingredient that hasn't been surveyed.

DR. BERGFELD: Can we propose a recension of the first motion and a new motion please?

DR. COHEN: Sure. The motion will be insufficient data and our data need is concentration of use.

DR. BERGFELD: Second?

DR. BELSITO: Second.

DR. ROSS: There was no method of manufacture in there if you want to add that.

DR. COHEN: We can ask for method of manufacture. Yeah, I think all those -- we didn't have method of manufacture.

DR. BERGFELD: Okay. That's a great add. Okay. Anything else? All right. We're going to take a vote on insufficient and I'm going to ask first for opposing? Abstaining? Approved. It is approved. Thank you very much for that discussion.

SEPTEMBER 2023 PANEL MEETING - DRAFT TENTATIVE AMENDED REPORT

Belsito's Team Meeting – September 11, 2023

DR. BELSITO: Then, 5-Amino-4-Chloro-*O*-Cresol, our last hair dye. So, this one, at the March 2023 meeting, we determined the data were insufficient. We wanted a method of manufacture and concentration. We didn't get it because it's not in use. And we need to reach our conclusion to be determined. I just had a number of comments here. So we're insufficient still, I think, for concentration of use and method of manufacturing.

DR. SNYDER: Correct.

MS. BURNETT: Well, we received data that there are uses, so there's no concentration.

DR. SNYDER: No uses.

DR. BELSITO: Right.

DR. RETTIE: And we needed the concentration of use to anchor anything.

DR. BELSITO: Right. Well, the SCCS took a different approach because they've allowed it at 1.5 percent, right.

MS. BURNETT: Correct.

DR. BELSITO: So they did that based upon a No Observed Adverse Effect Level from a 90-day oral study in percutaneous absorption under use conditions, and applying a margin of safety for the systemic tox based upon the 90-day oral, which was negative. We have DART data that's negative. We have genotox data that's plus and minus. Quite honestly, if we took an EU approach, we probably could clear this as safe rather than just asking the concentration of use. Which again gets back to some of the point that I made with Don earlier. Basing these safety assessments as safe as used, that's 1970s.

DR. SNYDER: I mentioned this morning, I think it's wrong. We have to do something different.

DR. BELSITO: Yeah. But I'm fine with continuing the conclusion that we had said before, that it's insufficient for concentration of use and method of manufacturing. But, when we have data that would allow us to come up with a conclusion that a certain concentration of this material being used as a whatever is safe, and just because industry hasn't given us the concentration --

DR. SNYDER: Well, I think this one is problematic because in 2004 we said it was safe as used.

DR. BELSITO: Right.

DR. SNYDER: And we got no new data. Now we completely changed to insufficient.

DR. BELSITO: Well, but we had grouped it with a whole bunch of other hair dyes.

DR. SNYDER: But I think the Discussion needs to capture some of that because, on its face, it looks --

DR. BELSITO: Yeah. But all of these we had said were safe as used.

DR. SNYDER: I know.

DR. KLAASSEN: We probably should end up with one of them being safe.

DR. BELSITO: We did.

DR. EISENMANN: Yes.

DR. KLAASSEN: We have already one. I have no problem of making this safe and giving it a number like the Europeans have.

DR. RETTIE: Despite the mixed genotox signals?

MS. FIUME: I know we did it when we didn't have concentrations of use, where the concentration was set.

DR. RETTIE: The only mixed toxin that was the immunogenicity --

MS. FIUME: This is a different situation because, just because you don't have concentration of use doesn't mean that you can't deem it safe if it were to be used in the future. So you could either rely on the previous concentration, or you can set a concentration based on the data in the report.

But, right now, the reason that it was going insufficient was for method of manufacture. So, if that is no longer a reason, you can give it some type of conclusion, it would just be a conclusion with a restriction, with a qualification.

DR. BELSITO: But, again, we haven't done the margin of safety calculations. We could potentially disagree with the factors that EU applied. I think all too often we've relied on the SCCS and their calculations in our reports rather than doing our own.

MS. FIUME: And, if that's the case in the past, you have relied when an ingredient goes out of use. But you've had concentration of use from when you've reviewed it previously. You've done it, it just that it would have to be handled somehow in the Discussion as to the fact that you're referring back to that concentration.

DR. SNYDER: Yeah. I think leave sleeping dogs lie because we still don't have any method of manufacture.

DR. BELSITO: Okay.

DR. SNYDER: And there's no uses, so I think it's --

DR. BELSITO: So insufficient for concentration --

DR. SNYDER: Method of manufacture.

DR. BELSITO: -- of use for the hydrochloride and method of manufacture?

DR. SNYDER: Yeah.

DR. BELSITO: Okay. I just, again, wanted to have this discussion because I really think we need to.

MS. FIUME: So can I clarify? So you don't have concentration of use for either, right?

DR. SNYDER: Either, for either one. Correct.

DR. BELSITO: Right.

MS. BURNETT: Correct.

MS. FIUME: But you've received information saying that there is no reported concentration of use. So do you still want that in the insufficient listing? And, therefore, would it be for both ingredients, or would it only be method of manufacture that's listed for the reason for insufficiency?

DR. BELSITO: Well, I think it's still insufficient because we're being told that there is no concentration of use. But is that every single company that manufactures a hair dye? If it were to be used, what concentration would it be used at is, I think, what we would need to look at. Our usual safe-as-used conclusion rather than doing -- we'd still have to probably do a margin of safety as per the SCCS, given the plus and minus genotox studies that we have, and go off of the negative 90-day oral, which is what Europe did.

So I think, despite the fact we're told there's no concentration of use, if it were to be used, what is that concentration?

MS. FIUME: So, then, for Christina's use for the Discussion, that would be part of the list as well as a paragraph. And, then, does the fact that there is a margin of safety in here need to be addressed as to why? I just don't want it to come back next time.

DR. BELSITO: Well, first of all, it's not used. It appears not to be used. Industry doesn't seem to want to support it.

MS. FIUME: Okay.

DR. BELSITO: Let's let sleeping dogs lie, but it's just all part of the discussion we had with Don earlier today. That I think we need to start moving the Panel into the realm of looking at the science behind all of this. And that's what the SCCS did where they said, okay, this would be a safe level for this.

We have the information that we can derive a safe level. We don't need industry to tell us what they're using it at. Based upon the information we have, using it at 1.5 percent of an oxidative hair dye would not pose a human health risk. And, I think, if we looked at it, we probably could come up with that conclusion as well.

DR. SNYDER: There's a whole new paradigm for it. It's the way we look at this data.

DR. BELSITO: Right.

DR. SNYDER: Whole new paradigm.

DR. BELSITO: That was just the point that I wanted to raise by questioning this conclusion and bringing up the SCCS data. I don't think we should put that in the Discussion because then it looks like we have defaulted, which we sort of have.

DR. RETTIE: Well, with respect to that, is it a potential teaching moment for us if we were to take up the burden of identifying our own margin of safety? Who would do that? How would we get that done? It would give us something to compare with the European.

DR. BELSITO: Well, yeah. Who would do that? What you'd have to do is you have to look at the composition of the SCCS. Okay. It is a very large group, and they have epidemiologists and statisticians on this group that can do those calculations for them.

DR. RETTIE: Don't we have people on the Panel that can do this type of calculation?

DR. BELSITO: I certainly can't.

DR. RETTIE: I certainly can't either.

DR. SNYDER: I think David is quite confident doing it. But that's only one.

DR. RETTIE: Do we ask David to run a test case for us just for our own edification as we go down this path?

DR. SNYDER: Well, I think it's a good discussion for tomorrow. But, again, it's part of a larger discussion, broader discussion, for this new paradigm I think.

DR. RETTIE: I mean, it's a real baby step towards actually doing something rather than talking about it.

DR. BELSITO: Right.

DR. RETTIE: I'm sure Dr. Ross would pick this up.

DR. BELSITO: Okay. So, just for the purposes of moving this forward, my motion is going to be method of manufacturing, concentration of use for insufficiency for the conclusion.

MS. BURNETT: Go ahead.

DR. BELSITO: No, you.

MS. BURNETT: I was just going to ask because I had drafted a --

DR. SNYDER: Discussion.

MS. BURNETT: -- discussion. And I'm not sure if all that needs to stay, if it's going to be insufficient, what discussion points you would like to keep and which to delete? Because I had a few that needed further development. And, if it's insufficient --

DR. BELSITO: I didn't change anything.

MS. BURNETT: Yeah, the most important point I need developed is --

DR. SNYDER: The dermal absorption.

MS. BURNETT: Yeah.

DR. SNYDER: Yeah. I think I would just strike that.

MS. BURNETT: Just strike it?

DR. SNYDER: I think so.

DR. BELSITO: What line are we on with the dermal --

DR. SNYDER: It's fourth or fifth paragraph in the Discussion.

MS. BURNETT: Yeah. It's only one sentence.

DR. SNYDER: Fourth. It's just a single sentence. A short sentence. This one right here.

DR. BELSITO: Oh.

DR. SNYDER: With or without an oxidizing agent.

DR. BELSITO: Yeah. So we're going to strike that?

DR. SNYDER: I think so. I mean it's not really relevant because we don't have any use data.

DR. BELSITO: Right. Okay. So let's look at the TBDs in the draft discussion. The first is in the paragraph above, the lack of method of manufacturing, no current use, and the original safety assessment.

DR. SNYDER: That's all fine.

MS. BURNETT: I'll tie that in with the paragraph about --

DR. SNYDER: Yep.

DR. BELSITO: Reported to be used at up to one percent in hair dyes and colors after mixing with hydrogen peroxide, period.

DR. SNYDER: And then a typical coal tar -- I mean a hair dye epidemiology, I think it's all fine, and respiratory.

MS. BURNETT: I'll combine the second and third paragraph since we will list the insufficiencies.

DR. SNYDER: Mm-hmm. I take that out about the genotox, right?

DR. BELSITO: Where are we?

DR. SNYDER: At the second paragraph, a reported function of oxidative hair dye in coloring products. In this amended report, the Panel concluded that the available data are insufficient due to the two issues. And just leave it at that.

MS. BURNETT: Okay.

DR. SNYDER: I wouldn't bring that genotox in, do we?

DR. BELSITO: No.

DR. SNYDER: It's not factored into any conclusion.

MS. BURNETT: Okay.

DR. SNYDER: So just take it out.

DR. BELSITO: So for manufacturing and concentration of use?

DR. SNYDER: Yeah.

MS. FIUME: So I do have one question about it. Typically, when a point such as carcinogenicity or something like that is missing, we refer back to why that was not included as part of the insufficient data request. And I think that sentence addressing the genotox explained that.

DR. BELSITO: Yeah. I think that's fine to leave it in.

DR. EISENMANN: I don't like the word mixed. That doesn't give you much information. I think if you go back, there were some positives in vitro, but the results of the in vivo were negative, if I remember correctly, for this one. So you could be a little bit more specific, other than just saying mixed.

DR. BELSITO: I mean, look, I didn't pick that up, Carol. It's genotox.

DR. SNYDER: Bacterial positive.

MS. BURNETT: Yeah.

DR. BELSITO: In vivo. We had one in vivo that was not genotox. So in vitro mixed, one in vivo negative.

DR. SNYDER: I just think it opened -- I mean, I'd ask Tom, but I think that puts too much emphasis on it because it was only in the Ames test. The lymphoma cell and the hamster lung was negative. Oh, no, it was genotox. Okay. All right.

DR. RETTIE: Yeah. It was two and two.

DR. SNYDER: Two, yeah. All right.

DR. BELSITO: So the in vitro was mixed, but the in vivo was negative, right?

MS. BURNETT: Yes.

DR. SNYDER: Yes.

DR. BELSITO: But there was only one in vivo.

MS. BURNETT: Correct.

DR. RETTIE: Only one in vivo micronucleus.

DR. BELSITO: Okay. So we'll bring up adding that to the Discussion. We can hear what Tom says tomorrow.

DR. KLAASSEN: Tom said before that it was okay. He was okay with the mutagenicity as a, quote, overall, no.

DR. BELSITO: I don't understand that. He was okay, but we didn't need additional mutagenicity?

DR. SNYDER: Correct.

DR. KLAASSEN: Right. That was on Page 13 of the previous notes.

DR. BELSITO: Okay.

DR. SNYDER: I mean, I always looked at these things as tiered. So, we get to a certain point where we clear it, but as we get more data then we may open up other data needs. We just can't throw out a garbage can list that this is everything we need because it's all based upon the exposures, what this the concentration is used at, I think.

DR. KLAASSEN: Mutagenicity is a hazard assessment. It is not a risk assessment.

DR. BELSITO: Right. Okay. But we're going out insufficient for manufacture and concentration of use. Anything else in the discussion that needs clarification, Christina?

DR. SNYDER: That is everything.

MS. BURNETT: That was it.

Cohen's Team Meeting – September 11, 2023

DR. COHEN: So, the next one is 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol Hydrochloride. We had a protracted discussion at the March meeting. And the Panel determined that the data were insufficient to support the safety of the hair dye ingredient, with additional needs of method of manufacturing and concentration of use. We've since received notice that for 5-Amino-4-Chloro-*o*-Cresol Hydrochloride, it has no reported concentration of use. And the VCRP from 2023 had no uses.

So, I know I found this to be a little bit of a quandary. When we adjudicated this one ourselves before we went into full panel, we had cleared this as safe as a hair dye at a concentration of up to 1.0 percent. It wasn't until we got the group together that we agreed to have these insufficiencies. So what's the group feel about the disposition of this report now?

DR. ROSS: Well, I thought the --

DR. COHEN: Go ahead, Susan.

DR. ROSS: Yeah, go ahead, Susan.

DR. TILTON: So, the insufficiencies were primarily due to lack of concentration data and max use that we could anchor to in the hopes that we might get some information for that. We discussed before that there were really no concerns with the toxicity data, the genotox was largely negative, particularly for the in vivo hydrochloride salt.

So, I would be comfortable with safe as used anchoring back to the last reported use concentration from 1994, the one percent. I mean, I guess that's the primary question, is how to anchor concentration.

DR. ROSS: I agree with that. That was exactly my sense of it. I thought since the use and the concentrations were a little vague in here, we have to get quite specific. I put out safe as used in final concentrations up to 1.0 percent as a component of oxidative hair dye preparations.

Just specifying the use, specifying the anchor concentrations, reiterating what Susan said, 1.0 percent. And I'm not worried about the method of manufacture because the purities are 97 to 99 percent anyway, and I think that was a fairly minor comment that we just had it on. So, I'd be okay going with that conclusion as I stated.

DR. COHEN: Tom?

DR. SLAGA: I agree with the last statement.

DR. COHEN: See, now, this is how we went in last time.

DR. ROSS: Yeah, I think it's --

DR. COHEN: It's exactly the same.

DR. ROSS: Yeah, we're being consistent.

DR. COHEN: No, we're being consistent. I think there was the issue of why were we comforted by the SCCP. I don't know if we were comforted by it, they had a 1.5 percent, we didn't suggest --

DR. ROSS: They did.

DR. COHEN: -- 1.5 percent. I think we'll go in with this the same way we did last time and let's hear what their objection is.

DR. SLAGA: Yeah.

DR. ROSS: If there is an objection. Could we be a bit more specific on the use as well?

DR. COHEN: What's that, again?

DR. ROSS: Could we be a bit more specific on the --

DR. COHEN: Oh, because of final concentration of 1.0 percent in an oxidative hair dye?

DR. ROSS: Yeah.

DR. COHEN: Yeah. Okay.

MS. BURNETT: And because the question will be asked, then, what's the feeling on the use in a non-oxidative hair dye? Or is that something to address in the Discussion? I believe this one is reported to be used for both. I'm not sure. I can go back. Yes. It might be just oxidative.

DR. ROSS: I have in my notes it's only used in oxidative, actually. But I felt it needed to be specified in our conclusion. If I'm wrong there, Christina, let me know.

MS. BURNETT: I think you're right. I'm sorry. Since this was broken out of six other ingredients I have them kind of jumbled together.

DR. COHEN: Well, 2004 it mentioned -- it cleared it for non-oxidative hair dye.

MS. BURNETT: Right. Yeah, the original conclusion says it supports the safety for use in oxidative and non-oxidative hair dyes.

DR. ROSS: Yeah. I was coming back to that margin of safety in the EU of 947, up to 1.5 percent, but under oxidative conditions. And that's why I put that in our conclusion. Now, that might be an item for discussion tomorrow. I don't know.

DR. TILTON: Yeah, we previously noted that it was a moderate sensitizer for non-oxidative formulations. So I don't know if that's something that's addressed in the discussion or requirement of a patch test or if the recommendation is only for oxidative formulations.

DR. COHEN: I don't think the sensitization would've held it up because all of the hair dyes have a patch test warning and they're sensitizers.

DR. TILTON: Yeah.

MS. BURNETT: So, there is a disparity in the data for dermal absorption between oxidative and non-oxidative that I need the panel to flesh out for the discussion section.

DR. COHEN: That's what came up, I think, in our discussion last time.

DR. ROSS: And what's the PDF on that?

DR. COHEN: PDF 18 --

MS. BURNETT: Yes.

DR. COHEN: -- has a description of the high absorption in rats that was substantially mitigated through oxidation. Huh?

MS. BURNETT: You mean 24 -- PDF 24 or 18?

DR. ROSS: Twenty-four.

DR. COHEN: Yeah, I had 18 but is it 24?

DR. ROSS: Twenty-four.

DR. COHEN: Let me see where -- what is on 18. Oh, you know what it is, I'm not in the PDF I'm in the web browser.

DR. ROSS: And so, your specific question was -- what did you need clarification on?

MS. BURNETT: I know in the last meeting the Panel noted that there was a difference in the absorption rate between oxidative and non-oxidative, and to make it a discussion point. But I don't know what to say about that. Like, is there a concern? If there's not a concern, why is there not a concern?

DR. COHEN: I think we see this a fair amount. This isn't the only circumstance where we see higher absorption in the non --

DR. ROSS: I mean, you'd predict that. I mean, because the oxidative it's going to change.

DR. HELDRETH: I think -- and I may be wrong. But I think what Christina is getting at, is typically our conclusions for a hair dye will be something like safe as used as a hair dye. But if we're going to pair it down and be more specific to only oxidative hair dye use, the reader is going to want to look to the discussion and say, why? Why is it only for oxidative?

Now, I don't think we need to delve deeply into it and explain it, since there's no reported uses at all in oxidative or non-oxidative, but it probably would benefit from just having some explanation why we've selected oxidative specifically.

I think it can be rather brief, too.

DR. COHEN: So, David, I had it safe as a hair dye. And was the reason you colored it was because of absorption?

DR. ROSS: No, I don't think so. I think I was going with the EU conclusion, up to 1.5 percent when used under oxidative conditions. I think that's where I pulled that from.

DR. HELDRETH: We essentially had that opinion in our conclusion in 1994. I mean, it says when used at up to 1 percent in a hair dye in combination with hydrogen peroxide. So that's max -- we're talking about an oxidative hair dye, but --

DR. COHEN: I thought the conclusion originally said oxidative and non-oxidative. Based on the available animal and clinical data the Panel concluded it's safe as used in oxidative and non-oxidative hair dyes.

DR. HELDRETH: Sorry, I was talking about that set conclusion. I meant the industry survey in 1994 showed that it was with hydrogen peroxide.

DR. COHEN: I don't know if we have to specify it to that degree.

DR. ROSS: I think that's what they use for the margin of safety calculation. They use that 1.6 percent for the MOS.

DR. COHEN: Was it because of the absorption and that was the calculation?

DR. ROSS: I think so.

DR. COHEN: Okay. Then we need to identify that for the Discussion because we are making a very specific recommendation. Do you know what PDF page that is discussed on from?

DR. ROSS: It's 24.

DR. COHEN: That's the absorption. I'm talking about the SCCP adjudication.

DR. ROSS: Oh.

MS. BURNETT: Margin of safety is on PDF Page 26.

DR. ROSS: Yeah, it's gotta be just after that. Yeah.

MS. BURNETT: It's mid-page.

DR. COHEN: Margin of safety?

DR. ROSS: Yeah, 1.5 percent under oxidative, yeah.

DR. COHEN: It's because of absorption, right?

DR. ROSS: Yeah.

DR. COHEN: 16.47 micrograms per centimeter squared.

DR. ROSS: I mean, they weren't huge differences were they?

DR. COHEN: They were big, massive differences like two orders of magnitude. Right? So, the question on the table right now is, what do you want in the Discussion?

MS. BURNETT: Specifically on the dermal absorption, if you want to keep that in the Discussion. Currently I have an open sentence that was proposed for the Panel to weigh in on. If you would like me to delete the sentence, I can do that. If you want me to add onto the discussion of the oxidative hair use, I can do that.

DR. COHEN: You have here after mixing with hydrogen peroxide.

DR. ROSS: So, the absorption goes down from 3.2 percent to 1.6 percent?

DR. COHEN: At 3.2? I thought it was much higher than that.

DR. ROSS: 3.9, sorry. 3.92. No, 3.9 is with (inaudible). That's how I'm reading this.

DR. COHEN: Mean skin absorption was 32 percent.

MS. BURNETT: I think on PDF Page 24, it's the data from the original report on the animal study that really shows, I think --

DR. ROSS: Oh, okay.

MS. BURNETT: -- the difference between the absorption. I'm trying to read fast here.

DR. ROSS: Thirty-two percent, yeah. Right, 32 percent to one percent.

DR. COHEN: Yeah, it was a --

DR. ROSS: Big difference. Yeah.

DR. COHEN: -- huge difference.

DR. ROSS: I mean, you could say the specification was made for oxidative conditions due to the decreased absorption. Or due to the lower absorption under these conditions. Some sort of generic statement like that. If you want the sentence in there, if you think we have to specify.

DR. COHEN: Well, again, we usually will say safe as a hair dye.

DR. ROSS: I see.

DR. COHEN: Right? We usually say safe as a hair dye. We're saying safe as an oxidative hair dye. The margin of safety has to do with the absorption, so we should at least say why we're doing that. We don't even know if we can get that to pass tomorrow but -- do you need more?

MS. BURNETT: I think I can work with that. Thanks.

DR. COHEN: Can you?

MS. BURNETT: I looked at him and he nodded, so yeah.

DR. COHEN: I saw that. Okay, so tomorrow we'll have this discussion.

DR. ROSS: Is this you tomorrow? Are you presenting this?

DR. COHEN: No, it's not.

DR. ROSS: It's not you.

DR. COHEN: It's not. I want to be fully informed and ready to go.

DR. TILTON: David, could you make sure your microphone is on.

DR. COHEN: I'm back on. Mine is definitely going off on its own because I never shut it off. But it's maybe timing out. Or if many people turn on, I see it sometimes shut off. Whatever. Absorption, non-oxidized. So, it's a margin of safety issue. Okay. Let's move on.

DR. BERGFELD: So, what are you going to do there?

DR. COHEN: I think we're going to call it safe as used as an oxidative hair dye.

DR. ROSS: At 1.0 percent.

DR. COHEN: Huh?

DR. ROSS: At 1.0 percent, right?

DR. COHEN: At 1.0 percent. And in the discussion, we'll talk about why we didn't clear it with non-oxidative.

DR. BERGFELD: Because of absorption at 32 plus percent.

DR. COHEN: Margin of safety on the absorption.

DR. ROSS: The margin of safety calculation was done with the oxidative absorption, I believe, at 1.6 percent.

DR. COHEN: It's clearly outlined in the body of the report.

DR. ROSS: Yeah.

DR. HELDRETH: Do we have anything we want in the discussion about why we chose the one percent?

DR. COHEN: It's where we anchored from our last report, isn't it?

DR. ROSS: Yeah.

DR. COHEN: Because we don't have any other data to anchor to.

MS. BURNETT: It does -- I'll have to reconfigure some of the sentences in the draft Discussion, but on the third paragraph I said you noted the lack of method of manufacturing and no current uses. The original safety assessment had reported use up to 1.0 percent in hair dyes and colors after mixing with hydrogen peroxide. So, I can recreate it.

DR. COHEN: Yeah. That's the to be further developed. That was for us to come up with something.

Full Panel Meeting – September 12, 2023

DR. BELSITO: Yes. This is a draft tentative amended report on the safety of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol Hydrochloride as used in cosmetics. At the March meeting, we issued an insufficient data, the additional data being method of manufacturer and concentration of use for the hydrochloride. We have not gotten those and we are going with insufficient for the same data needs.

DR. BERGFELD: Motion is second?

DR. COHEN: No, we went through this again. The last time our conclusion was safe as used at a final concentration of 1.0 percent as an oxidative hair dye. I thought that we don't have any concentration of use because we don't have any uses, but the report before that was safe, we didn't think there was any data to change that and we --

DR. BELSITO: But they were combined with a whole bunch of other for which we had data. And we read across incorrectly.

DR. COHEN: All right, so other than method of manufacturing, and I'd ask you to clarify how important that was, but the concentration of use, I think, was anchored to 1.0 percent at the last report. The SCCP had it at 1.5 percent. And if we anchored to the prior report at 1.0 percent, why couldn't we clear that, because we have no data that it's going to be more than that, and the report anchors to a lower concentration. We did have a provision as an oxidative hair dye because there is substantially more absorption of the non-oxidized one, so there was a margin of safety issue.

DR. BELSITO: The SCCS did that based upon calculation of a margin of safety. We have not done that. I mean, and if we're going to do it, since there's no concentration of use, if we come up with a margin of safety the same as the SCCS, then we

should give it a limit. Because right now we're saying, what, safe as used in nineteen eighty something? because we don't have any use concentrations for it.

DR. COHEN: We come across this, though, a fair amount when we're reopening reports where we have no use and we anchor back to the original report's concentration. We do that a lot.

DR. ROSS: I think you were specifying in your motion the concentration.

DR. COHEN: I did.

DR. ROSS: Yeah, at 1.0 percent.

DR. COHEN: Safe as used at a final concentration of 1.0 percent in an oxidative hair dye.

DR. BELSITO: I mean we had this discussion, so I'll let my teammates comment. I mean we have a 90-day oral with a NOAEL, which is what the SCCS based their margin of safety off of. The DART is negative. We have plus and minus genotox studies, but we thought overall they were fine. So, I'll let them comment.

DR. SNYDER: I can acquiesce to that. I mean, the overall toxicity profile is very benign, and I'm just a little uncomfortable without having data and then coming up with a percentage. And I think that incorrectly the percentage was linked to an old report, which was more broad, instead of what was used in these concentrations. But we just don't -- I mean, we have to be careful.

We usually go IDA if we don't have method of manufacturing. We can't be inconsistent on our request because all of a sudden we'll start getting nothing.

DR. COHEN: We've had no method of manufacturing in some of our reports before if we have the impurity data. And this impurity data, I think, if I recall --

DR. ROSS: It was 97 to 99 percent pure.

DR. COHEN: Yeah, we had pretty good impurity data.

DR. ROSS: So that's why we decided against needing that method of manufacture when we looked at the purity data.

DR. BELSITO: And are you going to request that a margin of safety be included in this report so we can justify?

DR. ROSS: I think it was in there anyway, wasn't it?

DR. BELSITO: It was referred as the SCCS. So are we just going to sit here and say whatever the SCCS says is fine with us?

DR. ROSS: No, but it was in the report, so that's what we looked at.

DR. COHEN: No, but it is data.

DR. KLAASSEN: Well we can calculate an MOS.

DR. SNYDER: It's not going to be any different.

DR. ROSS: It's going to be the same.

DR. KLAASSEN: Most likely it's going to come out 947 --

DR. ROSS: Because we don't have any new data, yeah.

DR. RETTIE: I think I volunteered you, Dr. Ross, to do the MOS.

DR. ROSS: I'm sure Kurt and I could take care of that, and Paul. But, yeah, we just felt that that was data in front of us in the report, so we looked at it.

DR. BELSITO: I'll only say that there are reports where the data has been incorrect on the sensitization index for methylisothiazolinone. It got us into huge problems in 2005.

So, David, if you want to do your own calculation and come up with a margin of safety that shows that's fine, I'm okay with going forward with a safe as used. But I will not accept a report in the literature of margin of safety without actually checking it ourselves.

DR. COHEN: We're at a stage in this report where we could do that and bring it up as a final, right?

DR. BELSITO: I'm fine with that, but we calculate our own margin of safety and not take what's been written in the literature as correct.

DR. COHEN: Okay. So, Don, if --

DR. BERGFELD: Is your movement to table then?

DR. BELSITO: Was this a final?

DR. COHEN: No, this is a tentative final, so we have another --

DR. BELSITO: We're just asking for the Panel's calculation of the margin of safety to verify that it's within the range of what the EU found.

DR. COHEN: So, it's insufficient for that?

DR. BELSITO: For calculation of margin of safety.

DR. HELDRETH: And I see no reason why Dr. Ross couldn't provide his calculation and his returns, and then that way it could be incorporated at the next iteration.

DR. BERGFELD: So, officially we're putting this on hold, but what are we calling it?

DR. COHEN: No, we're going to call it insufficient.

DR. BERGFELD: Insufficient? It'll go out insufficient?

DR. COHEN: Our data needs are internal. We're going to internally calculate this and then bring it back as a final. Put that in there and perhaps go with the safe as used as a oxidative hair dye.

DR. SNYDER: Christina, to capture the discussion regarding why we didn't ask for method of manufacturer, because of the impurity data was not --

DR. ROSS: And I think I would just add that I volunteered Dr. Snyder and Dr. Klaassen to help with that calculation. Is that okay with you, gentlemen?

DR. COHEN: Yes, we second that motion.

DR. SNYDER: We will peer review your calculations.

DR. KLAASSEN: And I will suggest that we have two significant figures, therefore, it will be different than the present one.

DR. ROSS: We're going to be using the same data.

DR. COHEN: Yeah, but I think as Don said, we should corroborate the data. It's very reasonable.

DR. ROSS: Yeah, I think it's a reasonable point. But what are we going to do with all these risk assessments that we get from European agencies that are in our dossiers? So, now we going to delete them?

DR. BELSITO: No, I mean, I think they're fine. But what we're doing here is we're just passing on -- we're agreeing that this is safe based on a margin of calculation done by the SCCS, and the fact that they said it could be used up to 1.5 and the old report had it at 1.0 percent.

You know, we were burned because there was an inaccurate report that had the SI for methylisothiazolinone as being ten times higher, you know, less sensitizing than it was. It was a decimal point error in a report and everyone worked off of that. And we were fortunate, unfortunate in a sense, that using that concentration, a hundred patients got through an HRIPT with negative results.

And we went out and allowed it to be used at a hundred parts per million, this is before QRA, which would've predicted, with the correct sensitization index, that we would've caused issues in wipes and a lot of other products. So, I just don't like accepting other people's numbers without looking very carefully at them.

DR. ROSS: Well I think the two representatives from both the teams, we can look at that and come up with our own. Is that okay with you, gentlemen?

DR. BELSITO: That's fine.

DR. BERGFELD: So we have a decision?

DR. SNYDER: Well, to Kurt's point, though, that the SCCS anchored to 1.5 percent, we're going to anchor to 1.0 percent.

DR. ROSS: We are.

DR. BELSITO: We're just going to say, you know, safe is used or --

DR. COHEN: 1.0 percent.

DR. BELSITO: Yeah.

DR. ROSS: Under oxidizing conditions. I mean, we wanted to specify that.

DR. COHEN: Under oxidizing conditions.

DR. RETTIE: So you'll come up with a different MOS number at 1.0 percent?

DR. ROSS: Kurt wants to go to two significant figur- -- no, we will look at it and we'll --

DR. BELSITO: Since we don't have a concentration of use, if we come up with a margin of safety that indicates 1.5, we can go with 1.5.

DR. COHEN: I'm okay with that. Yeah, that's fine.

DR. BERGFELD: All right, let's bring this to a close, these comments. Let's have Dr. Belsito repeat what we're going to do right now so we all understand it. Insufficient?

DR. BELSITO: Were insufficient for the Panel's internal calculation of the margin of safety, and we'll determine a safe concentration of use based upon that.

DR. BERGFELD: And second on it's agreeable? I think we'll just vote on this. All those in favor of this decision? All right, this is unanimous.

DECEMBER 2-3, 1998 PANEL MEETING

Dr. Belsito recalled that the following informal data requests on this group of ingredients were issued at the September 10, 1998 Team meeting:

(1) Concentration of use
(2) Physical and chemical properties
(3) Method of manufacture
(4) Impurities data, especially regarding the presence of *m*-cresol
(5) UV absorption data; if absorption occurs in the UVA or UVB range, photosensitization data may be needed
(6) Types of hair dye products (semi-permanent or oxidative) and the rate of reaction (bioavailability)
(7) Metabolism data; if metabolism is not similar to that of 4-Amino-2-Hydroxytoluene and *p*-, *m*-, and *o*-Aminophenol (ingredients already reviewed by CIR), the following data are needed:
    a. 28-day dermal toxicity data with histopathology
    b. dermal reproductive toxicity data
    c. two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity study performed using NTP methods.

Dr. Belsito noted that because these ingredients are used in hair dyes and because hair dyes are exempt from sensitization and photosensitization testing as long as the requirement of testing prior to use appears on the label, his Team determined that item 5 above could be deleted. Dr. Belsito said that item 5 should be deleted, because, even if the UV absorption data were positive, the Panel would not have the authority to ask for photosensitization data.

Dr. Schroeter agreed with the revised list of data requests (item 5 deleted).

Dr. Bailey said that he is unsure of how the legal and regulatory status of an ingredient impacts the CIR review process. He said that if there are data that relate to safety, regardless of whether the FDA has legal authority to act, these data should still be of concern to the Panel.

Dr. Belsito said that even if the ingredients were found to be photosensitizers, this would not be a reason for saying that they are unsafe for use in hair dyes, because hair dyes carry a warning about possible sensitization and the need to test prior to use.

Dr. Bailey said that photosensitization is not necessarily being referred to in this case, but, more so, contact sensitization.

Dr. McEwen said that the CIR Procedures do not preclude the Panel from requesting any data that are needed. He said that the Panel needs to determine whether the patch test requirement on the product label sufficiently addresses the Panel's concern about photosensitization, not from a theoretical standpoint, but from the use standpoint of hair dyes.

Concerning the list of data needs included at the beginning of this section, Dr. Belsito said that items 1-4 and 6-7 should be requested for all of the ingredients included in the review. He also reiterated that if the metabolism of these ingredients is not similar, then additional data (e.g. 28-day dermal toxicity data) will be needed.

Dr. McEwen asked if the Panel could use the information on skin penetration from Dr. Walters' presentation to do some modeling on these ingredients to determine if 28-day dermal toxicity data would be needed. In other words, he wanted to know if the Panel would agree to review skin penetration modeling data before requesting 28-day dermal toxicity data.

Dr. Andersen said that after reviewing skin penetration modeling data, the Panel has the option of issuing an Insufficient Data Announcement if these data are not found to be sufficient.

Dr. Belsito said that Dr. Walters presented models that were based on absorption against a barrier of the stratum corneum and data indicating that the forehead is a very absorptive surface, more so than other areas of the body. Dr. Belsito also noted that the follicular shunting mechanism (which is discounted by the models, because, in general, it is not a major area of absorption) would be much more important for a hair dye. Dr. Belsito said that if the skin modeling results indicated a high extent of ingredient absorption, then the 28-day dermal toxicity data would be needed. However, he said that if the results indicated low absorption, he would still want to know what the results would be in a mouse or human, both of which have many hair follicles. He concluded that the computer-generated model would not be useful to him in the present safety assessment.

Someone in the audience commented that the models were generated on specific chemical compounds with similar structures, and that it is possible that the Panel will need absorption data on all four hair dyes included in the safety assessment in order to generate the model.

Dr. Klaassen said that having heard the presentation on skin absorption, he would like for the Panel to include the octanol/water partition coefficient in its request for data on chemical and physical properties. He said that this is the most important chemical parameter that the Panel could have on any ingredient.

Dr. Bailey urged the Panel to be very cautious and be sure to ask certain questions before compounds (especially aromatic amines) are grouped for review in a single report and, potentially, data on one ingredient are wrongfully extrapolated to others.

Dr. Andersen said that the effort by CIR to maximize the benefit from the effort of each review may lead to the creation of as large a family of ingredients as is reasonable. He noted that during reviews by the Panel, any Panel member has an opportunity to recommend the exclusion any ingredient(s) that should not be included in the review.

Dr. Bailey recommended that for ingredients that are reviewed as groups, a table should be created (as part of the report) that indicates which tests have been done on which ingredients.

Dr. Bergfeld said that it was brought to her attention by Dr. Belsito and others that there was a recent hair dye study (4,000 individuals) showing some safety parameters that should be incorporated into CIR's data bank and, perhaps, should be made available for use in the present safety assessment.

Dr. Bailey said that another hair dye study by the American Cancer Society will be published soon. He said that this is a follow-up study to one that was done a few years ago.

Based on the preceding discussion, the following data are needed for completion of the safety assessment on 6-Amino-m-Cresol, 6-Amino-o-Cresol, 4-Amino-m-Cresol, 5-Amino-4-Chloro-o-Cresol, 5-Amino-6-Chloro-o-Cresol, and 4-Chloro-2-Aminophenol (data needed on all ingredients):

(1) Concentration of use
(2) Physical and chemical properties
(3) Method of manufacture
(4) Impurities data, especially regarding the presence of m-cresol
(5) Types of hair dye products (semi-permanent or oxidative) and the rate of reaction (bioavailability)
(6) Metabolism data; if metabolism is not similar to that of 4-Amino-2-Hydroxytoluene and *p*-, *m*-, and *o*-Aminophenol (ingredients already reviewed by CIR), the following data are needed:
    a. 28-day dermal toxicity data with histopathology
    b. dermal reproductive toxicity data
    c. two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity study performed using NTP methods.

Note: The Panel responded to a suggestion that skin penetration modeling might help resolve some of the questions by noting that such an approach probably would not be useful for products that are used on the hair follicle rich scalp and could also contact the skin of the forehead.

An Insufficient Data Announcement containing the preceding data requests will be issued.

JUNE 14-15, 1999 PANEL MEETING

Dr. Belsito recalled that an insufficient data announcement with the following data requests was issued at the December 2-3, 1998 Panel meeting.

(1) Concentration of use
(2) Physical and chemical properties
(3) Method of manufacture
(4) Impurities data, especially regarding the presence of *m*-cresol
(5) Types of hair dye products (semi-permanent or oxidative) and the rate of reaction (bioavailability)
(6) Metabolism data; if metabolism is not similar to that of 4-Amino-2-Hydroxytoluene and *p*-, *m*-, and *o*-Aminophenol (ingredients already reviewed by CIR), the following data are needed:
    a. 28-day dermal toxicity data with histopathology
    b. dermal reproductive toxicity data
    c. two genotoxicity studies, one using a mammalian system; if positive, a 2-year dermal carcinogenicity study performed using NTP methods.

Note: The Panel responded to a suggestion that skin penetration modeling might help resolve some of the questions by noting that such an approach probably would not be useful for products that are used on the hair follicle rich scalp and could also contact the skin of the forehead.

Dr. Belsito noted that, of the data requests listed, current concentration of use data and impurities data (only on 4-amino-*m*-cresol) were received from the cosmetics industry. He also stated that the CIR report contains a good amount of genotoxicity data on some, but not all, of the ingredients and that there is no information indicating how these chemicals are metabolized. Thus, his Team concluded that the current report is insufficient for arriving at a conclusion on the safety of these ingredients in cosmetics.

Dr. Belsito said that if the Panel continues to need data on chemical and physical properties, including the octanol/water partition coefficient, then impurities data (especially, regarding the presence of *m*-cresol and other organic molecules and heavy metals - modification of item 4 above) are needed. He noted that the impurities data are needed on all ingredients except 4-amino-*m*-cresol (data already received on this ingredient). Dr. Belsito added that the Panel still needs items 5 and 6 from the list of data needs, and that item 6c should refer to genotoxicity studies on 5-Amino-4-Chloro-o-Cresol and 5-Amino-6-Chloro-o-Cresol.

Dr. Schroeter said that his Team requested that 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol also be added to item 6c.

Dr. Shank said that a mammalian mutagenicity assay is needed on 4-Chloro-2-Aminophenol and that both mammalian and bacterial mutagenicity assays are needed on 6-Amino-*o*-Cresol.

The Panel voted unanimously in favor of issuing a Tentative Report with an insufficient data conclusion on 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol. The data needed in order for the Panel to complete its safety assessment of this group of ingredients are listed in the report discussion as follows:

(1) Physical and chemical properties, including the octanol/water partition coefficient
(2) Impurities data, for all except 4-Amino-m-Cresol, especially regarding the presence of heavy metals, *m*-cresol, and other organic molecules
(3) Types of hair dye products (semi-permanent or oxidative) in which these ingredients are used and the rate of reaction (bioavailability) in the hair dye product
(4) Metabolism data; if metabolism is <u>not</u> similar to that of 4-Amino-2-Hydroxytoluene and *p*-, *m*-, and *o*-Aminophenol (ingredients already reviewed by CIR), the following data are needed:

a. 28-day dermal toxicity data with histopathology
b. dermal reproductive and developmental toxicity data
c. for 5-Amino-6-Chloro-*o*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, and 6-Amino-o-Cresol, two genotoxicity studies, one using a mammalian system; for 4-Chloro-2-aminophenol, one genotoxicity study in a mammalian system; if any of these tests for any ingredient are positive, a 2-year dermal carcinogenicity study performed using NTP methods may be needed.

DECEMBER 20-21, 1999 PANEL MEETING

Because a significant amount of data was received one week before the Panel meeting, the Panel voted in favor of tabling any further discussion on this group of ingredients until the February 14-15, 2000 Panel meeting.

FEBRUARY 14-15, 2000 PANEL MEETING

Dr. Belsito noted that the report on this group of ingredients was tabled at the December 20-21, 1999 Panel meeting because of the large data submissions on 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol that were received. He also noted that additional data on 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol were received prior to today's meeting. Some of the information received indicates that these two dyes could be used in oxidative hair dyes. However, information indicating whether or not they are used in nonoxidative or semipermanent hair dyes was not received.

After reviewing all of the data on the safety of these ingredients, Dr. Belsito's Team concluded that all six are safe as used in oxidative hair dyes and that the following ingredients are safe as used in nonoxidative hair dyes: 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, and 5-Amino-6-Chloro-*o*-Cresol. The Belsito Team also concluded that the available data are insufficient for determining the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in nonoxidative hair dyes, and that the data needs that were included in the Tentative Report (issued at June 14-15, 1999 Panel meeting) are applicable to these two ingredients.

Dr. Andersen noted that the Belsito Team's conclusion differs significantly from the conclusion that was issued in the Tentative Report (i.e., insufficient data conclusion on all six ingredients). Thus, if the proposed conclusion is approved, the Panel should issue a Revised Tentative Report.

It was moved and seconded that 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, and 5-Amino-6-Chloro-*o*-Cresol are safe as used in oxidative and non-oxidative hair dyes, that 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol are safe as used in oxidative hair dyes, and that the available data are insufficient for supporting the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in non-oxidative hair dyes. The data that are needed in order for the Panel to complete the safety assessment of these two ingredients are listed in the discussion section of the report as follows:

(1) Physical and chemical properties, including the octanol/water partition coefficient
(2) Impurities data, especially regarding the presence of m-cresol, other organic molecules, and heavy metals
(3) Metabolism data; if the metabolism is not similar to that of 4-Amino-2-Hydroxytoluene and/or *p*-, *m*-, and *o*-Aminophenol (ingredients already reviewed by CIR), the following data are needed:
  (a) 28-day dermal toxicity data with histopathology
  (b) dermal reproductive toxicity data
  (c) an *in vitro* genotoxicity study for 6-Amino-o-Cresol, and a genotoxicity study in a mammalian system for 6-Amino-o-Cresol and 4-Chloro-2-Aminophenol (if any of these data are positive, a two-year dermal carcinogenicity study performed using NTP methods may be needed)

The Panel voted unanimously in favor of issuing a Revised Tentative Report with the conclusions stated in the preceding paragraph.

SEPTEMBER 11-12, 2000 PANEL MEETING

Dr. Belsito recalled that at the February 14-15, 2000 Panel meeting, the Panel concluded that the available data support the safety of 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, and 5-Amino-6-Chloro-*o*-Cresol as used in oxidative and non-oxidative semipermanent hair dyes, and that the available data also support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol as used in oxidative hair dyes. The Panel also concluded that the available data are insufficient to support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in nonoxidative semipermanent hair dyes. The issuance of a Revised Tentative Report with these conclusions was unanimously approved. Dr. Belsito noted that no data submissions in response to the insufficient data conclusion have been received.

The Panel voted unanimously in favor of issuing a Final Report on this group of ingredients with the following conclusion: The CIR Expert Panel concludes that the available data support the safety of 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, and 5-Amino-6-Chloro-*o*-Cresol as used in oxidative and non-oxidative (semi-permanent) hair dyes. The available data also support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol for use in oxidative hair dyes, but are insufficient to support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in non-oxidative (semi-permanent) hair dyes. The data that are needed in order for the Panel to complete its safety assessment of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol are listed in the discussion section of the report as follows:

(1) Physical and chemical properties for all ingredients, including the octanol/water partition coefficient
(2) Impurities data, especially regarding the presence of m-cresol, other organic molecules, and heavy metals for all ingredients except 4-Amino-*m*-Cresol
(3) Metabolism data; if metabolism is not similar to that of 4-amino-2-hydroxytoluene and/or *p*-, *m*-, and *o*-aminophenol (ingredients already reviewed by CIR), the following data may be needed:
  a. 28-day dermal toxicity with histopathology
  b. dermal reproductive toxicity data
  c. an *in vitro* genotoxicity study for 6-Amino-o-Cresol and one genotoxicity study in a mammalian system for 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol; if positive, a 2-year dermal carcinogenicity study using National Toxicology Program methods may be needed.

Dr. Belsito recommended that the last paragraph in the report discussion, which includes the data needs stated above, be reworded to clarify that the data needs listed refer to the data that are needed in order for the Panel to assess the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol for use in non-oxidative hair dyes.

Amended Safety Assessment of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: November 9, 2023
Panel Meeting Date: December 4-5, 2023

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, 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. This safety assessment was prepared by Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

1620 L Street, NW, Suite 1200 ◊ Washington, DC 20036-4702 ◊ ph 202.331.0651
cirinfo@cir-safety.org

ABBREVIATIONS

ADME	absorption, distribution, metabolism, and excretion
A_{max}	absorbance maximum
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI)
EC_3	estimated concentrations for a SI of 3
EU	European Union
FDA	Food and Drug Administration
HPLC	high-performance liquid chromatography
LLNA	local lymph node assay
MOS	margin of safety
NMR	nuclear magnetic resonance
NOAEL	no-observable-adverse-effect-level
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
SCCP	Scientific Committee on Consumer Products
SED	systemic exposure dose
SI	stimulation index
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl, which are reported to function as hair dyes in cosmetic products. The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl under the intended conditions of use as hair dye ingredients.

INTRODUCTION

5-Amino-4-Chloro-*o*-Cresol, which according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*) is reported to function in cosmetics as a hair colorant,[1] was previously reviewed by the Expert Panel for Cosmetic Ingredient Safety (Panel) as part of a safety assessment of 6 amino-cresol hair dye ingredients that was published in 2004.[2] At that time, the Panel concluded that "the available data … support the safety of 5-Amino-4-Chloro-*o*-Cresol… for use in oxidative and nonoxidative (semi-permanent) hair dyes." In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to several of the other amino-cresol hair dye ingredients that were included in the original 2004 report being banned for use in cosmetics by the European Commission.[3] However, because the Panel determined that data for these amino-cresol hair dye ingredients could not be read-across, rather than including all 6 ingredients in one amended report, re-reviews of each hair dye will be presented as individual stand-alone reports.

Much of the data on 5-Amino-4-Chloro-*o*-Cresol in the original report was actually on the salt, 5-Amino-4-Chloro-*o*-Cresol HCl. Accordingly, 5-Amino-4-Chloro-*o*-Cresol HCl has been added to this amended report because in situ and in formulation the salt and free base are identical. Excerpts from the summaries of the previous report on 5-Amino-4-Chloro-*o*-Cresol are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (These data are not included in the tables or the Summary.)

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 July 2023. 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.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

CHEMISTRY

Definition and Structure

According to the *Dictionary*, 5-Amino-4-Chloro-*o*-Cresol (CAS No. 110102-86-8) is the organic compound that conforms to formula in Figure 1.[1] 5-Amino-4-Chloro-*o*-Cresol HCl (CAS No. 110102-85-7) is the hair colorant that is the hydrochloride salt of 5-Amino-4-Chloro-*o*-Cresol. However, the use of regiochemical terms such as "*ortho*-" (i.e., the "-*o*-" in 5-Amino-4-Chloro-*o*-Cresol) is vague and inappropriate when an aromatic system such as a benzene ring has more than 2 substituents. (5-Amino-4-chloro-2-methylphenol is the systematic name for 5-Amino-4-Chloro-o-Cresol).

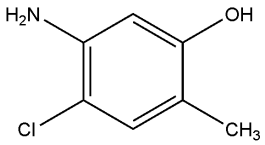

Figure 1. 5-Amino-4-Chloro-*o*-Cresol

5-Amino-4-Chloro-*o*-Cresol HCl is a precursor in oxidative hair dye systems.[4] It reacts with primary intermediates to form the final hair-reactive dye. The reaction can be accelerated by addition of an oxidizing agent (e.g., hydrogen peroxide), but can also be achieved by air oxidation.

Chemical Properties

Chemical properties for 5-Amino-4-Chloro-*o*-Cresol (molecular weight 157.59 g/mol) and 5-Amino-4-Chloro-*o*-Cresol HCl (formula weight 194.06 g/mol) are summarized in Table 1. 5-Amino-4-Chloro-*o*-Cresol is reported to be soluble in water, propylene glycol, and triethanolamine.[2] 5-Amino-4-Chloro-*o*-Cresol has a symmetrical absorption peak below 300 nm, which falls off sharply above 300 nm.

Method of Manufacture

Method of manufacturing data for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

Composition and Impurities

The specification of 97% purity for 5-Amino-4-Chloro-o-Cresol is supported by high-performance liquid chromatography (HPLC) analysis; impurities include an early peak identified as 2-methyl-5-aminophenol (2%), and two unidentified peaks (1% combined), one of which was close to the peak of the ingredient and one that eluted later.[2]

5-Amino-4-Chloro-*o*-Cresol HCl

The purity (general) of 5-Amino-4-Chloro-*o*-Cresol HCl is reported to be > 97% (w/w) through nuclear magnetic resonance (NMR) spectroscopy and > 99% (peak area) through HPLC.[4] Chloride and sulfate content are 18% (w/w) and 0.1% (w/w), respectively. Solvent content as water is < 0.1% (w/w) and as ethanol < 0.3% (w/w). Sulfated ash content is 0.6% (w/w). 4-amino-2-hydroxytoluene (up to 2%) is reported as an impurity. Heavy metal content was reported as the following: lead < 20 ppm; nickel and antimony < 10 ppm; arsenic and cadmium < 5 ppm; and mercury < 1 ppm.

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 these ingredients in cosmetics and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2023 VCRP data[5] and the concentration of use surveys conducted by the Council in 2021 and 2023,[6,7] 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl have no reported uses. When the original safety assessment was published in 2004, 5-Amino-4-Chloro-*o*-Cresol was reported to have no uses, according to 1998 VCRP data.[2] However, according to industry survey data submitted in 1994, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors in combination with hydrogen peroxide.

Although products containing this ingredient may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of this ingredient (and without consumer habits and practices data or particle size data related to this use technology), the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

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 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.[8,9] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the Food, Drug, and Cosmetic Act.

In the European Union (EU), 5-Amino-4-Chloro-*o*-Cresol is not specifically restricted from use in cosmetic products, but subject to the general provisions of the EU Cosmetic Regulation.[3] 5-Amino-4-Chloro-*o*-Cresol HCl is categorized in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. For this ingredient, the regulation states that the maximum concentration applied to hair must not exceed 1.5% (calculated as hydrochloride) after mixing under oxidative conditions. The Scientific Committee on Consumer Products (SCCP) concluded that 5-Amino-4-Chloro-*o*-Cresol HCl, at a maximum concentration of 1.5% on the head, does not pose a risk to the health of the consumer.[4]

TOXICOKINETIC STUDIES

Dermal Absorption

In Vitro

The dermal absorption/percutaneous penetration potential of [^{14}C]5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) through excised pig skin (750 µm thick) was determined from a cream formulation mixed with a developer containing hydrogen peroxide.[4] The study was performed in accordance with Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 428. The concentration of 5-Amino-4-Chloro-*o*-Cresol HCl in the final application formulation was 1.6%. Using Franz diffusion cells, 20 mg formulation per cm^2 pig skin (dose of test substance was approximately 0.32 mg/cm^2 skin; skin discs were 1.0 cm^2) was applied for 30 min. Application of the test material was terminated by gently rinsing with 0.01% Tween 80 solution and water. The formulation was analyzed in 2 experiments with 4 replicates per experiment for adsorbed, absorbed, and penetrated amount of the test material. The receptor fluid (Dulbecco's phosphate buffered saline; pH 7.35) was analyzed at defined intervals for up to 48 h post-application.

Both the amounts absorbed and penetrated were considered systemically available. The amount of 5-Amino-4-Chloro-*o*-Cresol HCl systemically available from a standard cream formulation mixed with a developer was found to be 12.47 $\pm$ 1.82 µg/cm^2 (range 10.60 to 16.47 µg/cm^2), which is equivalent to 3.90 $\pm$ 0.69% (range 3.12 to 5.29%) of the applied dose. The SCCP stated that the number of chambers used was too few, and therefore an absorbance maximum (A_{max}) of 16.47 µg/cm^2 in an oxidizing formulation (equivalent to 5.29% of the applied dose in a final application formulation containing 1.6% active) was used for the calculation of the margin of safety.[4]

Animal

Skin absorption of [^{14}C]5-Amino-4-Chloro-o-Cresol HCl was studied in female rats.[2] A formulation containing the radiolabeled ingredient (with p-toluenediamine sulfate, basic fatty acid emulsion, propylene glycol, water, and ammonia) was diluted 1:1 with water to make a final test ingredient concentration of 1.85%. The test material was applied for 72 h under semi-occlusive conditions. The amount of ingredient on intact, clipped skin was 0.41 mg/cm^2. The mean skin absorption was 32.7%. 5-Amino-4-Chloro-o-Cresol was excreted via urine (92%) and feces (8%). The concentration in kidneys (0.003%) at 72 h was the greatest of any of the organ/tissue samples. The stratum corneum at the site of application, obtained by tape stripping, had 0.22% of the radioactivity. A similar rat study was performed using the above formulation diluted 1:1 with a developer consisting of 6% hydrogen peroxide before application. The skin absorption in this case was only 1.28%. Excretion via urine (91%) and feces (9%) accounted for all that was absorbed; the concentration in organs/ tissues was at or near the detection limit of the radiolabel. The stratum corneum had 0.2% of the radioactivity and the dermis had 0.2%.

Absorption, Distribution, Metabolism, and Excretion (ADME) Studies

In an oral metabolism study in rats, a 1.27% solution of [^{14}C]5-Amino-4-Chloro-o-Cresol HCl was readily absorbed in the intestine (91.7%).[2] The test material was excreted via urine (94%) and feces (6%). The greatest concentration recovered in the organ/tissue samples was 0.001% in the liver.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

In an acute oral toxicity study, male and female rats received 5-Amino-4-Chloro-o-Cresol HCl by gavage at doses of 1184, 1539, and 2000 mg/kg.[2] For males, the LD_{50} was between 1539 and 2000 mg/kg and for females, the LD_{50} was >2000 mg/kg.

Acute toxicity studies of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not found in the updated literature search, and unpublished data were not submitted.

Subchronic Toxicity Studies

Oral

In a 90-d oral study, male and female rats received 5-Amino-4-Chloro-o-Cresol HCl by gavage at doses of 0, 20, 60, and 180 mg/kg/d.[2] No clinical observations or pathological findings indicative of systemic toxicity were observed. Only minor deviations in a few biochemical and hematological parameters were noted. The no-observable-adverse-effect-level (NOAEL) was 180 mg/kg/d.

Repeated-dose toxicity studies of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not found in the updated literature search, and unpublished data were not submitted.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

The only maternal effect observed in pregnant rats dosed with aqueous 5-Amino-4-Chloro-o-Cresol HCl (up to 500 mg/kg/d) by gavage on days 6 to 15 of gestation was a brown discoloration of the urine.[2] In fetuses, no developmental toxicity was associated with treatment with 5-Amino-4-Chloro-o-Cresol HCl.

Development and reproductive toxicity studies for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not found in the updated literature search, and unpublished data were not submitted.

GENOTOXICITY STUDIES

5-Amino-4-Chloro-o-Cresol was mutagenic with metabolic activation in an Ames test evaluating concentrations of up to 2500 µg/plate of 5-Amino-4-Chloro-o-Cresol HCl dissolved in water and up to 1200 µg/plate of 5-Amino-4-Chloro-o-Cresol dissolved in dimethyl sulfoxide.[2] No increases in the number of mutations were observed in a cell gene mutation test at the HGPRT locus in V79 Chinese hamster lung cells exposed to 5-Amino-4-Chloro-o-Cresol HCl dissolved in ethanol at up to 60 µg/ml without metabolic activation and up to 550 µg/ml with metabolic activation. In an in vivo micronucleus test in mice, 5-Amino-4-Chloro-o-Cresol HCl did not induce micronuclei after a single oral dose of up to 500 mg/kg bw.

Additional in vitro and in vivo genotoxicity studies on 5-Amino-4-Chloro-*o*-Cresol HCl summarized here are detailed in Table 2. In an Ames test, 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was mutagenic in strain TA98 with metabolic activation at up to 5000 µg/plate; the test material did not induce an increase in the number of revertant colonies in strains TA100, TA102, TA1535, or TA1537, at any concentration tested, with or without metabolic activation.[4] 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was not genotoxic in a L5178 mouse lymphoma cell assay at the *tk* locus at up to 500 µg/ml without metabolic activation or with up to 375 µg/ml with metabolic activation. In an in vitro mammalian cell micronucleus test, a clear dose-dependent increase in cells with micronuclei was observed following exposure of 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) at up to 1000 µg/ml without metabolic activation and up to 500 µg/ml with metabolic activation in V79 Chinese hamster lung cells. However, an in vivo micronucleus test found that 5-Amino-4-Chloro-*o*-Cresol HCl (purity not reported) did not induce micronuclei in mice that received a single intraperitoneal dose of 500 mg/kg bw.

CARCINOGENICITY STUDIES

Carcinogenicity data for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Very slight erythema and edema were observed following a 4-h semi-occlusive patch test of 5-Amino-4-Chloro-o-Cresol HCl (concentration not reported) in 3 rabbits.[2] No signs of erythema, edema, eschar formation or systemic toxicity were observed in a 2-h dermal irritation study of a 10% aqueous formulation containing 5-Amino-4-Chloro-o-Cresol HCl in 6 rabbits. In a repeated application study in mice, no primary skin irritation was observed to a 10% dilution of 5-Amino-4-Chloro-o-Cresol HCl, adjusted to pH 8 with ammonia.

The irritation potential of a 10% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol HCl (purity not reported) was assessed in 5 male New Zealand albino rabbits.[10] The test material was adjusted to pH 8 with ammonia and applied as a single dose (0.5 ml) to 6.25 cm^2 intact skin. Occlusive patches were applied and left in place for 4 h. The test sites were then rinsed. The skin was examined for erythema, eschar formation, and edema at 1, 24, and 48 h after the patches were removed. No reactions were observed. It was concluded that a 10% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol HCl was non-irritating.

Sensitization

Animal

5-Amino-4-Chloro-o-Cresol HCl (induced at up to 5% and challenged at 2%; in aqueous solution) was a moderate sensitizer in a guinea pig maximization test.[2] In additional guinea pig maximization tests, formulations containing 5-Amino-4-Chloro-o-Cresol HCl and oxidizing agents (induced at up to 0.2% and challenged at up 20% in formulation diluted 1:1 with 6% hydrogen peroxide) were non-sensitizing. 5-Amino-4-Chloro-o-Cresol in ethanol (63% as paste) was not considered to be a sensitizer in a Buehler guinea pig test.

A local lymph node assay (LLNA) was performed using 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure).[4] Female CBA/CaOlaHsd mice were divided into groups of 4 and received 5, 10, or 20% of the test material in ethanol:water (7:3, v/v) on the ear surface (25 µl) once daily for 3 consecutive days. α-Hexylcinnamaldehyde was used as the positive control and a negative control group received just the vehicle. Five days after the first topical application, all animals were injected intravenously with [^{3}H]methyl thymidine and the proliferation of lymphocytes in the draining lymph nodes was measured. The stimulation indices (SI) were calculated to be 1.18, 0.87, and 0.87 for the 5, 10, and 20% dose groups, respectively. The

estimated concentrations for a SI of 3 (EC_3) was not calculated. The controls yielded expected results. It was concluded that 5-Amino-4-Chloro-*o*-Cresol HCl was not sensitizing when tested at up to 20% in mice.

OCULAR IRRITATION STUDIES

Animal

Aqueous 5-Amino-4-Chloro-o-Cresol HCl (5%) instilled into the conjunctival sac of male albino New Zealand rabbits had no effects on the cornea or the iris, and only slight conjunctival erythema and edema up to 24 h were observed.[2]

In an ocular irritation study performed in accordance with OECD TG 405, 4 male New Zealand White rabbits received 0.1 ml of 5% aqueous 5-Amino-4-Chloro-*o*-Creol HCl (purity not reported) in the conjunctival sac of the right eye.[10] The eye was not rinsed and the left eye served as the control. Ocular reactions were recorded at 1, 6, 24, and 48 h after instillation. Slight redness of the conjunctiva was reported in 3 rabbits within 6 h of instillation, which resolved in all animals by 24 h. Exudate was observed in all rabbits 1 h after instillation, in 3 rabbits after 6 h, and in 1 rabbit until 24 h. No reactions were observed in the cornea or iris. It was concluded that 5% aqueous 5-Amino-4-Chloro-*o*-Cresol HCl was a slight ocular irritant.

In another ocular irritation study, approximately 51 mg of 5-Amino-4-Chloro-*o*-Cresol HCl (> 99% pure) were instilled into the conjunctival sac of one eye in one male New Zealand White rabbit.[4] The eye was not rinsed. The other eye served as the control. The eye irritation reactions were scored 1, 24, 48, and 72 h and 7 d after instillation of the test material. The test material caused severe eye irritation immediately after instillation. Instillation of the test material affected the cornea, iris, and conjunctivae. The opacity of the cornea, injection of the iris, and the irritation of the conjunctivae were irreversible within the study period of 7 d. There was evidence of ocular corrosion and staining with fluorescein revealed corneal epithelial damage in the animal. Under the conditions of the study, undiluted 5-Amino-4-Chloro-*o*-Cresol HCl was extremely irritating to the rabbit eye.

MARGIN OF SAFETY

The SCCP calculated the margin of safety (MOS) for 1.5% 5-Amino-4-Chloro-*o*-Cresol HCl (on head) under oxidative conditions to be 947 (which is considered protective).[4] This calculation is based on the NOAEL of 180 mg/kg bw/d from a 90-d oral rat study and a systemic exposure dose (SED) of 0.19 mg/kg bw (skin area surface of 580 cm^2 x absorption through skin of 16.47 µg/cm^2 x 0.001 (unit conversion)/typical human bw of 60 kg). The Panel confirmed this MOS calculation.

In consideration of the absence of dermal absorption data for 5-Amino-4-Chloro-*o*-Cresol HCl at the maximum use concentration of 1% reported by the Council, the Panel performed a more conservative calculation, under the assumption of 100% dermal absorption, the usage of 100 ml of permanent hair dye per application, and a retention factor of 0.1.[11] This yielded an SED value of 1.66 mg/kg. By employing the NOAEL of 180 mg/kg bw/d derived from the 90-d oral rat study, the MOS was calculated to be 113. Such cautious estimation illustrates that even when presumed that there is 100% absorption and the product is used daily, the resulting MOS is greater than 100. This figure is generally accepted as the threshold for considering a product safe to use.

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. 5-Amino-4-Chloro-*o*-Cresol and its chloride salt 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

5-Amino-4-Chloro-*o*-Cresol and its salt, 5-Amino-4-Chloro-*o*-Cresol HCl, are reported to function in cosmetics as hair colorants. 5-Amino-4-Chloro-*o*-Cresol was previously reviewed by the Panel as part of a safety assessment of 6 amino-cresol hair dye ingredients that was published in 2004. At that time, the Panel concluded that according to the available data (in that report), 5-Amino-4-Chloro-*o*-Cresol is safe for use in oxidative and non-oxidative hair dyes. In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years, and it has been at least 15 years since this assessment has been issued. In June 2022, the Panel determined that this safety assessment should be re-opened for re-evaluation due to several of the other amino-cresol hair dye ingredients that were included in the original 2004 assessment being banned for use in cosmetics by the European Commission.

According to 2023 VCRP survey data, 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol HCl have no reported uses. The results of the concentration of use surveys conducted by the Council in 2021 and 2023 for the free base and the HCl salt, respectively, also reported no uses for these ingredients. When the original safety assessment was published in 2004, 5-Amino-4-Chloro-*o*-Cresol was reported to have no uses, according to 1998 VCRP. However, according

to industry survey data submitted in 1994, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors (after mixing with hydrogen peroxide).

According to the EU, 5-Amino-4-Chloro-*o*-Cresol is not specifically restricted from use in cosmetic products, but subject to the general provisions of the EU Cosmetic Regulation. 5-Amino-4-Chloro-*o*-Cresol HCl is categorized in Annex III, the list of substances which cosmetic products must not contain except subject to the restrictions laid down. For this ingredient, the regulation states that the maximum concentration applied to hair must not exceed 1.5% (calculated as the hydrochloride) after mixing under oxidative conditions. The SCCP concluded that 5-Amino-4-Chloro-*o*-Cresol HCl, at a maximum concentration of 1.5% on the head, does not pose a risk to the health of the consumer.

In a dermal absorption/percutaneous penetration study, a cream formulation containing [^{14}C]5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) and hydrogen peroxide was applied to excised pig skin with the final concentration of the radiolabel reported as 1.6%. The amount of 5-Amino-4-Chloro-o-Cresol HCl systemically available was found to be 12.47 $\pm$ 1.82 µg/cm^2 (range 10.60 to 16.47 µg/cm^2), which is equivalent to 3.90 $\pm$ 0.69% (range 3.12 to 5.29%) of the applied dose.

5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was mutagenic in strain TA98 with metabolic activation in an Ames test at up to 5000 µg/plate; the test material did not induce an increase in the number of revertant colonies in strains TA100, TA102, TA1535, or TA1537, at any concentration tested with or without metabolic activation. 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was not genotoxic in a L5178 mouse lymphoma assay at the *tk* locus at up to 500 µg/ml without metabolic activation or with up to 375 µg/ml with metabolic activation. In an in vitro mammalian cell micronucleus test, a clear dose-dependent increase in cells with micronuclei was observed following exposure of 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) at up to 1000 µg/ml without metabolic activation and up to 500 µg/ml with metabolic activation in V79 Chinese hamster lung cells. However, an in vivo micronucleus test found that 5-Amino-4-Chloro-*o*-Cresol HCl (purity not reported) did not induce micronuclei in mice that received a single intraperitoneal dose of 500 mg/kg bw.

5-Amino-4-Chloro-*o*-Cresol HCl (10% aqueous solution; purity not reported) was non-irritating in a 4 h dermal irritation study in rabbits. In an LLNA, 5-Amino-4-Chloro-*o*-Cresol HCl (98% pure) was not sensitizing when tested at up to 20%. When tested as a 5% aqueous solution, 5-Amino-4-Chloro-*o*-Cresol HCl was a slight ocular irritant to rabbit eyes; however, when instilled undiluted to a rabbit eye, 5-Amino-4-Chloro-*o*-Cresol HCl (> 99% pure) was extremely irritating.

An MOS for 1.5% 5-Amino-4-Chloro-o-Cresol HCl (on head) under non-oxidative conditions was calculated by the SCCP to be 947. This calculation was based on an NOAEL of 180 mg/kg bw/d from a 90-d oral rat study and an SED of 0.19 mg/kg bw. The Panel calculated a more conservative MOS of 113 using the same NOAEL and an SED of 1.66 mg/kg bw, which was based on the maximum use concentration of 1% and 100% absorption; this demonstrated that even when presumed that there is 100% absorption and the product is used daily, the resulting MOS is greater than 100.

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.

Method of manufacture and carcinogenicity studies on 5-Amino-4-Chloro-*o*-Cresol (or the HCl salt) were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

DISCUSSION

In accordance with its Procedures, the Panel evaluates the conclusions of previously-issued reports approximately every 15 years. In 2004, the Panel published a final report on 5-Amino-4-Chloro-*o*-Cresol and concluded that the available data supported the safety of this ingredient for use in oxidative and nonoxidative (semi-permanent) hair dyes. This report has been reopened for re-evaluation because several of the other amino-cresol hair dye ingredients that were included in the original 2004 report are banned for use in cosmetics by the European Commission. Much of the data on 5-Amino-4-Chloro-*o*-Cresol in the original report was actually on the salt, 5-Amino-4-Chloro-*o*-Cresol HCl. Accordingly, 5-Amino-4-Chloro-*o*-Cresol HCl has been added to this amended report because in situ and in formulation the salt and free base are identical.

At the September 2023 meeting, the Panel concluded that the available data are insufficient to make a determination of safety for these two hair dye ingredients, stipulating that the margin of safety for 5-Amino-4-Chloro-*o*-Cresol HCl needed to be verified. The Panel noted that these ingredients are reported to function as oxidative hair dyes in hair coloring products; however, no use of these ingredients was reported according to 2021 and 2023 concentration of use surveys and 2023 VCRP frequency of use data. In the original (2004) safety assessment, 5-Amino-4-Chloro-*o*-Cresol was reported to be used at up to 1% in hair dyes and colors (after mixing with hydrogen peroxide). Accordingly, to estimate the risk for using these ingredients, the Panel performed a conservative MOS calculation using the assumption of 100% absorption of 5-Amino-4-Chloro-*o*-Cresol HCl and daily application. The resulting MOS is 113, which is considered protective.

In vitro genotoxicity studies yielded mixed results, and results of in vivo micronucleus studies were negative; however, concern for these mixed results was mitigated by the weight-of-evidence of negative results for other toxicity endpoints. The Panel noted the lack of method of manufacturing information, but data on composition and impurities for these ingredients and the high degree of reported purity obviated this need.

The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act), when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures. The Panel considered concerns that such self-testing might induce sensitization, but agreed that there was not a sufficient basis for changing this advice to consumers at this time.

In considering hair dye epidemiology data, the Panel concluded that the available epidemiology studies are insufficient to scientifically support a causal relationship between hair dye use and cancer or other toxicological endpoints, based on lack of strength of the associations and inconsistency of findings. Use of direct hair dyes, while not the focus in all investigations, appears to have little evidence of any association with adverse events as reported in epidemiology studies.

The Panel's respiratory exposure resource document (available at https://www.cir-safety.org/cir-findings) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the available data are insufficient to make a determination of safety for 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-4-Chloro-*o*-Cresol under the intended conditions of use as hair dye ingredients.

Tables

Table 1. Chemical properties

Property	Value	Reference
	5-Amino-4-Chloro-o-Cresol	
Physical Form	Brown crystals	[2]
Molecular Weight (g/mol)	157.59	[2]
Melting Point (ºC)	248 (decomposition)	[2]
	5-Amino-4-Chloro-o-Cresol HCl	
Physical Form	Beige to light brown amorphous powder	[4]
Formula Weight (g/mol)	194.06	[4]
Boiling Point (ºC)	> 240 (decomposition)	[4]
Water Solubility (g/l @ 20 ºC)	< 1	[4]
Other Solubility (g/l @ 20 ºC)	ethanol: 50-200; dimethyl sulfoxide: > 100	[4]
log P_{ow}	-1.90 (estimated)	[4]

Table 2. Genotoxicity studies

Ingredient	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
5-Amino-4-Chloro-*o*-Cresol HCl; 98% pure	3 - 5000 µg/plate	deionized water	*Salmonella typhimurium* strains TA98, TA100, TA 102, TA1535, TA1537	Bacterial reverse mutation test in accordance with OECD TG 471; with and without metabolic activation	Mutagenic in strain TA98 with metabolic activation; moderate, dose-dependent increase in revertant colonies observed. Toxic effects observed at higher concentrations (not specified) without metabolic activation observed in strains TA98, TA100, TA102, and TA1537, but test material did not induce an increase in number of revertant colonies in the other strains at any concentration tested, with and without metabolic activation. Negative and positive controls in accordance with the guideline	[4]
5-Amino-4-Chloro-*o*-Cresol HCl; 98% pure	Test 1: up to 500 µg/ml without metabolic activation and up to375 µg/ml with metabolic activation Test 2: up to 375 µg/ml without metabolic activation and up to 350 µg/ml with metabolic activation	deionized water	L5178 mouse lymphoma cells	Mammalian cell gene mutation test at the *tk* locus in accordance with OECD TG 476; with and without metabolic activation	Not genotoxic. In cells treated for 4 h without metabolic activation, an increase in the mutant frequency occurred at intermediate dose, but the increase was not reproducible and the mutant frequency was within normal parameters at the higher doses. This effect was not considered biologically relevant. Cells treated for 4 h with metabolic activation had an increase in mutant frequency at highest concentration tested; however, the increase was within historical control range and not reproducible when cells were treated with test material for longer durations or with expression periods. This effect was also not considered biologically relevant. Negative and positive controls were in accordance with the guideline.	[4]
5-Amino-4-Chloro-*o*-Cresol HCl; 98% pure	up to 1000 µg/ml without metabolic activation and up to 500 µg/ml with metabolic activation	deionized water	V79 Chinese hamster lung cells	Mammalian micronucleus test in accordance with draft OECD TG 487 and 473; with and without metabolic activation	Genotoxic; a clear dose-dependent increase in cells with micronuclei observed with and without metabolic activation at concentrations below 250 µg/ml. Precipitation observed at 250 µg/ml and above. Negative and positive controls were in accordance with the guideline.	[4]
			IN VIVO			
5-Amino-4-Chloro-*o*-Cresol HCl; purity not stated	0 and 500 mg/kg bw	distilled water	7 CFW 1 (Winkelmann) mice per sex	Mammalian erythrocyte micronucleus test in accordance with OECD TG 474; single intraperitoneal dose; groups of animals killed at 24, 48, or 72 h post-treatment; appropriate negative and positive controls used	Not genotoxic; test material did not induce micronuclei. No mortalities observed; clinical signs included reduced activity, ruffled fur, and abdominal position; orange colored urine observed after 20 h.	[4]

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Final Report on the Safety Assessment of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol[1]

Each of these ingredients function as hair colorants. 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol are identified as oxidative hair dyes, that is, they are combined with an oxidizing agent before being applied to the hair. 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, and 5-Amino-4-Chloro-*o*-Cresol are used in oxidative hair dyes, but it is not known if they are also used in nonoxidative (semipermanent) hair dyes. No toxicologically significant impurities are present with these two ingredients. To supplement the safety test data on these ingredients, available data on related ingredients (4-amino-2-hydroxytoluene and *p*-, *m*-, and *o*-aminophenol) previously found safe as used by the Cosmetic Ingredient Review (CIR) Expert Panel were summarized. 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol do not absorb significant ultraviolet radiation in the UVB region and none in the UVA region, although 4-Amino-*m*-Cresol had a symmetrical UV absorption peak at 300 nm. Percutaneous penetration of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol alone was significant, but when combined with oxidative developer, skin absorption was extremely low. Both of these dyes are excreted rapidly via the urine. Repeated exposure of animal skin to 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol failed to produce any cumulative irritation and single exposures up to 10% were not irritating to animal skin. 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol combined with oxidizer were not sensitizers in guinea pig maximization tests. Ocular irritation resulted from exposure of animals to undiluted 5-Amino-4-Chloro-*o*-Cresol, but not to a 5% solution. Only minor irritation was observed with 5% 5-Amino-6-Chloro-*o*-Cresol. Subchronic toxicity testing in animals using 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Amino-*m*-Cresol did not yield any adverse reactions. 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol were generally not mutagenic in in vitro and in vivo tests. Exposure to 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol from cosmetics were several orders of magnitude below developmental toxicity no-observed-adverse-effect levels (NOAELs). Although irritation data on several ingredients are absent, products containing these ingredients must include a caution statement and patch test instructions for determining whether the product causes skin irritation. The Expert Panel expects that following this procedure would identify individuals who would have an adverse reaction and allow them to avoid significant exposures. These compounds, when tested alone, are moderate skin sensitizers, but when combined with the developer, these ingredients are not sensitizers in animal tests. This information, coupled with the available animal test data, supports the safety of these ingredients in oxidative hair dyes. In the absence of systemic toxicity data, however, the available data are insufficient to support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in semipermanent hair dyes. The types of data required for these two ingredients for this use include (1) physical and chemical properties, including the octanol/water partition coefficient; (2) impurities data, especially regarding the presence of *m*-cresol, other organic molecules, and heavy metals; (3) data demonstrating that the metabolism is similar to that of 4-amino-2-hydroxytoluene and/or *p*-, *m*-, and *o*-aminophenol, or 28-day dermal toxicity with histopathology, dermal reproductive toxicity data, and an in vitro genotoxicity study for 6-Amino-*o*-Cresol and one genotoxicity study in a mammalian system; if positive, a 2-year dermal carcinogenicity study using National Toxicology Program methods may be needed.

INTRODUCTION

This report reviews the safety of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol, all of which function as hair colorants (Pepe, Wenninger, and McEwen 2002).

Data from the Cosmetic Ingredient Review (CIR) reports on 4-amino-2-hydroxytoluene and *p*-, *m*-, and *o*-aminophenol, and relevant data on other structurally similar ingredients (including the hepatotoxicity of acetaminophen derivatives), are included in this review. Elder (1989) found 4-amino-2-hydroxytoluene and Elder (1988) found *p*-, *m*-, and *o*-aminophenol safe in the present practices of use and concentrations. For purposes of comparison with the ingredients reviewed in this safety assessment, 4-Amino-2-hydroxytoluene was used in hair dyes and tints at concentrations $\leq$5% and *p*-, *m*-, and *o*-aminophenol were

Received 12 February 2004; accepted 4 June 2004.

[1]Reviewed by the Cosmetic Ingredient Review Expert Panel. Monice Zondlo Fiume and Torill A. Yamarik prepared this report. Address correspondence to F. Alan Andersen, PhD, Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

International Journal of Toxicology, 23(Suppl. 2):1–22, 2004

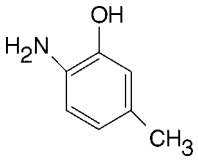
ISSN: 1091-5818 print / 1092-874X online
DOI: 10.1080/10915810490499037

used in hair tints and hair dyes and colors at concentrations of ≤1%, ≤5%, and ≤1%, respectively.

CHEMISTRY

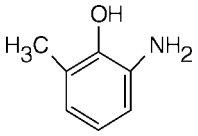
Definition and Structure

6-Amino-*m*-Cresol (CAS no. 2835-98-5) is the substituted aromatic compound that conforms to the formula (Pepe, Wenninger, and McEwen 2002):



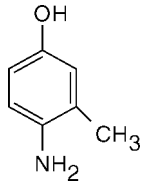
6-Amino-*m*-Cresol is also known as 4-Amino-3-Hydroxytoluene; 2-Amino-5-Methylphenol; Phenol, 2-Amino-5-Methyl-; 2-Hydroxy-4-Methylaniline (Pepe, Wenninger, and McEwen 2002); *m*-Cresol, 6-Amino; 6-Amino-3-Cresol; 6-Amino-3-Methylphenol; 2-Hydroxy-*p*-Toluidine; 5-Methyl-2-Aminophenol (Regulated Chemicals Listing 1998); 6-Amino-*meta*-Cresol; 4-Amino-3-Oxy-1-Methyl-Benzol; 4-Amino-3-Oxy-Toluol (Beilstein File of Organic Compounds 1998); and Toluene, 4-Amino-3-Hydroxy (CRC Handbook of Data on Organic Compounds 1998).

6-Amino-*o*-Cresol (CAS no. 17672-22-9) is the substituted aromatic compound that conforms to the formula (Pepe, Wenninger, and McEwen 2002):



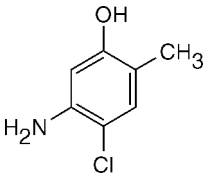
6-Amino-*o*-Cresol is also known as 3-Amino-2-Hydroxytoluene; 2-Amino-6-Methylphenol; Phenol, 2-Amino-6-Methyl-; 6-Amino-2-Methylphenol; Phenol, 6-Amino-2-Methyl-; 2-Hydroxy-3-Methylaniline (Pepe, Wenninger, and McEwen 2002); *o*-Cresol, 6-Amino; 6-Methyl-2-Aminophenol (Regulated Chemicals Listing 1998); 3-Amino-2-Oxy-1-Methylbenzol; and 3-Amino-2-Oxy-Toluol (Beilstein File of Organic Compounds 1998).

4-Amino-*m*-Cresol (CAS no. 2835-99-6) is the substituted aromatic compound that conforms to the formula (Pepe, Wenninger, and McEwen 2002):



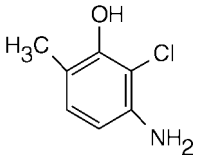
4-Amino-*m*-Cresol is also known as 2-Amino-5-Hydroxytoluene; 4-Amino-3-Methylphenol; Phenol, 4-Amino-3-Methyl-; 4-Hydroxy-*o*-Toluidine (Pepe, Wenninger, and McEwen 2002); 3-Methyl-4-Aminophenol (James Robinson Ltd. 1998); *p*-Amino-*m*-Cresol; *m*-Cresol, 4-Amino-; 4-Hydroxy-2-Methylaniline; *p*-Hydroxy-*o*-Toluidine; *m*-Methyl-*p*-Aminophenol; 3-Methyl-4-Aminophenol; 2-Methyl-4-Hydroxyaniline (Regulated Chemicals Listing 1998); 4-Amino-*meta*-Cresol; 6-Amino-3-Oxy-1-Methylbenzol; 6-Amino-3-Oxy-Toluol; *p*-Hydroxy-*o*-Toluidine; and Toluene, 2-Amino-5-Hydroxy (CRC Handbook of Data on Organic Compounds 1998).

5-Amino-4-Chloro-*o*-Cresol (CAS no. 110102-86-8) is an organic compound that conforms to the formula:



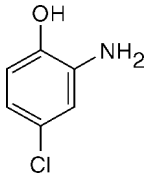
5-Amino-4-Chloro-*o*-Cresol is also known as 5-Amino-4-Chloro-2-Methylphenol; Phenol, 5-Amino-4-Chloro-2-Methyl- (Pepe, Wenninger, and McEwen 2002); and 2-Methyl-4-Chlor-5-Aminophenol (Henkel KGaA 1994).

5-Amino-6-Chloro-*o*-Cresol (CAS no. 84540-50-1) is an organic compound that conforms to the formula:



5-Amino-6-Chloro-*o*-Cresol is also known as 3-Amino-2-Chloro-6-Methylphenol; Phenol, 3-Amino-2-Chloro-6-Methyl- (Pepe, Wenninger, and McEwen 2002; Regulated Chemicals Listing 1998); 2-Chloro-3-Amino-6-Methylphenol; 2-Chloro-6-Methyl-3-Aminophenol; 3-Amino-2-Chlor-6-Methylphenol; 2-Methyl-5-Amino-6-Chlorophenol (Regulated Chemicals Listing 1998); 2-Hydroxy-3-Chloro-4-Aminotoluene; 2-Hydroxy-3-Chlor-4-Aminotoluol; and 5-Amino-6-Chlor-Benzol (Henkel KGaA 1996).

4-Chloro-2-Aminophenol (CAS no. 95-85-2) is the hair colorant that conforms to the formula:

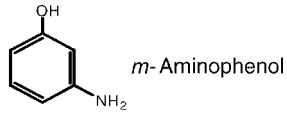


4-Chloro-2-Aminophenol is also known as 2-Amino-4-Chlorophenol; Phenol, 2-Amino-4-Chloro-; 2-Hydroxy-5-Chloroaniline; CI 76525 (Pepe, Wenninger, and McEwen 2002; Regulated Chemicals Listing 1998); 5-Chloro-2-Hydroxyaniline; *o*-Amino-*p*-Chlorophenol; *p*-Chloro-*o*-Aminophenol; and C.I. Oxidation Base 18 (Regulated Chemicals Listing 1998).

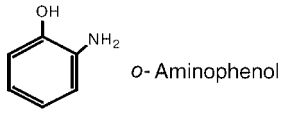
TABLE 1
Physical and chemical properties of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol (Henkel KGaA 1994, 1996)

	Description	
Property	5-Amino-4-Chloro-*o*-Cresol	5-Amino-6-Chloro-*o*-Cresol
Form	Brown crystals	Beige crystals
Melting point	248°C (with decomposition)	144–183°C
Odor	None	None
Solubility	Soluble in water, propylene glycol, and triethanolamine	Soluble in water
Purity	97% (by HPLC)	>94% (by HPLC)
Molecular weight	157.59 (free base)	194.07 (hydrochloride)

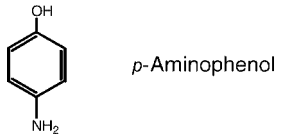
Structure of Related Ingredients



m-Aminophenol



o-Aminophenol



p-Aminophenol

The structures of *p*-, *m*-, and *o*-aminophenol are given above for comparison purposes. These ingredients were found safe in the present practices of use and concentrations (Elder 1988). Those use concentrations were ≤1%, ≤5%, and ≤1% for *p*-, *m*-, and *o*-aminophenol, respectively, in hair tints and hair dyes and colors.

Physical and Chemical Properties

6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, and 4-Amino-*m*-Cresol all have a molecular weight of 123.07 and 4-Chloro-2-Aminophenol has a molecular weight of 143.01 (Spectral Database Information System 1998). Other data on the physical and chemical properties of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol were not available. 6-Amino-*m*-Cresol (purum grade not defined) is a solid at room temperature (Goel, Kansal, and Sharma 1979). 4-Amino-*m*-Cresol has a melting point of 176°C to 178°C, is soluble in water and organic solvents, and a 1% solution had a pH of 8.2 (James Robinson Ltd. 1998).

Physical and chemical properties of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol are shown in Table 1.

The melting point for 6-Amino-*m*-Cresol is 163°C (CTFA 1999a). It is slightly soluble in water and soluble in many organic solvents. It is 99.9% pure as determined by elemental analysis. 6-Amino-*m*-Cresol is a crystalline powder with a beige to reddish-brown color. Upon exposure to air it becomes darker. The ultraviolet (UV) absorption data for 6-Amino-*m*-Cresol indicated absorption maxima at 210, 235, and 291 nm in ethanol. Physical and chemical properties of 6-Amino-*m*-Cresol are listed in Table 2.

The melting point for 4-Amino-*m*-Cresol is 178°C (CTFA 1999b). It is slightly soluble in water and is a crystalline powder with a reddish-brown color. It is 99.9% pure as determined by elemental analysis. When heated to decomposition it emits toxic fumes of NO. 4-Amino-*m*-Cresol is stable at normal conditions and hazardous polymerization will not occur. According to the classification of the European Directive on Classification of Hazardous Preparations, 90/492/EEC, 4-Amino-*m*-Cresol is not

TABLE 2
Physical and chemical properties of 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol (CTFA 1999a, 1999b)

	Description	
Property	6-Amino-*m*-Cresol	4-Amino-*m*-Cresol
Form	Beige to reddish-brown crystals	Reddish-brown crystals
Melting point	163°C	178°C
Odor	Not available	Emits toxic fumes of NO when heated
Solubility	Slightly soluble in water, and many organic solvents	Slightly soluble in water
Purity	99.9% (by HPLC/GC)	99.9% (by HPLC/GC)
Molecular weight	123.16	123

a dangerous substance. The UV absorption data for 4-Amino-*m*-Cresol indicated absorption maxima at 206, 234, and 300 nm in ethanol. Physical and chemical properties of 4-Amino-*m*-Cresol are also listed in Table 2.

Manufacture and Production

Published data on the manufacture and production of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, or 4-Chloro-2-Aminophenol were not found.

Analytical Methods

6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol have each been separated using capillary electrophoresis and high-performance liquid chromatography (HPLC) utilizing crown ethers (Nishi et al. 1997). 4-Amino-*m*-Cresol has been determined using thin-layer chromatography, and identified in urine using HPLC (Son, Everett, and Fiala 1980).

Ultraviolet Absorbance

Published data on the UV absorbance of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol were not found. 6-Amino-*m*-Cresol has maximum absorption peaks at 210, 235, and 291 nm in ethanol (CTFA 1999a). 4-Amino-*m*-Cresol had a symmetrical absorption peak at 300 nm (James Robinson, Ltd. 1998) and maximum absorption peaks at 206, 234, and 300 nm in ethanol (CTFA 1999b).

5-Amino-4-Chloro-*o*-Cresol has a symmetrical absorption peak below 300 nm, which falls off sharply above 300 nm (Henkel KGaA 1994), and 5-Amino-6-Chloro-*o*-Cresol has a similar pattern with an even sharper fall off (Henkel KGaA 1996).

4-Amino-2-hydroxytoluene has a maximum UV absorbance at approximately 285 nm (Elder 1989).

Impurities

Published data on the impurities of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, or 4-Chloro-2-Aminophenol were not found.

The impurity limits for 4-Amino-*m*-Cresol specify >99.5% solid content, <1.0% sulfated ash, and <50 ppm iron, with assay of >98.0% (James Robinson Ltd. 1998). The typical analysis was >99.9% solid content, <0.5% sulfated ash, and <10 ppm iron, with assay of 98.5% to 99.5%. No *m*-cresol was detected by HPLC.

The specification of 97% purity for 5-Amino-4-Chloro-*o*-Cresol is supported by HPLC analysis; impurities include an early peak identified as 2-Methyl-5-Aminophenol (2%), and two unidentified peaks (1% combined), one of which was close to the peak of the ingredient and one that eluted later (Henkel KGaA 1994).

An HPLC analysis of 5-Amino-6-Chloro-*o*-Cresol yielded 94.19% of the ingredient in one peak. Near the major peak were small peaks for 5-Amino-4-Chloro-2-Methylphenol (2.76%) and *p*-Amino-*o*-Cresol (1.99%). The only other significant peak (0.83%) was identified as a dichloro derivative (Henkel KGaA 1996).

USE

Cosmetic

6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol function as hair colorants (Pepe, Wenninger, and McEwen 2002).

5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol are specifically for use in oxidative hair dyes, with the former being used in combination with hydrogen peroxide (Henkel KGaA 1994, 1996).

The product formulation data submitted by the Food and Drug Administration (FDA) in 1998 stated that 6-Amino-*m*-Cresol was used in two hair dye and color formulations (FDA 1998). The other ingredients reviewed in this assessment were not reported to FDA as being used in 1998.

Concentration of use values are no longer reported to the FDA by the cosmetic industry (FDA 1992); the last reported concentration of use data available to CIR is from 1984 (FDA 1984). None of the ingredients reviewed in this report, however, were listed as being used in 1984.

Current information from industry indicated that 6-Amino-*m*-Cresol was used at a concentration of 2.4%, 6-Amino-*o*-Cresol was used at a concentration of 0.7%, and 4-Amino-*m*-Cresol was used at a concentration of 0.3% in all types of hair dye and colors (which require a caution statement and patch test) (CTFA 1999c).

In addition, 5-Amino-4-Chloro-*o*-Cresol is reported to be used in oxidation hair dye formulations at concentrations up to 2%, but because it is combined with hydrogen peroxide, the use concentration is only up to 1% (Henkel KGaA 1994). 5-Amino-6-Chloro-*o*-Cresol is also reported to be used in oxidative hair dyes formulations up to a final concentration of 2% (Henkel KGaA 1996).

Hair-coloring formulations are applied to or can come in contact with hair, skin (particularly at the scalp), eyes, and nails. Individuals dyeing their hair could use such formulations once every few weeks, whereas hairdressers could come in contact with products containing these ingredients several times a day. Under normal conditions of use, skin contact with hair dye is restricted to 30 min.

The hair dyes containing 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol, as coal tar hair dye products, are exempt from the principal adulteration provision and from the color additive provisions 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. The following caution statement should be displayed conspicuously on the labels of coal tar hair dyes:

> **Caution**—This product contains ingredients that 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 eyelashes or eyebrows; to do so may cause blindness.

The 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 h after application of the test material and prior to the use of a hair dye formulation.

Because 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 consensus among dermatologists that screening 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). 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 48 and 72 h 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 cosmetic industry should change its recommendation for the evaluation of the open patch test from 24 h to 48 h 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 cosmetic 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.

6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol do not appear in Annex II (list of substances which must not form part of the composition of cosmetic products) or Annex III (list of substances which cosmetic products must not contain except subject to the restrictions and conditions laid down) of the *Cosmetics Directive of the European Union* (European Union 1995).

Noncosmetic

No uses for these ingredients other than in cosmetics were found.

GENERAL BIOLOGY

Absorption, Distribution, and Metabolism

*6-Amino-*m-*Cresol, 6-Amino-*o-*Cresol, and 4-Amino-*m-*Cresol*

Published data on the absorption, distribution, metabolism, and excretion of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, or 4-Amino-*m*-Cresol were not found.

*5-Amino-4-Chloro-*o-*Cresol*

Skin absorption of radioactive (^{14}C) 5-Amino-4-Chloro-*o*-Cresol was studied using six female Sprague-Dawley rats (mean weight 189.5 g). A formulation containing the ingredient, with *p*-toluenediamine sulfate, basic fatty acid emulsion, propylene glycol, water, and ammonia, was diluted 1:1 with water to make a final test ingredient concentration of 1.85%. This formulation (0.2 g) was applied to an intact, clipped area of skin (9 cm^2) for 72 h under semiocclusive conditions. The concentration of ingredient on the skin was 0.41 mg/cm^2.

Feces and urine were monitored for 72 h, after which time the animals were sacrificed and adrenal glands, blood, brain, fat, bone, heart, kidneys, liver, lungs, muscle tissue, ovaries, spleen, thyroid glands, untreated skin, and the remaining carcass were analyzed. The mean skin absorption was 32.7%. 5-Amino-4-Chloro-*o*-Cresol was excreted via urine (92%) and feces (8%). The concentration in kidneys (0.003%) at 72 h was the greatest of any of the organ/tissue samples. The stratum corneum at the site of application, obtained by tape stripping, had 0.22% of the radioactivity (Henkel KGaA 1994).

A similar study was performed using the same strain of female rats of the same weight range except that the formulation was diluted 1:1 with a developer consisting of 6% hydrogen peroxide before application. After 30 min contact, the test material was rinsed off. Samples were taken as above. The skin absorption in this case was only 1.28%. Excretion via urine (91%) and feces (9%) accounted for all that was absorbed; the concentration in organs/tissues was at or near the detection limit of the ^{14}C. The stratum corneum had 0.2% of the radioactivity and the dermis, likewise, had 0.2% (Henkel KGaA 1994).

In a third study, the metabolism of ingested 5-Amino-4-Chloro-*o*-Cresol Hydrochloride was investigated using six female Sprague-Dawley rats (mean weight 200 g). A 1.27% solution of ^{14}C 5-Amino-4-Chloro-*o*-Cresol Hydrochloride in a 1:1 propylene glycol/water solution was given by oral administration at a dose of 21.5 mg/kg. Feces, urine, organs, and tissues were examined as described above. 5-Amino-4-Chloro-*o*-Cresol Hydrochloride was readily absorbed in the intestine (91.7%). It was excreted via urine (94%) and feces (6%). The greatest concentration in the organ/tissue samples was 0.001% in the liver (Henkel KGaA 1994).

*5-Amino-6-Chloro-*o-*Cresol*

Skin penetration/absorption of radioactive (^{14}C) hydrochloride was determined in a study using 12 female Wistar rats (mean weight 231 $\pm$ 7 g). Test animals were clipped and their skin

anesthetized with an i.m. injection of Ketanest® (12 ml/kg). In addition to the radioactive test ingredient, the formulation contained fatty alcohol, anionic surfactant, ammonium sulfate, water, and ammonia. The test article concentration was 1.14% and the pH was adjusted to 9.5. A dose of 20 mg/cm^2 was applied for 48 h without occlusive patches. Urine fractions were taken 0–8 h, 8–24 h, and 24–48 h. Feces were sampled daily. After 48 h, the animals were sacrificed and the skin and carcass assayed for radioactivity.

5-Amino-6-Chloro-*o*-Cresol hydrochloride was readily absorbed (93.2%). Radioactivity was excreted in urine (87.7%) and feces (2.22%). Only 0.48% was found in the carcass. The recovery rate of ^{14}C from the urine samples was 115% of the applied ^{14}C. An additional two animals were treated in the same manner, except that their expired CO_2 was monitored. No detectable ^{14}C was found in the expired CO_2 (Henkel KGaA 1996).

A similar study in six rats (mean body weight 217 ± 7 g) was conducted, except that the formulation was mixed 1:1 with 3% hydrogen peroxide developer solution prior to application. The test material was applied at a concentration of 15.3 mg/cm^2 and washed off after 30 min. Samples were collected as above. The skin penetration was only 0.116% (Henkel KGaA 1996).

The metabolism of radioactive (^{14}C) 5-Amino-6-Chloro-*o*-Cresol was determined in five female Wistar rats (weight 254 to 270 g). A single subcutaneous (s.c.) injection of 1 g of a 5-Amino-6-Chloro-*o*-Cresol solution (0.25% in water) was given into the neck. Urine, expired CO_2, and feces were collected over a period of 96 h. The animals were sacrificed and the skin and carcasses analyzed for residual radioactivity. Excretion was mainly via urine (88.5%) of which most (88.1%) was eliminated in the first 24 h. Only 3.97% was excreted in feces, and 0.674% was in the carcass and 0.04% in the injection site skin. No detectable radioactivity was found in expired CO_2 (Henkel KGaA 1996).

Metabolism was further studied using a single oral application of ^{14}C 5-Amino-6-Chloro-*o*-Cresol to 5 male Wistar rats (weight 321 to 336 g). Each animal received 49.4 mg/kg of the test article (1.7% in water) by gavage. Urine, expired CO_2, and feces were collected as daily fractions for 96 h. The animals were sacrificed and the gastrointestinal tract and the remaining carcass were analyzed. Excretion was again mainly via urine (90.93%) and mostly (90%) in the first 24 h. There was 6% in the gastrointestinal tract and 0.58% in the remaining carcass. No ^{14}C was detected in expired CO_2 (Henkel KGaA 1996).

The organ distribution of ^{14}C after a single oral dose of ^{14}C 5-Amino-6-Chloro-*o*-Cresol was studied in five male Wistar rats (mean weight 323 ± 9 g). A single dose of the test article (1.7% in water) was delivered by gavage. One rat was sacrificed at each of 1, 6, 24, 48, and 96 h after administration. Whole body autoradiography was used to detect the distribution of ^{14}C. Urine and feces were collected. One hour post administration the skin, kidneys, and the content of the intestine, liver, and especially the content of the stomach were collected for analysis. After 6 h, radioactivity was in the stomach, intestine, or colon content, and in the caecum. After 24 and 48 h, only residual radioactivity was found in the colon, caecum, and kidneys. After 96 h, excretion was nearly complete and only a small amount of label appeared (in bone). Within the first 24 h, 91% of the radioactivity was excreted via urine (Henkel KGaA 1996).

4-Amino-2-Hydroxytoluene and p-*Aminophenol*

Elder (1989) reported the percutaneous absorption of radioactive 4-amino-2-hydroxytoluene in a hair dye applied to the dry hair of humans under normal use conditions. The total excretion of 4-amino-2-hydroxytoluene was 0.2% ± 0.1%. This is contrasted with the oral administration in humans of radioactive 4-amino-2-hydroxytoluene in which there was a 94% recovery of the radioactivity in the urine. Elder (1988) reported the percutaneous absorption of 4-amino-2-hydroxytoluene (nonradioactive) coupled with radioactive *p*-aminophenol. The resultant ^{14}C-indamine was determined in rats under the conditions of oxidative hair dyeing. As much as 11% of the radioactivity introduced as ^{14}C-*p*-aminophenol was detected in the excreta, viscera, and skin of rats (Elder 1988); the penetration of *p*-aminophenol was similar when not coupled with 4-amino-2-hydroxytoluene. The ^{14}C-indamine formed during the oxidation did not substantially penetrate the cutaneous barrier.

Immunological Effects

4-Chloro-2-Aminophenol

The response of leukocytes from female guinea pigs treated with 4-Chloro-2-Aminophenol was evaluated using the leukocyte adherence inhibition (LAI) technique (Naniwa 1982). Both 4-Chloro-2-Aminophenol and *p*-aminophenol were conjugated with protein by similar condensation reactions. Significantly greater amounts of LAI were found for *p*-aminophenol–protein conjugates in the treated guinea pigs, indicating that 4-Chloro-2-Aminophenol–sensitized lymphocytes could not differentiate between 4-Chloro-2-Aminophenol–and *p*-aminophenol–protein conjugates. This suggested that cross-sensitization can occur with *p*-aminophenol.

Nephrotoxicity

4-Chloro-2-Aminophenol

Renal cortical slices from male Fischer 344 rats were used in gluconeogenesis and lactate dehydrogenase (LDH) release studies (Hong et al. 1996). The tissue slices were incubated with 0.01 to 0.5 mM 4-Chloro-2-Aminophenol in dimethyl sulfoxide (DMSO), 4-amino-2-chlorophenol, or vehicle. Renal gluconeogenesis was inhibited by ≥0.01 mM 4-Chloro-2-Aminophenol and ≥0.05 mM 4-amino-2-chlorophenol. LDH leakage was increased at concentrations of ≥0.5 mM 4-Chloro-2-Aminophenol and ≥0.1 mM 4-amino-2-chlorophenol.

p-*Aminophenol*

Hong et al. (1996), in an introduction to their study of chloro amino phenols, characterized *p*-Aminophenol as an acute

nephrotoxicant and a mild hepatotoxicant; *o*-Aminophenol as not toxic to the kidney or liver; and neither 4-Amino-3-chlorophenol nor 2-amino-5-chlorophenol as marked nephrotoxicant(s).

Hepatotoxicity

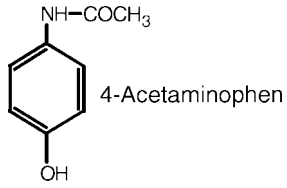
No data were available on ingredients in this safety assessment, but data on related ingredients are summarized below.

p-*Aminophenol and* o-*Aminophenol*

Elder (1988) reported that *p*-Aminophenol induces mild hepatotoxicity characterized by a twofold increase in serum transaminase levels, but that *o*-Aminophenol has no toxic effects on kidney or liver.

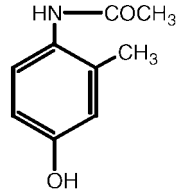
Acetaminophen

Acetaminophen, structure shown below, is somewhat similar to ingredients considered in this report and can be hepatotoxic in humans and experimental animals at large doses (Harvison, Forte, and Nelson 1986).

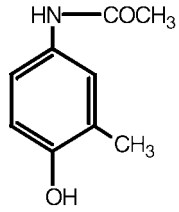


4-Acetaminophen

In a study to examine the role of mono-methylation in both the analgesic effect and hepatotoxicity of acetaminophen, Harvison, Forte, and Nelson (1986) prepared the following analogues that are structurally very similar to ingredients in this report:



4-Acetamino-*m*-Cresol



4-Acetamino-*o*-Cresol

Male Swiss-Webster mice (20 g) were injected intraperitoneally (i.p.) with either acetaminophen or the analogues shown above at various doses from 400 to 1000 mg/kg. Animals had been pretreated with either phenobarbital or cobaltous chloride and received a single i.p. dose of piperonyl butoxide 30 min before receiving the test substances. Animals were sacrificed and liver and kidney samples were taken and fixed in buffered formalin. Paraffin sections were prepared and stained with hematoxylin and eosin and examined for severity of necrosis.

The hepatotoxicity of 4-Acetamino-*o*-Cresol was comparable to that seen with acetaminophen, but 4-Acetamino-*m*-Cresol was less hepatotoxic. To the extent that these acetamino cresols are predictive of the hepatotoxicity of amino cresols, the results of these studies indicate that no greater hepatotoxicity would likely occur with the hair dye than is seen with acetaminophen, which isn't seen until g/kg doses are reached (Fethke, personal communication[2]).

ANIMAL TOXICOLOGY

Published data on the toxicity of 6-Amino-*o*-Cresol in animals was not found.

Acute Intraperitoneal Toxicity

4-Chloro-2-Aminophenol

Four male Fischer 344 rats per group were given a single i.p. injection of 0.4, 0.8, or 1.2 mmol/kg 4-Chloro-2-Aminophenol hydrochloride in 50% DMSO in distilled water, 0.4, 0.8, or 1.0 mmol/kg 4-amino-2-chlorophenol hydrochloride in distilled water, or vehicle (Hong et al. 1996). The animals were killed 48 h after dosing. 4-Chloro-2-Aminophenol had very few effects on renal function; no apparent morphological damage was observed at nonlethal doses of <0.8 mmol/kg. Changes in hepatic function or morphology were not observed. A dose of 1.2 mmol/kg 4-Chloro-2-Aminophenol killed 75% of the animals, but little evidence of nephrotoxicity was observed in the surviving animals. However, 4-amino-2-chlorophenol induced marked changes in renal function and morphology in a dose-dependent manner; no effect on hepatic function or hepatic morphology was observed.

Acute Dermal Toxicity

4-Amino-2-Hydroxytoluene

In an acute dermal toxicity study, 4-amino-2-hydroxytoluene did not produce any systemic/dermal toxicity in rabbits at a dose of 5 g/kg (Elder 1989).

p-*Aminophenol*

The dermal LD_{50} of *p*-aminophenol was >8 g/kg for rabbits (Elder 1988).

Acute Oral Toxicity

5-Amino-4-Chloro-o-*Cresol*

Male and female Wistar rats (average body weight of 164 g for females and 183 g for males) were given 5-Amino-4-Chloro-*o*-Cresol hydrochloride by gavage at doses of 1184, 1539, and 2000 mg/kg. Observations included apathy, piloerection, cyanosis, tremor, crouch, diarrhea, semiclosed eyes, and impaired hearing. Gross observations included brightened coloration of the liver and kidneys, ulcerations in the glandular

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

stomach, hydrometra, brown-colored hydrocele in the intestine, and emphysema (in the one animal that died). For males, the LD_{50} was between 1.54 and 2.0 g/kg and for females, the LD_{50} was >2.0 g/kg (Henkel KGaA 1994).

*5-Amino-6-Chloro-*o*-Cresol*

Male albino TNO-Wistar rats (average body weight of 200 g) were given 5-Amino-6-Chloro-*o*-Cresol hydrochloride by gavage at doses of 501, 1000, 1250, 1580, and 1999 mg/kg. Observations included apathy, staggering, rapid breathing, dyspnea (at later stages), and yellow-orange discoloration of the urine. The LD_{50} was 1.36 g/kg (Henkel KGaA 1996).

*4-Amino-*m*-Cresol*

Male CD-1 mice were dosed for 2 consecutive days (6 mice/group, route of administration not specified) with 1000, 1200, 1440, 1728, or 2074 mg/kg 4-Amino-*m*-Cresol. At 4 hours through day 2 of dosing, the following observations were observed: piloerection was observed in all groups; hypokinesia was observed in all but the low-dose group; ataxia occurred in the 1440- and 2074-mg/kg dose groups; and only mice in the 1200-mg/kg dose group had prostration. At least one mouse in all groups survived until day 14, but most mice died on day 1 or 2. The LD_{50} value was calculated as 1000 mg/kg (Holmstroem 1980).

*6-Amino-*m*-Cresol*

Holmstroem (1980), using the same protocol described above, calculated the LD_{50} of 6-Amino-*m*-Cresol as 1500 mg/kg.

In a pre-experiment toxicity study, Völkner and Heidemann (1991) dosed NMRI mice (2/sex/group) once with 500, 750, 1000, and 1500 mg/kg 6-Amino-*m*-Cresol in polyethylene glycol 400. Toxic reactions were observed in all groups and included reduction of spontaneous activity, eyelid closure, abdominal position, tremor, and death. One death occurred in each of the 750-, 1000-, and 1500-mg/kg groups by 6 h posttreatment. No deaths occurred in the 500-mg/kg group and the only toxic reaction observed in this group was reduction of spontaneous activity. Therefore, the 500-mg/kg group was estimated to be the maximum tolerated dose.

Leimbeck and Grötsch (1991) dosed two male and two female mice orally with 666 mg/kg 6-Amino-*m*-Cresol. In the first two hours all animals had tremor, anemia, and a slight to moderate reduction in activity. No animals died 72 h post application.

Fautz (1994) dosed two male rats once orally with 1200 mg/kg 6-Amino-*m*-Cresol in 1% carboxymethylcellulose. The rats had reduction of spontaneous activity, abdominal position, eyelid closure, and piloerection. In another experiment, two male rats each received a single oral dose of 1500 or 2000 mg/kg 6-Amino-*m*-Cresol in 1% carboxymethylcellulose, respectively. The animals in the 1500 mg/kg group had no toxic reactions except brown-colored urine. One animal in the 2000-mg/kg group died 24 h after treatment. The 1500-mg/kg group was estimated to be the maximum tolerated dose.

4-Amino-2-Hydroxytoluene

Using rats, 10% to 20% 4-amino-2-hydroxytoluene was slightly toxic in three separate acute oral studies (Elder 1989).

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

The oral LD_{50} values for rats of *p*-, *m*-, and *o*-aminophenol were 671–1270, 812–1660, and 1300 mg/kg, respectively (Elder 1988).

Short-Term Oral Toxicity

*6-Amino-*m*-Cresol*

Male and female Wistar rats (15/sex/group) were dosed orally with 50, 250, and 500 mg/kg 6-Amino-*m*-Cresol daily for 4 weeks (Forschungs GmbH 1985). The control group was dosed with 1 ml/100 g body weight 0.5% carboxymethylcellulose (CMC). Prior to study initiation and after 4 weeks, 10 rats/sex/group had ophthalmological and reflex examinations (5/sex/group), hearing tests and blood tests.

No significant observations occurred in the 50-mg/kg group. The 250-mg/kg group had increased activity 10 min after dosing during the third and fourth week of treatment and increased, discolored urine excretion. Water consumption was also increased. Significant results included reduced erythrocyte counts in males (highly significant) and females; increased reticulocytes in females; decreased hemoglobin in males and a highly significant decrease in females; increased hematocrit in both sexes, but highly significant in males; decreased iron in females; increased hepatic weight in females; increased kidney weight in males and females; and increased spleen weights in both sexes, but highly significant in females.

The 500-mg/kg group had initial decreased activity during week 1 and later increased activity as in the previous group. Increased, discolored urine excretion was also observed. Borderline significant results were observed for decreased body weight gain and food consumption during weeks 1 and 2 in females. Highly significant results were reported for increased water consumption in both sexes at all phases of the study; decreased erythrocytes and hemoglobin and increased reticulocytes in both sexes; and decreased hematocrit in males and females, although females were within normal range. The mean corpuscular volume (MCV) and prothrombin time was significantly increased in females, but still in the normal range. Iron was significantly reduced in females. At necropsy, dark, discolored spleens were observed (sex not specified). Liver, kidney, and spleen weights were all increased in both sexes. No treatment related observations were observed at microscopic evaluation. The no-observed-adverse-effect level (NOAEL) for 6-Amino-*m*-Cresol was established at 50 mg/kg.

Subchronic Dermal Toxicity

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

The dermal toxicity of hair dyes containing *m*-, *o*-, and/or *p*-aminophenol was determined using New Zealand white rabbits (Burnett et al. 1976). A dose of 1 ml/kg of oxidative hair dyes containing 0.7% *m*-aminophenol and 1.0% *p*-aminophenol, 0.7% *m*-aminophenol, 0.3% *o*-aminophenol, or 1.0% *N*-methyl-*p*-aminophenol sulfate mixed with an equal volume of 6% hydrogen peroxide or semipermanent hairdyes containing 0.09% and 0.2% *m*-aminophenol and p-aminophenol, respectively, or 0.02%, 0.04%, and 0.05% *m*-aminophenol, *p*-aminophenol, and *N*-methyl-*p*-aminophenol, respectively, were applied topically to the intact or abraded skin on the shaved backs of each animal twice weekly for 13 weeks, and no evidence of systemic toxicity was observed after application of the hairdyes.

Subchronic Oral Toxicity

5-Amino-4-Chloro-o-*Cresol*

Male and female Sprague Dawley rats (males, 152 to 160 g; females, 128 to 135 g) were given 5-Amino-4-Chloro-*o*-Cresol hydrochloride by gavage daily, 5 days a week, for 90 days. Daily doses were 0, 20, 60, and 180 mg/kg. No clinical observations or pathological findings indicative of systemic toxicity were observed. Only minor deviations in a few biochemical and hematological parameters were noted. The NOAEL was established at the highest dose of 180 mg/kg (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol*

Male and female Wistar rats (males, 102 to 149 g; females, 98 to 138 g) were given 5-Amino-6-Chloro-*o*-Cresol hydrochloride with tragacanth (1%) by gavage daily, 5 days a week, for 13 weeks. Daily doses were 50 mg/kg. No clinical observations, biochemical alterations, or pathological findings were indicative of systemic toxicity. The NOAEL was established at the highest dose of 50 mg/kg (Henkel KGaA 1996).

4-Amino-m-*Cresol*

Male and female Wistar rats were dosed orally with 15, 60, or 120 mg/kg 4-Amino-*m*-Cresol for 13 weeks (Forschungs GmbH 1984a). A control group was also included. The control group and the 120-mg/kg group had 25 rats/sex/group and the low- and mid-dose groups had 20 rats/sex/group. Prior to study initiation and again at 6 and 13 weeks, 5 rats/sex/group had ophthalmological, hearing, and reflex examinations. Blood samples were taken at the same time intervals on 20 rats/sex/group. Urinalyses were performed on 5 rats/sex/group.

No specific observations occurred in the 15-mg/kg group. The 60- and 120-mg/kg groups had dark, discolored urine due to compound discoloration in both sexes from treatment weeks 8 to 13. The 120-mg/kg group had significantly increased creatinine values in the female rats after 13 weeks of treatment, although the values were still within the normal range. The spleen weights were significant in female rats and increased in male rats. No observations attributed to the test compound were found during microscopic evaluation. The NOAEL was established at the mid-dose, 60 mg/kg.

4-Amino-2-Hydroxytoluene

Elder (1989) reported that the administration of 4-amino-2-hydroxytoluene in the diet of rats at concentrations of $\leq$3% for 3 to 6 months caused reduction in body weight, a slight anemia, and sporadic microfollicular goiter. Feeding rats $\leq$0.7% *p*-aminophenol for 3 to 6 months resulted in decreased body weights and feed consumption, increased relative liver and kidney weights, and nephrosis. Feeding rats $\leq$1% *m*-aminophenol 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.

Acute Dermal Irritation

6-Amino-m-*Cresol, 6-Amino*-o-*Cresol, 4-Amino*-m-*Cresol, and 4-Chloro-2-Aminophenol*

Published data on the dermal irritation potential of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, or 4-Chloro-2-Aminophenol were not found.

5-Amino-4-Chloro-o-*Cresol*

The acute dermal toxicity of 5-Amino-4-Chloro-*o*-Cresol was determined using 3 adult female albino New Zealand white (SPF) rabbits. A 0.5-ml aliquot of 5-Amino-4-Chloro-*o*-Cresol was applied to intact, shaved skin on the dorsal back of each animal. A semiocclusive patch was applied. After 4 h the patch was removed and the site rinsed. The skin was examined immediately after patch removal and then at 1, 24, 48, and 72 h thereafter. Only very slight erythema and edema were seen at 24 h, which disappeared at 48 and 72 h. Brown-yellow/yellow staining was seen at the application site. No information on systemic toxicity was provided (Henkel KGaA 1994).

The acute dermal irritation of 5-Amino-4-Chloro-*o*-Cresol was determined using six adult male albino New Zealand rabbits. A 0.5-ml aliquot of a 10% formulation (3 g of 5-Amino-4-Chloro-*o*-Cresol, 10 ml of distilled water, and 5 ml ammonium sulfate dissolved to a total volume of 30 ml in 96% ethanol) was applied to intact, shaved skin on the dorsal back of each animal. An occlusive patch was applied for 2 h. The skin was examined immediately after patch removal and then at 24 and 48 h. No signs of erythema, edema, or eschar formation were seen and the animals had no signs of systemic toxicity (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol*

The acute dermal toxicity of 5-Amino-6-Chloro-*o*-Cresol was determined using six adult male albino New Zealand rabbits. A 10% aqueous formulation (3 g of 5-Amino-6-Chloro-*o*-Cresol, 10 ml distilled water, and 5 ml ammonium sulfate dissolved to a total volume of 30 ml in 96% ethanol) was applied to a shaved area (0.5 ml/10 cm^2) on the dorsal back of each

animal. An occlusive patch was applied for 2 h. The skin was examined immediately after patch removal and then at 24 and 48 h. No signs of erythema, edema, or eschar formation were seen and the animals had no signs of systemic toxicity (Henkel KGaA 1996).

Repeated Dermal Application

5-Amino-4-Chloro-o-*Cresol*

Five adult male hairless mice (hr/hr strain) were used to assess skin irritation associated with repeated application of a 10% dilution of 5-Amino-4-Chloro-*o*-Cresol hydrochloride, adjusted to pH 8 with ammonia. Applications (one or two drops only) were made to the same area of the back once a day for 5 working days and twice a day for 4 working days for a total of 9 consecutive working days. Animals were examined before each application and the responses scored. No primary skin irritation was observed (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol*

Five adult male hairless mice (hr/hr strain) were used to assess skin irritation associated with repeated application of a 10% aqueous formulation (3 g of 5-Amino-6-Chloro-*o*-Cresol, 10 ml distilled water, and 5 ml ammonium sulfate dissolved to a total volume of 30 ml in 96% ethanol). One drop was applied to the same spot on the dorsal back, twice per day, for 5 consecutive days. No signs of primary skin irritation were observed (Henkel KGaA 1996).

Repeated application of 5-Amino-6-Chloro-*o*-Cresol to 6 adult male New Zealand rabbits was studied by Henkel KGaA (1996). One drop of a 10% aqueous formulation (3 g of 5-Amino-6-Chloro-*o*-Cresol, 10 ml distilled water, and 5 ml ammonium sulfate dissolved to a total volume of 30 ml in 96% ethanol) was applied to the same shaved area of the dorsal back every 30 s for a total of 60 applications. No signs of primary irritation were observed.

4-Amino-2-Hydroxytoluene

Elder (1989) reported that a concentration of 2.5%, 4-amino-2-hydroxytoluene was essentially nonirritating.

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

Elder (1988) reported that *p*- and *m*-Aminophenol were mildly irritating to rabbit skin; that *p*- and *o*-Aminophenol were both nonirritating when applied to intact and abraded rabbit skin under occlusive patches and to intact rabbit skin under semiocclusive patches; and that *m*-Aminophenol, 3%, was not irritating when applied to the backs of rabbits.

Sensitization

6-Amino-m-*Cresol, 6-Amino*-o-*Cresol, and 4-Amino*-m-*Cresol*

Published data on the sensitization potential of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, or 4-Amino-*m*-Cresol were not found.

4-Chloro-2-Aminophenol

The sensitization potential of 4-Chloro-2-Aminophenol and cross-sensitization potential with *p*-aminophenol was determined using guinea pigs (Naniwa 1982). (4-Chloro-2-Aminophenol and *p*-aminophenol belong to the same amino derivative class and have common side chains on the benzoic ring.) Fifteen female guinea pigs were first injected with an emulsion of 200 mg of 4-Chloro-2-Aminophenol in 0.5 ml *N*,*N*-dimethylformamide and 0.5 ml Freund's complete adjuvant. At 2 or 3, 4, and 6 weeks after treatment, the animals were patch tested with 0.1%, 0.5%, and 1.0% 4-Chloro-2-Aminophenol in equal volumes of dioxan and acetone. The solutions, 0.05 ml, were applied to the shaved dorsal area of each animal, and the sites were not covered. The test sites were scored 24 h after application of 4-Chloro-2-Aminophenol. Following patch testing with 4-Chloro-2-Aminophenol, a 1.0% *p*-aminophenol solution was applied using the same procedure. Five animals that were not treated were patch tested with 4-Chloro-2-Aminophenol and *p*-aminophenol and served as a control group.

One test animal died by week 6 of the study (reason for death not stated.) At weeks 2 to 3, 1, 1, and 3 of the 15 test animals had reactions (weak or strong erythema) at the 0.1%, 0.5%, and 1.0% 4-Chloro-2-Aminophenol sites, respectively. During the fourth week of the study, 2, 8, and 13 animals had reactions at the 0.1%, 0.5%, and 1.0% 4-Chloro-2-Aminophenol sites, respectively. During the sixth week of the study, 2, 7, and 13 of the 14 remaining test animals had reactions at the 0.1%, 0.5%, and 1.0% 4-Chloro-2-Aminophenol sites, respectively. None of the test animals reacted to *p*-aminophenol and none of the control animals reacted to 4-Chloro-2-Aminophenol or *p*-aminophenol.

5-Amino-4-Chloro-o-*Cresol*

Henkel KGaA (1994) conducted a guinea pig maximization study of 5-Amino-4-Chloro-*o*-Cresol using 20 female Pirbright White animals. Fifteen animals were used to determine the minimum irritant and maximum nonirritant concentration. Induction was done with injection of 0.1 ml of a 0.25% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol (adjusted to pH 8 with ammonia) as the minimum irritant concentration and two injections of 0.1 ml of a 0.5% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol diluted 1:1 with Freund's complete adjuvant (FCA). Controls were treated with FCA and vehicle only. The second topical induction was done 1 week later with 1.0 ml of a 5% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol under an occlusive patch for 48 h. The challenge was done 14 days after the second induction with 0.2 ml of a 2% aqueous solution of 5-Amino-4-Chloro-*o*-Cresol applied to the animals' flanks under an occlusive patch. Animals were examined at 24 and 48 h after removal of the patch.

After the first and second inductions, all animals had typical reactions to FCA. Almost 50% of the test animals (9/19; no explanation provided for the fate of the 20th animal) had slight erythema 24 h after challenge, but only 5 animals had

this minimal effect after 48 h. It was concluded that 5-Amino-4-Chloro-*o*-Cresol is a moderate sensitizer in the maximization test.

Henkel KGaA (1994) performed a second maximization study using a hair dye formulation containing *p*-toluidine diamine and 5-Amino-4-Chloro-*o*-Cresol hydrochloride. The hair dye formulation was diluted 1:1 with 6% hydrogen peroxide before use in the experiment. As in the previous study, 15 female Pirbright White guinea pigs were used to determine irritant concentrations and 20 animals were included in the maximization test. Intradermal induction was done with injection of 0.1 ml of a 0.1% aqueous solution of the hair dye/oxidizer combination and two injections of a 0.2% solution diluted 1:1 with FCA. Controls were treated only with FCA and vehicle. The second, topical induction was done 1 week later with 1.0 ml of the test substance (hair dye/oxidizer combination) under an occlusive patch for 48 h. The challenge was done 14 days after the second induction using 0.2 ml of a 2.5% aqueous solution of the test material on the flank under an occlusive patch for 24 hours.

After the inductions, animals had typical reactions to FCA. None of the animals exposed to the test substance had any reactions. As found in a hair dye formulation mixed with an oxidizer, 5-Amino-4-Chloro-*o*-Cresol was a non-sensitizer in the maximization test.

Henkel KGaA (1994) conducted a third maximization test with a second hair dye formulation containing 2,4,5,6-tetraamino-pyrimidine and 5-Amino-4-Chloro-*o*-Cresol. The hair dye formulation was diluted 1:1 with 6% hydrogen peroxide as an oxidizer before use in the experiment. As above, 15 female Pirbright White guinea pigs were used to determine irritant concentrations and 20 animals were included in the maximization test. Intradermal induction was done with injection of 0.1 ml of a 0.1% aqueous solution of the hair dye/oxidizer combination and two injections of a 0.2% solution diluted 1:1 with FCA. Controls were treated only with FCA and vehicle. The second, topical induction was done 1 week later with 1.0 ml of a 20% aqueous solution of the test substance (hair dye/oxidizer combination) under an occlusive patch for 48 h. The challenge was done 14 days after the second induction using 0.2 ml of a 2.5% aqueous solution of the test material on the flank under occlusive patches for 24 hours.

After the inductions, animals had typical reactions to FCA. None of the animals exposed to the test substance had any reactions. As found in this second hair dye formulation mixed with an oxidizer, 5-Amino-4-Chloro-*o*-Cresol hydrochloride was a nonsensitizer in the maximization test (Henkel KGaA, 1994).

Henkel KGaA (1994) also performed a Buehler method sensitization test using Dunkin-Hartley guinea pigs. Four animals were used to determine minimum irritant and maximum nonirritant concentrations and 20 animals were used in the sensitization test proper. Topical induction was done on the left body side on days 1, 8, and 15 with 0.5 ml of an ethanolic paste consisting of 5-Amino-4-Chloro-*o*-Cresol in ethanol (63% w/w) under occlusive patches for 6 h. Control animals were dosed with ethanol only. The challenge was done 14 days later by exposing the animals' flanks to 0.5 ml of the paste for 6 h under occlusive patches. Animals were examined 24 and 48 h after patch removal.

Neither test animals nor controls had reactions on challenge, so 5-Amino-4-Chloro-*o*-Cresol was not considered to be a sensitizer in this test (Henkel KGaA 1994).

*5-Amino-6-Chloro-*o*-Cresol*

Henkel KGaA (1996) conducted a guinea pig maximization study of 5-Amino-6-Chloro-*o*-Cresol hydrochloride using 20 female Pirbright White animals. Induction was done with injection of 0.1 ml of a 5.0% aqueous solution of 5-Amino-6-Chloro-*o*-Cresol and two injections of 0.1 ml of a 5.0% aqueous solution of 5-Amino-6-Chloro-*o*-Cresol diluted 1:1 with FCA. Controls were treated with FCA and vehicle only. The second topical induction was done 1 week later with 1.0 ml of a 5% cream of 5-Amino-6-Chloro-*o*-Cresol in petroleum jelly under an occlusive patch for 48 h. The challenge was done 14 days after the second induction with a 25% cream of the test substance applied to the animals' flanks under an occlusive patch. Animals were examined at 24 and 48 h after removal of the patch.

After the first and second inductions, all animals had typical reactions to FCA. One quarter of the test animals had slight erythema 24 h after challenge, but no effects were evident after 48 h. It was concluded that 5-Amino-6-Chloro-*o*-Cresol is not a sensitizer in the maximization test (Henkel KGaA 1996).

Using guinea pigs, 4-amino-2-hydroxytoluene was a mild sensitizer in a maximization test and a very weak sensitizer in a test using an open epicutaneous method (Elder 1989). Application to guinea pigs of 0.1% to 2% *p*-aminophenol in petrolatum under occlusive patches resulted in a concentration-dependent incidence of sensitization, with 3 of 10 animals sensitized with 0.1% and 9 of 10 animals sensitized at 2% *p*-aminophenol (Elder 1988). *p*-Aminophenol, 3% in deionized water, was not a sensitizer in guinea pigs. In an open epicutaneous test using guinea pigs, 3% *p*-aminophenol produced weak reactions in 4 of 20 animals and 3% *m*-aminophenol was not a sensitizer. In a maximization test, moderately strong cross-reactions to *o*-aminophenol application were observed in some guinea pigs previously sensitized with *p*-phenylenediamine.

Photosensitization

Published data on the photosensitization potential of ingredients reviewed in this safety assessment were not found.

4-Amino-2-Hydroxytoluene

Elder (1989) reported that 4-Amino-2-hydroxytoluene, with induction and challenge concentrations of 5% and 10%, respectively, was not a photosensitizer when evaluated using guinea pigs.

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

Elder (1988) reported that *p*-Aminophenol and *m*-aminophenol, both with induction and challenge concentrations of 10% and 5%, respectively, were not photosensitizers, but they did induce a contact hypersensitivity reaction.

Ocular Irritation

6-Amino-m-*Cresol, 6-Amino*-o-*Cresol, 4-Amino*-m-*Cresol, and 4-Chloro-2-Aminophenol*

Published data on the ocular irritation potential of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, or 4-Chloro-2-Aminophenol were not found.

5-Amino-4-Chloro-o-*Cresol*

A volume of 0.1 ml of 5% aqueous 5-Amino-4-Chloro-*o*-Cresol hydrochloride was instilled into the conjunctival sac of six male albino New Zealand rabbits; no rinsing was done. Eye irritation reactions were scored 2, 6, 24, and 48 h after exposure. No effects on the cornea or the iris, and only slight conjunctival erythema and edema up to 24 h were observed (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol*

A quantity of 51 mg of 5-Amino-6-Chloro-*o*-Cresol hydrochloride was instilled into the conjunctival sac of the right eye of one female albino New Zealand rabbit; none of the eyes were rinsed. Ocular irritation reactions were scored 1, 24, 48, and 72 h after exposure. Instillation of the undiluted ingredient produced immediate severe ocular irritation, and additional study was terminated. Corneal opacity, injection of the iris, and irritation of the conjunctivae persisted throughout the duration of the study. Undiluted 5-Amino-6-Chloro-*o*-Cresol hydrochloride was considered a severe ocular irritant (Henkel KGaA 1996).

In a second study, a volume of 0.1 ml of 5% aqueous 5-Amino-6-Chloro-*o*-Cresol hydrochloride was instilled into the conjunctival sac of four male albino New Zealand rabbits; none of the eyes were rinsed. Ocular irritation reactions were scored 1, 6, 24, and 48 h after exposure. No effects on the cornea or the iris, and only slight conjunctival erythema up to 6 h were observed. Exudation was observed after 1 h in all four animals, in three animals at 6 h, and in one animal at 24 h; the effect was not seen at 48 h. The researchers considered 5% 5-Amino-6-Chloro-*o*-Cresol hydrochloride to be very slightly irritating (Henkel KGaA 1994).

4-Amino-2-Hydroxytoluene, m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

At a concentration of 2.5%, 4-amino-2-hydroxytoluene (Elder 1989), *p*-aminophenol, and *m*-aminophenol (Elder 1988) were essentially nonirritating to rabbit eyes. In Draize tests, *p*-aminophenol (powder form) was not an eye irritant and *o*-Aminophenol did not irritate the cornea or iris and produced a cumulative conjunctival irritation score of 3.3/20.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Published data on the reproductive and developmental toxicity of 6-Amino-*o*-Cresol or 4-Chloro-2-Aminophenol were not found.

Dermal

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

The teratogenic potential of hair dyes containing *m*-, *o*-, and/or *p*-aminophenol were determined using rats (Burnett et al. 1976). A dose of 2 ml/kg of oxidative hair dyes containing 0.7% *m*-aminophenol and 1.0% *p*-aminophenol, 0.7% *m*-aminophenol, 0.3% *o*-aminophenol, or 1.0% *N*-methyl-*p*-aminophenol sulfate mixed with an equal volume of 6% hydrogen peroxide or semipermanent hair dyes containing 0.09% and 0.2% *m*-aminophenol and *p*-aminophenol, respectively, or 0.02%, 0.04%, and 0.05% *m*-aminophenol, *p*-aminophenol, and *N*-methyl-*p*-aminophenol sulfate, respectively, were applied topically to the animals on days 1, 4, 7, 10, 13, 16, and 19 of gestation. The hair dyes were not teratogenic or embryotoxic.

Burnett and Goldenthal (1988) conducted a two-generation reproduction study using rats. Twice weekly, 0.5 ml of oxidative hair dye formulations containing 0.7% *m*-aminophenol and 1.0% *p*-aminophenol, 0.7% *m*-aminophenol, 0.3% *o*-aminophenol, or 1.0% *N*-methyl-*p*-aminophenol sulfate mixed with an equal volume of 6% hydrogen peroxide was applied to a shaved area of the back of each animal. Successive applications were made to adjacent areas to minimize dermal irritation. When the rats were 100 days old, they were mated to produce an F_{1a} generation that was eventually used in a carcinogenicity study. The F_0 generation was reduced and re-mated to produce an F_{1b} generation. Rats from the F_{1b} litters were mated after 100 days to produce F_{2a} and F_{2b} litters. Male and female F_2 parents were selected and mated to produce an F_3 generation. However, a viral infection resulted in poor reproductive performance for all groups, including controls, invalidating the results. Dermal irritation consisting of intermittent mild dermatitis was noted during the treatment period in each generation. The topical application of oxidative hair dye formulations did not have an adverse effect on reproductive performance or on the health and survival of the developing fetus and postnatal animals.

Oral

6-Amino-m-*Cresol*

Female Sprague-Dawley rats were dosed orally with 5, 50, or 200 mg/kg 6-Amino-*m*-Cresol from days 6 to 15 of gestation (Hazleton Laboratories 1982). A control (distilled water) and positive control (vitamin A, 15 mg/kg) were also included. The control, positive-control, and 5- and 50-mg/kg groups had

23 animals per group, whereas 26 animals were used in the high-dose group. Rats were killed on day 19 of gestation.

No mortalities were attributed to treatment effects. No clinical changes were observed in any group. Body weight gain of all treated groups was comparable to the control group. No significant changes were observed at necropsy. No effect on pregnancy incidence was observed in the treated groups. The mean number of corpora lutea and the mean number of implantations per dam (preimplantation loss) were comparable to control groups. Postimplantation loss was not affected by 6-Amino-*m*-Cresol and postimplantation loss was lowest in the 200-mg/kg group. The number and sex of the fetuses and the litter and mean fetal weights in the treatment groups were comparable to the control group. Fetal defects, visceral and skeletal variations were the same as the control group. No malformations occurred in the treated groups. The positive control group had marked teratogenic effects: the majority of fetuses had exencephaly. 6-Amino-*m*-Cresol did not elicit embryotoxicity, embryolethality, or teratogenicity.

5-Amino-4-Chloro-o-*Cresol*

Pregnant Wistar/HAN rats (190 to 238 g) were dosed with 5-Amino-4-Chloro-*o*-Cresol hydrochloride in water (10 ml/kg) daily by gavage on days 6 to 15 of pregnancy (period of major organogenesis in the fetus). Four groups of 25 animals each received doses of 0, 20, 100, or 500 mg/kg/day of 5-Amino-4-Chloro-*o*-Cresol hydrochloride. Maternal mortality and body weight gain were recorded. The dams were killed on day 21 of gestation and the fetuses removed for examination. The number of alive and dead fetuses, fetal weight, sex, site of implantation in the uterus, early and late resorptions, and number of corpora lutea were determined. Half of the fetuses were selected at random and examined for visceral and brain abnormalities. The remaining fetuses were examined for abnormalities after staining with alizarin.

The only maternal effect seen was a brown discoloration of the urine. At examination of the fetuses, no developmental toxicity was associated with treatment with 5-Amino-4-Chloro-*o*-Cresol hydrochloride (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol*

Pregnant Wistar/HAN rats (186 to 234 g) were exposed to 5-Amino-6-Chloro-*o*-Cresol hydrochloride in water daily by gavage on days 6 to 15 of pregnancy (period of major organogenesis in the fetus). Four groups of 25 animals each received doses of 0, 30, 90, or 270 mg/kg/day of 5-Amino-6-Chloro-*o*-Cresol hydrochloride. Maternal mortality and body weight gain were recorded. The dams were killed on day 21 of gestation and the fetuses removed for examination. The number of alive and dead fetuses, fetal weight, sex, site of implantation in the uterus, early and late resorptions, and number of corpora lutea were determined. Half of the fetuses were selected at random and examined for visceral and brain abnormalities. The remaining fetuses were examined for abnormalities after staining with alizarin.

The only maternal effects were slight reduction in feed consumption and reduced body weight gain in the highest dose group. The NOAEL was considered to be 90 mg/kg/day. No developmental toxicity was associated with treatment with 5-Amino-6-Chloro-*o*-Cresol hydrochloride (Henkel KGaA 1994).

4-Amino-m-*Cresol*

Female rats (strain BOR:WISW-SPF TNO) were dosed orally with 10, 40, or 80 mg/kg 4-Amino-*m*-Cresol from days 5 to 15 of gestation (Forschungs GmbH 1984b). A control group was included. Positive proof of sperm in the vaginal smear was considered day 0 of gestation. Each group consisted of 24 animals. Dams were killed on day 20 of gestation.

No abnormal clinical observations were found during the study and no mortalities occurred. Body weight gain and food consumption had no significant intergroup differences. No abnormalities were observed at gross necropsy. No significant differences were observed between groups in mean number of fetuses per dam, left-right intrauterine distribution, sex ratio, birth position, weight, death of fetuses and live birth index, number of resorptions, resorption indices, implantations, postimplantation loss index, corpora lutea and placenta, gravid uteri, and uteri weights. External and skeletal examination of fetuses revealed no malformations. Visceral examination included one fetus in the 40-mg/kg group with hydrocephaly and two fetuses in the 80-mg/kg group with minor visceral anomalies (increased renal pelvic cavitation). The malformation index for all groups was 0, except the 40-mg/kg group, which had a malformation index of 0.56%. The NOAEL was established at the high dose, 80 mg/kg.

4-Amino-2-Hydroxytoluene

Oral administration of $\leq$3% 4-amino-2-hydroxytoluene produced maternal toxicity but was not teratogenic (Elder 1989).

m-*Aminophenol and* p-*Aminophenol*

Oral administration of 250 mg/kg *p*-aminophenol resulted in reduced maternal body weight gains and teratogenicity in offspring (external, skeletal, and visceral malformations) in a study using rats (Elder 1988). Chronic feeding of 0.7% *p*-aminophenol in the diet of rats produced embryotoxicity mediated by maternal toxicity. Chronic feeding of $\leq$1% *m*-aminophenol to rats resulted in maternal toxicity during gestation, but teratogenic effects were not observed. Oral administration of 100 to 200 mg/kg *p*-aminophenol to gravid hamsters did not produce teratogenic effects.

Parenteral

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

Elder (1988) reported that intravenous and i.p. administration of 100 to 200 mg/kg *p*-aminophenol induced fetal malformations; i.p. administration of *o*-aminophenol to hamsters resulted in teratogenic effects; but that no conclusive evidence was found for *m*-aminophenol using i.p. administration.

GENOTOXICITY

In Vitro

*6-Amino-*m*-Cresol*

The mutagenic potential of 6-Amino-*m*-Cresol was evaluated in an Ames test using *Salmonella typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (Noser 1979a). Concentrations of 30 to 1000 μg 6-Amino-*m*-Cresol, alone and with equal amounts of 6% hydrogen peroxide, were tested with and without metabolic activation. Negative and positive controls were used. 6-Amino-*m*-Cresol was slightly mutagenic towards *S. typhimurium* TA100 with and without metabolic activation. It was not mutagenic towards the other strains.

Saccharomyces cerevisiae diploid D7 cell cultures were exposed to 0.1 ml of 6-Amino-*m*-Cresol in DMSO at concentrations of 0.6, 3.0, and 15.0 μg/ml with and without metabolic activation (Bootman 1984a). Negative (DMSO) and positive (ethyl methanesulphonate) controls were used. 6-Amino-*m*-Cresol was highly toxic to the yeast cells, but it did not induce increases in the frequency of convertant or aberrant colonies with or without metabolic activation.

Mouse lymphoma L5178Y cells were treated for 2 h with 400 ml of 12.5 to 200 μg/ml 6-Amino-*m*-Cresol in DMSO with and without metabolic activation (Martin 1983). DMSO was used as the negative control and benzopyrene with metabolic activation and 4-nitroquinoline-1-oxide without metabolic activation were used as the positive controls. All microtitre plates were incubated for 2 weeks, after which wells with viable clones were counted. Cell viability was measured by adding ouabain and 6-thioguanine to cell suspensions 48 h and 7 days after treatment, respectively. 6-Amino-*m*-Cresol did induce an increase in mutation to both ouabain and 6-thioguanine resistance in the presence of metabolic activation; however, the increase was not considered significant with or without metabolic activation.

The clastogenic potential of 6-Amino-*m*-Cresol hemisulfate was determined using cultured male human peripheral lymphocytes (Bootman 1984b). Cell cultures were incubated for 24 h with 25 μl of the test compound dissolved in DMSO at concentrations of 0.6, 3.0, and 15.0 μg/ml with and without metabolic activation. DMSO was used as the negative control and cyclophosphamide with metabolic activation was used as the positive control. 6-Amino-*m*-Cresol hemisulfate did not significantly increase the number of aberrations as compared to controls.

*4-Amino-*m*-Cresol*

The mutagenic potential of 4-Amino-*m*-Cresol was evaluated in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (Noser 1979b). Concentrations of 15 to 600 μg/plate 4-Amino-*m*-Cresol, alone and with equal amounts of 6% hydrogen peroxide, were tested with and without metabolic activation. Negative and positive controls were used. 4-Amino-*m*-Cresol was not mutagenic with or without metabolic activation.

In an unscheduled DNA synthesis (UDS) assay, male rat primary hepatocytes were incubated with 1.0, 3.33, 10.0, 33.33, or 100.0 μg/ml 4-Amino-*m*-Cresol in DMSO (Miltenburger 1986). Negative controls were untreated or incubated with solvent and positive controls were incubated with 7,12-dimethylbenz(a) anthracene. 4-Amino-*m*-Cresol did not induce UDS in rat hepatocytes.

4-Chloro-2-Aminophenol

The mutagenic potential of 4-Chloro-2-Aminophenol in DMSO was determined in a preincubation assay (Zeiger et al. 1988). Concentrations of 10 to 1500 μg/plate were tested using *S. typhimurium* strains TA100, TA1535, TA97, and TA98 without and with metabolic activation. 4-Chloro-2-Aminophenol was weakly mutagenic.

*5-Amino-4-Chloro-*o*-Cresol*

The mutagenic potential of 5-Amino-4-Chloro-*o*-Cresol hydrochloride was evaluated in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (Henkel KGaA 1994). Concentrations of 4 to 2500 μg/plate with the 5-Amino-4-Chloro-*o*-Cresol hydrochloride dissolved in water and 75 to 1200 μg/plate with the 5-Amino-4-Chloro-*o*-Cresol (the free base) dissolved in DMSO were tested with and without metabolic activation by Aroclor 1254–induced rat liver enzymes. Positive controls were used as follows: Sodium azide for TA 100 and TA 1535; 9-aminoacridine for TA 1537; 4-nitro-*o*-phenylenediamine for TA 98 and TA 1538; and 2-aminoanthracene for all strains. Toxic effects were noted at the greatest concentration tested (2500 μg/plate). Table 3 has a summary of the results of this study. On the basis of these data, the investigators concluded that the free base was mutagenic with metabolic activation.

V79 Chinese hamster lung cells were used to examine the mutagenicity of 5-Amino-4-Chloro-*o*-Cresol hydrochloride. Mutations to 6-thioguanine resistance at the *HGRPT* locus with

TABLE 3
5-Amino-4-Chloro-*o*-Cresol Ames test results (Henkel KGaA 1994)

	With metabolic activation		Without metabolic activation	
Strain	Hydrochloride in water	Free base in DMSO	Hydrochloride in water	Free base in DMSO
TA 98	Neg	Weak pos	Neg	Neg
TA 100	Weak pos	Pos	Neg	Neg
TA 1535	Neg	Neg	Neg	Neg
TA 1537	Neg	Weak pos	Neg	Neg
TA 1538	Neg	Pos	Neg	Neg

Neg, negative; Pos, positive.

TABLE 4
5-Amino-6-Chloro-*o*-Cresol Ames test results (Henkel KGaA 1996)

Strain	With metabolic activation		Without metabolic activation
	Phenobarbital	Aroclor 1254	
TA 98	Neg	Pos	Neg
TA 100	Neg	Pos	Neg
TA 1535	Neg	Neg	Neg
TA 1537	Neg	Neg	Neg
TA 1538	Neg	Pos	Neg

Neg, negative; Pos, Positive.

and without metabolic activation were measured. 5-Amino-4-Chloro-*o*-Cresol hydrochloride dissolved in ethanol at 6 to 60 μg/ml without metabolic activation and 55 to 550 μg/ml with metabolic activation (Aroclor 1254–induced rat liver enzyme fraction) were used. Ethyl methanesulfonate (EMS) and dimethylbenz[a]anthracene (DMBA) served as positive controls. At no concentration or metabolic activation status were any increases seen in the number of mutations (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol*

The mutagenic potential of 5-Amino-6-Chloro-*o*-Cresol hydrochloride was evaluated in an Ames test using *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 (Henkel KGaA 1996). Concentrations of 4 to 2500 μ g/plate with the 5-Amino-6-Chloro-*o*-Cresol hydrochloride was tested with and without metabolic activation by Aroclor 1254 or phenobarbital induced rat liver enzymes. Positive controls were used as follows: Sodium azide for TA 100 and TA 1535; 9-aminoacridine for the other strains. Table 4 presents the results of this study. On the basis of these data, the investigators concluded that 5-Amino-6-Chloro-*o*-Cresol hydrochloride was mutagenic with metabolic activation.

V79 Chinese hamster lung cells were used to examine the mutagenicity of 5-Amino-6-Chloro-*o*-Cresol hydrochloride. Mutations to 6-thioguanine resistance at the *HGRPT* locus with and without metabolic activation were measured. 5-Amino-4-Chloro-*o*-Cresol hydrochloride dissolved in ethanol at 0, 35, 100, 200, and 300 μg/ml without metabolic activation and 0, 25, 100, 200, and 300 μg/ml with metabolic activation (Aroclor 1254–induced rat liver enzyme fraction) were used. EMS and DMBA served as positive controls. At concentrations $\geq$50 μg/ml, the plating efficiency of the cells was slightly reduced. At no concentration or metabolic activation status were any increases seen in the number of mutations (Henkel KGaA 1996).

V79 Chinese hamster lung cells were used to examine the mutagenicity of 5-Amino-6-Chloro-*o*-Cresol hydrochloride at concentrations from 10 to 1100 μg/ml. Chromosomes were prepared 7 (high dose), 18 (low, medium, and high dose), and 28 (high dose) h after the start of a 4-h treatment. Treatment was done with and without Aroclor 1254–induced rat liver enzymes. EMS was used as a positive control. Concentrations of 1000 and 3000 μg/ml were toxic in range finding studies, with and without metabolic activation. Although no chromosome aberrations were seen at 7 h, chromosome aberrations were increased in all dose groups at 18 h and at 28 h. The authors concluded that 5-Amino-6-Chloro-*o*-Cresol hydrochloride does induce chromosome aberrations in the V79 line independent of metabolic activation (Henkel KGaA 1996).

Unscheduled DNA synthesis (a measure of DNA damage) was measured in rat liver hepatocytes exposed to 5-Amino-6-Chloro-*o*-Cresol hydrochloride at concentrations ranging from 6.67 to 2000 μg/ml. Six cultures were used for each concentration and the experiments were repeated three times. Cells were incubated without the test compound for 1 h, at which time tritiated thymidine and the test substance were added and incubated a further 3 h. 2-Acetylaminofluorene (2-AAF) served as a positive control. Cells were washed, nuclei isolated, and the incorporated radioactivity was measured. Total DNA content was determined colorimetrically. No indications of a dose-related increase in unscheduled DNA synthesis were observed (Henkel KGaA 1996).

In Vivo

6-Amino-m-*Cresol*

In a micronucleus test, male CD-1 mice (10 per group) were dosed orally with 30, 150, or 750 mg/kg 6-Amino-*m*-Cresol in 0.5% carboxymethylcellulose at a volume of 10 ml/kg once daily for 2 days (Holmstroem 1980). The mice were dosed during two separate studies 6 and 30 h before they were killed. The vehicle was used as a negative control and 100 mg/kg cyclophosphamide was used as a positive control. Body weights did not vary by more than 1 g during the study. 6-Amino-*m*-Cresol did not increase the frequency of micronuclei.

In another micronucleus test, groups of six male and female NMRI mice were orally dosed with 500 mg/kg 6-Amino-*m*-Cresol in polyethylene glycol 400 (Völkner and Heidemann 1991). Three negative and one positive control (cyclophosphamide) were dosed orally once at 10 ml/kg. Bone marrow smears for the treated groups and negative control were prepared 24, 48, and 72 h post treatment. Bone marrow smears for the positive control were prepared 24 h post treatment. 6-Amino-*m*-Cresol did not induce micronuclei.

Groups of five male and five female NMRI mice were dosed orally with 666 mg/kg 6-Amino-*m*-Cresol in carboxymethylcellulose in a third micronucleus test (Leimbeck and Grötsch 1991). One negative and one positive control (cyclophosphamide, 40 mg/kg) were used. Bone marrow smears were evaluated 24, 48, and 72 h post administration. Again, 6-Amino-*m*-Cresol did not induce micronuclei in bone marrow cells.

A chromosome aberration study was conducted using groups of five male and five female Chinese hamsters (King and

Harnasch 1991). The animals were dosed once orally with 3200 mg/kg 6-Amino-*m*-Cresol in 4% gum arabic, and slides were prepared 6, 24, and 48 h post treatment. One negative control group was dosed with 20 ml of 4% gum arabic per kg body weight and one positive control was dosed i.p. with 30 mg/kg cyclophosphamide. Preparations from the positive control group were made at 24 h. A cytotoxic effect was observed, which indicated a strongly decreased ratio of polychromatic and normochromatic erythrocytes in the bone marrow (55% reduction compared to control animals). 6-Amino-*m*-Cresol did not induce chromosome aberrations in Chinese hamster bone marrow cells.

A bromodeoxyuridine pellet was implanted subcutaneously into male CD rats, and 2 h later groups of five animals were given a single oral dose of 60, 192, or 600 mg/kg 6-Amino-*m*-Cresol hemisulfate in distilled water (McGregor 1985). A negative-control group was given vehicle and a positive-control group was dosed with 5 mg cyclophosphamide. The animals were injected with colchicine 20 h after implantation, and killed 2 h after injection. 6-Amino-*m*-Cresol hemisulfate did not cause sister chromatid exchanges (SCEs) in rat bone marrow chromosomes.

An unscheduled DNA synthesis assay was performed using groups of five male Wistar Hanlbm:WIST (SPF) rats (Fautz 1994). The animals were given a single oral dose of 6-Amino-*m*-Cresol in 0.5% aqueous carboxymethylcellulose at a volume of 10 ml/kg. For the 2 h treatment, a dose of 1500 mg/kg was given and for the 16 h treatment, doses of 150 and 1500 mg/kg were used. A negative control (carboxymethyl cellulose) and a positive control, 100 mg/kg 2-AAF, were used. One of the animals in the 1500-mg/kg dose group died within 16 h of treatment and the other animals in the group had signs of toxicity. Additionally, the hepatocyte viability of two animals out of the 1500-mg/kg group was decreased. 6-Amino-*m*-Cresol did not induce UDS.

4-Amino-m-*Cresol*

In another micronucleus test, groups of six male and six female NMRI mice were given a single oral dose of 100, 333, or 1000 mg/kg 4-Amino-*m*-Cresol in DMSO (Miltenburger and Völkner 1988). Vehicle was used as the negative control and cyclophosphamide was used as the positive control. Femoral bone marrow cells were prepared 24 h after dosing for all groups and 48 and 72 h after dosing for the high-dose and control groups. 4-Amino-*m*-Cresol did not induce micronuclei.

In a micronucleus test, CD-1 mice were dosed with 20, 100, or 500 mg/kg 4-Amino-*m*-Cresol (Holmstroem 1980). The mice were dosed during two separate studies 6 and 30 h before they were killed. The vehicle control was 0.5% carboxymethylcellulose. The positive control was cyclophosphamide, which induced a small but significant increase in micronucleus frequency. Body weights did not vary by more than 1 g during the study. 4-Amino-*m*-Cresol did not increase the frequency of micronuclei in polychromatic erythroblasts.

In an SCE assay, groups of $\leq$25 male Chinese hamsters were dosed orally with 100, 300, 1000, 1500, or 2000 mg/kg or i.p. with 10, 30, 100, 300, or 400 mg/kg 4-Amino-*m*-Cresol hemisulfate in double distilled water (Bracher et al. 1984). Water was used as a negative control and 2-AAF was used as a positive control. Doses of 1500 and 2000 mg/kg p.o. and 400 mg/kg i.p. had cytotoxic effects, and a dose of 500 mg/kg i.p. was "partly lethal." 4-Amino-*m*-Cresol hemisulfate did not cause SCEs, regardless of administration.

A UDS assay was performed in which groups of five male Wistar rats were dosed with 4-Amino-*m*-Cresol in "aqua bidest" at a dose of 1000 mg/kg for the 4 h treatment and doses of 60 and 600 mg/kg for the 16 h treatment (Fautz and Völkner 1991). A negative control and a positive control (substances not specified) was used. 4-Amino-*m*-Cresol did not induce UDS.

Five male Wistar rats per group were dosed with 1000 mg/kg 4-Amino-*m*-Cresol and killed 4 hours post treatment and 60 and 600 mg/kg and killed 16 hours posttreatment (Fautz and Völkner 1991b). The negative-control group received DMSO/PEG 400 and the positive-control group received 2-AAF. The rats were killed at the designated times by liver perfusion. Three animals from each group were used in the UDS assay. Hepatocytes were cultured with ^{3}H-radiolabeled thymidine (^{3}HtdR) for 4 h. The hepatocytes were washed and incubated overnight prior to autoradiography. The nuclear and net grain counts of the treated groups were in the range of the corresponding controls, therefore a statistical evaluation was not performed. 4-Amino-*m*-Cresol did not induce DNA damage leading to repair synthesis in the hepatocytes of treated rats.

5-Amino-4-Chloro-o-*Cresol*

An in vivo micronucleus test for chromosome mutations was conducted using adult CFW1 mice (20–32 g). Seven male and seven female mice were used at each dose. The test substance was dissolved in water at doses of 50, 250, and 500 mg/kg of 5-Amino-4-Chloro-*o*-Cresol hydrochloride was administered once by gavage. Bone marrow extracted from the femurs was prepared 24, 48, and 72 h after dosing in the case of the highest dose group and at 24 h for the other two dose groups. Endoxan® was the positive control and the vehicle was the negative control. Analysis was done of 1000 polychromic erythrocytes per animal. No induced micronuclei were found at any dose. The investigators concluded that 5-Amino-4-Chloro-*o*-Cresol hydrochloride was not mutagenic in this assay (Henkel KGaA 1994).

5-Amino-6-Chloro-o-*Cresol Hydrochloride*

An in vivo micronucleus test for chromosome mutations was conducted using adult OF1 mice (28.7–37.8 g for males and 21.6–30.0 g for females). Five male and five female mice were used. The test substance was dissolved in water and administered once by gavage to a final dose of 1200 mg/kg of 5-Amino-6-Chloro-*o*-Cresol hydrochloride. Bone marrow extracted from the femurs was prepared 24, 48, and 72 h after dosing in the case of the highest dose group and at 24 h for the other two dose groups. Cyclophosphamide (10 mg/kg) was the positive control and the vehicle was the negative control. Analysis was done of

1000 polychromic erythrocytes per animal. The ratio of chromatic/polychromatic erythrocytes was slightly increased, suggesting some toxicity to the bone marrow, but the investigators concluded that 5-Amino-6-Chloro-*o*-Cresol hydrochloride was not mutagenic in this assay (Henkel KGaA 1994).

4-Amino-2-Hydroxytoluene

In Ames tests, 4-amino-2-hydroxytoluene was not mutagenic using *S. typhimurium* strain TA1535 without and with metabolic activation; 4-amino-2-hydroxytoluene was not mutagenic in some studies using strains TA98 and TA100 without and with metabolic activation, but was mutagenic in one study towards strains TA98, TA97, and TA100 (Elder 1989). Negative results were obtained in a micronucleus assay and a dominant lethal study using 4-amino-2-hydroxytoluene. No significant effect on SCEs or increase in chromosomal aberrations was observed in human lymphocytes obtained from subjects that repeatedly dyed their hair with a formulation containing 4-amino-2-hydroxytoluene.

p-*Aminophenol*

Elder (1988) reported that *p*-Aminophenol was strongly mutagenic in an assay for SCEs (human peripheral blood lymphocytes, $\leq 10^{-4}$ M), was mutagenic in a DNA synthesis inhibition assay (Epstein-Barr virus–transformed lymphoblastoid cells, j0.5 mM), three assays for DNA structural alterations (human lymphoblastoid cells, 0.05 to 0.5 mM; mouse bone marrow cells; plant cells), two erythrocyte micronucleus tests ($\leq$2 mmol/kg; 3%), and a sperm head abnormality test (200 to 400 mg/kg), was slightly mutagenic in an Ames assay without metabolic activation and one assay for SCEs, and was nonmutagenic in an Ames assay without and with metabolic activation ($\leq$2 μmol/plate), an *Escherichia coli* genetic repair assay, two assays for SCEs (Chinese hamster bone marrow cells, 5 mg/kg; metaphase human fibroblasts, 5 to 50 μM), one erythrocyte micronucleus test (0.5%), a thymidine kinase reversion assay (1% with metabolic activation), and a sperm head abnormality test (0.5 to 2.0 mmol/kg).

m-*Aminophenol*

Elder (1988) also reported that *m*-Aminophenol was mutagenic in an assay for DNA structural alterations (human lymphocytes); was slightly mutagenic in an assay for SCEs (human lymphocytes, 6.6 μg/ml); and was nonmutagenic in an Ames assay ($\leq$1 mg/ml agar with metabolic activation), an *E. coli* genetic repair assay, a DNA synthesis inhibition assay (rat hepatocytes, $\leq$500 nmol/ml), an assay for DNA structural alterations (human lymphocytes, 6.6 μg/ml), two SCE induction assays (Chinese hamster cells, 0.5–2 $\times$ 10^{-2} mM; Chinese hamster bone marrow cells, 5 mg/kg), two erythrocyte micronucleus tests (0.5–2 mmol/kg; 0.5%), a dominant lethal assay ($\leq$1%), and a sperm head abnormality test (0.5 to 2 mmol/kg). Also, no significant effect on SCEs or increase in chromosomal aberrations was observed in human lymphocytes obtained from subjects that repeatedly dyed their hair with a formulation containing *p*- or *m*-aminophenol (Elder 1988)

o-*Aminophenol*

Elder (1988) reported that *o*-Aminophenol was mutagenic in one Ames assay (7 to 100 μg/ml with metabolic activation), an *E. coli* genetic repair assay, three assays for SCE induction (human fibroblasts, 0.01 to 0.3 mM; Chinese hamster cells, 0.5–2 $\times$ 10^{-2} mM; human lymphocytes, 1.6 to 6.6 μg/ml), an erythrocyte micronucleus test (0.5 to 2 mmol/kg), and a sperm head abnormality test (0.5 to 2 mmol/kg) and was nonmutagenic in two Ames assays (0.5 to 2.0 μg/plate without and with metabolic activation; with metabolic activation), a DNA synthesis inhibition assay (rat hepatocytes, $\leq$100 nmol/ml), one SCE induction assay (Chinese hamsters, 5 mg/kg), and an assay for DNA structural alterations (implanted Ehrlich ascites tumor cells).

CARCINOGENICITY

Published data on the carcinogenicity of the ingredients reviewed in this safety assessment were not found. Data from previous safety assessments of related ingredients are summarized.

m-*Aminophenol,* o-*Aminophenol, and* p-*Aminophenol*

The carcinogenic potential of an oxidative hair dye containing 0.5% and 1.5% *p*-amino-*o*-cresol and *p*-aminophenol, respectively, was determined using mice (Jacobs et al. 1984). A dose of 0.5 ml of the dye mixed with an equal volume of 6% hydrogen peroxide was applied to the skin of each mouse once weekly for 20 months. The oxidative dye was not carcinogenic.

The carcinogenic potential of hair dyes containing *m*-, *o*-, and/or *p*-aminophenol were determined using mice (Burnett et al. 1980). A dose of 0.05 ml of oxidative hair dyes containing 0.7% *m*-aminophenol and 1.0% *p*-aminophenol, 0.7% *m*-aminophenol, 0.3% *o*-aminophenol, or 1.0% *N*-methyl-*p*-aminophenol sulfate mixed with an equal volume of 6% hydrogen peroxide were applied once weekly for 21 months and 0.05 ml of semipermanent hair dyes containing 0.09% and 0.2% *m*-aminophenol and *p*-aminophenol, respectively, or 0.02%, 0.04%, and 0.05% *m*-aminophenol, *p*-aminophenol, and *N*-methyl-*p*-aminophenol sulfate, respectively, were applied once weekly for 23 month. The hair dyes were not carcinogenic, and toxicity was not observed.

Burnett and Goldenthal (1988) also conducted a study to determine the carcinogenic potential of oxidative hair dye formulations containing 0.7% *m*-aminophenol and 1.0% *p*-aminophenol, 0.7% *m*-aminophenol, 0.3% *o*-aminophenol, or 1.0% *N*-methyl-*p*-aminophenol sulfate using the F_{1a} generation of rats from their reproduction study that was previously summarized. The formulations were mixed with equal volumes of 6% hydrogen peroxide and twice weekly a dose of 0.5 ml was applied topically to a shaved area of the back for approximately 2 years. Successive applications were made to adjacent areas to minimize dermal irritation.

The incidence of mammary gland adenomas was significantly increased for the female test animals as compared to the animals in one of three control groups; however, this value was not considered statistically different from the other two control groups. The incidence of pituitary adenomas significantly increased for female test animals as compared to all three control groups. The researchers noted that the "incidence of this tumor is known to be high and variable in untreated female Sprague-Dawley rats. The fact that no pituitary carcinomas occurred in this group suggests that the distribution of these tumors was not related to the experimental treatments." The oxidative hair dye formulations were not considered carcinogenic.

CLINICAL ASSESSMENT OF SAFETY

Irritation and Sensitization

Published data on the clinical irritation and sensitization potential of 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, or 5-Amino-6-Chloro-*o*-Cresol were not found.

4-Chloro-2-Aminophenol

Thirty-one factory workers were patch tested with 4-Chloro-2-Aminophenol, as well as with four other compounds (*p*-aminophenol, p-nitrophenol, *p*-dichloronitrobenzene, and 3′-chlorodiphenylamine-2-carboxylic acid) used or produced at the factory (Naniwa 1979). (4-Chloro-2-Aminophenol, *p*-amin ophenol, and 3′-chlorodiphenylamine-2-carboxylic acid are amino derivatives of aromatic compounds and *p*-nitrophenol and *p*-dichloronitrobenzene are nitro derivatives of them.) Using adhesive plasters, 0.1%, 0.5%, and 1.0% 4-Chloro-2-Aminophenol (and the other four compounds) in petrolatum was applied to the back of each subject for 48 h. The tests sites were scored 20 min after removal of the patches. A challenge test was performed by dropping 0.1 ml of 0.1% dinitrochlorobenzene (DNCB) in acetone onto the flexural antibrachium of each person, and the reaction was evaluated 48 h after application. A group of five control subjects was tested in the same manner.

Of the 31 subjects tested, 7 had positive reactions to 0.1%, 0.5%, and 1.0% 4-Chloro-2-Aminophenol, 6 had positive reactions to 0.5% and 1.0%, 2 had positive reactions to 0.1% and 0.5%, 1 had a positive reaction to 1.0% only, and one had a positive reaction to 0.1% and 1.0%. Six of the seven subjects that reacted to all three concentrations of 4-Chloro-2-Aminophenol had been directly exposed to it on repeated occasions. Some cross-sensitization might have occurred between 4-Chloro-2-Aminophenol and *p*-aminophenol (four cases), *p*-nitrophenol (one case), *p*-dichloronitrobenzene (three cases), and 3′-chlorodiphenylamine-2-carboxylic acid (two cases). None of the test subjects had a cross-sensitization reaction with DNCB. None of the control subjects had a primary irritation reaction to any of the tested compounds.

4-Amino-2-Hydroxytoluene

In modified Draize repeat-insult patch tests (RIPTs), two aqueous solutions containing 2.0% 4-amino-2-hydroxytoluene produced one (although not reconfirmed at challenge) and two significant cases of dermatitis using 23 and 31 subjects, respectively (Elder 1989). In two semiocclusive (open) RIPTs with 3% *m*-aminophenol, slight irritation during induction and no sensitization reactions at challenge were observed in one study and some irritation and a low degree of sensitization in 2/99 subjects was observed in the other study.

EPIDEMIOLOGY

Between 35% and 45% of American women dye their hair, often at monthly intervals, over a period of years (Cosmetic, Toiletry, and Fragrance Association [CTFA] 1993). This estimate is drawn from market research data on hair dye product use, generally from females aged 15 to 60.

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, although direct hair dyes are a preformed color. The ingredients addressed in this safety assessment are oxidative hair dyes.

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.

In 2003, an updated review of the available epidemiology literature was prepared (Helzlsouer, Rollison, and Pinney 2003). This review considered 83 literature citations available since the IARC review. 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 bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma. These findings, however, were not consistently observed across studies. The authors concluded that the available evidence is insufficient to conclude a causal association between personal hair dye use and bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma. With respect to other cancers, including leukemia, breast cancer, or childhood cancers, and autoimmune disease or adverse developmental/reproductive effects, the

authors concluded that the evidence also did not demonstrate a causal association with hair dye use.

A case-control study (Gago-Dominguez et al. 2001, 2003), described in this 2003 review, 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. The review authors noted that these results were based on small sample sizes.

The 2003 review authors recommended the replication of studies to better understand the observed associations, but concluded that the available evidence is insufficient to conclude the association between personal hair dye use and the health outcomes discussed is causal.

In considering this information, the CIR Expert Panel agreed that the available epidemiology studies are insufficient to conclude there is a causal relationship between hair dye use and cancer and other end points described in the Helzlsouer, Rollison, and Pinney (2003) review.

The Panel stated that use of direct hair dyes, although not the focus in all investigations, appear to have little evidence of an association with adverse events as reported in epidemiological 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 epidemiological 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 replicate these studies, along with further studies to examine the possibility of susceptible subpopulations. Additional studies examining bladder cancer, non-Hodgkin's lymphoma, and multiple myeloma and hair dye use are underway and it is the intent of the CIR Expert Panel to periodically review hair dye epidemiological studies and update this section.

Occupational

4-Chloro-2-Aminophenol

Blood samples were taken from 21 workers that handled 4-Chloro-2-Aminophenol (and other compounds) (Tomoda, Tomioka, and Minami 1989). Half-oxidized hemoglobins, such as $(\alpha^{2+}\beta^{3+})_2$ and $(\alpha^{3+}\beta^{2+})_2$, and methemoglobin were significantly increased in circulating erythrocytes of some workers.

Exposure Assessment

*5-Amino-4-Chloro-*o*-Cresol*

Considering that 5-Amino-4-Chloro-*o*-Cresol hydrochloride is used in oxidative hair dye formulations up to a maximum concentration of 2%, Henkel KGaA (1994) assessed the risks that such exposure might pose. Dilution with an oxidant 1:1 reduces the available concentration to 1%. It was estimated that a maximum of 100 ml of this dyeing mixture would be applied monthly. It was further noted that color development is completed within 30 min and the resulting oxidized hair dye is fixed at the hair cortex, with any excess rinsed off (80% to 90% of the dyeing mixture).

From the available percutaneous absorption data in rats (Henkel KGaA 1994), in which dilution with an oxidizer was done to produce a 1.85% hair dye solution and rinsing off after 30 min exposure was done, an intake of 5-Amino-4-Chloro-*o*-Cresol hydrochloride of 5.21 μg/cm^2 was determined. Assuming a scalp surface of 500 cm^2, the total absorbed hair dye would be 2.6 mg. This quantity may be extrapolated to 2.8 mg if a hair dye solution at 2% were applied. Using this latter value and considering a 60-kg user, the dose is 47 μg/kg. Comparing this dose with, for example, the 180-mg/kg dose reported to produce no observable effects in a 90-day oral toxicity study in rats, these investigators concluded a substantial safety factor was available for 5-Amino-4-Chloro-*o*-Cresol.

*5-Amino-6-Chloro-*o*-Cresol*

Considering that 5-Amino-6-Chloro-*o*-Cresol hydrochloride is used in oxidative hair dye formulations up to a maximum concentration of 2%, Henkel KGaA (1996) assessed the risks that such exposure might pose. Dilution with an oxidant 1:1 reduces the available concentration to 1%. It was estimated that a maximum of 100 ml of this dyeing mixture would be applied monthly. It was further noted that color development is completed within 30 min and the resulting oxidized hair dye is fixed at the hair cortex, with any excess rinsed off (80 to 90% of the dyeing mixture).

From the available percutaneous absorption data in rats (Henkel KGaA 1996) in which dilution with an oxidizer was done to produce a 1.14% hair dye solution and rinsing off after 30 min exposure was done, only 0.116% of 5-Amino-6-Chloro-*o*-Cresol hydrochloride was absorbed. Assuming a scalp surface of 500 cm^2, 100 ml of hair dye mixture applied, concentration of dye of 1.14%, and absorption of 0.116%, the total absorbed hair dye can be calculated to be only 8.87 μg. This quantity may be extrapolated to 17.75 μg if a hair dye solution at 2% were applied. Using this latter value and considering a 60-kg user, the dose is 0.3 μg/kg. Comparing this dose with, for example, the 50-mg/kg dose that was reported to produce no observable effects in a 90-day oral toxicity study in rats, the investigators concluded that a substantial safety factor was available for 5-Amino-6-Chloro-*o*-Cresol.

SUMMARY

6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol function as hair colorants. 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol are identified as oxidative hair dyes, that is, they are combined with an oxidizing agent before being applied to the hair. Information is not available to determine if 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, and 5-Amino-4-Chloro-*o*-Cresol

are used only in oxidative hair dyes or have application as nonoxidative (commonly referred to as semipermanent) hair dyes.

In 1998, frequency of use data submitted by FDA indicated that 6-Amino-*m*-Cresol was used in two hair dye formulations. More recent data available from the industry indicate that 6-Amino-*m*-Cresol was used at 2.4%, 6-Amino-*o*-Cresol was used at 0.7%, and 4-Amino-*m*-Cresol was used at 0.3% in 1999. Recent data from industry also reports that 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol were used at a maximum concentration of 2% in oxidizing hair dyes, which is effectively reduced to 1% with the addition of oxidizing agents.

5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol do not absorb significant UV radiation in the UVB region and none in the UVA region, although 4-Amino-*m*-Cresol had a symmetrical UV absorption peak at 300 nm. Both 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol produce virtually a single peak in HPLC and no small peaks were identified as *m*-cresol. 4-Amino-*m*-Cresol did not contain *m*-cresol when analyzed using HPLC.

Percutaneous penetration of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol alone was significant, but when combined with oxidative developer, the absorption was extremely low. Both of these dyes are excreted rapidly via the urine.

The hair dyes containing 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Chloro-2-Aminophenol, as coal tar hair dye products, are exempt from the principal adulteration provision and from the color additive provisions 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. The following caution statement should be displayed conspicuously on the labels of coal tar hair dyes:

> **Caution**—This product contains ingredients that 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 eyelashes or eyebrows; to do so may cause blindness.

Repeated exposure of animal skin to 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol failed to produce any cumulative irritation and single exposures up to 10% were not irritating to animal skin.

The response of leukocytes from guinea pigs using the LAI technique suggested that cross-sensitization might occur between 4-Chloro-2-Aminophenol and *p*-aminophenol. However, in testing using guinea pigs in which induction was with 4-Chloro-2-Aminophenol and the animals were challenged first with 4-Chloro-2-Aminophenol and then *p*-aminophenol, animals reacted to 4-Chloro-2-Aminophenol but not *p*-amino phenol. In clinical testing using factory workers, some cross-sensiti zation was observed between 4-Chloro-2-Aminophenol and *p*-aminophenol, as well as *p*-nitrophenol, *p*-dichloronitrobenzene, and 3′-chlorodiphenylamine-2-carboxylic acid. Guinea pig maximization tests of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol combined with oxidizer demonstrate no sensitization.

Ocular exposure of animals to undiluted 5-Amino-4-Chloro-*o*-Cresol was irritating, but exposure to a 5% solution produced no irritation. Only minor irritation was observed with 5% 5-Amino-6-Chloro-*o*-Cresol.

Subchronic toxicity testing in animals using 5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, and 4-Amino-*m*-Cresol did not yield any adverse reactions.

6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol were generally negative in in vitro and in vivo mutagenicity tests. The only exception was 6-Amino-*m*-Cresol was slightly mutagenic in an Ames assay towards *S. typhimurium* strain TA100 with and without metabolic activation. 4-Chloro-2-Aminophenol was weakly mutagenic in a preincubation assay. 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol were positive in some Ames test strains, but were negative in the HGPRT test in mammalian cells. 5-Amino-4-Chloro-*o*-Cresol did not induce chromosome aberrations in mammalian cells, but 5-Amino-6-Chloro-*o*-Cresol induced chromosome aberrations in mammalian lung cells but not in bone marrow erythrocytes. Neither of these hair dyes induced unscheduled DNA synthesis.

5-Amino-4-Chloro-*o*-Cresol, 5-Amino-6-Chloro-*o*-Cresol, 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol were not developmental toxins.

An exposure assessment that compared likely exposure levels of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol with adverse effects data found that exposure would be several orders of magnitude below NOAEL levels.

DISCUSSION

The Expert Panel recognizes that irritation and sensitization data on 6-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, 4-Amino-*m*-Cresol, and 4-Chloro-2-Aminophenol are absent from this report. However, the hair dyes containing the ingredients included in this report, as coal tar hair dye products, are exempt from the principal adulteration provision and from the color additive provisions 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. The Expert Panel expects that following this procedure will identify individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures.

The information available on the use of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol in hair dye formulations indicate that these ingredients are reacted with a developer and are not available for absorption into the skin of the scalp. These compounds, when tested alone, are moderate skin sensitizers, but when combined with the developer, these ingredients are not sensitizers in animal tests. In addition, no toxicologically significant impurities are present with these two ingredients. This information, coupled with the available animal test data,

support the safety of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol for use in oxidative hair dyes.

Were 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol to have application in nonoxidative (semipermanent) hair dyes, there is concern about the potential for skin sensitization because these ingredients are moderate sensitizers. Because individuals would be pretested to determine if they would develop skin sensitization and because there is an absence of any significant systemic toxic effects in animal tests, the Panel believes that these two ingredients could be used safely in semipermanent hair dyes. Even though there is currently no use of these ingredients as semipermanent hair dyes, the Panel believes it useful to conclude that they could be used safely.

Although 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol appear to be used only in oxidative hair dyes, it is not clear whether 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 6-Amino-*o*-Cresol, and 4-Chloro-2-Aminophenol are used solely in oxidative hair dyes where they would be reacted with a developer and would not be available for absorption into the skin. Therefore, the Expert Panel has considered each ingredient separately for use in oxidative hair dyes and in semi-permanent hair dyes.

Because 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol would be chemically reacted with a developer in oxidative hair dyes, and because the available information has consistently shown that such reactions make the starting ingredient unavailable for skin absorption, the CIR Expert Panel believes these ingredients would present no safety concerns if used in oxidative hair dyes.

The use of 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in semipermanent hair dyes, however, could lead to skin absorption that would raise the need to assess systemic toxicity.

Such data are available for 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol, i.e., there are no toxic impurities, the ingredients themselves are not significantly toxic when absorbed into the skin, and there is no reproductive or developmental toxicity or genotoxicity associated with exposure to them. Therefore, it is possible to conclude that 6-Amino-*m*-Cresol and 4-Amino-*m*-Cresol can also be used safely in semi-permanent hair dyes.

Such data are not available to assess the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol for use in semipermanent hair dyes. In this situation, where the ingredients would not be chemically reacted before they are absorbed into the skin, available data do not provide all the information needed. The types of data required for each ingredient include

1. Physical and chemical properties for all ingredients, including the octanol/water partition coefficient
2. Impurities data, especially regarding the presence of *m*-cresol, other organic molecules, and heavy metals
3. Metabolism data, if the metabolism is not similar to that of 4-amino-2-hydroxytoluene and/or *p*-, *m*-, and *o*-aminophenol (ingredients already reviewed by CIR), the following data may be needed:
   a. 28-Day dermal toxicity with histopathology
   b. Dermal reproductive toxicity data
   c. An *in vitro* genotoxicity study for 6-Amino-*o*-Cresol and one genotoxicity study in a mammalian system for 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol; if positive, a 2-year dermal carcinogenicity study using National Toxicology Program methods may be needed.

CONCLUSION

The CIR Expert Panel concludes that the available data support the safety of 6-Amino-*m*-Cresol, 4-Amino-*m*-Cresol, 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol as used in oxidative and nonoxidative (semipermanent) hair dyes. The available data also support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol for use in oxidative hair dyes, but are insufficient to support the safety of 6-Amino-*o*-Cresol and 4-Chloro-2-Aminophenol in nonoxidative (semipermanent) hair dyes.

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