Amended Safety Assessment of 4-Chloro-2-Aminophenol as Used in Cosmetics

Status:	Draft Final Amended Report for Panel Review
Release Date:	August 15, 2025
Panel Meeting Date:	September 8-9, 2025

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.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Thomas J. Slaga, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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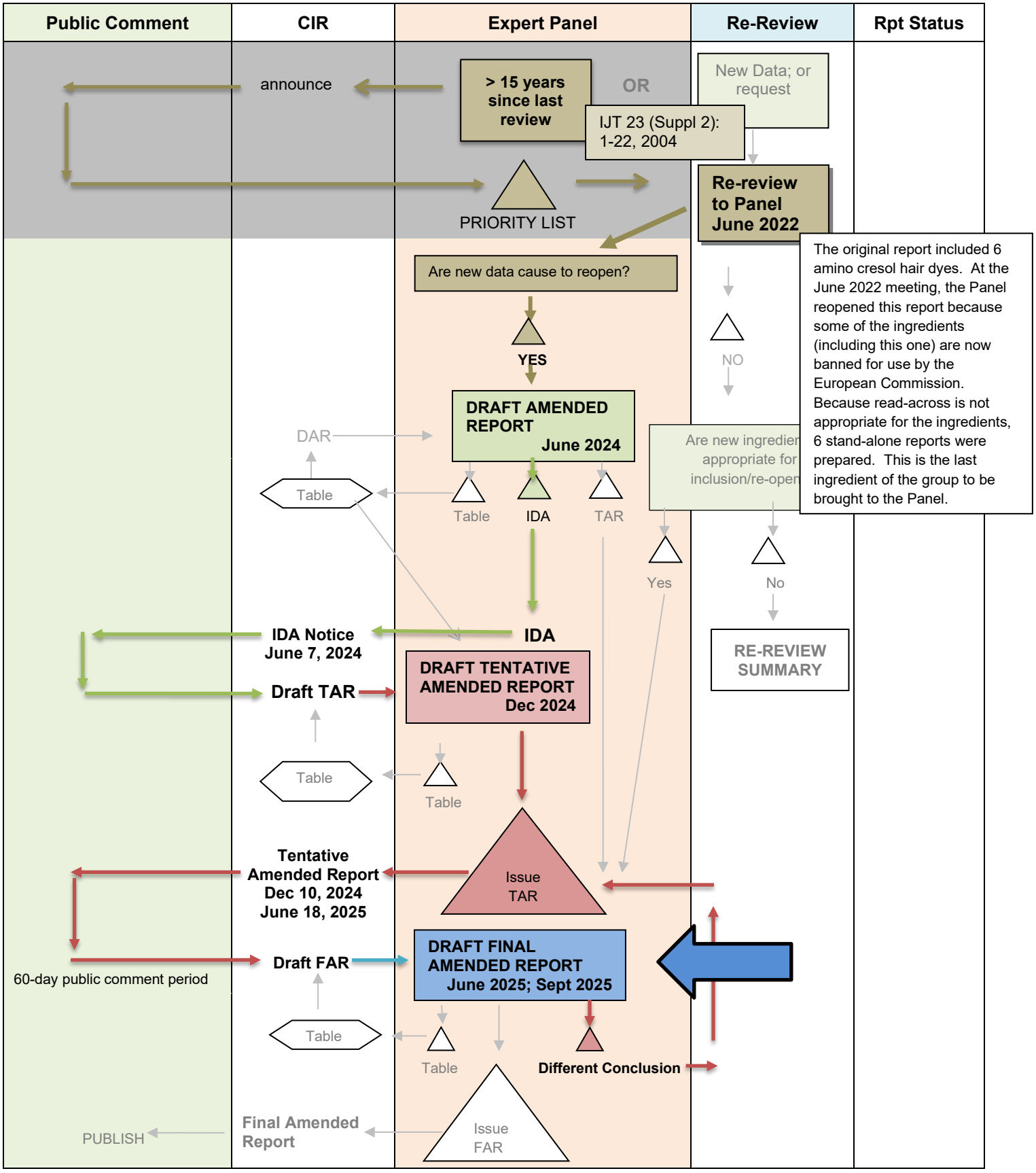
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY 4-Chloro-2-Aminophenol

MEETING September 2025



Cosmetic Ingredient Review

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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: August 15, 2025
Subject: Amended Safety Assessment of 4-Chloro-2-Aminophenol as Used in Cosmetics

Enclosed is the Draft Final Amended Report on the Safety Assessment of 4-Chloro-2-Aminophenol as Used in Cosmetics. (It is identified as *report_4-Chloro-2-Aminophenol_092025* in the pdf document.) At the June 2025 meeting, the Panel issued a revised Tentative Amended Report for public comment with the conclusion that 4-Chloro-2-Aminophenol is unsafe for use as a hair dye ingredient. The Panel determined that while absorption data are lacking, it is likely that this aromatic amine will absorb to some extent. Positive genotoxicity results were observed, specifically in Ames tests, and bladder tumors were observed in an oral carcinogenicity study in rats.

Since the June meeting, CIR has received no new data. No uses have been reported for this ingredient by the FDA RLD, FDA VCRP, or the Council.

Additional supporting documents for this report package include a flow chart (*flow_4-Chloro-2-Aminophenol_092025*), the original report (*originalreport2004_4-Chloro-2-Aminophenol_092025*), report history (*history_4-Chloro-2-Aminophenol_092025*), a search strategy (*search_4-Chloro-2-Aminophenol_092025*), a data profile (*dataprofile_4-Chloro-2-Aminophenol_092025*), transcripts from the meetings at which the current report was discussed (*transcripts_4-Chloro-2-Aminophenol_092025*), and the minutes from all the meetings at which 4-Chloro-2-Aminophenol was discussed during the original review (*originalminutes_4-Chloro-2-Aminophenol_092025*).

The Panel should carefully review the Abstract, Discussion, and Conclusion, and issue a Final Amended Report.

4-Chloro-2-Aminophenol 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 4-Chloro-2-Aminophenol is safe as used in oxidative hair dyes, but the data were insufficient to support the safety of this ingredient in nonoxidative (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 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Commission.

June 2024 – The Panel issued an Insufficient Data Announcement. The additional data needs were:

- Maximum concentration of use
- Composition/impurities data
- Toxicokinetics data, especially dermal absorption data
    - If absorbed, additional data, including developmental and reproductive toxicity data, are needed
- Micronucleus genotoxicity data

December 2024 – The Panel issued a Tentative Amended Report for public comment with the conclusion that the available data are insufficient to make a determination that 4-Chloro-2-Aminophenol is safe under the intended conditions of use in hair dye formulations. The Panel determined that the data needs from the Insufficient Data Announcement issued following the June 2024 Panel meeting remain unmet. In order to come to a conclusion of safety for this hair dye, the following data are needed:

- Maximum concentration of use data
- Composition/impurities data
- Toxicokinetics data, especially dermal absorption data
    - If absorbed, additional data, including developmental and reproductive toxicity data, may be needed
- Micronucleus genotoxicity assay data

June 2025 - The Panel issued a revised Tentative Amended Report for public comment with the conclusion that 4-Chloro-2-Aminophenol is unsafe for use as a hair dye ingredient. The Panel determined that, while the absorption data is lacking, it is likely that this aromatic amine will absorb to some extent. Positive genotoxicity results were observed, specifically in Ames tests, and bladder tumors were observed in an oral carcinogenicity study in rats.

4-Chloro-2-Aminophenol Data Profile* – September 2025 – 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
4-Chloro-2-Aminophenol		X	X	X							X				XO			X					O						

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

4-Chloro-2-Aminophenol

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
4-Chloro-2-Aminophenol	95-85-2	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed (From 2002 forward)
(4-chloro-2-aminophenol) OR (95-85-2[EC/RN Number]) – 25 hits, 1 relevant

Typical Search Terms (this is informational – not for inclusion for search strategy that goes to the Panel)

- INCI names
- CAS numbers
- chemical/technical names
- additional terms will be used as appropriate

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
- Connected Papers - https://www.connectedpapers.com/
- DeepDyve - https://www.deepdyve.com/

Pertinent Websites

- wINCI - https://incipedia.personalcarecouncil.org/winci/ingredient-custom-search/
- FDA Cosmetics page - https://www.fda.gov/cosmetics
- eCFR (Code of Federal Regulations) - https://www.ecfr.gov/
- FDA search databases: https://www.fda.gov/industry/fda-basics-industry/search-databases
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- GRAS listing: https://www.fda.gov/food/food-ingredients-packaging/generally-recognized-safe-gras
- SCOGS database: https://www.fda.gov/food/generally-recognized-safe-gras/gras-substances-scogs-database
- Inventory of Food Contact Substances Listed in 21 CFR: https://www.cfsanappsexternal.fda.gov/scripts/fdcc/index.cfm?set=IndirectAdditives
- Drug Approvals and Database: https://www.fda.gov/drugs/development-approval-process-drugs/drug-approvals-and-databases
- FDA Orange Book: https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book
- OTC Monographs - https://dps.fda.gov/omuf
- Inactive Ingredients Approved For Drugs: https://www.accessdata.fda.gov/scripts/cder/iig/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- 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/
- EUR-Lex - https://eur-lex.europa.eu/homepage.html
- Scientific Committees (SCCS, etc) opinions: https://health.ec.europa.eu/scientific-committees_en https://health.ec.europa.eu/scientific-committees/scientific-committee-consumer-safety-sccs_en
- ECHA (European Chemicals Agency – REACH dossiers) – https://echa.europa.eu/
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- EFSA (European Food Safety Authority) - https://www.efsa.europa.eu/en
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) IRIS library - https://apps.who.int/iris/
- a general Google and Google Scholar search should be performed for additional background information, to identify references that are available, and for other general information - www.google.com https://scholar.google.com/

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.

JUNE 2024 PANEL MEETING – DRAFT AMENDED REPORT

Belsito's Team Meeting – June 3, 2024

DR. BELSITO: Okay. Then we're going to 4-Chloro-2-Aminophenol. God. Okay, I'm having an issue now because it's not allowing me to save this. I don't know what to do here. Hold on. I need to figure out something. Okay. I guess we'll just leave that open and move on.

So, 4-Chloro-2-Aminophenol. Can one of you take over because I'm having issues right now with this. Curt or Allan, can you take over? I'm having some computer issues.

DR. KLAASSEN: Okay, I'll start off, and then anybody can add on. So, 4-Chloro-2-Aminophenol is a compound that has no reported uses. It is a hair dye. I think the biggest question has to do with mutagenicity and carcinogenicity. So, it is mutagenic, and IR said it's a possible carcinogenic.

One of the problems and questionable points about this, is this carcinogenicity? And where you see the carcinogenicity is squamous cell papilloma in the forestomach both in male mice and in male rats. But this forestomach that we see in rodents doesn't have a similar structure in humans, and so how one interprets that is always questionable. And that's kind of where I will stop for right now.

Paul, would you like to add to that?

DR. SNYDER: No, I fully agree, Curt. But the forestomach in rodents doesn't exist in humans, and so the relevance of that finding to human, in the absence of any other data to support carcinogenicity, has to be taken with that in mind.

DR. KLAASSEN: Allan, you have anything you wanted to add?

DR. RETTIE: No, I just agree with what you said about this. It's, first look at this, insufficient on many fronts, very little data with no dermal penetration data. There was some dermal irritation found. There's no sensitization data in guinea pigs, no other irritation data, ocular irritation data out there. And the mutagenicity, chromosomal aberration data gets your attention. So, I expect we have many data needs if we go with insufficient here, which we probably must do. Is it worthwhile just moving on to listing those needs? I could start off and leave Curt and Paul to chime in.

I think I'd like to see some ADME data, some dermal irritation and sensitization, ocular irritation, genotox. Do we want an in vivo micronucleus test? We have in vitro micronucleus but not anything else. And DART is negative on the data here -- not negative; it's just not there. So, probably DART. It's a long list.

Paul, you got any other adds to that?

DR. SNYDER: No, I do not.

DR. EISENMANN: See, this is one where I would not expect any data. And it's one where we'd like to see your procedures get modified to have an offramp so you don't have to review things like this. But that has to be worked on.

DR. RETTIE: Hundred percent agree.

DR. KLAASSEN: Yeah, I agree also. And the chemical is not being used, theoretically at least, and we've spent a lot of time on it. But I think to go through the process as we have now the best thing to do is to ask for these things. We won't receive any data, and then we can write it off.

DR. SNYDER: I think the only thing I would qualify that with is this is banned in the EU.

DR. BELSITO: Yeah, which I thought we should just ban too. But you're telling me that the carcinogenicity studies you don't think are real.

DR. SNYDER: Well, no, I said what we need is to put them in the right context. The genotox data is real. And as Allan alluded to, they're trying to get additional data to support that. Yeah, that's my only comment.

DR. KLAASSEN: Okay. If we are kind of done with that one, we've asked for these various things, and we'll move on.

DR. BELSITO: So, are you keeping the notes, Curt, because I'm still having problems?

DR. KLAASSEN: I'm not keeping any notes. Allan will be able to add that in a minute.

DR. RETTIE: I'm writing it down at least.

MS. BURNETT: I can repeat what I heard the data needs to be.

DR. RETTIE: Yeah.

MS. BURNETT: I heard ADME, dermal irritation and sensitization, ocular, genotoxicity for in vivo micronucleus test.

DR. RETTIE: That's what I had.

MS. BURNETT: Okay. When we come to the next iteration of the report, I did want to point out the butoxyethanol report that we just finished. In the last re-review, NTP data came in and there was forestomach carcinogenicity that was addressed in that re-review summary and pointed out how it was relevant to humans. So I can go look at that wording and see.

DR. RETTIE: And pull that over.

MS. BURNETT: Yeah.

DR. KLAASSEN: Yeah, that a same concept, same controversy let's say.

DR. HELDRETH: All right. So, the Cohen team will lead this one tomorrow. So, the assumption is that we'll be seconding an insufficient data announcement for these needs then is what I'm hearing.

DR. RETTIE: So, Curt we got quite a few of these in our report, species selective toxicities. Kind of wondering if we should have a document that we could look up. I mean, you know them, I don't. Look them up and things like the forestomach carcinogenicity and others we've talked about in recent iterations of this meeting.

DR. KLAASSEN: There are two of them that come up quite often. For the one, it's forestomach. The second is renal carcinoma in male rats that's due to the alpha-2-globulin.

DR. RETTIE: Right. That's the one I was thinking about.

DR. KLAASSEN: Those are the two --

DR. RETTIE: But beyond that -- is it just those two really?

DR. KLAASSEN: Let me think some more. Paul, do you have any others to add to that list that we see relatively common?

DR. SNYDER: Those are the two most common, Curt. There are a couple related to cell types that don't exist, like the large granular lymphocytic leukemia and stuff like that. But those are the two most important ones.

DR. RETTIE: Maybe I can remember those two.

DR. KLAASSEN: Yeah, you can remember up to two.

DR. RETTIE: Only two.

Cohen's Team Meeting – June 3, 2024

DR. COHEN: Speaking of hair dye chemicals, we'll move on to 4-chloro-2-aminophenol. So, this comes out of our assessment in June of 2022 to reopen a large panel of hair dye chemicals and decided to split them out. We've gone through many of them since then. For 4-chloro-2-aminophenol, the 2023 VCRP data has no reported uses and the Council's survey in 2021 has no uses. And the original safety assessment published in 2004 had no uses.

DR. BERGFELD: Well, didn't they also say that the oxidative dyes were safe and that it was insufficient for the semi-permanent in the previous document?

DR. COHEN: In the old document?

DR. BERGFELD: Yeah.

DR. COHEN: Yes. The data were insufficient to support the safety of the ingredient in non-oxidative dyes. So, we have some additional information here. Some ocular irritation. I guess just to cut through to this, should we go to a use not supported in this? We have no uses.

DR. BERGFELD: I don't think we can do that right away. We have to do it after two years.

MS. FIUME: If it comes out insufficient and there's zero use after two years it goes to use not supported.

DR. COHEN: Okay. Hopefully.

MS. FIUME: It's a CIR procedure line item.

DR. COHEN: So, we need an IDA with everything in it?

DR. ROSS: Well, you've got a lot of data. I looked at this and data's already summarized. The fact that it's got no uses, no reported concentrations. If you look at its genotoxicity, it's positive in the end, it's positive in the Chinese hamster ovary cells. If you look at its status as a carcinogen, it's IARC 2B. It's properly carcinogenic. It's on the California Prop65 list. It's E.U. Annex II. It's prohibited in cosmetics.

When the actual carcinogenesis study was done; it's a two-year dietary study in mice. Carcinogenic in males, not in females. But in rats, clear evidence of carcinogenicity in males and some evidence in females. So, I'm looking at this and I'm thinking, what more evidence do we need to come to a conclusion of unsafe? We know this is genotoxic; we know it's carcinogenic. But then I thought, well, we don't have concentrations of use. So, how am I going to determine that this thing is unsafe when I don't know what concentration it's being used at.

And so, then I sort of diverted well, maybe it's an IDA. It's an insufficiency but I'm sort of in between the unsafe and insufficiency.

DR. BERGFELD: I don't think you can go to unsafe until you go out for an IDA, right?

DR. ROSS: You think?

DR. BERGFELD: Yeah.

DR. ROSS: Okay.

DR. BERGFELD: I think it gives industry a chance and then move on it after.

DR. COHEN: Well, if you think industry had a chance this is no use. There's no reported uses. Multiple times.

DR. BERGFELD: But do we call for -- we do an initial, do we not? We call for unpublished or --

MS. FIUME: I think the tendency is to go to an IDA if there's a chance you might get information that would give you a different conclusion. If you have sufficient information, you can make whatever conclusion the data supports. It's the purview of the Panel.

DR. ROSS: But the only thing I'm lacking is the concentrations of use. Everything else is unsafe.

DR. COHEN: So, what concentration of use would give you comfort around the carcinogenicity and the genotoxicity?

DR. ROSS: How about zero? No, I --

DR. BERGFELD: Zero?

DR. TILTON: I mean, the carcinogenicity is oral. I was going to say, you know what we don't have is anything about dermal penetration, toxicokinetics, or dermal carcinogenicity.

DR. COHEN: The IDA's dermal tox.

DR. TILTON: So, I guess more information about the kinetics in terms of the relevance --

DR. ROSS: Absorption?

DR. TILTON: Yeah.

DR. ROSS: So, you need dermal absorption. You need 28-day dermal toxicity, Susan?

DR. BERGFELD: If absorbed.

DR. ROSS: If absorbed, yeah.

DR. TILTON: If absorbed.

DR. ROSS: And additional data may be needed. Genotox and carcinogenicity.

DR. TILTON: Yeah.

DR. ROSS: I mean, you've already got carcinogenicity data.

DR. BERGFELD: Did you say concentrations because you lead with that.

DR. ROSS: Yeah.

DR. BERGFELD: Okay.

MS. FIUME: But because carcinogenicity is oral, would you need dermal carcinogenicity?

DR. COHEN: Yeah, dermal.

DR. ROSS: Yeah. Exactly, Monice.

DR. TILTON: Yeah.

DR. ROSS: Yeah. Good point.

DR. COHEN: Dermal carc.

DR. TILTON: Yes.

MS. FIUME: You said genotox as well?

DR. TILTON: I didn't list dermal genotox. I mean, if there --

DR. COHEN: It's possible.

MS. FIUME: There's no --

DR. ROSS: It's in vitro.

MS. BURNETT: It's only in vitro.

DR. ROSS: In vivo genotox you put.

DR. COHEN: Okay.

DR. ROSS: I was way down the road of unsafe here before I came back because --

DR. TILTON: I mean, I came to that conclusion too, but we don't have a lot of inf- -- I feel like for other hair dyes we've had more information about what happens to it under oxidative conditions and then how much exposure there might be, and we really have nothing related to that here to change from a prior conclusion of safe under oxidative conditions.

DR. COHEN: Usually, we get that for the absorption data, right, under oxidative or non-oxidative conditions.

DR. TILTON: Yeah. So, I'm assuming that a lot of that was from sort of the read across from the group which we're no longer doing. So, we don't have that for this.

DR. ROSS: Yeah. No. I think Susan's dead on. And, I think, with that data, Susan, we would be able to calculate a margin of safety previously known as margin of you know. A quantitative safety factor which would address safety. We would do an MOS, for example, with all the other dyes. I think we've looked at pretty much all of them. We don't have the data to do that here.

DR. COHEN: You're not going to have that data but okay we'll go up with the IDA on this.

MS. BURNETT: This is already banned in the E.U. so chances are we're not going to get much data. So.

DR. BERGFELD: Well, let's talk about that banned in Europe again. Let's make sure that hits our discussion.

DR. ROSS: I'm assuming that one was because they didn't have any data rather than because of cause, right? Maybe it was cause, I don't know.

MS. BURNETT: I don't believe so. We didn't -- I think I went and checked, and I think it's just lack of a dossier.

DR. COHEN: Okay.

MS. BURNETT: Yeah. There's no data on it.

DR. BERGFELD: We can say (inaudible) review of safety.

DR. COHEN: I must say, though, it's these kind of reports that we need to revise our protocols a little bit. We're going to go for a process that we already know I'm running full speed into a brick wall.

DR. ROSS: Yeah.

DR. COHEN: It's unnecessary bandwidth. We have no reported uses for, like, 20-some odd years, right, and we're going through the process of writing this report.

DR. BERGFELD: We can send a note to the Steering Committee and ask for another category.

MS. FIUME: That is an item that we are now discussing with the steering committee. What can we do with these?

DR. COHEN: Should we bring it up tomorrow?

DR. BERGFELD: Yeah. I think it should be done in the minutes.

DR. COHEN: Yeah.

MS. FIUME: So -- not that we'll probably get anything, but just to make sure that it's complete. So, on PDF page 22, it lists the insufficient information from the last time this was reviewed, and one was impurities data, especially the presence of m-cresol and heavy metals. Are those items that would also be needed for the IDA to be complete, or is this list that you came up with today sufficient?

DR. BERGFELD: I think we should add those, actually, because they're hair dye.

DR. COHEN: Just impurities we'll go with.

DR. BERGFELD: Yeah.

DR. TILTON: It says that there are listed impurities. I don't know.

DR. COHEN: It says it's greater than 95 percent, but we don't know what the other five percent is.

DR. BERGFELD: The other thing that would be interesting to know when we look back at those that we've called unsafe -- the hair dyes -- and I think there are five of them or six of them and the reasons why we called it, may be interesting because this may be going that way.

DR. ROSS: I kind of like Dave's conclusion of use not supported. You don't think we can go down that route?

DR. BERGFELD: I don't know.

MS. FIUME: After two years --

DR. BERGFELD: After two years.

MS. FIUME: -- if there's no use, it switches from insufficient to use not supported.

DR. COHEN: But why can't we change that (inaudible)?

DR. BERGFELD: We have to have the steering committee put it in. It's in the administrative writing so we don't have it there. We have to have a new category.

DR. COHEN: Yes, because this is taking up a lot of time for literally filed under circular file. It's literally going in the garbage after all this work.

MS. BURNETT: Right. And we have a report from the last meeting that was from the same group -- tat the same situation. No uses. We put out an insufficient data announcement for it and we're just going to have the same result.

DR. COHEN: Right. If we're supposed to protect the safety of people and work collaboratively with industry. We have industry not caring about it and no access for patients. What am I doing this report for? Who am I writing this report for?

DR. BERGFELD: You're doing the process that's been established. That's what you're doing.

DR. COHEN: No, no. It's okay, but every now and again when the process makes no sense --

DR. BERGFELD: Then we have to amend it.

DR. COHEN: -- and it burdens bandwidth. Like we have important things we're doing, and this is not. Right?

DR. BERGFELD: I know. But we can't move until we have that adjustment.

DR. COHEN: No, no. We call for it.

DR. BERGFELD: Yeah. We send --

DR. COHEN: (Inaudible) president of PCPC?

DR. BERGFELD: Yeah, we want this changed.

DR. ROSS: Yeah. Well, we've got ingredients with zero uses and then some fairly -- zero uses for how many years?

DR. BERGFELD: Twenty plus.

DR. ROSS: Twenty years and we have some --

DR. COHEN: We're writing supports. We have --

DR. ROSS: We have (inaudible) --

DR. COHEN: -- staff going through it.

DR. ROSS: -- some fairly major tox data in there which shows toxicity varies endpoints and we should be able to go directly to use not supported.

DR. COHEN: Now, of course, with MoCRA there are going to be new reported uses that we didn't know about. That's the possibility.

DR. TILTON: That is a possibility.

DR. MAGNA: Yes, everything you're seeing is VCRP so far.

DR. ROSS: Yeah.

DR. COHEN: Okay. I have that one tomorrow and I have PPD tomorrow.

Full Panel Meeting – June 4, 2024

DR. COHEN: Okay, 4-Chloro-2-Aminophenol, and we'll have a further discussion about this after the motion. But for a matter of historical perspective, the Panel previously reviewed 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 in an assessment that was published in 2004.

In June of 2022 the Panel reopened a safety assessment for these ingredients due to some of these hair dyes including 4-Chloro-2-Aminophenol being banned for use by the European Commission. Because the Panel determined that the data for these amino-cresol hair dyes could not read-across, rather than including all six in one amended report, the rereviews of each of these would be presented as stand-alone reports. And, I'm glad to say, this is the last one from that group.

This is a Draft Amended Report for the safety of 4-Chloro-2-Aminophenol. Of note, the Panel concluded that 4-Chloro-2-Aminophenol is safe for used in an oxidative hair dye originally, but the data were insufficient to support the safety of this ingredient in nonoxidative, semi-permanent, hair dyes. I already mentioned the ban in the EU. It currently has no usages and no concentration of use currently, and for what we could gather the last 25 years. Since the June 2022 meeting, no new data had been submitted. We have evidence of genotoxicity and carcinogenicity.

Our motion is for an IDA for dermal absorption and if absorbed further tox, concentration of use, impurities, dermal carcinogenicity and in vivo genotox. We can discuss the reason for this IDA after.

DR. BELSITO: Well, I'll let Paul and Curt speak, but we felt the carcinogenicity was not relevant to humans because it was forestomach.

DR. COHEN: Okay.

DR. BELSITO: And our insufficiencies were for absorption. We asked for in vivo micronucleus test, and some DART data if absorbed.

DR. ROSS: (Inaudible).

DR. COHEN: Well, we had in vivo genotox and dermal carc.

DR. ROSS: I think Don said that.

DR. BELSITO: In vivo micronucleus.

DR. COHEN: Okay. Sorry. And the dermal carcinogenicity we were not together on?

DR. BELSITO: Absorption ADME, genotox, and in vivo micronucleus, and DART data if absorbed.

DR. COHEN: And impurities.

DR. BELSITO: Impurities, sure.

DR. COHEN: You have that.

DR. BERGFELD: You accept all that?

DR. COHEN: Yeah, I accepted it, yeah.

MS. BURNETT: I'll read back.

DR. COHEN: Yeah, let's get the read.

MS. BURNETT: Dermal absorption ADME data and if absorbed more toxicity endpoints potentially?

DR. BELSITO: Well, DART, if absorbed DART and in vivo micronucleus regardless.

MS. BURNETT: Yes, concentration of use, even though the survey is going out?

DR. COHEN: Right.

DR. BELSITO: Yeah.

MS. BURNETT: And impurities composition.

DR. BELSITO: Fine.

MS. BURNETT: Okay.

DR. SNYDER: Don, my notes say we had an ocular.

DR. BELSITO: Paul, we can't hear you.

DR. SNYDER: My notes say something about needing something with ocular. Was there an ocular issue that we needed concentration or something, because I have ocular down question mark? No?

DR. BELSITO: We didn't talk about that.

DR. SNYDER: Okay.

DR. ROSS: I don't think we had ocular, Paul. I don't think we had ocular on there.

DR. SNYDER: Okay, disregard.

DR. BERGFELD: Okay, so we have an Insufficient Data Announcement and the needs have been gone over and expanded. And so do we have any other comments?

DR. COHEN: We have a second on my motion, right?

DR. BERGFELD: Yes.

DR. BELSITO: Right.

DR. RETTIE: Dr. Bergfeld?

DR. BERGFELD: Yes.

DR. RETTIE: Would this report be a poster child for the catch-and-kill that you referred to in the --

DR. COHEN: Exactly.

DR. BERGFELD: Yes.

DR. RETTIE: Yeah.

DR. COHEN: We didn't have it worded like that, but I do like it. We are hoping for a category where we could have immediate use not supported. So use not supported requires that it sits out there for a few years. It requires us to go through the iterations of the draft to a tentative to a final. And, for 25 years there's no reported use and no concentration of use, yet, this is going to come back as a Tentative Report to us. Right. We need to have a little freedom to operate to not have to go through that.

DR. BERGFELD: (Inaudible) official (inaudible) will be like a special steering committee to give us this again?

DR. RETTIE: Okay, thank you.

DR. EISENMANN: We would like it to be slightly different terminology than use not supported, because you already have a category and we understand what that is. This is really no need to review it because you're not even assessing safety. You're just not reviewing it because it's no longer in use.

DR. COHEN: Right, but it does have to articulate that you don't have a pass to use it.

DR. EISENMANN: Correct, right, right some statement you no longer consider the conclusion of the old report valid.

DR. COHEN: Right, yeah, use not supported sort of says it all, but we need a similar says-it-all. Because if we just withdraw the report, it's -- it's like we don't support the use, because, you know, the prior report is cancelled, and you can't use, you know, we're not supporting the use. Somehow, I'm sure the steering committee can come up with something.

DR. EISENMANN: And the important part is you're not reviewing it anymore.

DR. COHEN: Right.

DR. BELSITO: But the current status on it is that it's out there and it's approved for use.

DR. EISENMANN: Right, probably why there must be some statement that it includes that the previous report is no longer valid or something like that.

DR. COHEN: Even more resolute than that, I think.

DR. BELSITO: It would have to be some type of statement that would be picked up on PubMed, so if someone is doing a search they wouldn't simply see the old report. They would see the report as well stating that the conclusion of the old report is no longer considered valid, and that whatever further statement we want to make.

DR. COHEN: Don's point is very important that it's got to look like almost a rereview document where it's published as -- it's not an errata but it's like an amendment or a rereview.

DR. HELDRETH: Yeah, my thought just now was that it could be something rather akin to a Rereview Summary?

DR. COHEN: Yeah.

DR. HELDRETH: Where the Panel looks at it and like, we don't want to reopen this, the data doesn't give us any cause for concern. And then it would go out as a Rereview Summary. So, it could be a similar process of, we looked at the data, nobody's using this thing, and so now we want to say that, you know, our safety assessment is now expired. You know, don't rely on us if you decide to go use this ingredient without the right use of data.

DR. ROSS: No one is using this, Bart, but also there are no concentrations of use, zero concentration of use, zero usages. It's very difficult for both teams do a toxicological assessment when you don't have a concentration of use. So, I'd like that recorded.

DR. KLAASSEN: If the concentration of use is zero, it's very safe.

DR. COHEN: Well, where we have no concentration of use. The absence of data is not data, right?

DR. BERGFELD: All right, if we could close the discussion.

DR. SNYDER: Bart, I have a question.

DR. BERGFELD: I will call the vote, all those in favor of this Insufficient Data Announcement with the needs that were listed?

DR. HELDRETH: Okay, yes, thank you.

DR. BERGFELD: Thank you.

DR. HELDRETH: But, I just had one more thought. To save us the trouble right here and now, even before we get information back from the steering committee and it was you've reopened it now. You have it in front of you. You can say the data are insufficient and our conclusion is going to be, you know, in the Rereview Summary that nobody's using this. We're not expecting to get any data back. And you can be done with this now and just call it conclusion insufficient.

DR. BELSITO: If we go out with an insufficient, aren't we required to have it come back and we look at it in 60 days to see if anyone did respond?

DR. COHEN: It's a draft report.

DR. HELDRETH: Just an idea.

DR. BERGFELD: Okay, well, moving forward --

DR. COHEN: Why don't we just maul that around for a while it'll, you know.

DR. BERGFELD: Yeah, it may end up that way.

DR. COHEN: Yeah.

DR. BERGFELD: All right, we're going --

DR. BELSITO: To clarify, it comes back to us. We get no data. We issue a final insufficient.

DR. BERGFELD: Yeah.

DR. BELSITO: It sits there for two year and then it becomes not supported.

DR. BERGFELD: Right.

DR. BELSITO: Which is what we want to do anyway, right, essentially?

DR. ROSS: Two years and 60 days left.

DR. BELSITO: It's better than nothing.

DR. BERGFELD: All right, closing that discussion.

DECEMBER 2024 PANEL MEETING – DRAFT TENTATIVE AMENDED REPORT

Belsito's Team Meeting – December 2, 2024

DR. BELSITO: So, then we'll move onto 4-chloro-2-aminophenol. So, at the June 2024 meeting we determined that the data were insufficient to support the safety of this hair dye ingredient. The data we needed were maximum concentration of use, composition/impurities data, toxicokinetic data including dermal absorption, and if absorbed developmental and repro tox data and a micronucleus genotoxicity assay. We've gotten no new data, no uses have been reported for this ingredient by the FDA RLD, FDA VCRP, or the council.

So, I guess the question here is if we have this new protocol now, no uses, and conclusion for use is not supported and then do we just close this document or do we just go ahead with an insufficient announcement? And I'll turn this over to Bart. What do we do here, Bart?

DR. HELDRETH: I think the imagined new pathway was for the Panel's use at the time of the re-review proposal and I think we've went past that at this point. The reports already reopened, and Christina's already drafted a whole new report here. I think probably the most appropriate way would be to go forward. If the conclusion is intended to stay insufficient, then to issue a tentative amended report with an insufficient data conclusion.

MS. BURNETT: Right. This report was last of the six amino cresols that were in one report together. So, we've already done five others and at least one or two of which are going to have the same conclusion because they have no uses. So, I feel because they already packaged it together at one point this would have to go the same way.

DR. BELSITO: Okay, I'm fine with that. I just wanted to bring up the question. On PDF page 32, we said that, "The available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer." And do we want to say that for this ingredient since there's some cancer carcinogenicity signals?

I mean, in particular since we're going unsafe or insufficient rather --

DR. SNYDER: The last sentence, Don, of that discussion, first paragraph, does say that although we noted those it was mitigated because of the observed effects are not relevant to humans. Is that sufficient for those effects?

DR. BELSITO: Okay.

DR. SNYDER: That's what I took it as.

DR. BELSITO: Let me look at that language again, Paul. What is the PDF number?

DR. SNYDER: PDF page 32, the draft discussion. The first paragraph -- the last sentence of the first paragraph. It's highlighted in yellow.

DR. BELSITO: Okay. Yeah. That's the epi data. But for this we have two-year studies and genotox data that suggests that it may be different for this hair dye and since there are no uses that could be part of the reason, no? That is --

DR. SNYDER: Agreed. Agreed.

DR. BELSITO: -- in fact genotoxic and carcinogenic. I mean, because we have banned a product for carcinogenicity in the past and I think it was a hair dye ingredient was it not?

DR. KLAASSEN: I think so.

DR. BELSITO: I would just -- you know, we're going to say it's insufficient. I was just concerned with the genotox and carcinogenicity data that we had on this studies that this IARC -- so it's in proposition 65 in California based on sufficient evidence in experimental animals IARC stated in 2020 monograph that 4-chloro-2-aminophenol is possibly carcinogenic to humans, category 2B.

And then we're just using epi data for generic hair dye use to try and say, well, it's not an issue with this ingredient. I'm not sure that it's not an issue with this ingredient based on the data we have in this report and so, I mean, epi data is nice when we don't have data directly on an ingredient. I don't know. I just thought I would be more comfortable striking that language. We're going to go use not supported anyway, right?

DR. SNYDER: Yeah. I agree. Do we know what was the basis for it being banned in Europe?

DR. BELSITO: Probably lack of data submission but I don't know that. I mean, they don't really say but --

DR. SNYDER: Okay. I'm okay with your proposed language.

MS. BURNETT: So, you'd like to strike both the hair dye epidemiology section and the boilerplate language in the discussion?

DR. BELSITO: Yeah, I would.

MS. BURNETT: Insufficient data conclusion. Anything else you'd like in the discussion?

DR. BELSITO: Otherwise, I thought that the discussion was fine. We're going to -- yeah.

MS. BURNETT: Okay.

DR. BELSITO: Anything else?

DR. SNYDER: Nothing for me.

DR. BELSITO: Okay.

Cohen's Team Meeting – December 2, 2024

DR. COHEN: Now we have 4-chloro-2-amino. So, this is a draft tentative amended report for 4-chloro-2-aminophemol. At the June meeting we issued an IDA with multiple needs, and we've received no data. So, I think this would go out as a conclusion of use not supported or is this insufficient data? Just insufficient data?

MS. BURNETT: Insufficient data first. It would have a two-year clock once it goes final. Right?

MS. FIUME: Yeah, because there's use -- there's no use.

DR. BERGFELD: No use.

DR. ROSS: Yeah, but we can't go use not supported.

DR. BERGFELD: No data, no use.

DR. ROSS: I mean, we could -- if this came to us next year, we could go use not supported. Next meeting.

MS. FIUME: Use not supported.

DR. ROSS: But since we've already started the process, it has to be insufficient, I think.

MS. BURNETT: Well, and this was part of the six amino cresol ingredients. This was the last one and we have already had some of the ingredients that went down a similar path so probably want to keep at least those six in the same format.

MS. FIUME: Christina, did any of those not have use? They did? Okay.

MS. BURNETT: Correct, yes. 6-amino -- it was either *o*- or *m*-cresol. I can't remember which one.

DR. COHEN: Okay.

DR. BERGFELD: So, are we going insufficient or we going not supported?

DR. COHEN: Insufficient and then the two-year clock runs and then it's use not supported after that, right?

MS. BURNETT: Correct.

DR. COHEN: Okay.

DR. ROSS: I had one addition/amendment I guess. Last time we talked about the carcinogenicity of this stuff in mice and rats, and we talked about the four stomach carcinogenicity not relevant to humans, et cetera. But there was also bladder tumors, I see, in male rats -- admittedly at high doses -- but I thought that should be added to the discussion. I think Christina it's in our data summary. Let me just pull it up here. Yeah, it's PDF 30 in the data summary.

MS. BURNETT: Under 8,000 parts per million treated males.

DR. ROSS: Yeah, it's pretty high dose but --

DR. COHEN: What PDF is it, David?

DR. ROSS: That was page 30 in the data. You're right in the midst of the carcinogenicity data paragraph, the last paragraph. And I just wondered if we needed that in the discussion or summary also. Well, actually, I think it's in the summary, isn't it? No, I think we're good. Yeah. It's in the summary, forget I said it. We're good. We're good to go.

MS. BURNETT: Okay.

DR. COHEN: So, if this goes as insufficient, does the report get published?

MS. FIUME: Yes.

DR. COHEN: Gets published just like it is now?

MS. BURNETT: Correct.

DR. COHEN: Okay.

DR. ROSS: I mean, this thing is really the poster child for use not supported.

DR. BERGFELD: Right.

DR. ROSS: I mean, but the problem is we can't really revert back to that can we, Monice, since we've started this process?

MS. FIUME: Christina, based on the discussions it was to go with insufficient data?

MS. BURNETT: Correct.

MS. FIUME: Okay.

DR. COHEN: But we did get the memo contemporaneous with this meeting.

DR. ROSS: Yeah. If we want to push the envelope there, yeah.

MS. BURNETT: I mean, (inaudible) all the other ones but sure.

DR. COHEN: No, but the point is does that matter? I mean this, we just were given like permission from the council to do this, right?

MS. BURNETT: Sure.

DR. BERGFELD: New procedures.

MS. FIUME: Right.

MS. BURNETT: Procedures.

DR. COHEN: New procedures, contemporaneous with this meeting.

MS. FIUME: Christina, was whether or not it could go discussed in the other meeting?

MS. BURNETT: Yeah.

MS. FIUME: The use not supported. It was discussed?

MS. BURNETT: And Bart said probably should not since this is part of the other report split up.

DR. COHEN: Yeah, I don't know if that. I mean, by the way, who are we offending by doing this?

MS. FIUME: I think it's open for discussion tomorrow, David. I think that's an overall Panel conclusion.

DR. COHEN: Yeah.

DR. ROSS: I would be very happy to support that. I think last time I said I would be very happy to go with unsafe on this one, but we don't have the concentrations of use so how can you do that?

MS. BURNETT: If that were to go through then this would be the last time you'd see it.

DR. ROSS: Correct.

DR. BERGFELD: That's okay.

DR. COHEN: Yeah, what would be wrong with that?

MS. BURNETT: I mean, nothing for me. I'm a creature of habit in this. Whatever the Panel would like, that's fine.

MS. FIUME: Right. I think the point is it would be changing it mid-stream the route it followed.

DR. COHEN: We can have the discussion tomorrow. I don't think anyone's digging their heels in one way or the other.

MS. BURNETT: If this is to continue through the process, is the discussion as drafted okay, or you want anything else to it?

DR. ROSS: Good for me so far.

DR. BERGFELD: Looks okay.

DR. COHEN: Yeah, I thought it was okay too but that was under the assumption that we were going to probably see it again. But there's really nothing we would've changed on this or added to it by (inaudible).

Full Panel Meeting – December 3, 2024

DR. BELSITO: Yeah. So the June 2024 meeting we determined that the data were insufficient to support the safety of this hair dye and the data we needed were max concentration of use, composition, impurities data, toxicokinetic data, especially dermal absorption and, if absorbed, additional data such as DART, and micronucleus genotoxicity assays.

Since that insufficient data announcement we've gotten no new data. No uses have been reported for this ingredient by the FDA-RLD, FDA-VCRP or the Council? So the question I have for Bart is, is this one of these new ingredients that, you know, use not supported, or do we go with an insufficient announcement? And since it's already in the (inaudible) the recommendation was to go with insufficient for all the reasons that I've just listed.

DR. COHEN: Second.

DR. BERGFELD: Any further comment?

DR. BELSITO: Yeah.

DR. BERGFELD: Going ahead, Don.

DR. BELSITO: Yeah. I was just a little bit concerned in the draft discussion that we're using the hair dye epidemiology data and saying that the data is insufficient to scientifically support a causal relationship between hair dyes and cancer. But I'm a little bit concerned about this ingredient because the data suggests that it may be associated with cancer. And we have banned ingredients before because of their carcinogenicity. I would recommend that that hair dye epidemiology data be struck from this report.

DR. BERGFELD: David, yes?

DR. COHEN: Makes sense?

DR. BERGFELD: It's agreed. Yes. Anything else?

DR. ROSS: I had a question.

DR. BELSITO: No, that was it.

DR. BERGFELD: Okay. And who had a question?

DR. ROSS: It's me, Wilma. Dave Ross. I like Don's idea of use not supported. And we had the same discussion, Don, you know, about this was already in the process and so did we have to stay with sufficient or could we go with use not supported? I kind of like the use not supported. Is there a problem with that, Bart, going sort of back on the insufficiency now and going back to use not supported?

DR. HELDRETH: Yeah, it's not insurmountable, but I do see two issues with it. First, this new use not supported pathway is meant for when the Panel is faced with the re-review proposal stage, typically where the Panel was just saying reopen, don't reopen, and then you could go to use not supported at that stage. So we're past that stage, as Dr. Belsito already said, and I've already drafted this report.

The other reason that I would suggest not going into that pathway for this particular report, is that this is one of multiple ingredients that were split out of a previous report and we've already actually issued full reports on all of those other ingredients. And so, this one would be kind of an outlier from that whole process. It might be worthwhile to just let this one finish going down the road and save that option next time we have a re-review proposal in front of you.

DR. RETTIE: We had that exact same discussion. That was a nice summary, Bart.

DR. ROSS: Yeah.

DR. HELDRETH: Thank you.

DR. BERGFELD: Any other comments before we call the question? The final is insufficient. Are those opposed?

Abstaining? This is approved.

JUNE 2025 PANEL MEETING – 1ST DRAFT FINAL AMENDED REPORT

Belsito's Team Meeting – June 9, 2025

DR. SNYDER: The report that's under our consideration this afternoon is 4-Chloro-2-Aminophenol. It's a Draft Final Amended Report. In December of 2024, we issued an Insufficient Data Announcement.

We had four needs. We had maximum concentration use, composition and impurities, TK data, and micronucleus genotox data that we wanted to see. Since then, no new data has been received, so I think we just move forward with the insufficient data, right?

DR. BELSITO: Yeah.

DR. SNYDER: Everybody agree?

DR. KLAASSEN: Yes.

DR. SNYDER: Okay.

DR. BELSITO: And I thought the Discussion was okay.

DR. SNYDER: Likewise. Nice job, Christina, as always. All right.

Cohen's Team Meeting – June 9, 2025

DR. DAVID COHEN: 4-Chloro-2-Aminophenol. That's the last one from that group, right? When did we start this?

MS. BURNETT: 2023, I think.

DR. DAVID COHEN: This is a Draft Final Amended report for 4-Chloro-2-Aminophenol. In December, we concluded that the available data were insufficient to make a determination of safety. The data requirements were listed and no data has been received to address any of these insufficiencies. Consequently I suggest we go with an Insufficient Data Conclusion again.

DR. SAM COHEN: I think we should leave it because it's not safe.

DR. DAVID COHEN: I think just technically we just issue an Insufficient Data Conclusion; it goes out that way. If in two years there's no additional data, then safety is not supported, correct?

MS. FIUME: Right. So this has no uses. Is that right? No?

DR. SAM COHEN: Good.

MS. BURNETT: Correct.

MS. FIUME: Oh no, it has no reported uses.

DR. DAVID COHEN: So, could we go as use not supported?

DR. EISENMANN: It goes under no use.

MS. FIUME: Yeah, it's under no use so I think technically it becomes use not supported. Is that how it's reported online, Carol?

DR. EISENMANN: No use is reported as --

MS. FIUME: Yeah. So no use is the use not supported categorization, basically.

DR. SAM COHEN: It's a positive Ames test. It's an aromatic amine and it causes bladder tumors in animals. This is a carcinogen that's not going to be used in humans. So, it shouldn't be used in humans.

MS. FIUME: I totally defer to the Panel for the conclusion.

DR. DAVID COHEN: That's a very good point, Sam. If we got all of the data requests, you still wouldn't -- you would not clear this?

DR. SAM COHEN: Not at all. You've got a genotox, Ames positive. It's causing bladder tumors in the rat and it's an aromatic amine. Aromatic amines are the most well-known cause of bladder cancer in humans.

DR. DAVID COHEN: So team, that's highly provocative and I'd like for you guys comment on that.

DR. ROSS: We discussed not approving this.

DR. BERGFELD: Or calling it unsafe?

DR. DAVID COHEN: No, well we issued an insufficient data.

DR. ROSS: That was the -- but we discussed the possibility of calling it unsafe. I don't remember --

DR. DAVID COHEN: We asked for micronucleus genotoxicity data.

DR. ROSS: But we actually were considering calling it unsafe. The conclusion, there was some reason why that was not -- maybe the request had already been done for insufficiency.

DR. TILTON: But we did talk about lack of toxicokinetics, so I don't know if it was just --

DR. DAVID COHEN: Right, if it's not absorbed.

DR. TILTON: Yeah. There is no new data.

DR. DAVID COHEN: Right. If it's not absorbed, how do you get bladder tumors?

DR. SAM COHEN: Yeah. If it's not absorbed at all.

DR. ROSS: I'm not sure you can say that.

DR. SAM COHEN: I'd be surprised if it's not absorbed.

DR. ROSS: Yeah, I would agree with Sam. I think it will be absorbed looking at it.

DR. SAM COHEN: It won't be absorbed a lot, but some of it will be.

DR. DAVID COHEN: I know, but we asked for toxicokinetic data in the Insufficient Data Conclusion, right?

DR. SAM COHEN: If it's absorbed at all, it will be enough to cause bladder tumors.

DR. DAVID COHEN: That's an if, right?

DR. SAM COHEN: Yeah.

DR. DAVID COHEN: It's if.

MS. BURNETT: So that's your unknown.

DR. DAVID COHEN: Right. So I think use not supported. Use not supported means you shouldn't use it.

DR. BERGFELD: It doesn't mean it's unsafe. It doesn't mean it's unsafe, though.

DR. ROSS: But it's two different conclusions, yeah.

DR. BERGFELD: Yeah.

DR. DAVID COHEN: It doesn't mean it's unsafe, but does it clear use?

DR. SAM COHEN: So it would accomplish the same thing.

DR. DAVID COHEN: Right. You'd have to petition to reopen this, right?

MS. FIUME: Yes. Yes, you'd have to show use.

DR. DAVID COHEN: Right. I'm looking at this from the consumer end of this. Could the consumer be exposed to this with a use not supported? And I think they're protected with a use not supported, right? Well, I mean, anyone could put it in, but it's not being used because of our document.

DR. ROSS: I have notes here on 12/24. It says, "I'm happy to reach a conclusion of unsafe."

MS. FIUME: I'm looking at --

DR. ROSS: But I didn't have a -- you know, particularly, because I didn't have a concentration of use. How can I reach a conclusion of unsafe without having a concentration of use?

DR. DAVID COHEN: And absorption data.

DR. ROSS: Yeah. So that was one of the issues. I mean, clearly, this is not a great compound to be putting in cosmetics.

DR. SAM COHEN: No, this is not a safe compound.

DR. ROSS: No.

DR. SAM COHEN: And as a hair dye you're going to have some oral ingestion, you're going to get some inhalation exposure of which has been shown to cause bladder cancer.

DR. ROSS: But looking at this you could twist it around. Could you conclude if you didn't have concentration of use? Well, not usually. Can you conclude unsafe if you don't have a concentration of use?

DR. SAM COHEN: I think the only way you could declare this as safe is if there's absolutely no absorption. It would have to be zero.

DR. ROSS: I think that's very unlikely.

DR. SAM COHEN: David, I agree. I don't think -- this chemically is going to get absorbed.

DR. ROSS: It's going to get absorbed.

DR. SAM COHEN: Not a lot, but it must be substantial.

DR. DAVID COHEN: So what are the technical boundaries here?

MS. FIUME: I'm looking back through the transcripts and this exact conversation has happened.

DR. SAM COHEN: Yes.

DR. DAVID COHEN: We're consistent if anything.

MS. FIUME: If you feel there is no concentration that is safe, then I don't see why you couldn't go unsafe, if you feel there is no concentration that is safe. How you explain it in the Discussion, that's going to depend on your expertise, right?

DR. SAM COHEN: It's Ames positive, bladder carcinogen in rats, it's an aromatic amine. Any other aromatic amine that causes bladder cancer in rats is considered a human carcinogen.

MS. FIUME: So, it comes down to the expertise of the Panel is what it comes down to.

DR. ROSS: We could have the discussion tomorrow.

DR. DAVID COHEN: No, no, but we need to make a motion.

MS. FIUME: Right.

DR. BERGFELD: Unsafe.

MS. BURNETT: And then it will go back out and come back, so.

DR. ROSS: Yeah.

DR. DAVID COHEN: What?

MS. BURNETT: The report will go out for comment and then come back again.

DR. ROSS: It'll come back to us again.

DR. DAVID COHEN: Because we're changing the conclusions.

DR. ROSS: Exactly.

MS. FIUME: Being more restrictive. Does industry feel the need to weigh in on this?

DR. SAM COHEN: It's not being used.

DR. EISENMANN: We were hoping it would go in the new category.

DR. DAVID COHEN: Use not supported.

DR. EISENMANN: Use not supported, so it wouldn't have to come back to you anymore. But, because it had already been opened, you decided it couldn't go in that category. I don't think we object to unsafe with this one. Nobody's using it.

DR. DAVID COHEN: Probably because it's unsafe.

DR. ROSS: Well, why don't we make the motion of unsafe.

DR. EISENMANN: We'd rather you not spend time on it.

DR. ROSS: Yeah, exactly.

DR. DAVID COHEN: This one probably wouldn't spend -- we wouldn't spend a lot of time on this.

DR. ROSS: I'm fine with unsafe.

DR. DAVID COHEN: If it looped around, would it be a lot of staff time?

MS. BURNETT: No. Just fixing Discussion and the Conclusion.

DR. DAVID COHEN: I think there's value, Sam, in what you brought forward. And I think there's value to the public and value for what we do here.

DR. ROSS: I agree.

DR. DAVID COHEN: I'm going to make a motion of unsafe. Because there's no absorption that you're going to be happy with.

DR. SAM COHEN: No. If there's any absorption, it would be unsafe.

DR. DAVID COHEN: And inhalation is going to be hard to get around.

DR. SAM COHEN: Right.

DR. DAVID COHEN: What do you think, Wilma?

DR. ROSS: I had some points, Christina, on some clarification needed on dose levels of forestomach tumor induction in the males. And it's in the Discussion. And I'll send you the comments. It just seemed contradictory.

MS. BURNETT: Okay.

DR. ROSS: It goes back to the original Japanese study which I pulled out, but it just needs a bit of clarification.

MS. BURNETT: Okay.

DR. DAVID COHEN: Sam, could you just list the reasons why. So you have positive Ames.

DR. SAM COHEN: Positive Ames, bladder tumors in rats, aromatic amine is a human carcinogen, likely to be a human carcinogen. And it's been banned in Europe for that reason.

DR. DAVID COHEN: I know but we have our own --

DR. SAM COHEN: Yeah. What I'm saying, this would be -- this would never get by any Panel, EPA or FDA.

DR. BERGFELD: It'll be nice to know how many unsafe ingredients we've actually ruled on during this course of this year.

MS. BURNETT: About a dozen.

MS. FIUME: Eleven or 13. Yeah, right?

MS. BURNETT: That's about a dozen.

MS. FIUME: Yeah, it's 11 or 13.

DR. DAVID COHEN: So we have a baker's dozen now.

MS. FIUME: And some of them are the hair dyes that are out there.

DR. BERGFELD: Yeah, there are about three of them, I think, as I recall.

DR. ROSS: Well, I think this one is quite deserving.

DR. DAVID COHEN: Okay, so we're done.

Full Panel Meeting – June 10, 2025

DR. DAVID COHEN: Thank you. This is a Draft Final Amended Report on the safety of 4-Chloro-2-Aminophenol. In our December 2024 meeting, we concluded that the available data are insufficient to make a determination of safety. The data requirements to come to a conclusion of safety were as follows: Maximum concentration of use, composition and impurities, toxicokinetics and further information based on that, and micronucleus genotoxicity data.

Since the Tentative Amended Report was issued, the CIR has received no new data. No uses have been reported for this ingredient by the RLD, the VCRP or the Council.

We deliberated this a great deal. And based on it being an aromatic amine, positive Ames test, bladder tumors in rats and a likely human carcinogen, since there was no toxicokinetic data that would satisfy a safe conclusion, our motion is unsafe for use.

DR. BERGFELD: Is there a second or a comment?

DR. SNYDER: Don, do you have a comment regarding the unsafe versus the insufficient data?

DR. BELSITO: Yeah, David, I understand what you're saying, but do you actually have data showing that it is genotoxic or carcinogenic to make that call unsafe.

DR. DAVID COHEN: I think we had enough corroborating data based on its structure, its Ames test, bladder tumors and it being a likely human carcinogen. If we had kinetic data that showed minimal exposure, and we'd expect at least some exposure, we would not clear this.

DR. BERGFELD: Other comments, Sam?

DR. SAM COHEN: I think that from what I understand in the previous discussion with this, it was considered as unsafe also. And I think given the combination of it being an aromatic amine, which is a well-known class of bladder carcinogens, the fact it produced bladder cancer in rats and it was Ames positive, this is a genotoxic, mutagenic, bladder carcinogen, and it's likely to be so in humans.

DR. BELSITO: If it's absorbed.

DR. SAM COHEN: There is some evidence that it is absorbed. There were a couple of documents that referred to its absorption. Given its chemical structure, I can't imagine that at least some of this isn't absorbed.

DR. BERGFELD: Any other comments from the Belsito team? Are you seconding?

DR. SNYDER: Allan, Curt, any comments?

DR. BERGFELD: Are you seconding or you're not seconding? You're still deliberating?

DR. SNYDER: Are you comfortable seconding it, Don?

DR. BELSITO: I'm not a genotoxic carcinogenicity person. I mean, there were a lot of other hair dyes that are aromatic amines that we've allowed to go through. So just saying it's an aromatic amines and --

DR. SAM COHEN: No, it's an aromatic amine that also was positive in the Ames assay and caused bladder tumors in rats. There's a lot of aromatic amines that do not produce a positive Ames assay, and they're not N-hydroxylated so you don't get the DNA reactivity, and they don't produce bladder tumors.

In fact, we endogenously produce a couple of these anthranilic acid and kynurenine and their hydroxy analogs which are analogs of this compound. But those do not N-hydroxylate and there's been a lot of work done by a guy at the University of Louisville, Dr. Hein, that looked at the structure activity relationships of these. And pretty much those that are able to anti-hydroxylate are the ones that are Ames positive and are bladder carcinogens.

In fact, most of the time in rats they are liver or mammary gland carcinogens and not bladder carcinogens. So given that background of information, it's very likely -- I mean, there's no evidence absolutely proving it, but it's very likely that this would be a human carcinogen even if it's absorbed only a little bit.

DR. SNYDER: Curt, any comment?

DR. KLAASSEN: I agree with that.

DR. SNYDER: So I guess procedurally, will this then come back around to us? Because I would like to see the Discussion elaborate on all these points and everything to support that. And we don't currently have that in the document.

DR. HELDRETH: Yes, if it's voted on and the Panel agrees to this conclusion, it would go out as a Revised, Tentative Amended Report. And then come back to the Panel again at a future meeting as a Revised, Draft Final Amended Report.

DR. BELSITO: I'm still concerned that we don't have data on absorption under use conditions. You know, when mixed with peroxide and put on the scalp for 20 to 30 minutes and washed off, which is very different from feeding an animal. I hear where you're coming from in terms of the genotoxicity and carcinogenicity.

DR. ROSS: Could I just make a comment, maybe help this along a bit. I think we've seen this a number of times. One of the previous times, I think, we discussed going unsafe, but we didn't have a concentration of use, and so we got hung up on that.

In our discussions yesterday with Sam and David and Susan, we felt we really couldn't come up with a concentration that would be safe because we know this stuff is going to get absorbed. So that's how we remove that obstacle, if you like, and we came to our conclusion of unsafe. Maybe that helps.

DR. SNYDER: Go ahead, Allan.

DR. RETTIE: But to go back to the use conditions, do you have a different conclusion, under oxidative conditions, where presumably very little, if any, of the actual compound we're talking about here has systemic availability?

DR. BELSITO: That's my point. We don't have that. I mean it's one thing just to look at the pure compound, it's another to look at as used. I mean again, I just don't think we have the data. But it'll go away anyway, right? I mean, if we say that it's insufficient, no one's using it, and after two years, use not supported, right? Is that correct, Bart?

DR. HELDRETH: Yes. If we get a final Insufficient Data Conclusion, it eventually would be considered use not supported.

DR. BELSITO: I can't hear you.

DR. HELDRETH: Yes, it would eventually be considered use not supported if no one comes forward with the data to meet the insufficiency.

DR. DAVID COHEN: We've had, you can recall, compounds similar to this, even in oxidative conditions, that have had zero systemic absorption. From my recollection, the oxidative process markedly reduces absorption. I don't recall no absorption. But maybe I'm missing one.

DR. RETTIE: I don't recall either.

DR. DAVID COHEN: Yeah, I don't either.

DR. BERGFELD: Do we have a motion to second?

DR. SNYDER: I'm not comfortable seconding it. Is that what you, Don -- ? Is that what you're saying?

DR. BELSITO: Yeah, again, I just -- I think that we're a scientific, data-driven Panel. And yes, we have a concern about absorption, and if absorbed, you know, there's the genotoxic potential. And you know, you can't do margins of safety for genotox.

I mean, I guess you could say that it's likely that at least some would be absorbed and therefore you can't do a MOE and it's unsafe. But again we don't -- I'm just disturbed by the fact that we asked for data on dermal absorption, we asked for data on concentration, we didn't get it, and yeah, I mean we've changed our opinion before. I have to concede to Sam on his feelings about the -- yeah, I mean clearly it's in the document, right? It's genotoxic and there is bladder cancer in rats when it's fed.

DR. ROSS: What's the IARC conclusion?

DR. BELSITO: There's not a study where it's applied dermally.

DR. BERGFELD: David or Sam?

DR. ROSS: Just Sam can comment. Sam, what's the IARC classification?

DR. SAM COHEN: The IARC classification, I think it's 2B just because there's no human data on this. But I think just given its chemical structure, and even under oxidative conditions, some of this would get absorbed. There's the potential also for some inhalation. And certainly aromatic amines by inhalation are well known to cause bladder cancer. And cigarette smoking is the most notable of these.

You're right that there's very little dermal information on the aromatic amines. But I just think that given the fact that there would be some systemic exposure -- not a lot, but there would be some -- that this is potentially a human carcinogen.

DR. BERGFELD: Any other comments? We have a motion that has not been seconded. Do you want to restate your motion? Or do you want to have someone on your team second it? How would you like to proceed?

DR. DAVID COHEN: Yes, so procedurally anyone can second this?

DR. BERGFELD: Right. Yeah.

DR. DAVID COHEN: Okay. Do you want to second it, Curt?

DR. KLAASSEN: Yes, I'll second it.

DR. BERGFELD: Okay. Now the motion has been seconded to call this ingredient unsafe. I'm going to call the question. All those to vote as unsafe, please raise your hand. Okay. Abstaining? Against?

DR. DAVID COHEN: Don, are you abstaining or voting against?

DR. BELSITO: I guess I'll abstain.

DR. BERGFELD: One abstaining and one against. So it passes.

DR. DAVID COHEN: Two abstains. Two abstains.

DR. BERGFELD: Two abstains? He didn't vote against? Okay. Two abstains in the remainer for that. So it passes as unsafe and moves forward. And you'll again restate how it moves forward?

DR. HELDRETH: Yes.

DR. BELSITO: It comes back to us.

DR. HELDRETH: That's right. With this new conclusion it will go out for public comment as a Revised, Tentative Amended Report. And then in a future meeting it will come back to the Panel as a Revised, Draft Amended Final Report.

DR. BERGFELD: Thank you.

DR. BELSITO: And David, what is your plan for the Discussion in terms of this likely absorption and genotoxic carcinogenic when fed to rats?

DR. DAVID COHEN: All of those. It's aromatic amines. The data you just outlined. And the likelihood of some absorption. And the fact that we could not come to terms with any concentration of use that we would clear it with. All those things would be in the Discussion.

DR. BERGFELD: Christina, did you have a comment or a question? You got it? Okay. Any other comments regarding this ingredient?

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 4-Chloro-2-Aminophenol as Used in Cosmetics

Status: Draft Final Amended Report for Panel Review
Release Date: August 15, 2025
Panel Meeting Date: September 8-9, 2025

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.; Samuel M. Cohen, M.D., Ph.D.; Curtis D. Klaassen, Ph.D.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Thomas J. Slaga, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D., and the Senior Director is Monice Fiume, M.B.A. This safety assessment was prepared by Christina Burnett, M.S., Senior Scientific Analyst/Writer, CIR.

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ABBREVIATIONS

CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMSO	dimethyl sulfoxide
DNCB	dinitrochlorobenzene
EPA	Environmental Protection Agency
EU	European Union
FD&C	Food, Drug, and Cosmetic
FDA	Food and Drug Administration
HTS	high-throughput screening
IARC	International Agency for Research on Cancer
JETOC	Japan Chemical Industry Ecology-Toxicology & Information Center
LAI	leukocyte adherence inhibition
LDH	lactate dehydrogenase
MoCRA	Modernization of Cosmetics Regulation Act
NIH	National Institutes of Health
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
RLD	Registration and Listing Data
TG	test guideline
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) reassessed the safety of 4-Chloro-2-Aminophenol, which is reported to function as a hair dye ingredient in cosmetic products. The Panel reviewed all data relevant to the safety of this ingredient. The Panel issued an amended report with a revised conclusion stating that 4-Chloro-2-Aminophenol is unsafe for use as a cosmetic ingredient.

INTRODUCTION

4-Chloro-2-Aminophenol, which according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (*Dictionary*) is reported to function in cosmetics as a hair colorant,[1] was previously reviewed by the 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 4-Chloro-2-Aminophenol for use in oxidative hair dyes, but are insufficient to support the safety of…4-Chloro-2-Aminophenol for use in 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 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Union.[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 were presented as individual stand-alone reports.

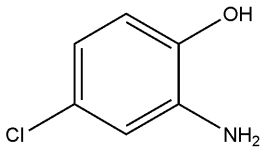
Excerpts from the summaries of the previous report on 4-Chloro-2-Aminophenol are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (These data are not included in the tables or the Summary.) The original report is available on the Cosmetic Ingredient Review (CIR) website (https://cir-reports.cir-safety.org/).

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 2025. 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 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*, 4-Chloro-2-Aminophenol (CAS No. 95-85-2) is the hair colorant that conforms to the structure in Figure 1.[1]



Chemical Properties

Chemical properties for 4-Chloro-2-Aminophenol are summarized in Table 1.[4,5] 4-Chloro-2-Aminophenol is a light brown crystalline solid with a molecular weight of 143.57 g/mol.[4] The melting point is 140˚C and the estimated log P_{ow} is 1.24.

Method of Manufacture

4-Chloro-2-Aminophenol is manufactured by converting 2,5-dichloronitrobenzene to 4-chloro-2-nitrophenol in a reaction with sodium hydroxide.[6] The product is then reduced with iron, hydrazine, or hydrogen with Raney nickel or platinum catalyst. It is not known if this method is used for preparation of cosmetic grade products.

Composition and Impurities

The International Agency for Research on Cancer (IARC) Working Group reported that the purity of 4-Chloro-2-Aminophenol to be greater than 95%.[5] No further details were provided. A supplier of 4-Chloro-2-Aminophenol for a subchronic and carcinogenicity study described in those sections of this report stated that their product was > 99.1% pure, and no impurities or degradation products were detected with gas chromatography analysis.[6]

USE

Cosmetic

The safety of the cosmetic ingredient 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 4-Chloro-2-Aminophenol in cosmetics. Data included herein were obtained from the FDA and in response to a survey of maximum use concentrations conducted by the

Personal Care Products Council (Council), and it is these values that define the present practices of use and concentration. Frequencies of use obtained from the FDA include data from the Voluntary Cosmetic Registration Program (VCRP) database as well as Registration and Listing Data (RLD). As a result of the Modernization of Cosmetics Regulation Act (MoCRA) of 2022, the VCRP was discontinued in 2023 and, as of 2024, manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-year period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products are not included in this exemption.[7] Please note, at this time, it is not appropriate to contrast data from the VCRP and RLD to determine a trend in frequency of use because there are numerous differences in the ways the data for the VCRP and the RLD were collected and processed, and because reporting frequency of use is now mandatory (as opposed to the past practice of voluntary reporting). Although the VCRP program is now defunct, trends in frequency of use from the RLD alone are not yet possible in that a baseline is currently not available.

According to 2024 RLD,[8] 2023 VCRP data,[9] and the results of the concentration of use survey conducted by the Council in 2021 (provided in 2022),[10] 4-Chloro-2-Aminophenol has no reported uses. 4-Chloro-2-Aminophenol was also reported to have no reported uses in the original (2004) safety assessment, according to 1998 VCRP data and 1999 industry survey data.[2]

This ingredient is considered a coal tar hair dye 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 (FD&C Act). In order to be exempt, the following caution statement must be displayed on all coal tar hair dye products:

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

Product labels shall also bear patch test instructions for determining whether the product causes skin irritation. However, whether or not patch testing prior to use is appropriate is not universally agreed upon. The Panel recommends that an open patch test be applied and evaluated by the beautician and/or consumer for sensitization 48 h after application of the test material and prior to the use of a hair dye formulation. Conversely, a report in Europe suggests that self-testing has severe limitations, and may even cause morbidity in consumers.[11,12] Hair dye products marketed and sold in the US, though, must follow the labeling requirements established by the FD&C Act.

Under European regulations for cosmetic ingredients, 4-Chloro-2-Aminophenol, when used as a substance in hair dye products, is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.[3]

Non-Cosmetic Use

4-Chloro-2-Aminophenol is reported to be used as an intermediate in the production of dyes used to color textiles and clothing fabrics, leather, and paper chemicals.[5] It is also used in inks and toners. 4-Chloro-2-Aminophenol is reported to be a synthetic precursor of the muscle relaxant chlorzoxazone.[13]

TOXICOKINETIC STUDIES

The IARC Working Group noted that while no experimental data were available on 4-Chloro-2-Aminophenol, it is expected that the material would be absorbed after oral administration and be eliminated via the kidneys.[5] No further details were provided.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Intraperitoneal

Groups of 4 male Fischer 344 rats were given a single intraperitoneal injection of 0.4, 0.8, or 1.2 mmol/kg 4-Chloro-2-Aminophenol hydrochloride in 50% dimethyl sulfoxide (DMSO) in distilled water or vehicle only.[2] *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.*

Subchronic Toxicity Studies

Oral

In a 13-wk study performed in accordance with the Organisation for Economic Co-operation and Development (OECD) test guideline (TG) 408, groups of 10 male and 10 female F344/DuCrlCrlj (Fisher) rats were fed a diet containing 0, 512, 1280, 3200, 8000, or 20,000 ppm 4-Chloro-2-Aminophenol (>99.1% pure).[6] The rats were observed daily for clinical signs of toxicity and mortality. Body weights and feed consumption were measured once a week. Urinalysis was performed near the end of the treatment period, and hematology and blood chemistry analysis were performed at the terminal necropsy. Blood levels of methemoglobin were determined. All animals underwent complete necropsy.

All treated rats of both sexes survived to the end of the 13-wk administration period. Terminal body weight was significantly decreased in the rats of both sexes fed 20,000 ppm and in the male rats fed 8000 ppm. Feed consumption was significantly lowered only in the 20,000 ppm males. Macroscopic examination at terminal necropsy revealed that all male and female 20,000 ppm rats had both enlarged spleens and a thickened forestomach walls. Relative weights of the kidneys and liver were significantly increased in the male rats fed 3200, 8000, or 20,000 ppm 4-Chloro-2-Aminophenol; relative weights of the lungs and spleen were significantly increased in the males given 8000 ppm and greater. The treated female rats exhibited a statistically significant increase in relative spleen and liver weights at 8000 and 20,000 ppm, and in relative kidney weight at 20,000 ppm. A statistically significant increase in methemoglobin levels was observed in the 8000 and 20,000 ppm male rats and in the 20,000 ppm females. A significant increase in reticulocyte counts were observed in males that were fed 1280 ppm or greater of 4-Chloro-2-Aminophenol and in females fed 3200 ppm and above. Red blood cell counts, hemoglobin concentration, and hematocrit were significantly decreased in the males fed ≥ 3200 ppm. In females, red blood cell counts were significantly decreased in the 1280 ppm and above dose groups, while hemoglobin concentration and hematocrit were significantly decreased in the 3200 ppm and above and 8000 ppm and above dose groups, respectively. The plasma level of total bilirubin was significantly increased in the 20,000 ppm dose group of both sexes. No hematuria occurred in any group of either sex.

Histopathological findings included hyperplasia of the forestomach observed in all rats of both sexes that received 8000 and 20,000 ppm of the test material, while the incidence of erosion/ulcer was significantly increased in the females of the 20,000 ppm dose group. In the urinary bladder, the incidence of transitional cell hyperplasia was significantly increased in males of the 20,000 ppm dose group, and two morphologically different types of hyperplasias, i.e., simple and papillary and/or nodular types, were observed. Crystalline or amorphous precipitate could not be detected in the urinary bladder of the 20,000 ppm male rats. Swelling of the transitional epithelium in the urinary bladder, indicating a degenerative change in the transitional cells, occurred in male and female of the 20,000 ppm dose group. A statistically significant incidence of splenic lesions, including hemosiderin deposition, extramedullary hematopoiesis, and erythrocyte engorgement, occurred in both sexes that received ≥ 3200 ppm of the test material. (Extramedullary hematopoiesis was not observed in the 3200 ppm females, but was observed in the 8000 and the 20,000 ppm females). No treatment-related lesions were observed in other organs, including the lungs, kidneys, and liver, in any dose group of either sex. The maximum tolerated dose was determined to be 8000 ppm.[6]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity data for 4-Chloro-2-Aminophenol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

GENOTOXICITY STUDIES

In Vitro

The mutagenic potential of 4-Chloro-2-Aminophenol in DMSO was determined in a preincubation assay.[2] *Concentrations of 10 to 1500 µg/plate were tested using Salmonella typhimurium strains TA100, TA1535, TA97, and TA98 with and without metabolic activation. 4-Chloro-2-Aminophenol was weakly mutagenic. (No further details were provided.)*

In an Ames test, the mutagenic potential 4-Chloro-2-Aminophenol (99% pure) was tested using *S. typhimurium* strains TA98, TA100, TA1535 and *Escherichia coli* strain WP2uvrA at concentrations up to 5000 µg/plate, with or without metabolic activation.[14] Statistically significant mutagenic effects were observed in strains TA100 and TA1537 with metabolic activation. No further details were provided.

4-Chloro-2-Aminophenol (99.9% pure) induced chromosomal aberrations in Chinese hamster lung cells.[15] The material was tested for 6 h with an 18 h recovery time at up to 0.1 mg/ml without metabolic activation and at up to 0.4 mg/ml with metabolic activation. Without metabolic activation, the material was also tested at up to 0.003 mg/ml for 24 h and 0.006 mg/ml for 48 h, both time periods without recovery time. No further details were provided.

CARCINOGENICITY STUDIES

Since 2019, 4-Chloro-2-Aminophenol has been included on the Proposition 65 list as a chemical known to the state of California to cause cancer.[16] Based on sufficient evidence in experimental animals, IARC stated in a 2020 monograph that 4-Chloro-2-Aminophenol is possibly carcinogenic to humans (Group 2B).[5] The studies that this IARC determination is based on are described below.

In a 2-yr study, groups of 50 male and 50 female B6D2F_1/Crlj mice were fed diets that contained 4-Chloro-2-Aminophenol (> 99.1% pure) at concentrations of 0, 512, 1280, or 3200 ppm (w/w).[17] The mice were observed daily for clinical signs of toxicity and mortality. Body weights and feed consumption were measured once a week for the first 14 wk, and then every 4 wk thereafter. Urinalysis was performed near the end of the treatment period, and hematology and blood chemistry analysis were performed at the terminal necropsy. All mice, including those found dead or in a moribund state as well as those that survived until the end of the 2-yr treatment period, underwent a complete necropsy.

Survival rates, body weights, and feed consumption were similar to controls for all dose groups. In male mice, the incidence of squamous cell papillomas in the forestomach was increased in the 3200 ppm dose group when compared to the control group. Additionally, the incidences of squamous cell papillomas in the forestomach in the males in all the treated groups were higher than

historical control data (statistical significance not reported). A slight increase in the incidence of squamous cell papillomas in the forestomach was also observed in the treated females, but those incidences were within the range of the historical control data. It was concluded that there was evidence of carcinogenic activity in the male mice treated with 3200 ppm 4-Chloro-2-Aminophenol, but there was no evidence of carcinogenic activity from the test material in the female mice.[17]

The same research group performed a carcinogenicity study in groups of 50 male and 50 female Fischer 344/DuCrlCrlj (Fisher) rats.[6,18] The rats were fed a diet containing 4-Chloro-2-Aminophenol (> 99.1% pure) at 0, 1280, 3200, or 8000 ppm for 2 yr. The methodology is the same as described in the mouse study above. Survival rates were similar to controls for all dose groups. There were no statistically significant differences in terminal body weights between any 4-Chloro-2-Aminophenol male dose groups and the male control; however, the 3200 and 8000 ppm females exhibited a statistically significant decrease in terminal body weight compared to the female control. Feed consumption was reduced in a statistically significant manner in the 3200 and 8000 ppm males and the 8000 ppm females. Yellow coloration of the fur was observed in all the male and female treated rats. The incidence of forestomach tumor (squamous cell carcinoma and papilloma) was increased in a statistically significant manner in male rats fed 3200 and 8000 ppm. The incidence of urinary bladder tumor was significantly increased in the 8000 ppm treated males. In females, the incidence of squamous cell papillomas in the forestomach was significantly increased in the 8000 ppm dose group. Non-neoplastic lesions observed included significantly increased incidence of squamous cell hyperplasia of the forestomach in the 3200 and 8000 ppm males and 8000 ppm females. Slight, non-statistically significant changes of anemic parameters including red blood cell count were noted in 3200 and 8000 ppm females, and deposition of hemosiderin in the spleen and significantly increased spleen weights were observed in the 8000 ppm females. It was concluded that there was clear evidence of carcinogenic activity in the male rats treated with ≥ 3200 ppm 4-Chloro-2-Aminophenol, and some evidence of carcinogenic activity from 8000 ppm of test material in the female rats.

High-Throughput Screening Assays

IARC conducted evaluations of bioactivity across various assay endpoints that are commonly associated with carcinogenic potential.[5] Six of 10 identified key characteristics of carcinogens have been examined for 4-Chloro-2-Aminophenol by high-throughput screening (HTS) assays (there are no assays available to test 3 of the characteristics, and no assays were completed to assess one characteristic) used by the US Environmental Protection Agency (EPA) and the US National Institutes of Health (NIH) (Table 2). 4-Chloro-2-Aminophenol was found to be active in 11 of 54 assays run. Specifically, 4-Chloro-2-Aminophenol was considered active in 5 of the 6 assay endpoints linked to the key characteristic of "is genotoxic." Furthermore, 4-Chloro-2-Aminophenol displayed activity in 4 assay endpoints related to the "modulates receptor-mediated effects" characteristic, as well as 1 endpoint associated with the "induces oxidative stress" characteristic and 1 endpoint related to the "alters cell proliferation, cell death, or nutrient supply" characteristic.

OTHER RELEVANT STUDIES

Immunological Effects

The response of leukocytes from female guinea pigs treated with 4-Chloro-2-Aminophenol was evaluated using the leukocyte adherence inhibition (LAI) technique.[2] *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

Renal cortical slices from male Fischer 344 rats were used in gluconeogenesis and lactate dehydrogenase (LDH) release studies.[2] *The tissue slices were incubated with 0.01 to 0.5 mM 4-Chloro-2-Aminophenol in DMSO or vehicle alone. Renal gluconeogenesis was inhibited by ≥ 0.01 mM 4-Chloro-2-Aminophenol. LDH leakage was increased at concentrations of ≥ 0.5 mM 4-Chloro-2-Aminophenol.*

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal Irritation

Dermal irritation data for 4-Chloro-2-Aminophenol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

Dermal Sensitization

The sensitization potential of 4-Chloro-2-Aminophenol and cross-sensitization potential with p-aminophenol was determined using guinea pigs.[2] *(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 wk after treatment, the animals were patch tested with 0.1, 0.5, and 1.0% 4-Chloro-2-Aminophenol in equal volumes of dioxane 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 served as a control group.*

One test animal died by week 6 of the study (reason for death not stated.) At 2 to 3 wk, 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.

OCULAR IRRITATION STUDIES

Ocular irritation data for 4-Chloro-2-Aminophenol were not included in the original report and were not found in the updated literature search, and unpublished data were not submitted.

CLINICAL STUDIES

Occupational

Blood samples were taken from 21 workers that handled 4-Chloro-2-Aminophenol (and other compounds).[2] *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.*

Thirty-one factory workers were patch tested with 4-Chloro-2-Aminophenol, as well as with four other compounds used or produced at the factory.[2] *Using adhesive plasters, 0.1, 0.5 and 1.0% 4-Chloro-2-Aminophenol 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 applying 0.1 ml of 0.1% dinitrochlorobenzene (DNCB) in acetone onto the flexural antebrachium of each person, and the reaction was evaluated 48 h after application. A group of 5 control subjects was tested in the same manner. Of the 31 subjects tested, 7 had positive reactions to all concentrations tested, 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% 4-Chloro-2-Aminophenol. Six of the 7 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 the other compounds tested. 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.*

SUMMARY

4-Chloro-2-Aminophenol is reported to function in cosmetics as a hair colorant. 4-Chloro-2-Aminophenol 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), 4-Chloro-2-Aminophenol is safe for use in oxidative hair dyes; however, the data were insufficient to support safety for use in 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 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Union.

According to 2024 RLD, 2023 VCRP survey data, and the results of the concentration of use survey conducted by the Council in 2021 (provided in 2022), 4-Chloro-2-Aminophenol has no reported uses. 4-Chloro-2-Aminophenol was also reported to have no reported uses in the original (2004) safety assessment, according to 1998 VCRP data and 1999 industry survey data.

Under European regulations for cosmetic ingredients, 4-Chloro-2-Aminophenol, when used as a substance in hair dye products, is categorized in Annex II, the list of substances prohibited in cosmetic products in Europe.

In a 13-wk study in male and female rats fed a diet containing up to 20,000 ppm 4-Chloro-2-Aminophenol, the maximum tolerated dose was determined to be 8000 ppm. All treated rats survived until study end. Macroscopic findings revealed that all male and females in the 20,000 ppm dose group had both enlarged spleens and thickened forestomach walls. Histopathological findings included hyperplasia of the forestomach in rats of both sexes at 8000 and 20,000 ppm 4-Chloro-2-Aminophenol. Incidences of transitional cell hyperplasia of the urinary bladder were significantly increased in males of the 20,000 ppm dose group. A statistically significant incidence of splenic lesions occurred in both sexes that received ≥ 3200 ppm of the test material. No treatment-related lesions were observed in other organs, including the lungs, kidneys, and liver, in any dose group of either sex.

In an Ames test, 4-Chloro-2-Aminophenol was mutagenic in *S. typhimurium* strains TA100 and TA1537 with metabolic activation when tested at up to 5000 µg/plate. 4-Chloro-2-Aminophenol induced chromosomal aberrations in Chinese hamster lung cells when tested at up to 0.1 mg/ml without metabolic activation and up to 0.4 mg/ml with metabolic activation.

Since 2019, 4-Chloro-2-Aminophenol has been placed on the Proposition 65 list as a chemical known to the state of California to cause cancer. Based on sufficient evidence in experimental animals, IARC determined that 4-Chloro-2-Aminophenol is possibly carcinogenic to humans (Group 2B). A 2-yr mouse study in which animals were fed a diet containing 512 – 3200 ppm 4-Chloro-2-Aminophenol reported increased incidences of squamous cell papillomas in the forestomach of male mice that received 3200 ppm 4-Chloro-2-Aminophenol. Results of a similar study in rats given diets containing 1280 – 8000 ppm 4-Chloro-2-Aminophenol reported increased incidences of squamous cell carcinomas and papillomas of the forestomach in male rats in groups dosed with 3200 and 8000 ppm 4-Chloro-2-Aminophenol. Male rats also had increased incidences of urinary

bladder tumors at 8000 ppm 4-Chloro-2-Aminophenol. Female rats had increased incidences of squamous cell papillomas in the forestomach at 8000 ppm. Non-neoplastic lesions observed included increased incidence of squamous cell hyperplasia of the forestomach in the 3200 and 8000 ppm males and 8000 ppm females. It was concluded that there was evidence of carcinogenic activity in male mice that received 3200 ppm, no evidence of carcinogenic activity in female mice, clear evidence of carcinogenic activity in male rats that received $\geq$ 3200 ppm, and some evidence of carcinogenic activity in female rats that received 8000 ppm 4-Chloro-2-Aminophenol.

HTS assays were utilized to assess the carcinogenic potential of 4-Chloro-2-Aminophenol. This ingredient was active in 11 of 54 assay endpoints.

Developmental and reproductive toxicity, dermal irritation data, and ocular irritation data on 4-Chloro-2-Aminophenol 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 re-evaluates the conclusions of previously-issued reports approximately every 15 years. In 2004, the Panel published a final report on 4-Chloro-2-Aminophenol and concluded that this ingredient was safe for use in oxidative hair dyes. However, the data available at the time were insufficient to support the safety of 4-Chloro-2-Aminophenol for use in non-oxidative (semi-permanent) hair dyes. This report was reopened for re-evaluation due to 4-Chloro-2-Aminophenol being banned for use in cosmetics by the European Commission. In this amended report, the Panel noted a lack of relevant safety data, specifically for the following:

- Maximum concentration of use
- Composition/impurities data
- Toxicokinetics data, especially dermal absorption data
    - If absorbed, additional data, including developmental and reproductive toxicity data, are needed
- Micronucleus genotoxicity data

However, the Panel determined that, while the absorption data is lacking, it is likely that this aromatic amine will absorb to some extent. Additionally, positive genotoxicity results were observed, specifically in Ames tests, along with an increased incidence of urinary bladder tumors in an oral carcinogenicity study in rats. Based on the overall weight of evidence - including the genotoxic potential and tumor findings - the Panel considers that 4-Chloro-2-Aminophenol poses a potential carcinogenic risk to humans, and, therefore, is unsafe for use as a cosmetic ingredient.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that 4-Chloro-2-Aminophenol is unsafe for use as a cosmetic ingredient.

TABLES

Table 1. Chemical properties

Property	Value	Reference
Physical Form	Light brown crystalline solid	[4]
Molecular Weight (g/mol)	143.57	[4]
Density/Specific Gravity (g/ml)	1.41	[5]
Vapor pressure (mmHg @ 25ºC)	0.0015	[4]
Melting Point (ºC)	140	[4]
Water Solubility (g/l @ 20ºC)	3	[4]
log P_{ow}	1.24 (estimated)	[4]

Table 2. Summary of activity of 4-Chloro-2-Aminophenol reviewed in the IARC monograph and tested in ToxCast and/or Tox21 HTS assays.[5]

Key characteristic	Number of positive results out of the number of assays completed*
1. Is electrophilic or can be metabolically activated	0 out of 1
2. Is genotoxic	5 out of 6
3. Alters DNA repair or cause genomic instability	*No assays available*
4. Induces epigenetic alterations	*not tested*
5. Induced oxidative stress	1 out of 3
6. Induces chronic inflammation	0 out of 1
7. Is immunosuppressive	*No assays available*
8. Modulates receptor-mediated effects	4 out of 22
9. Causes immortalization	*No assays available*
10. Alters cell proliferation, cell death, or nutrient supply	1 out of 21
Total hits out of total number of assays evaluated	**11 out of 54**

* Mapped HTS assay endpoints are available to assess 7 of the 10 identified key characteristics.[19]

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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

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[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.

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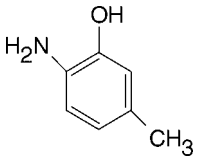
used in hair tints and hair dyes and colors at concentrations of ≤1%, ≤5%, and ≤1%, respectively.

CHEMISTRY

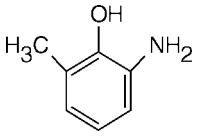
Definition and Structure

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



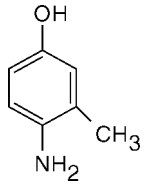
6-Amino-*m*-Cresol is also known as 4-Amino-3-Hydroxytoluene; 2-Amino-5-Methylphenol; Phenol, 2-Amino-5-Methyl-; 2-Hydroxy-4-Methylaniline (Pepe, Wenninger, and McEwen 2002); *m*-Cresol, 6-Amino; 6-Amino-3-Cresol; 6-Amino-3-Methylphenol; 2-Hydroxy-*p*-Toluidine; 5-Methyl-2-Aminophenol (Regulated Chemicals 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):



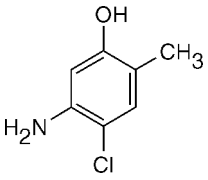
6-Amino-*o*-Cresol is also known as 3-Amino-2-Hydroxytoluene; 2-Amino-6-Methylphenol; Phenol, 2-Amino-6-Methyl-; 6-Amino-2-Methylphenol; Phenol, 6-Amino-2-Methyl-; 2-Hydroxy-3-Methylaniline (Pepe, Wenninger, and McEwen 2002); *o*-Cresol, 6-Amino; 6-Methyl-2-Aminophenol (Regulated Chemicals Listing 1998); 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):



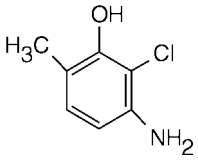
4-Amino-*m*-Cresol is also known as 2-Amino-5-Hydroxytoluene; 4-Amino-3-Methylphenol; Phenol, 4-Amino-3-Methyl-; 4-Hydroxy-*o*-Toluidine (Pepe, Wenninger, and McEwen 2002); 3-Methyl-4-Aminophenol (James Robinson Ltd. 1998); *p*-Amino-*m*-Cresol; *m*-Cresol, 4-Amino-; 4-Hydroxy-2-Methylaniline; *p*-Hydroxy-*o*-Toluidine; *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:



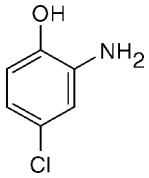
5-Amino-4-Chloro-*o*-Cresol is also known as 5-Amino-4-Chloro-2-Methylphenol; Phenol, 5-Amino-4-Chloro-2-Methyl- (Pepe, Wenninger, and McEwen 2002); and 2-Methyl-4-Chlor-5-Aminophenol (Henkel KGaA 1994).

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:

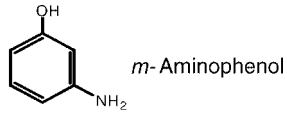


4-Chloro-2-Aminophenol is also known as 2-Amino-4-Chlorophenol; Phenol, 2-Amino-4-Chloro-; 2-Hydroxy-5-Chloroaniline; CI 76525 (Pepe, Wenninger, and McEwen 2002; Regulated Chemicals Listing 1998); 5-Chloro-2-Hydroxyaniline; *o*-Amino-*p*-Chlorophenol; *p*-Chloro-*o*-Aminophenol; and C.I. Oxidation Base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

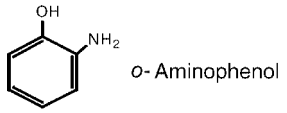
TABLE 1
Physical and chemical properties of 5-Amino-4-Chloro-*o*-Cresol and 5-Amino-6-Chloro-*o*-Cresol (Henkel KGaA 1994, 1996)

	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)

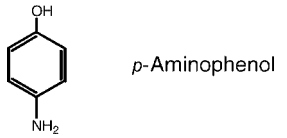
Structure of Related Ingredients



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

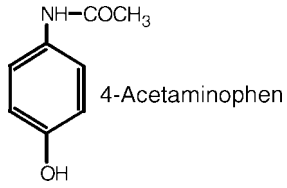
No data were available on ingredients in this safety assessment, but data on related ingredients are summarized below.

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.

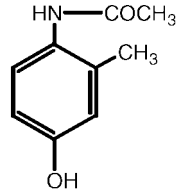
Acetaminophen

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).

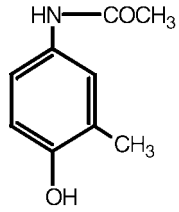


4-Acetaminophen

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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