Safety Assessment of Basic Brown 17 as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 13, 2020
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, CIR.

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Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst, CIR
Date: November 13, 2020
Subject: Safety Assessment of Basic Brown 17 as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Basic Brown 17 as Used in Cosmetics. (It is identified as *bbrown122020rep* in the pdf document.) At the June 2020 meeting, the Panel issued an Insufficient Data Announcement (IDA) for this ingredient. The additional data needed to determine safety were concentration of use and reported function for the non-coloring hair product uses that were reported in the FDA VCRP database. Since the issuance of the IDA, CIR has not received any new data.

Supporting documents for this report package include a flow chart (*bbrown122020flow*), report history (*bbrown122020hist*), transcripts from the previous meeting (*bbrown122020min*), a search strategy (*bbrown122020strat*), and a data profile (*bbrown122020prof*).

Based on the proceedings and comments from the June 2020 meeting, a draft Discussion has been included. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion.

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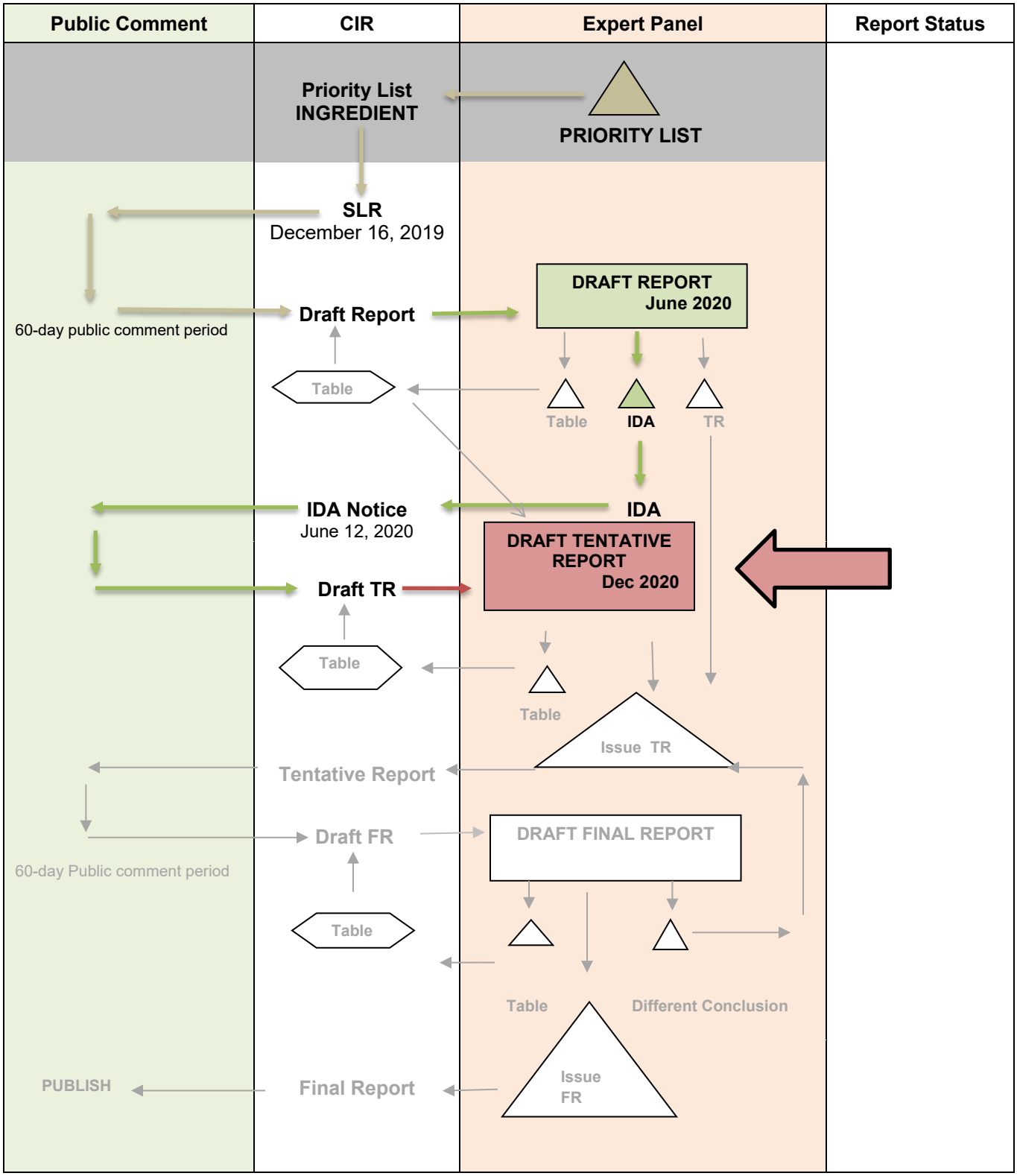
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Basic Brown 17

MEETING December 2020



Basic Brown 17 History

December 16, 2019 – Scientific Literature Review announced.

June 2020 - The Panel issued an Insufficient Data Announcement (IDA) for this ingredient. The additional data needed to determine safety were concentration of use and reported function for the non-coloring hair product uses that were reported in the FDA VCRP database.

Basic Brown 17, December 2020 – Christina Burnett

	Reported Use	Method of Mfg	Constituents	Impurities	Toxico-kinetics: Dermal Penetration	Toxico-kinetics: ADME	Acute Tox: Dermal	Acute Tox: Oral	Acute Tox: Inhalation	Repeated Dose Tox: Dermal	Repeated Dose Tox: Oral	Repeated Dose Tox: Inhalation	DART: Dermal	DART: Oral	Genotox: In Vitro	Genotox: In Vivo	Carci: Dermal	Carci: Oral	Dermal Irr.: In Vitro	Dermal Irr.: Animal	Dermal Irr.: Human	Dermal Sens.: In Vitro	Dermal Sens.: Animal	Dermal Sens.: Human	Phototoxicity	Ocular Irr.: In Vitro	Ocular Irr.: Animal	Clinical Studies: Retrospective/ Multicenter	Clinical Studies: Case Reports
Basic Brown 17	X		X	X	X		X	X			X			X	X	X				X			X			X	X		X

"X" indicates that data were available in a category for the ingredient

Basic Brown 17

Ingredient	CAS #	InfoBase	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Basic Brown 17	68391-32-2	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed

"Basic Brown 17" – 4 hits, 3 relevant

"68391-32-2" – 0 hits

Search updated October 2020.

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc

JUNE 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito's Team Meeting – June 8, 2020

DR. BELSITO: Okay. So then we're moving on from wheat to Basic Brown 17. So this is our hair dye for the day. So this is a hair dye, but, according to the document, there are other non-coloring hair products uses for it. So how do we deal with that?

DR. HELDRETH: Typically, we do, as I'm sure you're alluding to, focus our conclusion on safe as used or insufficient or what have you as used as a hair dye. Since there are more than just hair dye uses for this, we may have to address our conclusion to those other use types as well.

DR. BELSITO: Okay.

DR. HELDRETH: And it can be split. You may feel comfortable in one use type and not in another, just like any other report.

DR. BELSITO: Okay. So we'll look at that as we go through.

DR. ANSELL: Let me add that this is not an approved color for cosmetics in the U.S. So any non -- those applications would have to be non-colorant applications.

DR. BELSITO: It's not an approved color?

DR. ANSELL: Right. Hair dyes are regulated uniquely. So it can be used as a hair dye, but it could not be used as a color additive for a cosmetic.

DR. HELDRETH: So for instance, you couldn't take this ingredient and put it in an eye shadow where the intended purpose was to impart color onto the skin because this is not a recognized color by FDA. But you can use it as a colorant for hair dyes, as Jay is saying. Now, you could use it for other non-coloring purposes in other cosmetic types but not as a color.

DR. BELSITO: Pardon? Not as a --

DR. HELDRETH: Not as a non-hair color. A color for things other than hair.

DR. BELSITO: You could not use it?

DR. HELDRETH: Right, that's correct. It has to be a registered color with FDA. You know, FDA has strict guidelines about colors in cosmetics that aren't for hair dyes.

DR. BELSITO: So it's use as a non-coloring hair product, which we're told it's used as, would not be an FDA approved use of this material.

DR. HELDRETH: If it's not imparted in the color, then there's no problem, whether it's hair or skin. The only problem it would come up with is if the ingredient was used to impart color to, say, the skin, like in a mascara.

DR. SNYDER: Which is not the case for these three non-colorant uses.

DR. HELDRETH: Right, these are non-oxidative -- I mean, they're hair products.

DR. BELSITO: Okay. So we can't kick that out for not being an unapproved FDA use. That's fine. I mean, there was no sensitization alerts here. So I guess, the first comment I have, should we move right up to the front that it functions as a non-oxidative hair dye, rather than putting that a few sentences below in the introduction? It's under the chemistry, but shouldn't it be in the introduction that it's non-oxidative?

MS. BURNETT: Sure.

DR. LIEBLER: Yeah. First sentence in the introduction as a non-oxidative hair dye.

DR. BELSITO: Okay. And then under impurities, do any of those impurities bother you? These amines and naphthalenes? This is PDF page 8.

DR. LIEBLER: Yeah. I mean, not really at the low concentration specified.

DR. BELSITO: Okay. So should that be in our discussion? Yes? No?

DR. LIEBLER: I'm thinking.

DR. SNYDER: I mean, the Basic Red is not approved to be used in cosmetics, only as an impurity to a color. So we probably should have some discussion about what that is because Basic Red is not (inaudible) only as an impurity in Basic Brown 17. Is that not correct?

MS. BURNETT: That's the case in Europe.

DR. LIEBLER: The one potential impurity concern would be that first one listed, the nitrobenzene-1,4-diamine. But it's at a very low concentration in essentially a rinse off product. There are some notable aromatic amines that are famous -- or for azo compounds that are famous carcinogens. And then there are many more that are not at all.

I don't know if there are any data on nitrobenzene diamine that we could look at that would help in our assessment. I don't think the 7-hydrozy-N,N,N-trimethylnaphthalene-2-aminium chloride is likely to be a problem. It doesn't really contain a structure alert that would be of concern. That N,N,N-trimethylnaphthalene-2-aminium is -- that's not a structural alert for a carcinogen for example. Whereas, that 1,4-diamine would be potentially a concern -- the nitrobenzene-1,4-diamine. So maybe, Christina, you could look to see if there is any data on the nitrobenzene-1,4-diamine.

MS. BURNETT: Sure.

DR. BELSITO: Okay. Are we done with that point or are there more comments?

DR. LIEBLER: No, I think that covers that part.

DR. BELSITO: Okay. And then in a dermal penetration, the animal -- this is PDF page 9, first paragraph. It was below detection limits for the aqueous in the standard formulation. So nothing was in the receptive fluid. Is that what that's saying?

DR. SNYDER: I had the dermal absorption less than 0.5 percent. (Inaudible).

DR. BELSITO: You broke up, Paul. I didn't hear you. You had the dermal absorption what?

DR. SNYDER: At less than 0.5 percent.

DR. LIEBLER: Yeah. It basically appears to be not absorbed, as the data indicate.

DR. BELSITO: Okay.

DR. LIEBLER: And in fact, the top of PDF 10, it was concluded that Basic Brown 17 is not absorbed through the skin.

DR. BELSITO: Right. Okay.

DR. SNYDER: So I had it cleared with no absorption. We have lots of tox data for dermal, oral, acute and sub-chronic. We have developmental tox. It was all clean for very high NOEAL. We didn't have genotox data, and -- we had genotox data that cleared it. And we didn't have any carcinogenicity. So the absence of absorption in lieu of a genotox signal, I didn't have any issues with (Inaudible) data.

DR. BELSITO: Well, the genotox data was a little mixed though, right?

DR. KLAASEN: Yes.

DR. BELSITO: You had a positive Ames. You had a positive micronucleus. You had a positive comet. And then you had some negatives. I dealt with that by lack of absorption and short-term exposure, but, I mean, are there other ways around it? This is PDF page 12.

DR. KLAASEN: I agree with you, Don.

DR. LIEBLER: Yeah. The mammalian systems were negative on genotox, I believe.

DR. SNYDER: Yeah. I had it overall at Table 2 on PDF page 16.

DR. BELSITO: Okay. So is this something that should go in the discussion, though?

DR. LIEBLER: Sure. I think it's reasonable. We usually -- or we frequently do that in the discussion when we have a mix of genotox data.

DR. BELSITO: Okay.

DR. LIEBLER: That was one of my discussion points.

DR. BELSITO: Okay. And did you draft some language for that, Dan?

DR. LIEBLER: Just a few bullets for Christina. Generally favorable safety profile. Negative mammalian genotox mitigates concern about positive Ames and a lack of carcinogenicity data. Data indicates no dermal absorption so margin of safety 1000 with a conservative assumption on absorption -- very conservative. I think it was 50 percent absorption in the MOS calculation. The actual was closer to zero.

DR. BELSITO: Okay. Which margin of safety data are you looking at, Dan?

DR. LIEBLER: I'm looking at the SCCS calculation in the middle of PDF page 13, right between clinical studies and hair dye epi.

DR. BELSITO: Oh, yeah. Okay.

DR. LIEBLER: So it says bioavailability of 50 percent in that calculation -- the third line. But the actual is much lower than that, near zero. And even with that conservative assumption, they come up with a 1000 for the MOS.

DR. BELSITO: Okay. Then overall in the conclusion I thought it was safe as used, except I thought it was insufficient for other non-coloring hair products, because we had no concentration of use for those.

DR. SNYDER: I had 0.19 percent for the concentration of use for the three non-hair coloring --non-coloring uses. And those were shampoo and hair conditioner, I think, or something. I don't remember exactly.

MS. BURNETT: The VCRP categories were shampoo, conditioner, and other non-coloring hair products. And the concentration data was on the other hair coloring product -- that point 0.19 percent.

DR. BELSITO: Yeah. It wasn't on the non-coloring products.

DR. SNYDER: No, that was the non-coloring. At least what I had, that was the non-coloring.

DR. BELSITO: There's no table for this, right? It's just in the --

DR. SNYDER: PDF page 19. There's a table that has the hair dyes and colors. Hair shampoos -- coloring, and other hair coloring preparations -- 0.14 to 0.19.

MS. BURNETT: Yeah. So none of those are non-coloring products. Those are all under the hair dye category. So we don't have a concentration of use for those.

DR. BELSITO: These were all coloring, Paul.

DR. SNYDER: Okay. I misread that.

MS. BURNETT: So the three that are for the hair conditioner, the shampoo, and the other non-coloring hair preparations from the VCRP data is what we are missing. I think it could be a potential misclassification.

DR. BELSITO: Probably is, but I think the data are insufficient for that use given the lack of concentration. Paul, Curt, Dan?

DR. SNYDER: I mean, unless they're stating -- unless they're used within the range of concentration reported for the others coloring uses because of the low absorption and the high toxicity profile we have. High concentration (Inaudible).

DR. BELSITO: But, I mean, in this case can we assume that they're used in the same concentration since they're supposedly non-coloring?

DR. HELDRETH: You could go with two options. You could have it be a completely split conclusion and say safe for colorant use, insufficient for non-colorant use. Or you could say safe as used and have -- like we have in some of the other reports -- have a little asterisk on the conclusion that says for those ingredients where we don't know the concentration of use, they would have to be used within the same use-type category and concentration to be covered by this conclusion.

DR. BELSITO: But they're not used in the same use-type category. They're non coloring.

DR. HELDRETH: Sure, but they're all hair products, correct?

MS. BURNETT: Yes.

DR. BELSITO: Right.

MS. BURNETT: This is the first review, so we could issue the IDA on the concentration of use and see if either the uses get clarified in the VCRP or if we get concentration of use.

DR. LIEBLER: Yeah. I would favor that approach.

DR. BELSITO: Yeah.

DR. LIEBLER: That's our usual pathway.

DR. BELSITO: Okay. So safe as used for hair dyes and coloring. And we need concentration of use for the non-coloring hair products.

DR. HELDRETH: Okay. So we're going to be issuing an IDA at this point (inaudible). Is that correct?

DR. BELSITO: Yes. Anything else on this?

MS. BURNETT: Dr. Liebler, did you want the IDA to include more on the impurities or just do a simple search and figure that out ourselves?

DR. LIEBLER: Yeah. Let's just do a simple search ourselves. I'd just like to know if there are any data on that one impurity. The 250 PPM is a low number, but I'd just like to make sure that we don't get blindsided by something on that.

MS. BURNETT: Okay. Got it.

DR. BELSITO: And that was the amine impurity, right, Dan?

DR. LIEBLER: Yeah. The diamine. Don, can we take a five-minute break?

Marks' Team Minutes – June 8, 2020

DR. MARKS: And this is the first review of the direct semi-permanent, non-oxidative hair dye. My main comment is in -- this is probably aimed at you, Ron Shank -- is do we need method of manufacture when we have the constituents and impurities? So for me, if we don't have the method of manufacture in the past -- there's been some sticklers in terms of having method of manufacture. Is this an insufficient data announcement or is it a tentative report? Let's assume all the other data needs are taken care of. So Lisa, Ron, Tom, your comments?

DR. SHANK: Okay. This dye doesn't penetrate the skin to any significant extent. It was negative in acute toxicity, the peak toxicity, chronic toxicity, DART. It has little irritation potential and negative in skin sensitization tests. It gave mixed results in a variety of mutagenicity tests, but it's a rinse off. So it has very little genotoxic potential there. I would say safe as used. And method of manufacture, I can't see how that would change anything. So that's where I stand, safe as used.

DR. MARKS: Lisa?

DR. PETERSON: Yeah. I more or less support that, so I think all the data's there. I was more concerned about some of the impurities, but you've already reviewed them, too. There's documents that are on those.

And this is just more a parenthetical. There is a new epidemiological study that was published in 2020 from the sister study that suggest that frequency of use of hair dyes is associated with increased risk, which is -- it's just not part of your epidemiological summary. So that might want to be included.

But I agree that this is more or less safe. Then, if you are not worried about not having the manufacture for all the reasons stated, I'm comfortable with that.

DR. SHANK: Okay.

DR. MARKS: Yeah. We'll see. Dan Liebler is usually the stickler on method of manufacture, so we'll see what he says tomorrow. When you said more or less, you feel comfortable with safe, not equivocal. I know the epidemiologic study --

DR. PETERSON: No, I think the data -- the data on the parent compound look good. I don't --

DR. MARKS: Okay.

DR. PETERSON: -- I didn't really have any -- my note is that it looks like if the parent compound is safe.

DR. MARKS: Okay. And then we do update the hair dye epidemiology resource document, so this newest epidemiology study will go into it. Wilma, correct me, if the new studies create any significant issue, then the whole Panel deals with it, and we review those.

DR. BERGFELD: It's my understanding that when we start a review -- a re-review like this, that we all see it again and comment on it.

DR. MARKS: Yeah.

DR. BERGFELD: It just doesn't float out there without our knowledge.

DR. MARKS: So -- it sounds like --

DR. BERGFELD: A new article will generate a re-review.

DR. MARKS: Pardon?

DR. BERGFELD: So you could send it in. Lisa, if you can send the --

DR. PETERSON: Yeah, yeah, yeah. I'll put it in there. I have it. It's the *International Journal of Cancer*, 2020, so I have the reference, and I will put it --

DR. MARKS: What was the -- I'm sorry. What was the conclusion? Increased frequency of use resulted in increased potential frequency of cancer or not?

DR. PETERSON: An increase in breast cancer and it was caused by frequency of use. And this was in a population of -- it's a sister study, so one sister has breast cancer. And it pulls in all the sisters.

DR. MARKS: I see.

DR. PETERSON: So there is a predisposition, but African Americans were at increased risk because they had increased use of hair dyes as well as -- and straighteners were in there, too.

DR. MARKS: Yeah. Interesting. And more than likely I would --

DR. PETERSON: And it was a huge study. It was like tens of thousands of women.

DR. MARKS: Okay.

MS. BURNETT: Before we move on, I just wanted to ask. Dr. Peterson, what did you -- you were okay with the impurities you said?

DR. PETERSON: Well, I guess the impurity -- why was I worried --

DR. MARKS: What page is that, Christina?

MS. BURNETT: PDF page 8.

DR. MARKS: And Tom, I'm going to want your input either verbally or --

DR. PETERSON: So I guess the one impurity -- you know, it's just it's mostly a structural alert to me more than anything because these are -- aromatic amines and azo dyes have a history of having some issues. But this one more has -- all of the data are good except -- and then I just was wondering about this 2-nitrobenzenel 1,4-diamine, but you've reviewed that. And so I'm more reacting to the structural alerts than anything. That's what I'm reacting to.

MS. BURNETT: That's right. Okay.

DR. PETERSON: But the data presented here, I didn't see any concern.

MS. BURNETT: Okay. And then one other --

DR. PETERSON: I just wanted to alert you to that new publication because it's -- it made a big splash here in Minnesota.

DR. MARKS: Yeah. That's important. Thanks, Lisa.

MS. BURNETT: And then one other item. In the VCRP, there are three non-hair dye uses. They are still hair product uses, but they are not dye uses. Does the Panel want to discuss that at all?

DR. SHANK: Are they rinse off?

MS. BURNETT: One's a shampoo, one's a conditioner, and one is categorized as other, which we don't know if that's a rinse off or leave on. It could be miscategorized, and we don't have any concentration of use data on it.

DR. BERGFELD: You can always put in the discussion that these are considered rinse offs, and this one lacks absorption.

DR. SHANK: Yeah. That's a good way to handle it.

MS. FIUME: So that was -- that would actually -- may change how we give a conclusion for hair dyes because typically the ingredient --

DR. BERGFELD: No, no. It's a discussion.

MS. FIUME: I'm sorry, Wilma. I didn't hear you.

DR. BERGFELD: Discussion not conclusion.

MS. FIUME: No, no, but I was going to say, being that those aren't listed as hair dye uses, typically when we have a hair dye, we say safe as used in hair dye formulations. So that would just make this conclusion a bit different for this ingredient. And I don't know. Is there any concern?

And Christina, I don't remember how we categorized this when we look at them -- that one of the concentrations is in other hair coloring products. Do we know if that's a leave on or a rinse off?

MS. BURNETT: No. I don't believe so.

MS. FIUME: Carol, do you have any clarification on that?

DR. EISENMANN: No, sorry. I don't know what -- I mean, usually hair dyes are mostly rinse off. I mean it's -- I would suspect the other hair dye -- the other than the hair dye are a miscatagorization, but I don't know for sure. I mean there are hair coloring shampoos that somebody might have just put under the shampoo. I don't know.

MS. BURNETT: Yeah. There's ten uses in the other category.

DR. EISENMANN: Other hair dye?

MS. BURNETT: Other hair dye, yes. And 14 in hair coloring shampoos.

DR. MARKS: So Ron, Lisa, Tom, do we want to just use our standard hair dye conclusion and in the discussion say that our review of this ingredient is relevant to a hair dye and not to these other potential uses?

DR. BERGFELD: Well, as a woman, these shampoos with the color in them, I thought that these are a semi, non-oxidative product, usually layering the hair, temporary.

DR. MARKS: Yeah. And this is a non-oxidative hair dye. So actually, on the rinses, I didn't get concerned because, to me, you rinse and get a little color in there. So I didn't get an alert for that. I thought we could use just our standard hair dye conclusion. I don't think it changes our conclusion this is safe.

MS. FIUME: I guess, Jim, my concern was, with those other products, that there was a chance they were leave ons because they could be a type of spray sometimes when it says coloring product. So I just wanted to make sure that didn't get overlooked and either handled in the discussion or something in case it wasn't necessarily a rinse-off use.

DR. MARKS: Yeah.

DR. BERGFELD: But if it does absorb -- even if it layers and doesn't absorb, isn't that a level of safety? Lack of absorption.

DR. MARKS: Yeah. That's what I was going to say with Ron's reasoning right off the get-go of the lack of absorption. So that would be handled that way. Ron, is that --

DR. SHANK: Yeah.

DR. MARKS: -- did Wilma and I interpret what you said correctly?

DR. SHANK: Yes, you did.

DR. MARKS: Okay.

DR. PETERSON: So do you have to worry about the impurities in that case? And I don't know their safety, but I'm just asking. Because one impurity is the Basic Red 118, and that, you know, in Europe they have a -- I have they accepted it as an impurity.

DR. MARKS: Lisa, are you concerned about that impurity?

DR. PETERSON: I don't know if I'm -- I don't have enough information on it, but there is a report on it.

DR. SHANK: This is the first time we've seen this report. It wouldn't hurt to ask for impurities.

DR. PETERSON: Well, they do have the impurities are here.

DR. MARKS: I think what you're raising, Lisa -- are you concerned -- could these impurities -- are they at a concentration enough there starts to be toxicity from them?

DR. PETERSON: Right. Because I believe they've been reviewed by this panel before. There should be data on that. And I am sorry my notes aren't -- I should have made stronger notes.

DR. MARKS: That obviously will change what we would have --

DR. PETERSON: I think if it's leave on -- I mean that's why. I think if it's leave on, then it becomes a different -- you worry about the impurities more than if it's just rinse off --

DR. BERGFELD: So you need --

DR. PETERSON: **--** because I do believe the impurities are more penetrating. That's where I'm coming from.

DR. MARKS: Mm-hmm. Would you then rather -- I guess one tactic, Lisa, would be to issue an insufficient data announcement with the idea of -- I'm not sure that's the right thing -- more data on the impurities.

DR. PETERSON: Well, I think the data exists. Like I think -- I'm sorry. I can see how my note taking when I'm reviewing needs to shift with more detail because I have written in my notes that CIR has reviewed these impurities because they're additives in their own right.

DR. MARKS: I'll tell you what. Why don't we, between now and tomorrow, Lisa -- we're going to be seconding it tomorrow. If between now and tomorrow morning, if you could review those, and if the impurities are still an issue, why not bring it up tomorrow and we can proceed with that.

DR. PETERSON: Okay. I'll take a look at it.

DR. MARKS: Does that sound reasonable?

DR. PETERSON: Yeah. Sure.

DR. MARKS: Now, Tom, I haven't forgotten you. On the table now is seconding a tentative report with a safe conclusion. That's on the condition that, when Lisa looks up the impurities, there aren't any red flags there. Are you okay with that -- our team seconding that?

DR. SLAGA: Well, I know it's a hair dye. You know, if you look at the genotoxicity, all of the Ames assays were very positive. That has some concern to me because, you know, that is the greatest predictor -- the Ames. If you look at the battery of tests of Ames, they're all parts of it. It has over 80 percent relationship to carcinogenicity. Can you hear me?

DR. MARKS: Yeah. Kind of. So were you uncomfortable with a safe conclusion? Do you want more data?

DR. SLAGA: I know it's a hair dye. And we have accepted the genotoxic parts of the genotoxicity in the past. I understand that, but in this particular case, all the Ames cluster strands are positive in testing. And they even shifted dose responses. I have a little concern. I understand that hair dyes have a lot of (inaudible). To be carcinogenic, there would have to be a large amount of it.

DR. MARKS: Okay. So all that can be handled in the discussion.

DR. SLAGA: Right. Yeah.

DR. MARKS: Bottom line, did you think we could move forward with a safe, or do you think it should be unsafe or insufficient?

DR. SLAGA: I would rather go with insufficient until I had a little bit more time to look into the genotoxicity, which I'll do tonight.

DR. MARKS: Okay. I don't think Ron or Lisa -- go ahead, Wilma.

DR. BERGFELD: Well, I think there's another approach on the insufficiency is to go up to industry and say, "Define this group that is undefined in 'other' and define what the shampoos are."

DR. MARKS: That would still mean we'd do an insufficient data announcement.

DR. BERGFELD: Exactly, but we could do all of that at one time.

DR. MARKS: Oh, yeah. No, let me put that. So forget the tentative report. Ron Shank, we're going to change direction a little bit: insufficient data announcement. We want more use detail concerning non-hair dye uses.

DR. BERGFELD: Rinse off.

DR. MARKS: I think that captures it, doesn't it, Wilma?

DR. BERGFELD: Yep.

DR. MARKS: And we want to get a little bit more information on how it's being used as a non-hair. And Tom, you wanted more mutagenicity data?

DR. SLAGA: Well, if there is more genotox data, I would like to look at it.

DR. MARKS: Genotox, okay. And then I'll put in there, Tom, you want that. And then, Lisa, in some ways -- and I think if we're going to put in an insufficient data announcement, we obviously -- in the next rendition, we've got to include a discussion about that study that was just published you mentioned, Lisa, concerning the 2020 epidemiologic study. I suspect we need to discuss that more because it sounds pretty compelling.

The one thing that came to my mind as you were discussing it, you talked about blacks being more frequent in use. When frequency increases, potentially increase of breast cancer. I wonder also blacks -- they don't use a higher concentration of the dye than in nonwhites just because their hair is darker.

DR. PETERSON: Yeah. I mean it was sort of a complicated conclusion from the study, but, you know, there was a clear signal that held up. And it was related to use, and there were population differences in the outcomes.

DR. EISENMANN: If I remember correctly, there were some limitations to that study in that the shorter-term -- the shorter-term exposures had a greater risk than the longer term exposures, so it didn't really have much a dose response. My colleague will have more to say about it when we actually discuss it. Linda Loretz has looked into it a little bit more.

DR. PETERSON: Oh, okay. I mean, I knew that there were shortcomings, but sometimes -- yeah.

DR. EISENMANN: Well, it should be looked at. We agree that it should be looked at and discussed, but there were some shortcomings to the study.

DR. PETERSON: Yep. Yep.

DR. MARKS: Okay. Well, that changes things. So tomorrow, presumably, I'm doing to be seconding an insufficient data announcement. We want more use detail concerning non-hair dye uses. We want more details concerning non-hair dye uses of this ingredient, more genotox data. Tom, if they ask what you want, you can chime in -- and then review the recent 2020 hair epidemiology study. What journal was that in?

DR. PETERSON: It was The *International Journal of Cancer*, Volume 147, pages 383 to 391 and that was 2020.

DR. MARKS: Yeah. Okay. Any other comments?

DR. SLAGA: I'm good.

DR. MARKS: Ron Shank, is that okay with you?

DR. SHANK: Yeah. I'd like to see what the discussion's going to be tomorrow. We have 11 genotoxicity tests: half positive and half negative. So I don't know where that's going to go. I would say safe as used as a rinse-off hair coloring agent. But we can go -- this is the first time we're looking at it, so let's ask them to define what "other uses" means.

DR. MARKS: Although, I may mention that, Ron, tomorrow because, you know, I usually like to have potential anticipation where the Panel's going, particular our teams. So I think that we probably could -- Lisa, Tom could agree and I certainly would agree with you, Ron, that we could go with a tentative report with as safe as used as a hair coloring -- as a rinse-off you said?

DR. SHANK: Yes.

DR. MARKS: Rinse-off hair coloring agent -- and then, in the discussion, address the concerns about non-hair dye uses, but, of course, we've covered it in that conclusion. The genotox, Tom, I know you said you wanted more, but there's a fair number with some conflicting results, obviously. And then we will get the hair dye epi study. We'll certainly see that at the next review of this next rendition.

So we'll see what the Belsito team does. And then I think we've got it covered either way. It's going to either be an insufficient data announcement or a tentative report. And it may be what the conclusion a tentative report is. We'll have that discussion. Ron, I agree with you. It will be interesting to see how this goes tomorrow.

DR. SHANK: Right.

DR. MARKS: Let me see. Excuse me while I make a few notes here for a minute. I want to make sure I got this correct. I hate not to get -- tentative report safe.

Okay. Any other comments? That was a robust discussion. If not, we'll go on to the next ingredient.

Full Team Meeting – June 9, 2020

DR. BELSITO: Okay, so, the major issue that we had was the fact that it was used in other non-coloring hair products. So, we went safe as used, except insufficient for other non-coloring hair products. We will need concentration of use and data on the amine impurity, particularly nitrobenzene-1,4-diamine.

DR. MARKS: Second.

DR. BERGFELD: Second.

DR. PETERSON: May I interject? Dr. Belsito, I did a little search on the 2-nitrobenzene-1,4-diamine and that is also known as 2 nitro p phenylenediamine, which we have reviewed before.

DR. BELSITO: Okay. But, it's a hair dye, so, it's insufficient for other non-coloring hair products; we would need the concentration of use.

DR. MARKS: Yeah, our team basically comes to the same conclusion. We were concerned about non-hair dye uses also, and we just had the conclusion safe as use as a rinse-off hair coloring agent. But, Don, you're basically saying the same thing in a different way. So, if, I second your motion, Don; Lisa, Ron, Tom, is that fine with you?

DR. SHANK: Yes, fine with me.

DR. SLAGA: That's fine.

DR. PETERSON: It handles all my concerns.

DR. BELSITO: Safe as used as a hair dye, insufficient for non-coloring hair product use.

DR. MARKS: Yeah.

DR. BELSITO: What we would need is concentration of use.

DR. MARKS: Now, yesterday we had also discussed -- Tom, you've had a little bit more time, do you still want to see more genotox for the next rendition of this? This will go out as a tentative report then, correct?

DR. SLAGA: Correct. No, I just brought that up; it should be in the discussion. All the genotoxicity, with a battery of Ames tests, is positive that this is a hair dye, and I understand that. And, even though, if you go to the battery of Ames tests and they are all positive, it has the highest correlation to a carcinogenic effect. It's over 80 percent; no other thing comes close. It just brings some -- you know, we should discuss it so that people don't think that we're ignoring it.

If I had more bacterial-type of a comparison, we could go to the weight of evidence, so I'm just bringing that out as an issue. We've had this many times with hair dyes, in the past that they have some carcinogenic activity, mutagenic from the, you know, (inaudible).

DR. SHANK: There were several mutagenicity tests that were negative also.

DR. SLAGA: Mammalians. They were more clastogenic.

DR. BERGFELD: Curt, do you have a response?

DR. KLAASSEN: Well, I agree with Tom. In this committee we often talk about the bacterial test and the mammalian test. And maybe opposite of what one might think it's exactly what Tom said, is that the Ames tests, the bacterial test is -- much better correlates with mutagenicity than -- and carcinogenicity than does the mammalian test. So, when you have a number of Ames tests that are positive, it's of significant concern.

DR. BERGFELD: So what is the proposal here?

DR. SLAGA: My proposal is just we discuss it in the discussion so that it's brought out, that's all.

DR. BELSITO: And, so, we also had a lengthy discussion about the genotox and the very mixed results, and we pointed out that there's a lack of dermal absorption. And the SCCS, it's in our document, has looked at this and a margin of safety, assuming 50 percent absorption which this doesn't have; it's closer to zero absorption, even with 50 percent absorption the margin of safety would be 1,000. And, we put that in the discussion.

So, we did have a rather lengthy talk about the genotox and the mixed results. But we have that SCCS document in here that we can refer to and point out that they assumed 50 percent absorption (audio skip) it's much, much lower.

DR. SLAGA: (Inaudible) with you, Don.

DR. BERGFELD: Any other discussion? Jim?

DR. MARKS: Yes. Lisa pointed out yesterday a recent 2020 hair dye epidemiology study that was published in an *International Journal of Cancer, Volume 147*, beginning on Page 383. And, I know we update our hair dye epidemiology resource document, but I think the findings, Lisa, in that study are important to mention. And then, obviously, the epidemiology resource document is going to be updated, but I don't know if we should do more than just use our typical boilerplate language. Lisa, do you mind reviewing that study briefly?

DR. PETERSON: Oh, you're putting me on the spot because my (audio skip) stop working, I'm not going to get all the details right. But basically it was a very large study looking in at sister cohort, which is basically two sisters, one has breast cancer, one doesn't. And there was a signal for increased risk of breast cancer with high usage of hair

dyes. And, there was a difference between African American populations and white. And there was also an association with hair straighteners.

And I know that there are a lot of issues -- I mean, there are some concerns about this study, some shortcomings, I guess. You talked about, you know, it's a susceptible population first of all because there's an increased risk of breast cancer just by having a family member.

But I think there is a signal there that is concerning and needs to be followed up on. And I think somebody brought up yesterday that there's a difference between, you know, more recent use versus long-term use. And, I've been kind of thinking about that, and it could be a change in products that is causing the difference. I mean, we don't know; I just think there is a signal there. It was a huge study, so that sort of -- I don't know, it's something to be considered.

DR. MARKS: I think since this is going out as a tentative report that study can be delved into. And all the Panel members could get it and review it and be discussed in more detail the next time we see this.

DR. HELDRETH: Dr. Marks?

DR. MARKS: Yes.

DR. HELDRETH: So, just a couple things I wanted to add. Since this is a draft report, and we have an insufficiency, we can proceed -- we could actually put this out as an insufficient data announcement. And then, after the time period passes, CIR staff will present a draft tentative report to bring back to the Panel next time.

The other thing I wanted to mention is Jinqiu Zhu, our in-house staff toxicologist, who wrote the most recent epidemiology document, I think he has something to add here. Jinqiu, can you come on the line?

DR. ZHU: Yes, can you hear?

DR. HELDRETH: Yes.

DR. ZHU: Okay. So, Dr. Bergfeld forwarded this paper to us to late-early this year, right after it was published. So, note that there is also a commenter on this paper, published in the same journal, which raised the five issues. You know, major issues regarding the study design and the resulted justification.

And in addition, when asked if women should stop using the hair dye, the author of the paper answered that, "Where exposure too many things that could potentially contribute to breast cancer, and it is unlikely that any single factor explains a women's risk, where it's too early to make a firm recommendation." So, for us, I think we can definitely incorporate this new study into our resource document. But, I'm afraid that we cannot draw any conclusion based on this study at this moment.

DR. PETERSON: Yeah, I totally agree with all of that. You know, it's part of the data; you know, you put all the data together in here that I think you need to have. Again, if there's a signal there that needs to be followed up on. And, I think the author is right, to be very cautious about how you interpret it. But, I do think that when you see a signal it's something that just needs to call your attention to it.

DR. BELSITO: Sure.

DR. BERGFELD: Thank you, very much. Anything else to discuss before we sort of conclude the conclusion and vote on it?

DR. MARKS: Well, I'm not sure what the motion is now because Bart brings up a good point. I thought the motion, Don, you made was for a tentative report, but is it for an insufficient data announcement? And then, what's the insufficiency for the non-hair dye use?

DR. BELSITO: Concentration of use.

DR. BERGFELD: I thought the option was that it was safe as a hair dye, but insufficient for other uses.

DR. SHANK: Right.

DR. BERGFELD: Or is that just an option?

DR. BELSITO: It's safe as used for a hair dye, insufficient for non-coloring hair products, and the information that is needed is concentration of use.

And then, the question becomes -- and I think, Bart, we discussed this a little bit, perhaps you want to state more clearly what you said. I mean, the question is this, would this other use be in violation of FDA policy because it's not listed as an approved colorant. In which case it would be, you know, in violation of FDA regulations to use a non-approved colorant in a cosmetic. Am I quoting you correctly, Bart?

DR. HELDRETH: So, the first part is, yes, procedurally since this is a draft report and this is the first time that the Panel is making note of an insufficiency, this would proceed as an insufficient data announcement for the need that you requested.

If FDA would like to comment, I'm sure Dr. Katz is much more of an expert on this than I, but my understanding is that these other uses in hair products are not used as a colorant and therefore they're not going against FDA restrictions about unregistered colorants.

DR. BERGFELD: Linda Katz, are you there?

DR. KATZ: This is Linda. Can you hear me?

DR. BERGFELD: We can't hear you.

DR. KATZ: Can you hear me now?

DR. LIEBLER: No.

DR. BERGFELD: We still can't hear you.

DR. KATZ: I can try to call in separately on the call line, if that would work. I'm not sure if I can.

DR. KLAASSEN: We can actually hear you.

DR. KATZ: Can you hear me now?

DR. KLAASSEN: Yeah, just keep going.

DR. KATZ: Okay. The bottom line is that you're only (audio skip) a particular use. So that if something (audio skip).

MS. KOWCZ: She's breaking up.

DR. BELSITO: Linda, call in, we can't hear you.

DR. BERGFELD: We can't hear you, Linda.

DR. SNYDER: While Linda's calling in, Bart actually gave us two options that we could with a split conclusion, we're safe for hair dyes and coloring and insufficient for concentration of use for non-coloring. Or we could go with a single conclusion, saying that they were safe as used as long as the non-colorings were used at similar concentration.

DR. BERGFELD: You said Linda said that, or Bart said that?

DR. SNYDER: Bart.

DR. BERGFELD: Are we waiting for Linda?

DR. BELSITO: Yes.

DR. BERGFELD: Bart, Linda's on the phone?

DR. HELDRETH: Yeah, I'm not seeing her trying to connect yet. All right, here comes a number that's maybe her.

DR. KATZ: Can you hear me now?

DR. BERGFELD: Yes.

DR. KATZ: All right. The bottom line is -- I'm getting a lot of echoing.

MS. KOWCZ: Mute your computer.

DR. KATZ: I am muting; this is just not working very well.

DR. BERGFELD: We can hear you.

DR. KATZ: Okay. The bottom line is that you're only supposed to use a color for which it is approved. If you look in the regulations it will state which color can be approved for which types of indication. If the intent is to impart any color, and it has not been approved for that indication, it cannot be used. Does that answer the question?

DR. BERGFELD: Yes.

DR. KLAASSEN: Yep.

DR. BERGFELD: Thank you.

DR. KATZ: Okay.

DR. BERGFELD: All right. Don, since this is your ingredient, can you propose? You've had a motion of -- let's have you restate it.

DR. BELSITO: Well, I guess the major question is, as Bart said, it's not clear that these non-colorings, I mean, it's posed as non-coloring, so it presumably has some function other than color. I can't imagine what that is, but we don't know. You know, it's used in non-coloring hair products. Is it used to impart a color to those non-coloring hair products, or is it used for some other function?

So, it's insufficient, I guess, I would add for concentration of use and function of use in non-coloring hair products.

DR. BERGFELD: So the dye is safe, but the added ingredient -- or added use, we need more information.

DR. BELSITO: Right, concentration of use and purpose or function of use in a product. If it's used to impart a color, then it violates FDA regulations; it's not a registered color. If it's used for lord knows what, then we have to look at the safety data, but we don't know.

DR. BERGFELD: Okay. And, Jim Marks are you seconding that motion?

DR. MARKS: Yes, second.

DR. BERGFELD: Okay. Any other discussion regarding the safety and the needs, and the insufficient portion?

DR. BELSITO: Just that genotox discussion in our discussion as I mentioned before.

DR. BERGFELD: Genotox and the absorption, like (inaudible).

DR. BELSITO: Yes.

DR. BERGFELD: Okay, I'm going to call the question then, all those in favor of this report and conclusion? Any opposed? It'll be unanimous. All right, good discussion.

DECEMBER 2020 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Safety Assessment of Basic Brown 17 as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 13, 2020
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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel member involved in this assessment: James G. Marks, Jr., M.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer, CIR.

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DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Basic Brown 17, which is reported to function as a hair dye in cosmetic products. The Panel reviewed the available data to determine the safety of this ingredient. The Panel concluded that…TBD.

INTRODUCTION

Basic Brown 17 is reported to function as a non-oxidative hair dye in cosmetic products, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*).[1] 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 exhaustive search of the world's literature. 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 Expert Panel for Cosmetic Ingredient Safety (Panel) typically evaluates, is provided on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties. It should be noted that the European Commission's Scientific Committee on Consumer Products (SCCP), now known as the Scientific Committee on Consumer Safety (SCCS), has produced several opinions from which CIR has summarized data.[2-5] Only the most recent version (which also contains data from the 2008 and 2012 opinions) and the 2004 opinion (which has data not reported in the more recent versions because the material studied was either of an unknown purity or a lower purity than the material used in the more recent studies) are cited in this report.

CHEMISTRY

Definition

Basic Brown 17 (CAS No. 68391-32-2) is the monoazo color that conforms to the structure in Figure 1.[1] It is reported to function as a direct, non-oxidative hair dye in hair coloring products.[2,3]

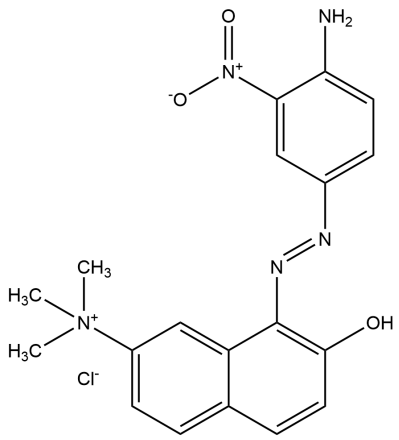

Figure 1.

Chemical Properties

Available chemical properties of Basic Brown 17 are provided in Table 1.[3,6] Basic Brown 17 is a dark brown fine powder with a formula weight of 401.85 Da (as the chloride) and an octanol/water partitioning coefficient of 2.73 at 25°C.

Method of Manufacture

No methods of manufacture were found in the public literature, and unpublished data were not provided.

Composition/Impurities

Impurities of Basic Brown 17 may include 2-nitrobenzene-1,4-diamine (also known as 2-nitro-*p*-phenylenediamine, another hair dye ingredient; < 250 ppm), Basic Red 118 (a 2-nitro isomer of Basic Brown 17; < 4.5% w/w), and 7-hydroxy-*N,N,N*-trimethylnaphthalene-2-aminium chloride (NBTRI; < 1% w/w).[3] A tradename mixture containing Basic Brown 17 may also contain saccharose to adjust color strength in formulation to a certain predefined value.

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 this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2020 VCRP survey data, Basic Brown 17 is used in a total of 54 formulations. Of these reported uses, 3 are in non-coloring hair products (specifically a shampoo, a conditioner, and an "other" non-coloring hair product) and the remaining 51 are in coloring hair products (specifically 5 in hair dyes and colors, 22 in coloring rinses, 14 in coloring shampoos, and 10 in "other" coloring hair products).[7] The results of the concentration of use survey conducted by the Council in 2019 indicate that Basic Brown 17 is used at up to 0.66% in hair dyes and colors, up to 0.065% in coloring shampoos, and up to 0.19% in "other" hair coloring products.[8]

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. 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. 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.

In 2012, a report was published regarding such self-testing for contact sensitization to hair dyes.[9] These authors concluded that, in its present form, the hair dye self-test has severe limitations. The authors issued the warning that, if the use of a hair dye self-test to predict contact sensitization becomes widespread, there is severe risk that a tool has been marketed that may cause morbidity in European consumers. An accompanying editorial performed on behalf of the European Society of Contact Dermatitis (ESCD) asserted that industry is focusing on predicting the risks from exposure to hair dyes by having millions of European consumers perform a self-test prior to each hair dying and stated that it is the opinion of the ESCD that attention must be given to reducing the risks of serious allergic reactions by improving the safety of the products themselves.[10]

In the European Union, Basic Brown 17 is restricted to use only in non-oxidative hair dye products at a maximum concentration of 2.0% in ready for use preparations.[11] The European Scientific Committee on Consumer Safety (SCCS), in 2014, concluded that Basic Brown 17 is safe for use in non-oxidative hair dye formulations with a maximum concentration of 2.0%, apart from possible sensitization potential.[3] Basic Brown 17 might contain up to 4.5% (w/w) Basic Red 118; Basic Red 118 is not permitted for use in cosmetics in Europe except as an impurity in Basic Brown 17 when used as a substance in hair dye products.

TOXICOKINETIC STUDIES

Dermal Penetration

Animal

The percutaneous penetration/dermal absorption potential of Basic Brown 17 (> 94% pure) was investigated in excised pig skin that was dermatomed to 400 μm thickness.[12] The test material was studied in an aqueous solution with methanol (1:1; 10 μl/cm^2) and in a representative standard formulation (10 mg/cm^2) in which the concentration of Basic Brown 17 was 2%. The receptor solution was physiological saline and ethanol (75:25), and the exposure area of the skin disks was 2.54 cm^2. Exposure was terminated by washing of the skin surface 30 minutes after application, and the receptor fluid was analyzed at defined intervals for up to 48 h post application. The majority of the applied test material was found in the terminal rinse 30 minutes after exposure (87.7% for aqueous solution and 90.9% for standard formulation). The percutaneous penetration of Basic Brown 17 was below detection limits (0.094%) for both the aqueous solution and the standard formulation. The penetration rate was < 0.004 μg/cm^2/h. Approximately < 0.11% of the aqueous solution and < 0.16% of the standard formulation were described as bioavailable in this study.

The dermal absorption of Basic Brown 17 (77.4% pure) in a hair dye formulation at 2.0% w/w was studied in excised dermatomed pig skin.[3] The hair dye formulation (21.18 mg/cm^2, equivalent to 20 mg/cm^{2}of the test article) was applied to skin from 2 male and 2 female pigs. The skin samples were then mounted into static diffusion cells (10 replicates) containing

sodium chloride (0.9% w/v) in the receptor chamber. The receptor fluid was collected at 0.5, 1, 2, 4, 6, and 24 h post-dosing. At 30 min and 24 h post-dosing, the skin surface was washed with a dilute shampoo solution and water. The skin was then removed from the static diffusion cells at 24 h, dried, and the stratum corneum was removed with 20 successive tape strips. After 24 h, the dermal bioavailability of Basic Brown 17 following topical application to pig skin was 0.48% (1.62 µg/cm^2) of the applied dose. The majority of the dose was removed by washing the skin.

Human

In a human dermal absorption study with10 male subjects, applications of 20 µl of 1 mM Basic Brown 17 in 40% aqueous isopropanol were made on 5 separate skin areas (5.3 cm^2) of the inner forearm (equivalent to about 1.5 µg/cm^2).[2] After 10 min and 24, 48, and 72 h, the test sites were subjected to 10 repeated tape strippings. During the intervals between sampling, the skin areas were protected by a special non-occlusive cover. The stripping-tapes were glued on white cardboard and kept in the dark until they were evaluated by densitometry. From the recovery rates, the amount of the test material that could possibly have penetrated the skin was estimated (details not provided). No test material was observed in the "horny layer" (stratum corneum). It was therefore concluded that Basic Brown 17 was not absorbed through the skin.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Basic Brown 17 (no vehicle; purity not reported) was studied in male and female Sprague Dawley rats.[6] Five male and 5 female rats received the test material on shaved skin at a dose of 2000 mg/kg bw. No signs of toxicity and mortality were noted during a 14-d observation period. The animals exhibited normal body weight gain through the study period of 14 d, and no abnormalities related to treatment were observed during gross pathological examination. The acute dermal LD_{50} of Basic Brown 17 was greater than 2000 mg/kg bw.

Oral

In an acute oral toxicity study, CF1 mice received Basic Brown 17 (purity not reported) once by gavage at three dose levels up to 5000 mg/kg bw, at a volume of 0.2 ml/10 g bw.[2] All animals were observed for a period of 7 d. During the observation period, no mortalities were recorded. The LD_{50} was reported to be greater than 5000 mg/kg bw in mice.

The acute oral toxicity of Basic Brown 17 (purity not reported) was studied in female Sprague Dawley rats.[6] Groups of 6 animals received Basic Brown 17 in distilled water at doses of 300 or 2000 mg/kg bw. No signs of toxicity or mortality were observed in any of the treated animals. Gross pathological examination did not reveal any abnormalities in any of the test animals. The acute oral LD_{50} of Basic Brown 17 was greater than 2000 mg/kg bw in rats.

In another acute oral study, the toxicity of Basic Brown 17 (purity not reported) was studied in groups of 4 male and 4 female CFY rats.[3] The rats received 0, 100, 1000, 4000, 8000, or 16,000 mg/kg bw Basic Brown 17 in 1% aqueous methylcellulose in a volume of 1 – 40 ml/kg bw. Clinical signs of toxicity observed during the 14 d after dosing were lethargy, piloerection, decreased respiratory rate, and hunched posture. Two male rats and 1 female rat in the 16,000 mg/kg bw dose group died. The LD_{50} in this study was determined to be between 8000 and 16,000 mg/kg bw.

Subchronic Toxicity Studies

Oral

In a 90-d feeding study, groups of 10 female CF1 mice received 1250, 2500, or 5000 mg/kg of Basic Brown 17 (purity not reported) mixed with diet.[2] A control group of 20 animals received untreated feed. All mice, with the exception of one animal in the highest group (5000 mg/kg), survived the treatment period. No changes in behavior were noted in the test group animals when compared to the controls. Feed intake and the results of hematological and biochemical tests were also comparable to controls. A decrease in body weight gains was observed in all treated groups, but based on a graphical presentation in data submitted to the SCCP, the reductions in body weight were not considered to be dose-related. No differences were observed in absolute or relative organ weights between control and treated animals. Yellow-brown urine was noted in all treated animals, which indicated gastrointestinal absorption of the test material. A yellow-brown discoloration of the stomach and intestines were observed macroscopically, and fatty infiltration of the liver and slight hemosiderosis in the spleen was noted in all the treated animals. It was concluded that dietary administration of 1250 mg/kg/d Basic Brown 17 was borderline for possible toxic effects in mice.

The potential adverse effects of Basic Brown 17 (77.4% pure) was investigated in a 90-d oral toxicity study in Wistar Hannover rats.[3] The study was performed in accordance with Organization for Economic Co-operation and Development (OECD) test guideline (TG) 408. Groups of 10 male and 10 female rats received 0, 60, 120, or 180 mg/kg/d of the test material in distilled water via gavage at 10 ml/kg bw. An extra 5 animals per sex were used for the control and high dose groups to assess recovery for 4 wk after the treatment period concluded. Two high dose males and 1 high dose female died during the treatment period. A necropsy of these animals found incomplete lung collapse in the female, with both lungs and the thymus dark/red in color. The necropsy of the males found the lungs, thymus, spleen, and thyroid dark/red in color, and

one had irregularities of the heart, liver, and prostate. No treatment-related changes in body weight gains and feed consumption were observed at up to 180 mg/kg/d. No clinical signs of toxicity were observed in any of the treated animals. No significant hematological changes were noted during the study. Moderate to marked alteration in aspartate aminotransferase was reported in 3 females and 3 males in the high dose group and in 2 females in the mid-dose group. Significantly raised gamma-glutamyl transferase, cholesterol, triglycerides, glucose levels, and lowered sodium were observed in the high dose group, but these parameters were similar to the controls at the end of the recovery period. Some of the high dose animals exhibited bilirubinuria, which was attributed to either the test substance or its metabolites found in the urine.

Necropsy of the treated animals found dark coloration in the brain, heart, kidneys, ovaries, skeletal muscle, spleen, and thyroid in the high dose rats, with the females more affected than the males. In the mid-dose group, both sexes had dark coloration of the spleen and thyroid, with some females exhibiting dark coloration in the heart and skeletal muscle. These effects were present after 4 wk of recovery. Yellow/brown pigmentation was observed in the heart, kidneys, liver, spleen, thyroid, Peyer's patches, and skeletal muscle of animals of both sexes that received $\geq$ 120 mg/kg bw/d when compared to controls. Yellow/brown pigmented macrophages were also observed in the lungs of females receiving $\geq$ 120 mg/kg bw/d. Males and females in the 180 mg/kg bw/d dose group and the recovery high dose group had yellow/brown pigmentation in the adrenals, ovaries, uterus, mesenteric/cervical lymph nodes and thymus. An increased incidence of extramedullary hemopoiesis in the spleen in all treated groups was observed. Absolute and relative thyroid weights were lower than the controls in females in the high dose group at the end of the recovery period; this group also had relative liver weights that were higher than controls. The no-observed-adverse-effect-level (NOAEL) for Basic Brown 17 (77.4% pure) in this study was calculated to be 46 mg/kg/d.[3]

In a 15-wk study, Basic Brown 17 (68% as chloride; dissolved in water) was administered 5 d/wk, by gavage, to 3 groups of 10 male and 10 female Sprague Dawley rats at doses of 50, 150, and 450 mg/kg bw.[2] Another group of 10 male and 10 female rats was given vehicle alone, and served as the control group. No adverse effects or mortalities occurred at doses of 50 or 150 mg/kg bw. Mortalities occurred at 450 mg/kg bw, either following general or central nervous system signs of toxicity, or without previous abnormal observations. Histological examination of the liver revealed individual pigment inclusions within Kupffer cells of some female rats given 50 mg/kg bw. At 150 mg/kg bw, deposits were seen in a number of tissues, but there were no accompanying degenerative or inflammatory changes. Examination of recovery groups (details not provided), maintained for a further 7 wk without treatment, showed that the deposits were persistent at 150 and 450 mg/kg bw/d, but not at 50 mg/kg bw/d. The NOAEL of this study was determined to be 150 mg/kg bw/d, and the no-observed-effect-level (NOEL) was determined to be 50 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES

Oral

In an oral teratogenicity study of Basic Brown 17 (77.4% pure), groups of 25 female Wistar HsdBrlHan rats received the test material in distilled water via gavage at doses of 0, 60, 120, or 240 mg/kg bw/d on day 5 through day 19 of gestation.[3] The animals were checked daily for clinical signs of toxicity, abortions, premature deliveries, and mortalities. Body weights and feed consumption were determined at periodic intervals throughout the study. All animals surviving to day 20 of gestation were necropsied, and fetuses were removed and studied.

One female died in the high dose group on gestation day 11. A macroscopic examination found enlarged adrenals, abnormal swollen intestinal tract content, and a dark color of the liver and spleen. In the remaining dams, scabs and hair loss were observed in the treated females, and occasionally in the controls. Abrasion and aggressive behavior were noted in 2 high dose females on gestation days 19 and 20, respectively. Dyspnea was observed in 1 low dose female on gestation day 7. No other adverse reactions to treatment were noted in the daily observations. Statistically significant reductions in body weights gains and feed consumption were noted in the high dose group on days 9 and 12, when compared to controls. Statistically significantly lower terminal body weight and absolute weight gain were observed in the high dose group when compared with the controls. Gravid uterus weights were not affected by the treatment. At necropsy, the spleen was dark and occasionally swollen in the high dose group, which was likely due to the color of the test material. Mean values for corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, fetal body weights, percent resorbed conceptuses, and percent live male fetuses were similar to the controls. There were no dead fetuses. Small fetuses (total of 13) were observed in the control (4), low dose (3), mid-dose (5), and high dose (1) groups. One mid-dose fetus had enlarged brain ventricles; this effect was considered incidental. No other adverse effects considered to be treatment-related were observed in the fetuses. For the test material, the maternal NOAEL was considered to be 120 mg/kg bw/d and the fetal NOAEL was > 240 mg/kg bw/d; when taking into account the purity of the test material, the NOAELs were 93 mg/kg bw/d and > 186 mg/kg bw/d, respectively.[3]

In another oral teratogenicity study, a group of 24 pregnant Sprague-Dawley CD rats received 50 mg/kg Basic Brown 17 (68% as chloride) via gavage daily on days 6 to 15 of gestation.[2] A control group of 26 rats received the vehicle alone (distilled water). On gestation day 20, the rats were killed and Caesarean sections were performed. The number of implantation sites, resorptions, living fetuses, and the number of corpora lutea were counted in each litter. The weights of the

placenta, uterus, fetuses, and dams, and the sex of the fetuses, were recorded. About one third of each litter was prepared and examined for soft tissue anomalies. The remaining fetuses were examined for skeletal abnormalities. The body weight gains were determined for each dam. No mortalities were reported in the dams. No differences in mean body weight gain were seen during the course of gestation in any group. There were no treatment-related effects concerning reproduction data or malformations of the fetuses. The level of skeletal variation or ossification in the test and control group was comparable. Basic Brown 17 was not considered teratogenic in rats at a dose of 50 mg/kg bw/d.

GENOTOXICITY STUDIES

In vitro and in vivo genotoxicity studies on Basic Brown 17 summarized here are detailed in Table 2. Genotoxicity was observed in Ames tests, a micronucleus test in human hepatoma (HepG2) cells, and in a comet assay in HepG2 cells.[2,3,6,13] Test results were negative for genotoxicity in mouse lymphoma assays (*tk* and *hprt* loci), a micronucleus test in Chinese hamster V79 cells, and a comet assay in reconstructed human skin tissue.[3] Basic Brown 17 was not clastogenic and/or aneugenic in a mouse erythrocyte micronucleus assay when tested at 5000 mg/kg bw via gavage.[2]

CARCINOGENICITY STUDIES

No carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

The dermal irritation potential of Basic Brown 17 (no vehicle; purity not reported) was assessed using 5 male and 5 female Sprague Dawley rats.[6] The test material was applied at 2000 mg/kg bw to shaved skin under an occlusive patch for 24 h. No signs of skin reactions were noted in a 14-d observation period. The test material produced a primary irritation index of 0.0 and was classified as non-irritating.

In a primary skin irritation/corrosion study, 3 male New Zealand White rabbits received 0.5 g of Basic Brown 17 (96.3% pure) moistened in water on shaved skin for 4 h under semi-occlusive patches.[3,6] The study was carried out in accordance with OECD TG 404. Observations were made 1, 24, 48, and 72 h after exposure. Very slight erythema and/or very slight edema and/or slight edema were observed on the treated areas, which resolved within 48 h. Yellow-brown staining of the treated skin by the test material was noted throughout the observation period. The study authors considered Basic Brown 17 to be not irritating in this study.

In a dermal irritation study performed in accordance with OECD TG 404, 100% Basic Brown 17 was applied undiluted (0.5 g/in^2) to shaved intact or scarified skin on the back of 6 albino rabbits of each sex.[2] The test site was covered by a linen cloth and plastic foil and left in place for 24 h. Readings were made upon removal of the test material, and then daily for the following 14 d. No irritation was observed.

Sensitization

Animal

The sensitization potential of Basic Brown 17 (purity = 77.4% by nuclear magnetic resonance spectroscopy (NMR)) was assessed in a local lymph node assay (LLNA) in 5 groups of 4 female mice.[3,6] The mice received the test material daily at concentrations of 0.2%, 0.5%, 1%, 3%, or 6% (w/v) in ethanol/water (7/3; v/v) by topical application to the dorsum of each ear lobe for 3 consecutive days. Two negative control groups, each of 4 female mice, were treated with the vehicle (ethanol/water (7/3; v/v)) only. Three positive control groups of 4 mice each were treated with 5%, 10%, and 25% (w/v) α-hexylcinnamaldehyde in acetone:olive oil (4:1, v/v) in a separate study. All treated animals survived the treatment period. No clinical signs of toxicity were observed in any animals of the control groups, the 0.2%, the 0.5%, or the 1% dose groups. On the third application day, slight erythema was observed at both dosing sites in all the mice of the 3% dose group. In the 6% dose group starting the second application day, moderate or slight erythema was observed at both dosing sites in all mice, persisting for the remainder of the in-life phase of the study. The stimulation indices (SI) for the 0.2%, 0.5%, 1%, 3%, and 6% dose groups were 1.0, 1.0, 1.3, 0.9, and 1.3, respectively. In the positive controls, the SI for 5%, 10%, and 25% were 2.4, 3.6, and 11.2, respectively. Effects noted in the 3% and 6% dose groups were determined to be due to irritation and not allergenic sensitization. The authors of the study concluded that Basic Brown 17 was not a sensitizer.[3,6]

In another LLNA performed in manner similar to that described above, 3 groups of 4 female mice received 1%, 5%, or 25% Basic Brown 17 (purity > 94%) topically.[2] The SI were 0.6, 0.7, and 1, respectively. A control group of 4 mice received water. It was concluded that Basic Brown 17 was not a sensitizer.

In a guinea pig maximization study, 10 female Dunkin-Hartley guinea pigs received Basic Brown 17 (purity not reported) in water at 0.1% w/v and as a 1:1 mixture with a solution Freund's complete adjuvant in water during intradermal induction (0.1 ml), 75% w/v during topical induction (0.4 ml; occluded for 48 h), and 25% w/v in distilled water during topical challenge (0.1 ml).[2] Reactions consisting of erythema with slight edema were observed on the skin of 7 animals. To

further evaluate the reactions, a second topical application was made 1 wk later using 0.1 ml of Basic Brown 17 at a concentration of 5% in distilled water. Erythema was observed on the skin of 2 animals at 24 h (only), and at 48 h (only) in a third animal. The authors of the study did not consider the test material sensitizing despite the observed reactions. In 2004, the SCCP determined that this study is inadequate due to the intradermal induction concentration being too low.

OCULAR IRRITATION STUDIES

In Vitro

The ocular irritation potential of Basic Brown 17 (purity not reported) was determined by the MatTek EpiOcular™ model in accordance with OECD TG 492.[6] Tissues were exposed to the test material (neat) and positive and negative controls (sterile ultrapure water and methyl acetate, respectively) for 30 min. The exposure was followed by a 12-min post-soak and approximately 2 h recovery after the post-soak. The viability of each tissue was determined by a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Basic Brown 17 was predicted to be non-irritating to eyes.

Animal

The ocular irritation/corrosion potential of Basic Brown 17 (no vehicle; 96.3% pure by high-performance liquid chromatography (HPLC)) was assessed using 3 male New Zealand White rabbits in accordance with OECD TG 405.[3,6] A single instillation of the test material (45 mg or approximately 0.1 ml) to unrinsed eyes resulted in effects on the iris in 2 animals and on the conjunctivae in all 3 animals. Iridial irritation grade 1 was observed, and resolved within 24 or 72 h. Irritation of the conjunctivae consisted of redness, chemosis, and discharge, which resolved within 7 d in all animals. Remnants of the test material were present on the outside of the eyelids 24 and 48 h after instillation in 1 animal. Yellow-brown staining on the fur caused by the test substance was noted. The study authors considered Basic Brown 17 to be non-irritating in this study.

In another ocular irritation study in rabbits, 0.1 ml of a 0.5 % (w/v) Basic Brown 17 in saline solution was instilled into the conjunctival sac of the left eye of each of 3 male and 3 female New Zealand White rabbits.[2] The right eye was treated with 0.1 ml of the vehicle and served as a control. The test material was not rinsed out. Reactions were read 30 and 60 min and 1 and 2 d following instillation of the test material, and were evaluated by the Draize method. Discoloration of the conjunctivae by the test substance was noted. No effects were observed to the cornea or the iris of any of the animals.

CLINICAL STUDIES

Case Report

A 57-year-old woman presented with eczema of the hands and feet.[14] The patient was a former hairdresser that still occasionally performed hair care services. The patient reported that she had a history of severe itching on the hands and in the ears, accompanied with a “bad taste” in the mouth, following use of a brand-name hair dye containing Basic Brown 17. Previous patch tests were positive for *p*-phenylenediamine, nickel, chromium, cobalt, and colophonium. The patient was patch tested again and had positive reactions to *p*-toluenediamine, methyldibromo glutaronitrile, and several extracts of a “hypoallergenic leather.” Skin prick testing was performed with the brand-name hair dye and its ingredients. Strong positive reactions were observed within 15 min to the hair dye and to Basic Brown 17 (1% aq.; ++ reaction). Repeated testing 2 mo later with just Basic Brown 17 resulted in another ++ reaction.

MARGIN OF SAFETY

The SCCS calculated the margin of safety for a hair dye (non-oxidative) containing 2% Basic Brown 17 (on-head concentration) to be 1000.[3] This calculation is based on an adjusted NOAEL of 23 mg/kg bw/d (46 mg/kg bw/d with a bioavailability of 50%) and a systemic exposure dose (SED) of 0.023 mg/kg bw (skin area surface of 580 cm^2 x absorption through skin of 2.37 $\mu g/cm^2$ x 0.001/typical human bw of 60 kg).

HAIR DYE EPIDEMIOLOGY

Hair dyes may be broadly grouped into oxidative (permanent) and direct (semi-permanent) hair dyes. The oxidative dyes consist of precursors mixed with developers to produce color, while direct hair dyes are a preformed color. Basic Brown 17 is a direct, non-oxidative hair dye ingredient. While the safety of individual hair dye ingredients is not addressed in epidemiology studies that seek to determine links, if any, between hair dye use and disease, such studies do provide broad information. The Panel determined that the available hair dye epidemiology data do not provide sufficient evidence for a causal relationship between personal hair dye use and cancer. A detailed summary of the available hair dye epidemiology data is available at https://www.cir-safety.org/cir-findings.

SUMMARY

Basic Brown 17 is reported to function as a hair dye in cosmetic products. According to 2020 VCRP survey data, Basic Brown 17 is used in a total of 54 formulations. Of these reported uses, 3 are in non-coloring hair products (specifically a

shampoo, a conditioner, and an "other" non-coloring hair product), and the remaining 48 are in coloring hair products (specifically 5 in hair dyes and colors, 22 in coloring rinses, 14 in coloring shampoos, and 10 in "other" coloring hair products). The results of the concentration of use survey conducted by the Council in 2019 indicate that Basic Brown 17 is used at maximum concentrations of up to 0.66% in hair dyes and colors, up to 0.065% in coloring shampoos, and up to 0.19% in "other" hair coloring products.

In dermal penetration studies of Basic Brown 17 (2%) in excised dermatomed pig skin, 0.11% of the aqueous test material and 0.066% of the representative formulation was absorbed in one study, and 0.48% of the formulation was absorbed in another study. In a human dermal absorption study, Basic Brown 17 was not absorbed through the skin when 1 mM of the material in 40% aqueous isopropanol was tested.

The acute dermal LD_{50} of Basic Brown 17 in rats was greater than 2000 mg/kg bw. The acute oral LD_{50} of Basic Brown 17 in mice was greater than 5000 mg/kg bw and in rats was between 8000 and 16,000 mg/kg bw.

In a 90-d feeding study in mice that received 1250, 2500, or 5000 mg/kg Basic Brown 17, a decrease in body weight gains and fatty infiltration of the liver and slight hemosiderosis of the spleen was observed in all treatment groups. The decrease in body weight gains was not dose-related. The NOAEL for Basic Brown 17 (77.4% pure) was 46 mg/kg/d in a 90-d oral toxicity study in rats. Adverse effects included an increased incidence of extramedullary hemopoiesis in the spleen in all treated groups. Absolute and relative thyroid weights were lower than the controls in females in the high dose group at the end of the recovery period; this group also had relative liver weights that were higher than controls. In a 15-wk study in rats, the NOAEL of Basic Brown 17 (68% as chloride) was determined to be 150 mg/kg bw/d and the NOEL was determined to be 50 mg/kg bw/d (the lowest dose tested).

In an oral teratogenicity study of Basic Brown 17 (77.4%), the maternal NOAEL was 120 mg/kg/d and the fetal NOAEL was > 240 mg/kg/d, which was corrected to 93 mg/kg/d and > 186 mg/kg bw/d when accounting for the purity of the test material. Maternal effects included a statistically significant lower terminal body weight and absolute weight gain and swollen spleens in the high dose group. In another oral teratogenicity study in rats, Basic Brown 17 (68% as chloride) did not produce adverse developmental effects when tested at 50 mg/kg bw/d.

Genotoxicity was observed in Ames tests, a micronucleus test in HepG2 cells, and in a comet assay in HepG2 cells. Test results were negative for genotoxicity in mouse lymphoma assays (*tk* and *hprt* loci), a micronucleus test in Chinese hamster V79 cells, and a comet assay in reconstructed human skin tissue. Basic Brown 17 was not clastogenic and/or aneugenic in a mouse erythrocyte micronucleus test when tested at 5000 mg/kg bw by gavage.

In dermal irritation studies in rats and rabbits, Basic Brown 17 (96.3% pure) was not irritating. Basic Brown 17 (purity > 94%) at up to 25% was not sensitizing in LLNA studies in mice. Basic Brown 17 was predicted to be non-irritating to human eyes in an EpiOcular™ study, and it was not irritating in rabbit eyes when the test material was tested neat or at 0.5% in saline solution.

A case study was reported in a former hairdresser that had eczema of the hands and feet following exposure to a hair dye containing Basic Brown 17. Skin prick test were positive for the hair dye and Basic Brown 17 (1% aq.).

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

No method of manufacturing or carcinogenicity studies were found in the published literature, and unpublished data were not submitted.

DRAFT DISCUSSION

[Please note, this discussion is in draft form and will be modified following the meeting.]

Basic Brown 17 is reported to function as a direct, non-oxidative hair dye in hair coloring products. The Panel recognizes that hair dyes containing this ingredient, as coal tar hair dye products, are exempt from certain adulteration and color additive provisions of the Federal Food, Drug, and Cosmetic Act, when the label bears a caution statement and patch test instructions for determining whether the product causes skin irritation. The Panel expects that following this procedure will identify prospective individuals who would have an irritation/sensitization reaction and allow them to avoid significant exposures. The Panel considered concerns that such self-testing might induce sensitization, but agreed that there was not a sufficient basis for changing this advice to consumers at this time.

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

The Panel expressed concern over the mixed results in the genotoxicity studies and the lack of carcinogenicity studies. However, the Panel noted that the toxicokinetic studies show that Basic Brown 17 does not absorb through the skin and a that

a conservative margin of safety calculation yielded a result of 1000. These findings, coupled with the short exposure time as a rinse-off product, helped mitigate the Panel's concern.

Remaining discussion to be determined…

CONCLUSION

To be determined…

TABLES

Table 1. Chemical properties for Basic Brown 17

Property	Value	Reference
Physical Form	Dark brown fine powder	[3]
Formula Weight (g/mol; as chloride salt)	401.85	[3]
Vapor Pressure (mmHg at 25°C)	0	[6]
Melting Point (°C)	200 - 202	[3]
Boiling Point (°C at 729.9 mmHg)	> 240	[6]
Water Solubility (g/l at 20°C and pH = 5.6)	16.1	[3]
log $P_{o/w}$ (temperature not given)	-0.1466	[3]
(at 25°C)	2.73	[6]
λ_{max} (nm)	216, 462	[3]

Table 2. Genotoxicity studies

Concentration/Dose/Vehicle	Species/Strain/Cell	Method	Results	Reference
In Vitro				
3-5000 µg/plate in deionized water or dimethyl sulfoxide (DMSO); purity = 77.4% (NMR)	*Salmonella typhimurium* strains TA 98, TA 100, TA 102, TA 1535, and TA 1537, with and without metabolic activation	Ames test; positive and negative controls were in accordance with OECD TG 471	Mutagenic; a substantial and dose-dependent increase in revertant colony numbers was observed following treatment in strains TA 98 and TA1537, with and without metabolic activation	[3,6]
4-5000 µg/plate in DMSO; purity = 68% as chloride	*S. typhimurium* strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538; with and without metabolic activation	Ames test, in accordance with OECD TG 471; appropriate positive and negative controls were used	Mutagenic; dose-related relevant increase in revertant numbers observed in strains TA 98, TA 100, TA 1537, and TA 1538, with and without metabolic activation	[2]
Experiment I: 8.1-97.5 µg/ml without metabolic activation and 16.3-198.0 µg/ml with metabolic activation Experiment II: 8.0-192.0 µg/ml without metabolic activation Tested in deionized water; purity = 77.4% (NMR)	L5178Y mouse lymphoma cells	Mouse lymphoma assay (*tk* locus), in accordance with OECD TG 476; appropriate positive and negative controls were used	Not mutagenic; no biologically-relevant and concentration dependent increase in the number of mutant colonies was observed with either experiment, with or without metabolic activation	[3]
Experiment I: 3.1-99.2 µg/ml without metabolic activation and 6.2-198.4 µg/ml with metabolic activation Experiment II: 3.1-49.6 µg/ml without metabolic activation and 3.1-99.2 µg/ml with metabolic activation Tested in deionized water; purity = 98.7% (area by HPLC)	L5178Y mouse lymphoma cells	Mouse lymphoma assay (*hprt* locus), in accordance with OECD TG 476; appropriate positive and negative controls were used	Not mutagenic; no biologically-relevant increase of mutant frequency was observed in either experiment, with or without metabolic activation	[3]
Experiment I: 31.3-4100.0 µg/ml without metabolic activation and 128.1-2050.0 µg/ml with metabolic activation Experiment II: 100.0-512.2 µg/ml without metabolic activation and 128.1-1025.0 µg/ml with metabolic activation Tested in deionized water; purity = 77.4% (NMR)	Chinese hamster V79 cells	Micronucleus test in accordance with OECD TG 487 (draft); appropriate positive and negative controls were used	Not genotoxic; test substance did not induce an increase in micronucleated cells	[3]
Experiment I: 20-500 µg/ml Experiment II: 100-2000 µg/ml; with and without metabolic activation Tested in DMSO; purity = 68% as chloride	Chinese hamster V79 cells	Mammalian cell gene mutation test (HPRT locus); appropriate positive and negative controls were used	Test material induced some increased mutant frequencies; however, precipitates were observed with metabolic activation lead to an error in the assessment of doses; the assay was considered unsuitable for genotoxicity evaluation by the SCCP	[2]

Table 2. Genotoxicity studies

Concentration/Dose/Vehicle	Species/Strain/Cell	Method	Results	Reference
Experiment I: 25-2500 µg/ml Experiment II: 3.33-333.33 µg/ml Experiment III: 0.03-3.33 µg/ml; incubated 3 h with ^{3}H-thymidine Tested in 0.9% NaCl, 68% of test material as chloride	Wistar rat hepatocytes	Unscheduled DNA synthesis (UDS) test in accordance with OECD TG 482; DMSO was negative control and 2-acetylaminofluorene was positive control	The authors concluded that Basic Brown 17 did not induce significant increases in DNA repair; however, the study was considered unsuitable for genotoxicity evaluation by the SCCP due to improper methodology	[2]
3.9, 7.8, or 15.6 µg/ml, dissolved in sterilized bi-distilled water and minimal essential medium	HepG2 cells isolated from human hepatoma	Cytokinesis-block micronucleus test; positive and negative controls utilized (no details)	Genotoxic; significant chromosomal damage was induced	[13]
3.9, 7.8, or 15.6 µg/ml, dissolved in sterilized bi-distilled water and minimal essential medium	HepG2 cells isolated from human hepatoma	Comet assay; positive control was methyl methanesulfonate in minimal essential medium (MEM) and the negative control was MEM with 1% of sterile water	Genotoxic	[13]
2000-8000 µg/ml in 70% ethanol; purity = 98.7% (area by HPLC; 77.4% by NMR)	Phenion® full-thickness reconstructed human skin tissue	Single-cell gel/Comet assay; appropriate positive and negative controls were included (no details)	Not genotoxic	[3]
In Vivo				
0 and 5000 mg/kg bw in 0.9% NaCl; test material purity was 68% as chloride	Groups of 5 male and 5 female CFW 1 mice	Mammalian erythrocyte micronucleus test in accordance with OECD TG 474; single dose via gavage; appropriate negative and positive controls were used	Not clastogenic and/or aneugenic; no clinical signs of toxicity were observed; a slight change in PCE/NCE ratio was observed, but no statistically significant increase in the frequency of PCE; controls yielded expected results	[2]

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2020 FDA VCRP Raw Data

BASIC BROWN 17	Hair Conditioner	1
BASIC BROWN 17	Shampoos (non-coloring)	1
BASIC BROWN 17	Other Hair Preparations	1
BASIC BROWN 17	Hair Dyes and Colors (all types requiring caution statements and patch tests)	5
BASIC BROWN 17	Hair Rinses (coloring)	22
BASIC BROWN 17	Hair Shampoos (coloring)	14
BASIC BROWN 17	Other Hair Coloring Preparation	10