BLUE

Safety Assessment of Chlorphenesin As Used in Cosmetics

CIR EXPERT PANEL MEETING

SEPTEMBER 10-11, 2012

Cosmetic Ingredient Review
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August 16, 2012

Memorandum

To: CIR Expert Panel

From: Wilbur Johnson, Jr.
Manager/Lead Specialist

Subject: Final Report (draft) on Chlorphenesin

A tentative report with a conclusion stating that chlorphenesin is safe in the present practices of use and concentration was issued at the June 11-12 Expert Panel meeting. After the meeting, a paragraph relating to the sensory irritation potential of chlorphenesin was added to the tentative discussion to address this issue, and should be reviewed. Additionally, a summary of a multicenter study of preservative sensitivity in patients with suspected cosmetic contact dermatitis, identified in a literature search, has been added to the Skin Irritation and Sensitization (human) section of this safety assessment for the Panel's review. This study has not been published, but will be published in August of this year **(J. Dermatol. 2012 Aug; 39(8):677-681)**. Technical comments on the tentative report, received from the Council, have been addressed.

A copy of the draft final report on this ingredient is included along with the CIR report history, literature search strategy, ingredient data profile, 2012 FDA VCRP data, minutes from the June Panel meeting, and technical comments received from the Council (pcpc1 pdf file).

After reviewing this safety assessment, the Expert Panel needs to determine whether a final report with a safe as used conclusion should be issued at this meeting.

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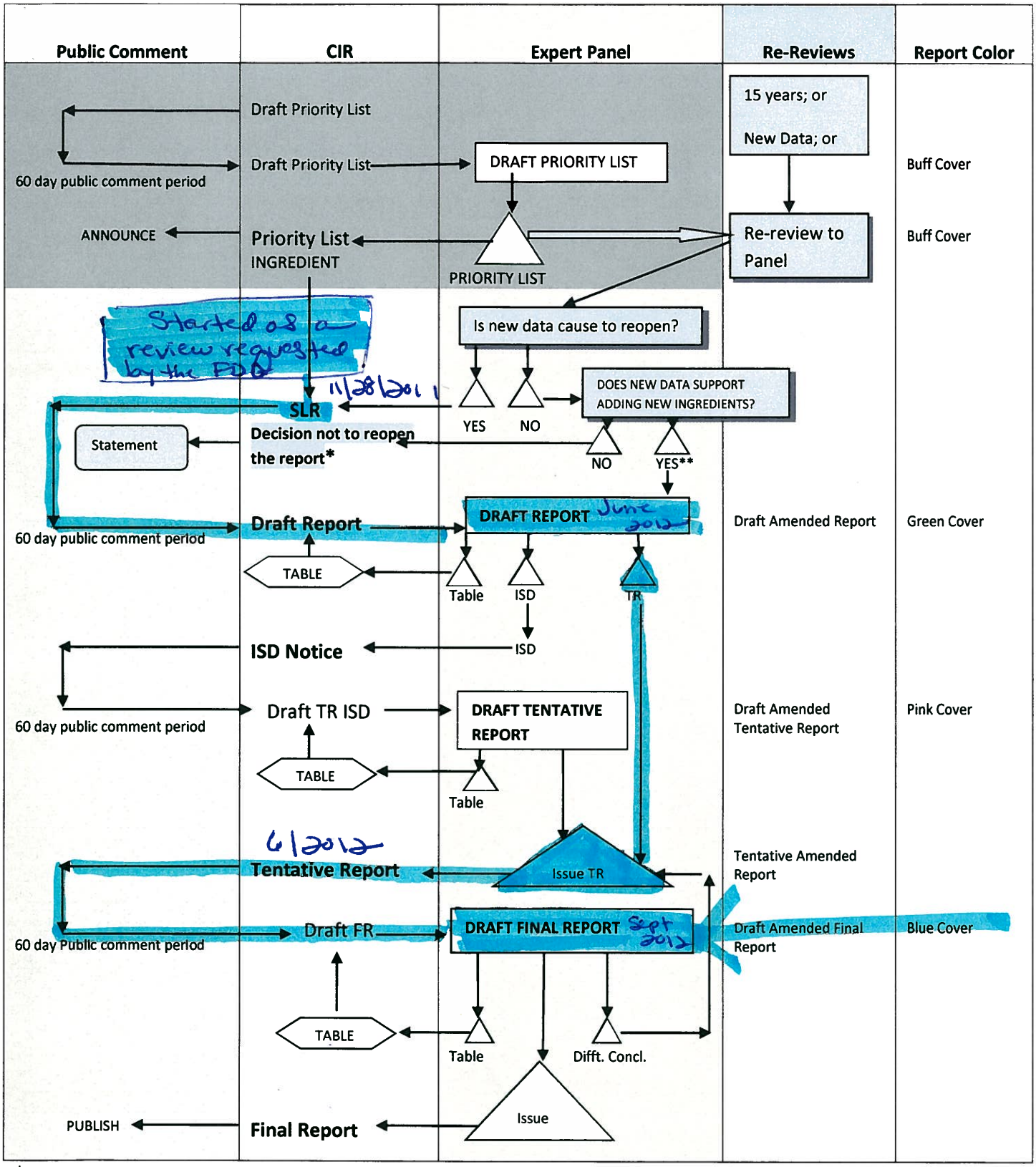
Chlorphenesin

SAFETY ASSESSMENT FLOW CHART

Sept 2012



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

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

△ Expert Panel Decision

▭ Document for Panel Review

⇨ Option for Re-review

CIR History of:

Chlorphenesin

A Scientific Literature Review (SLR) on Chlorphenesin was issued in November of 2011. Use concentration, chemical characterization, percutaneous absorption, antimicrobial activity, and safety test data received from the Council were incorporated prior to announcement of the SLR.

1st Review, Belsito and Marks Teams/Panel: June 11-12, 2012

The following data on Chlorphenesin (included in draft report) were received from the Council prior to announcement of the SLR: (1) Chemical characterization data submitted on 7-13-2011; (2) Chemical characterization, percutaneous absorption, and safety test data submitted on 9-6-2011; (3) 28-day oral toxicity study submitted on 9-6-2011; (4) Oral teratogenicity study submitted on 9-6-2011; (5) Genotoxicity and human skin irritation and sensitization data submitted on 9-6-2011; (6) Use concentration data submitted on 10-25-2011; and (7) Information on antimicrobial activity submitted on 2-8-2012.

The Panel issued a tentative report with a conclusion stating that chlorphenesin is safe in the present practices of use and concentration.

2nd Review, Belsito and Marks Teams/Panel: September10-11, 2012

After the June Panel meeting, a paragraph relating to the sensory irritation potential of chlorphenesin was added to the tentative discussion to address this issue. Additionally, a summary of a multicenter study of preservative sensitivity in patients with suspected cosmetic contact dermatitis, identified in a literature search, has been added to the Skin Irritation and Sensitization (human) section of the safety assessment for the Panel's review. This study has not been published, but will be published in August of this year **(J. Dermatol. 2012 Aug; 39(8):677-681)**. Comments on the tentative report were received from the Council.

Chlorphenesin Checklist forSeptember, 2012. Analyst – Wilbur Johnson																				
			Acute toxicity					Repeated dose toxicity				Irritation			Sensitization					
	Skin Penetration	Penetration Enhancement	ADME	Oral	Parenteral	Dermal	Inhale	Oral	Parenteral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Chlorphenesin	X		X	X				X				X	X	X	X	X	X	X	X	X

Literature Search on Chlorphenesin*

Ingre-dients	Toxline &PubMed	ChemIDplus	Multidatabase (See legend*)	DART	SciFinder	RTECS
CHL	54 (106)	1	0	5	22 (355)	1

*Data in Table: Publications found; Multidatabase = HSDB, CCRIS, ITER, IRIS, Gene-Tox, and LacMed

Searches Performed on10/12/2011
Search updated on 4/26/2012
Search updated on 7/30/2012

INGREDIENT

Chlorphenesin (CHL, abbreviation in Table)
3-(4-Chlorophenoxy)-1,2-Propanediol
1,2-Propanediol, 3-(4-Chlorophenoxy)-
p-Chlorophenyl Glyceryl Ether
104-29-0

Search Strings (NLM databases)

Chlorphenesin OR "3-(4-Chlorophenoxy)-1,2-Propanediol" OR "1,2-Propanediol, 3-(4-Chlorophenoxy)- " OR "p-Chlorophenyl Glyceryl Ether" OR 104-29-0

SciFinder Search Terms
Chlorphenesin

Transcript

Day 1 of the June 11-12, 2012 CIR Expert Panel Meeting – Dr. Marks' Team

Chlorphenesin

DR. MARKS: Let's move on to chlorphenesin. It's Green Book, also. This is also --

MR. HILL: Big Green Book.

DR. MARKS: A substantial Green Book, and that's not even -- don't have way too many in here, so we'll see if we have it. There are lots of uses --

MR. JOHNSON: Excuse me, Dr. Marks, before we conclude with tin oxide. We did receive some Wave 2 data on tin oxide, so I just want to confirm that you want those data incorporated into the safety assessment. We just have acute orotox, acute parental toxicity data, and additional data relating to non-cosmetic use. All on tin oxide.

DR. MARKS: That seems certainly to be relevant.

MR. HILL: I was going to say, why would we not put it in?

DR. MARKS: Yes.

MR. JOHNSON: Okay, I just wanted to.

DR. MARKS: Yeah, but none of it sent alerts, Ron. Obviously that Wave 2 wasn't a concern. So this is the first time --

MR. HILL: I'm looking at it right here.

DR. MARKS: This is the first time we've seen this draft report on chlorphenesin. So the first time we're reviewing this cosmetic ingredient. There are over 1,000 uses.

Just to clarify in the notes that Alan sent me, there is some confusion about the cosmetic ingredient chlorphenesin, and the drug mayolate musin, a central-acting muscle relaxant to treat muscle pain and spasm which is sometimes incorrectly called chlorphenesin, even though its correct chemical name is chlorphenesin carbomate. The drug chlorphenesin carbomate is not currently in use in the U.S. It's a biocide, it has over 1,000 uses.

So as we go through -- Wilbur, you'll obviously -- it's going to be important discussant that we're not talking about the drug here, we're talking about the cosmetic ingredient. So the issues of this central-acting muscle relaxant presumably are not applicable. But at any rate, Tom and Ron, do you have any insufficient data needs?

DR. SLAGA: There is bacterial mutagenesis, but no mammalian, and there's not a 28-day dermal study. And on the other I had the -- there are two baby products which, based on what you said, but it doesn't give any concentration for it. It says "not available."

MR. HILL: I noted that, too..

DR. MARKS: So --

DR. SLAGA: And it should have absorbed all these --

DR. SHANK: It does -- oh. But phototox --

DR. SLAGA: Yes.

DR. MARKS: Yes. So, let's go back. Impurities. Was that section okay? I had that there was -- let me see. When I looked over that, there's formaldehyde. Was that an issue in this?

DR. SLAGA: I don't have any issue.

DR. MARKS: Okay.

DR. SLAGA: I'm fine with it..

MR. HILL: Now, formaldehyde came up in production by oxidation with periodic acid, which is not relevant. I mean, yes you can do that well-known chemistry, but that shouldn't be occurring under any cosmetic use that I can imagine or envision.

DR. MARKS: So, Tom. You mentioned 28-day --

DR. SLAGA: Well, there's no data for that.

DR. MARKS: So 28-day dermal tox?

DR. SLAGA: And no mammalian mutagenesis.

DR. MARKS: Ron? 28-day dermal tox?

DR. SHANK: I didn't have that need. There is a carcinogenicity bioassay, anti-tumor --

DR. SLAGA: Yeah, it's anti-tumor. If you look at it as that particular study, there was two IP doses of chlorphenesin injected, but there was really no control for the, you know, chlorphenesin alone or, you know, other than those two injections. It has an anti effect on the DMBA TPA type of studies, but it to me wasn't really controlled for chlorphenesin.

DR. MARKS: So you would want mammalian?

DR. SLAGA: Well, we had bacterial. If we had mammalian, then the bacterial was, I believe, negative. If mammalian would be, then it would be a need for carcinogenicity.

MR. HILL: Let me add to that is that chlorphenesin carbonate is known to be converted to chlorphenesin in-vivo. So if we picked up the pharmacology -- we picked up some of that tox data, enough to suggest that we don't have a problem there, then we don't have to worry about it at all. But I made a note here. I put, we need to have captured what is known about chlorphenesin pharmacology, even though we're, you know -- the carbomate is what I meant to say. As a muscle relaxant, so we can relate it back to -- we're not going to see these problems because we're now talking dermal or incidental. The levels are much lower, like that. And I don't know this as a philosophical thing that we don't normally do that.

So, I don't know. Maybe I'm opening a can of worms here. But --

DR. SLAGA: Well, this is the first time we've seen it, so we should ask for whatever --

DR. MARKS: So specifically, you want mammalian --

DR. SLAGA: Mutagenicity.

MR. HILL: And I guess what I'm saying is, we may not need it if data from chlorphenesin carbomate suggests that there is no need for that, but we don't have that information in here captured and I didn't go out and search for it in preparation for this meeting.

DR. SLAGA: IT may be available, I don't know.

MR. HILL: If it was done with the carbomate, I think we can translate that easily to this particular molecule because that in vivo conversion is well characterized and known. But I don't know if that's opening a can of worms to an ingredient that we're not considering here. That's the only question I had.

But I think, you know, if you go back and look because that was in human use and drugs, if you go back for I don't know how many years it was on the market -- if you go back and look and determine that it's clean in that regard, then I don't see any reason to have to put on somebody to do those studies.

But I did note that our repeated dose toxicity was strictly oral. Grant you, the doses are high but again, I just keep reminding that rodents are extremely efficient at first-pass metabolism. And so just because you're giving 1,000 milligrams per kilogram and maybe it's not very soluble, we may not be getting much into the system, even at those high doses. So I think perhaps --

DR. SLAGA: I mean, overall, I didn't have concerns about this --

MR. HILL: My concern there was only that we were lacking concentration of use data in a number of these categories. If we'd known, yeah, okay, it's only a 2 percent on the skin, whatever.

DR. MARKS: So let's go back. It's interesting indirect -- not indirect, but an interesting data set. You suggest, Ron, that we could take the drug data and if that's not mammalian mutagenic, then that would satisfy.

DR. SLAGA: But they probably would have tested it for the carcinogen, wouldn't it?

DR. MARKS: Yeah, carbomate.

MR. HILL: Well but, I'm saying is if that's clean then this is clean because the carbomate is known to be converted facilely and relatively rapidly into chlorphenesin.

DR. SLAGA: Even in bacterial system, or mammalian cells?

MR. HILL: No, I'm suggesting --

DR. SLAGA: You're talking about going through the liver.

MR. HILL: Yeah, okay -- yes.

DR. MARKS: Yeah, and you're talking about if you put it directly on the skin.

MR. HILL: I guess I'm saying if in the studies they use to put that drug on the market, there was no hint. Then, do we really need it? Of course, it's --

DR. MARKS: Well, they ask for that data. So, the mammalian mutagenesis --

DR. SLAGA: I mean, even as Ron pointed out it's anti-tumorigenic if you inject it. So, you assume that there's nothing but it wasn't really controlled alone.

DR. MARKS: So, 28 -- so getting back. So, Tom. Where do you come down on this? Is this a data need and we can't go forward, this would be insufficient data if we don't get that? Or should we ask for it, see what comes, and then make a decision?

DR. SLAGA: Yeah, I think --

DR. MARKS: I think we may not get it unless you put out insufficient data and then we have to say in another -- the next time we review it, well, we really didn't look at this.

DR. SLAGA: We usually always like to see 28-derm and this is void of that.

DR. MARKS: Yeah. And, Ron, you said you didn't need a 28-day derm. Is that right?

DR. SHANK: Yeah, it was negative in everything else. There is immune activity, but actually it increases survival in the tumor study. It didn't increase infection rates in any of the studies. So, I wasn't concerned there.

The HRIPT sensitization data were negative. There were case reports that were positive, but you don't know what else was involved there.

DR. MARKS: Exactly, irritation --

DR. SHANK: So actually I didn't have any concerns. But I'll certainly go along with the mammalian genotox.

DR. MARKS: So, mutagenicity, so that's one. And then the concern about the concentration in baby products.

MR. HILL: Yeah, because I had a lot of --

MR. ANSELL: It couldn't exceed.3.

MR. JOHNSON: Let me say this, that would --

SPEAKER: That would be why? Because of its use as a preservative.

SPEAKER: Is there some actual use on this?

MR. HILL: Yeah, it just stood out glaring form that. I agree with you, it stood glaringly out in that table. We were lacking reports on underarm deodorant and those baby products. Everything else was.3 or below.

MR. JOHNSON: The current FDA data 2012 data indicate that it's no longer being used in baby products.

DR. MARKS: Oh, interesting. Okay.

DR. SHANK: Makes it easy enough. As long as we're on that table, Table 2.

DR. MARKS: Which page?

DR. SHANK: Report 11, Book 17.

DR. MARKS: Seventeen, yeah. Okay.

DR. SHANK: What we have for number of uses for nails, mucous membrane, less than one. How does that work? We have less than one use?

DR. MARKS: Maybe it means less than one geographic mucous membrane.

DR. SHANK: It's probably just -- oh, number of uses is 0.000 --

MR. JOHNSON: Okay, yes. That's a mistake. Yeah, that's a mistake.

DR. SHANK: I don't know if that -- that's a mistake.

DR. MARKS: That means that's an out -- okay, thank you.

DR. SHANK: For nails --

DR. ANDERSEN: Wilbur, you sent out the new VCRP data in Wave 2, so --

MR. JOHNSON: Yes.

DR. ANDERSEN: You got an update --

DR. MARKS: Somehow I didn't get that in here. Yeah, I missed it.

DR. ANDERSEN: But, yes.

DR. MARKS: I missed it on that.

DR. ANDERSEN: Probably is one or lower.

DR. MARKS: Okay. Well, that will be cleaned up, obviously, in the next rendition.

DR. SLAGA: There's really no real issue. Those were just --

DR. MARKS: Right, typos.

DR. SLAGA: No, no. I meant for the mammalian mutagenicity and 28 dermal. Those were -- I, like Ron, didn't have any trouble with it but those were glaring so I just --

DR. MARKS: So do we want to move forward with an insufficient data announcement for mammalian mutagenesis or do we want to do safe?

DR. ANDERSEN: Before you go there --

DR. MARKS: Oh, okay.

DR. ANDERSEN: -- talk to me about the immunosuppressant data. It seemed to contradict the findings on anti-tumorigenicity, but there's still a section here on immunosuppressive activity of chlorophenesin.

DR. MARKS: Which page are you on?

DR. SHANK: Page 7.

SPEAKER: Panel Book 7 -- oh, I'm sorry, Panel Book 13, Report 7.

DR. SLAGA: The top of the page.

DR. ANDERSEN: As I read it, the phenomenon seems to be linked when antigen and chlorphenesin are given simultaneously --

MR. HILL: Right.

DR. ANDERSEN: -- so I don't know how that impacts, but some comment would be useful.

DR. SHANK: Well, I did mention that there is immune activity there.

DR. MARKS: Right.

DR. SHANK: But in these longer-term studies, it actually increased the survival rate of the animals, which would not --

DR. SLAGA: An increased immunity in that space.

DR. SHANK: Yes.

MR. HILL: The note I had on that section was -- I'm sorry, go ahead. I thought you were finished.

DR. SHANK: I am finished.

MR. HILL: My note was, how do these concentrations compare to plasma or tissue concentrations observed in chronic dermal tox studies? Of course, there was a gap in time and I didn't realize we don't have chronic dermal tox studies. But I wrote, did the authors comment on the relevance of these concentrations. That's the question I had here.

And then I thought, I'm getting to the age where melanoma could be a real problem, this sounds like a promising thing.

DR. MARKS: So, Ron, how would you want to handle this? Ron Shank.

DR. SHANK: In the discussion. We certainly have to talk about these immune response studies. There are three of them. But that the rest of the -- especially the inter-tumorigenicity studies would not support immune suppression.

DR. SLAGA: It would be sufficient in the discussion.

DR. MARKS: So, you would point out there are studies that suggest immune suppression, but it did not have an adverse effect in terms of tumor promotion.

DR. SLAGA: Well, long -- synthesized the tumor promotion studies are longer-term than these studies under immunosuppression. And actually, as you said, the animals lived longer, too, at least.

DR. MARKS: Well, from an infectious point of view, is there a concern there, putting this on? So it doesn't seem from a tumorigenesis point of view it's an issue. From an infectious point of view, it says here when they -- what was it? If they did -- is it BCS or PPD for tuberculosis? BCS reaction. So, significantly reduced the tuberculant reaction in guinea pigs.

DR. SHANK: Somewhere in here it says decreased infection rates in animals.

MR. HILL: There was a study, at least in albino rabbits, where there was at least no increased susceptibility to infections. It was found -- I'm seeing it in the summary, I'm going back to the --

MR. ANSELL: Is the model relevant? Since these are all co-administered with antigen to cause these effects?

MR. HILL: Right. I thought that was where, you know, in the summary my note for that summary paragraph is this summary paragraph needs to leave an impression more consistent with the totality of the findings, especially no increased susceptibility to infections. It

didn't include the carcinogenicity results, but so it goes to what you were saying. I was just trying to find the original.

DR. SHANK: The infection is on report page 8, near the end of the paragraph that starts, "Female Swiss mice." That had a pronounced bearing effect on the mortality.

MR. HILL: That was leukemia infection.

DR. SHANK: Leukemia after infection with the virus.

MR. HILL: Microbial infections is on report page 7. It's right two sentences before reproductive and developmental toxicity. Effective as an immunosuppressant agent, only when administered joint with the antigen did not affect existing antibody levels or the secondary response and did not increase the susceptibility of the animals to infections.

DR. MARKS: Okay. So, I think we in the discussion, then, Wilbur, we would acknowledge that section under immune suppression, the results of that. But when one looks further there was no evidence that there was tumor promotion nor increased infections in animals that were exposed.

DR. SLAGA: In longer-term studies.

MR. JOHNSON: Just one more time so I just make sure I have that captured.

DR. MARKS: Yes. Essentially, we acknowledge that there's some studies that suggest that there's immunosuppression. That's on Panel Book page 12 and 13, but not only in that section where you pointed out, Ron Hill, about the infection. No increase or no promotion of infections were observed, nor was there tumor promotion observed in other studies. And you mentioned the chronic ones there.

So, I think it's the main thing that even though it appears to have this immunosuppressive potential, that we saw no consequences of this.

DR. SLAGA: Probably the function of the host.

DR. MARKS: The function of the host, yeah?

MR. ANSELL: Well, also two of those three studies were not with material alone.

DR. MARKS: Yeah.

MR. ANSELL: I mean, they were co-administered. So, I wonder about the relevance of the model for its use in cosmetic applications.

DR. MARKS: That's also an excellent point.

MR. HILL: And Wilbur, I mean, we don't have concentrations, of course, in the VCRP, but am I correct that deodorants disappeared and dropped off the map? I don't see it, but I'm -- baby products did, but?

MR. JOHNSON: The nail polish and the enamel. That category is no longer there.

MR. HILL: I don't see deodorants, either, and that was the other place where we didn't have a concentration of use.

MR. JOHNSON: Just the baby products and the nail products.

MR. HILL: So we don't know about deodorants but we think it shouldn't be above.3 percent like everything else?

DR. MARKS: So, tomorrow presumably I'm going to second a motion that we have a draft tentative report on chlorphenesin, that it is safe as used conclusion. Correct?

DR. SHANK: Even one from mammalian genotypes?

DR. SLAGA: First time around one should ask for it just so we're consistent.

DR. MARKS: So you want an insufficient data announcement. Yeah, okay. I wasn't -- okay. I guess on the sidebar up here I didn't hear you being firm about that.

DR. SLAGA: No, I'm not firm. It's so negative to everything else --

DR. MARKS: That gets back to what Jay says. If we don't get it the next time are we going to flip and say, oh we don't really need it?

DR. SLAGA: Then we'd get mad..

MR. ANSELL: So, insufficient for which?

DR. MARKS: The mammalian mutagen.

MR. ANSELL: Okay.

DR. MARKS: Mutagenesis.

MR. JOHNSON: So we don't need the 28-day dermal tox data?

DR. SLAGA: Ask for both.

DR. MARKS: Well, now. Wait a second. We usually don't -- I don't think we ask for it. We don't put insufficient data announcement unless we really need that data to come to a conclusion of safe. So, if we don't need the 28- day tox it's --

DR. SLAGA: We don't need the mammalian mutagenesis.

DR. MARKS: -- we don't need that either. So, I think we move forward with safe, then, if we don't really need it.

DR. SHANK: Okay.

DR. MARKS: Because if we don't have any more data next time and we say, well now we don't need it, what's changed? Okay.

DR. ANDERSEN: Very good question. I think if in the discussion tomorrow Tom has a kindred spirit on the other team --

DR. MARKS: Yes.

DR. ANDERSEN: -- that's saying, wait a minute, I want mammalian genotox, then you will be in synch and you can at that point change strategy. But where you are now --

DR. SLAGA: Sleep with the enemy? (Laughter)

DR. MARKS: They're playing their cards first, so I'm prepared to --

DR. SHANK: Strange bedfellows.

DR. MARKS: I'm prepared to second a motion that we issue a draft tentative report with a safe as used, and I'm prepared also to second a motion that insufficient data for the moment --

DR. SLAGA: If they ask for the 28 --

DR. MARKS: -- 28-day -- I'm not sure I'm going there. Ron Shank really said we don't need 28-day, nor did Ron Hill say we need that. So I think we're only going to do the mammalian mutagenesis. We're definitely in the discussion going to capture the sense of -- thank you, Alan, for pointing out how we need to deal with immune suppression. That may be the reason why the irritation and sensitization data is all clean, Ron. You know? Because it's immunosuppressive, so it wasn't a sensitizer or irritator. It doesn't allow the inflammatory response.

Day 1 of the June 11-12, 2012 CIR Expert Panel Meeting – Dr. Belsito's Team

Chlorphenesin

DR. BELSITO: Okay, so, next we have chlorphenesin. And this was brought up and sort of expedited at FDA's request and I guess it all has to do with confusion about chlorphenesin, the cosmetic ingredient and what clearly should be called chlorphenesin carbamate, which is a muscle relaxant. It always helps when you review a biocide that has over 1,000 uses and I'm not sure why it wasn't on our radar list anyway.

So the bottom-line, chlorphenesin, the cosmetic ingredient, has no muscle relaxant properties. And I looked. This was a huge book. I looked through it and thought it was safe as used and just required a discussion that chlorphenesin, the cosmetic ingredient, wasn't chlorphenesin carbamate, the muscle relaxant.

DR. LIEBLER: I agree. Safe as used. I had a couple of small deletions on data, suggested deletions. One is on Panel Book page 10, the cellular effects section on second messenger and histamine release. I just felt that they were of really doubtful relevance to human exposures, those experimental systems. And then also at the bottom of page 7, Panel Book page 7 on reactivity, that one sentence thing about production of formaldehyde by oxidation by periodic acid has been reported. That may be chemically true but not relevant to any kind of scenario that would occur in use of this product in a cosmetic ingredient.

DR. BELSITO: Paul, Curt, Rachel, anyone? Yes, sir.

DR. RUA: Diego Rua from FDA. So we have concentration of use data but it says here we are dealing with a nipple cream. Where would you get that concentration out of? I mean, what page was that, 453?

DR. BERGFELD: 451.

DR. RUA: 451. CIR Panel Book page 451 and 452. You have all the product categories and the maximum concentration of use. So I guess if we try to figure out whether there's a safety issue with a nipple cream, how would the panel go after that? I mean, would you look at maybe skin care perhaps? Would you think that the nipple cream probably had a 0.3 percent maximum concentration of chlorphenesin?

DR. BELSITO: Well, I think that for a nipple cream what we would be looking at is reproductive and developmental toxicity and, you know, the data was certainly clean in that regard. Of course, that always begs the question does the molecule cross the placenta? But then we also have significant, you know, repeated dose toxicity studies in animals that were pretty clean. So I didn't really have a sense that this represented a significant concern in terms of its uses in nipple cream. In terms of if your question is what concentration are we assuming that it would be used in, I would hope that where PCPC would have put this in would have been incidental ingestion as in nipple cream, and that it would be at the 0.3 level that's labeled in CIR Panel Book page 17, rather than at a dermal contact level. But the levels are really pretty much the same. I mean, the highest level is 0.3.

DR. EISENMANN: If you search on the internet for the specific product that FDA wrote the letter on, I think they've reformulated. But I don't think it contained -- and I don't know that anybody has submitted any information on what concentration in a nipple cream because that's not really a traditional cosmetic product that people are reporting. But for this specific one, I was trying to find information on it and I think they've reformulated because they got that letter.

DR. RUA: So, but the repro on developmental toxicities in utero. So that wouldn't really go to the issue here with babies.

DR. BELSITO: That's what I said. I said we rely on the repro but also since it's not clear necessarily that chlorphenesin would cross the placenta, that we also looked at the oral. And we have repeated oral toxicity data at fairly significant doses in relatively young animals, 42 days of age, I think.

DR. RUA: So on CIR Panel Book page 9, under acute oral toxicity where there's -- as part of the science, loss of reflex is mentioned, does that indicate any neurotoxicity? Any potential neurotoxicity?

DR. BELSITO: I'll let Paul address that.

DR. SNYDER: I'm looking at this again. It didn't raise any flags on my review. I mean, there were some minor changes and only noted in high dose animals. So I didn't feel that there was anything that was significant regarding low level exposures we'd expect at 0.3 percent. It's kind of non-specific (inaudible) at the high dose..

DR. KLAASSEN: You know, they were given 4 gm/kg here. It's a huge dose.

DR. SNYDER: And it was only in a high dose. And most of it is probably because they were getting such large doses. The hunspa should have normal gait, lethargy.

DR. BELSITO: It was gavage dosing though.

DR. RUA: Okay, thank you.

DR. LIEBLER: So was this whole thing because the FDA mistook chlorphenesin for chlorphenesin carbamate? Is that what happened here?

DR. BELSITO: That's my understanding, although in retrospect an ingredient that's used in over 1,000 products probably deserved to be up there anyway. And why it wasn't on our radar screen, I don't know. So it doesn't matter anymore.

DR. LIEBLER: Would it be the enforcement action and then the reason that we're looking at it?

DR. BELSITO: Yes. And I think it's very critical that we go ahead with this because if you go to the EWG website and you type up chlorphenesin, they still don't have that straight and it's pretty scary the information that they have. So I think, if anything, this document will point out that the cosmetic ingredient chlorphenesin is different from the pharmaceutical ingredient which more probably should be called chlorphenesin carbamate.

DR. RUA: And even if in the future there were cosmetic products where the baby would be exposed, a young baby would be exposed, you still wouldn't be concerned. Would that be --

DR. BELSITO: At the level that we're approving, which is 0.3 percent, I don't have a concern.

DR. RUA: Okay.

DR. LIEBLER: So for those reasons -- I didn't ask the question to embarrass anyone; more it was just to clarify. And I think the key point for us to make in this is what Don just said. The discussion needs to clarify that this widely used ingredient at the levels it's used in the context it's used is safe as used. That's it.

DR. BERGFELD: Don, Rachel has a question.

DR. BELSITO: Yes.

MS. WEINTRAUB: I mean I just wanted -- I think it's important to get a sense of FDA's response to this cream. I'm just not sure from their statements what FDA thinks happened here. So I'd really like to get a clear sense of their response.

MR. MILSTEIN: We can get that clarification for you. It's probably a matter of historical record at this point. We'll try to get you a clarification.

MS. WEINTRAUB: Because it seems -- I just want to fully understand that FDA -- we were to get a sense of FDA's concern about an infant's interaction with this ingredient and whether FDA is concerned that even at the doses that it seems like it could be included in various cosmetic products that that would potentially be problematic. So that's what I just would like to tease out also.

DR. RUA: FDA was not aware of the concentration of use of chlorphenesin in these products. I don't know if you want to add to that.

MR. MILSTEIN: Nothing at this time other than to note that there are other carbamates I think that are pharmaceutically active that do have neuromuscular activity as well.

DR. BRESLAWEC: For point of clarification I think it's important to put on the record that the product we're reviewing is chlorphenesin and not chlorphenesin carbamate. And also, the 2008 recall was that do you know what concentration the chlorphenesin was in that particular product and are you aware -- I guess this is information I think would be useful -- are you aware that that product is -- I'm just -- yeah, that product continues to be marketed? Because I think what Carol said is that we've searched for it and it's no longer -- we couldn't find it.

MR. MILSTEIN: I think the recall involved Mommy's Bliss Nipple Cream but it's exact marketing status now is not entirely clear to me at this point.

DR. BRESLAWEC: Right. And again, our understanding is it's been

reformulated. And if you have information that suggests otherwise, we would like to know that.

DR. LIEBLER: But I think it is important that the introduction be much more clear in stating that this cosmetic ingredient is chlorphenesin, not the carbamate. And it does sort of say that but it needs to say that really clearly and emphatically at the end. The issue here is not what was correct or incorrect about Mommy's Bliss but about the need for a safety assessment of chlorphenesin as a cosmetic ingredient.

DR. BELSITO: Okay.

MR. JOHNSON: Dr. Belsito, one question that I had on CIR Panel Book page 8, we have the structure of chlorphenesin carbamate.

DR. BELSITO: My, my, my. Get rid of that.

MR. JOHNSON: Okay.

DR. BELSITO: Yes. Anything related to chlorphenesin carbamate should be struck except to say that chlorphenesin is not chlorphenesin carbamate.

Day 2 of the June 11-12, 2012 CIR Expert Panel Meeting – Full Panel

Chlorphenesin

DR. BERGFELD: Are there any other additions, suggestions or edits? Seeing none, I'll for the question. All those in favor of safe approval of this ingredient? Thank you. Unanimous. Then moving on to the next green reports advancing, Dr. Belsito and the chlorphenesin.

DR. BELSITO: This ingredient was moved up at the request of FDA in part because of some confusion between the cosmetic ingredient chlorphenesin and a pharmaceutical ingredient chlorphenesin carbamate which is a muscle relaxant. Despite that, it has over a thousand uses, so I don't know how it escaped getting on our radar screen anyway. However, once that issue was clarified that this is not chlorphenesin carbamate, that it doesn't have muscle relaxant properties, we found that this was safe as used and that the discussion should very clearly point out that this confusion that exists between chlorphenesin carbamate, the cosmetic ingredient and chlorphenesin carbamate.

DR. BERGFELD: That's a motion?

DR. BELSITO: That's a motion.

DR. MARKS: Second.

DR. BERGFELD: Is there any discussion from any of the team members?

DR. MARKS: Yes. Our team yesterday as was pointed out by Dr. Andersen the potential immune suppression that this ingredient could cause and we felt that that did not raise safety concerns since there are areas of reports showing that there is no tumor promotion that has occurred from this ingredient and there is no infection promotion or increased infection. We note the immune suppression and feel that can be dealt with in the discussion.

DR. BERGFELD: Ron Hill?

DR. HILL: I was going to comment that chlorphenesin carbamate can be cleaved in vivo, is cleaved in vivo, to chlorphenesin so I think that the difference in terms of effect is that these are used at preservative levels up to.3 percent maximum and dermal absorption isn't expected to be all that efficient. It's a situation where systemic clearance probably occurs about as rapidly as absorption would occur. So I think it's not so much that we don't have the muscle relaxant effect potential. That drug was demarketed many, many years ago, but it's just a matter that you will never build up systemic levels to where that would come into play or whatever pharmacology is involved there.

DR. BERGFELD: Are you suggesting that short descriptor also be put into the discussion?

DR. HILL: I don't know right this moment. I had some debates with myself, because I think it does somewhere need to be acknowledged that chlorphenesin carbamate is cleaved in vivo to chlorphenesin. It actually happens to a large extent to my recollection when I was teaching that drug, but I don't know that that's relevant to these preservative levels in cosmetic ingredients. So I'm not sure what needs to be captured in the document in that regard. That may be true, but I think it is probably not relevant. One of the things that we talked about yesterday is that this whole situation appears to have arisen out of to some degree some confusion and I think the most important function of our report is not necessarily to talk about chlorphenesin carbamate and we should probably minimize our mention and discussion of chlorphenesin carbamate and focus on the safety of chlorphenesin. For that reason, although not that I disagree with you about what might be happening with the carbamate, it's a side issue and it's in the discussion it would cloud our message. I'm not sure that the mechanism is the pharmacological mechanism of even guaifenesin which is still on the market is 100-percent known actually how that muscle relaxant occurs. But the point is it's at systemic concentrations of chlorphenesin even if that is the effect or it's going to be very low and way below I think the levels that would cause any -- so I don't know about capturing it. I'd have to think about that some more. Not that I didn't think about it already, but I still have to think about it some more. We had a comment period, so I'll communicate anything.

MR. MILSTEIN: We did a little more research on the subject, the history of this confusion, and we're happy to try to alleviate that by observing that the issue emanated

apparently back in 2008 from issuance of a warning letter concerning an OTC drug product that was making unapproved new drug claims. You'll find that on our website.

DR. BERGFELD: Are there any other comments? We have had a second this for a safety review. All those then in favor of a safe conclusion, please raise your hand. Thank you. Unanimous.

Report

Safety Assessment of Chlorphenesin as Used in Cosmetics

Status: Draft Final Report for CIR Expert Panel Review
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The 2012 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is F. Alan Andersen, Ph.D. This report was prepared by Wilbur Johnson, Jr., M.S., Manager/Lead Specialist.

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ABSTRACT: Chlorphenesin functions as a preservative, and is used at concentrations up to 0.32% in rinse-off products and up to 0.3 % in leave-on products. The Expert Panel noted that chlorphenesin was well-absorbed when applied to the skin; however, concern over this finding was not warranted, taking into consideration the negative toxicity data included in this safety assessment. The Expert Panel concluded that chlorphenesin is safe in the present practices of use and concentration.

INTRODUCTION

Available data relevant to the safety of chlorphenesin as used in cosmetics are reviewed in this tentative safety assessment. As stated in the *International Cosmetic Ingredient Dictionary and Handbook*,[1] this ingredient functions as a biocide in cosmetic products. The Food and Drug Administration (FDA) initially requested the review because of the agency's previous recall of a nipple cream containing chlorphenesin, based on skeletal muscle relaxation, central nervous system depression, and respiratory depression in infants. The CIR Expert Panel opined that the drug chlorphenesin carbamate (CAS No. 886-74-8, also known as chlorphenesin) is known to have muscle relaxant effects, but such effects are not expected for the cosmetic ingredient, chlorphenesin (CAS No. 104-29-0). Based on the use concentration of chlorphenesin in cosmetics and the dermal route of exposure, serum concentrations would never reach levels that are needed to cause muscle relaxation.

CHEMISTRY

Definition and Structure

As given in the *International Cosmetic Ingredient Dictionary and Handbook*, chlorphenesin (CAS No. 104-29-0) is a chlorophenol derivative defined as the organic compound that conforms to the formula shown in Figure 1.:[1]

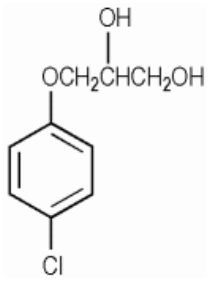

Figure1. Chlorphenesin

Other names for this chemical include: 3-(4-Chlorophenoxy)-1,2-Propanediol; 1,2-Propanediol,3-(4-Chlorophenoxy)-; and p-Chlorophenyl Glyceryl Ether.[1]

Chemical and Physical Properties

A UV spectral analysis of 0.01% aqueous chlorphenesin solution indicated maximum absorption at 279 nm.[2] Additional properties of chlorphenesin are found in Table 1.

Methods of Production

Chlorphenesin is prepared by condensing equimolar amounts of p-chlorophenol and glycidol in the presence of a tertiary amine or a quaternary ammonium salt as a catalyst.[3]

USE

Cosmetic

Chlorphenesin reportedly functions as a biocide in cosmetic products.[4] Reportedly, chlorphenesin (ELESTAB® CPN; concentration of use = 0.10 to 0.30%) has bactericidal activity against Gram (+) and Gram (-) bacteria, fungicidal activity against *Aspergillus niger* IMI 149007 and *Penicillium pinophilum* IMI 87160 (fungi), and is also active against *Candida albicans* NCPF 3179 and *Saccharomyces cerevisiae* NCPF 3275 (yeasts).[5]

According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2011, chlorphenesin is used in 1,386 cosmetic products.[6] These data are summarized in Table 2. Results from a survey of ingredient use concentrations provided by the Personal Care Products Council (also included in Table 2) in 2011 indicate that chlorphenesin is used at concentrations up to 0.32% in rinse-off products and up to 0.3 % in leave-on products.[7]

Cosmetic products containing chlorphenesin may be applied to the skin and hair, or, incidentally, may come in contact with the eyes and mucous membranes. Products containing these ingredients may be applied as frequently as several times per day and may come in contact with the skin or hair for variable periods following application. Daily or occasional use may extend over many years.

Chlorphenesin is used in hair, foot, and suntan sprays, and could possibly be inhaled. In practice, 95% to 99% of the aerosols released from cosmetic sprays have aerodynamic equivalent diameters in the 10 to 110 μm range, with propellant sprays yielding a greater fraction of droplets/particles below this range when compared to pump sprays .[8,9] Therefore, most aerosols incidentally inhaled from these sprays are deposited in the nasopharyngeal region and are not respirable to any appreciable level.[10,11]

According to the European Union Cosmetics Directive, chlorphenesin is listed among the preservatives that may be contained in cosmetic products marketed in the European Union (EU). The maximum authorized use concentration for this ingredient is 0.3%.[12]

Noncosmetic

Chlorphenesin is one of the ingredients in an antimicrobial product identified as Miol cream.[13]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

The absorption, distribution, and metabolic fate of chlorphenesin was evaluated using male Sprague-Dawley rats and Beagle dogs.[14] In the first experiment (4 rats), a16.7 mg oral dose of chlorphenesin-1,3-^{14}C (in physiological saline) was administered via stomach tube, after which concentrations in the blood were determined. In a second experiment, chlorphenesin-1,3-^{14}C (15.2 mg) was administered i.p. to one rat, and the distribution of administered radioactivity was determined. A third experiment was performed to isolate chlorphenesin metabolites from the urine. Non-radioactive chlorphenesin (500 mg/kg) was administered orally to 2 Beagle dogs and urine was collected for 24 h. Urine from 2 Beagle dogs was also collected after the animals received 2 i.p. injections of non-radioactive chlorphenesin (250 mg/kg, 6 h apart). In an experiment to identify conjugated metabolites, 4 male rats were injected i.p. with chlorphenesin UL-ring-^{14}C (30 mg) and urine was collected for 24 h. The relative radioactivity corresponding to each of the major metabolites was determined quantitatively in additional experiments in which chlorphenesin-1,3-^{14}C was administered to rats (capsule form) and Beagle dogs (i.p. dose).

Following oral ingestion, chlorphenesin-^{14}C was absorbed rapidly in the rat. Radioactivity reached a peak blood concentration in 30 min, and the half-life of serum radioactivity was approximately 140 minutes. Results of the distribution experiment indicated that over half of the administered i.p. dose of chlorphenesin-1,3-^{14}C in the rat was excreted in the urine after 4 h. The remainder was found primarily in the gastrointestinal tract and carcass. A small portion of the radioactivity was recovered as respiratory CO_2. The urinary end products identified after administration of the drug to rats or dogs were: 3-p-chlorophenoxylactic acid, p-chlorophenoxyacetic acid, and unchanged chlorphenesin. Additional urinary end products

identified as a conjugate of chlorophenol and a conjugate of chlorphenesin were observed after rats were injected i.p. with chlorphenesin UL-ring-^{14}C.[14]

Percutaneous Absorption

The percutaneous absorption of ^{14}C-chlorphenesin was evaluated using 16 male rats of the Sprague-Dawley CD strain (~ 6 weeks old).[15] ^{14}C-chlorphenesin (in 0.05% w/w cold cream; mean dose = 1.14 mg/kg [~ 14 µCi]) was applied topically to shaved skin on the back (9 cm^2). Application sites were occluded with aluminum foil until the animals were killed. After test substance application, the animals were placed in individual metabolism cages for the collection of urine and feces. Pairs of animals were killed at various intervals, beginning at 1 h and ending at 96 h. The mean total recovery of radioactivity (application site, excreta, selected tissues, and residual carcass) was 92.35% dose + 3.11 standard deviation (SD) after dosing. The proportion of administered ^{14}C-chlorphenesin dose that remained at the application site (in and on the skin) decreased from ~ 89% at 1 h to ~ 43% at 96 h. During the 0 to 96 h time period, ~ 48% (mean value) of the applied dose was excreted in the urine. Approximately 0.5% was excreted in the feces and ~ 0.7% was recovered in cage washings. Thus, practically all of the absorbed dose was excreted over a period of 96 h.

Not more than 1% of the applied dose was present in any of the tissues during the 1 h to 96 h time frame, though up to 57% of the dose was absorbed. At 96 h, ~ 7 to 8% of the administered dose remained and was subsequently eliminated from the body. Apparently, the radioactivity was absorbed biphasically, with initial and terminal half-lives for absorption of ~ 4 h and 126 h, respectively. The urinary excretion rate was proportional to plasma radioactivity concentrations during 0 to 96 h, suggesting that the renal clearance of radioactivity was constant. The terminal excretion half-life (~ 22 h) was considerably shorter than the terminal absorption half-life (~ 126 h). Thus, the excretion of radioactivity was absorption-rate limited.[15]

TOXICOLOGY

Acute Oral Toxicity

The acute oral toxicity of chlorphenesin (in 0.5% carboxymethylcellulose aqueous gel) was evaluated using 5 groups of 10 (5 males, 5 females/group; ~ 6 weeks old) Sprague Dawley rats.[16] The 5 groups received single oral doses of 1200, 1620, 2187, 2952, and 3985 mg/kg, respectively. Dosing was followed by a 14-day observation period, after which all surviving animals were killed. The following signs were observed after test substance administration of each dose: dyspnea, decrease in spontaneous activity, hypotonia, piloerection, and loss of reflex. Necropsy findings for animals that died were mainly an intestinal meteroism and lung congestion. A mean LD50 of 3,000 mg/kg 95% confidence interval: 2830 to 3180 mg/kg) was reported.

Repeated Dose Toxicity

A repeated dose oral toxicity study on chlorphenesin was performed using 4 groups of 16 rats of the Charles River Crl : CD(SD) BR strain (8 males, 8 females/group; 47 days old).[17] Chlorphenesin (suspension in 1% aqueous methylcellulose) was administered by gavage to 3 groups at doses of 10, 100, and 1000 mg/kg/day (dose volume = 10 ml/kg/day), respectively, for 28 consecutive days. Control rats were dosed similarly with 1% aqueous methylcellulose. Except for one animal killed during week 4, the animals were killed on day 29. Microscopic examination of the rat (high-dose male) killed during week 4 revealed renal tubular dilatation and necrosis of the papillary tip, both treatment-related. No microscopic changes were observed in high-dose female rats or the remaining high-dose male rats. Clinical findings in the highest dose group included: hunched posture, abnormal gait, pallor, lethargy, ptosis, a badly groomed appearance, noisy respiration, and piloerection. A badly groomed appearance was also observed in rats of the low dose (not toxically significant) and intermediate dose groups, and increased salivation was also observed in the intermediate dose group. Compared to controls, a statistically significant reduction ($P < 0.01$) in body weight gain was noted for male and female rats of the highest dose group. Significantly lower hemoglobin levels were reported for high-dose males and females and intermediate-dose males.

Statistically significant increases ($P < 0.01$) in glutamic pyruvic transaminase (GPT) were reported for high-dose males and females. Alkaline phosphatase levels in high dose males were slightly higher when compared to controls, but the difference was not statistically significant. Potassium and calcium ion concentrations were significantly lower ($P < 0.05$) in high-dose females. IgG and IgM serum levels in high-dose females, when adjusted for pre-dose levels, were significantly

higher than control values at the end of dosing. These changes were considered a reflection of hematological and biochemical changes due to treatment with chlorphenesin, and not a specific effect on the immune system. Absolute spleen weights (high-dose males and females) and thymus weights (high-dose males) were significantly lower ($P < 0.05$ or $P < 0.01$) when compared to controls. At macroscopic examination, general brown staining of the fur was observed in all 5 high-dose female rats examined, compared to the absence of this finding in controls. The only microscopic finding (in kidney) is mentioned in the preceding paragraph. The reported changes in the high and intermediate dose groups were considered treatment-related. A dose of 10 mg/kg/day was considered the no adverse effect level in this study.[17]

Ocular Irritation

The ocular irritation potential of chlorphenesin (1% [w/v] in distilled water) was evaluated using 3 New Zealand albino rabbits (ages not stated).[18] The test substance (0.1 ml) was instilled into the right eye of each animal, and the lids were held together for approximately 10 seconds. Untreated left eyes served as controls. The eyes were examined for ocular reactions at 1 h and then at days 1, 2, 3, 4, and 7 post-instillation. Slight conjunctival irritation (enanthema, chemosis, and lacrimation) was reported for each rabbit and these reactions had cleared by 24 h post-instillation. Chlorphenesin was classified as a weak ocular irritant (maximum ocular irritation index = 6 [at 1 h post-instillation]).

Skin Irritation

Non-Human

The skin irritation potential of chlorphenesin was evaluated using 6 male New Zealand albino rabbits (ages not stated). A 2.5 x 2.5 cm occlusive patch containing chlorphenesin (1% [w/v] in distilled water, 0.5 ml) was applied to the shaved flanks of each animal.[18] The right flank was abraded and the left remained intact. Patches were secured with fastening tape and the trunk was wrapped with an elastic bandage secured with adhesive tape. At 24 h, the patches were removed. Slight, reversible erythema was observed in 2 rabbits, and there was no evidence of structural modification. Chlorphenesin was classified as a non-irritant (primary irritation index [PII] = 0.1).

Human

A study was performed to investigate the side effects of cosmetic preservatives by evaluating objective and subjective skin irritants.[19] In a 24 h occlusive patch test involving 30 subjects (20 females, 10 males; mean age = 33.7 years), 2% chlorphenesin (20 µl) was applied to filter paper discs on IQ test chambers, and patches remained in contact with the forearm for 24 h. Reactions were evaluated at 30 minutes and 1 day after patch removal. A mean irritation score of 0.17 ± 0.38 was reported. A cumulative skin irritation test was performed using 15 healthy subjects (8 females, 7 males; mean age = 29.7 years). The formulations tested were emulsion bases with a preservative mixture consisting of 0.2% methylparaben, 0.1% propylparaben, and 0.25% chlorphenesin (Type 1) and emulsion bases containing 0.2% methylparaben, 0.1% propylparaben, 0.3% phenoxyethanol, and 0.25% chlorphenesin (Type 2). Each formulation (20 µl) was applied according to the preceding method 3 times per week over a 21-day period. Each subject received 9 applications (same site) of the test substance. For Type 1 formulations tested, the highest reported total cumulative irritation mean score was 0.40 ± 0.91. For Type 2 formulations, a mean score of 0.87 ± 1.19 was the highest reported.

A sensory irritation test was performed using 16 healthy subjects (6 females, 10 males; mean age = 28.3 years). A cotton swab soaked with 0.4% chlorphenesin (in 0.5% carbopol solution, 0.5 ml volume) was rubbed briskly and applied (under occlusion) to each side of the nasolabial fold and cheek. Any evidence of a stinging/burning reaction was recorded over a period of 9 minutes. Carbopol (0.5%) solution served as the vehicle control. The sensory irritation potential of 0.4% chlorphenesin (mean score = 0.54) was greater than the control (mean score = 0.22). Emulsion bases (with or without chlorphenesin in preservatives mixture) were tested according to the same procedure. Sensory irritation induced by the formula containing methylparaben, propylparaben, and chlorphenesin was greater when compared to the same formula without chlorphenesin.[19]

Facial sensory irritation testing was initially proposed by Frosch and Kligman.[20] In a previous CIR safety assessment of alpha hydroxy acids (AHA's),[21] it was concluded that the sensitivity of tissue around the area of the eye to sensory irritation was such that AHA-containing products intended for use near the eye be formulated in such a way to reduce stinging and burning reactions. AHA's were also demonstrated dermal irritants.

The acute dose skin irritation potential of 0.3% chlorphenesin (in water) was evaluated using 25 subjects (20 females, 5 males; 19 to 62 years old). An occlusive patch containing the test substance (0.1 ml) was applied to the back of

each subject for 48 h. Reactions were scored 20 minutes after patch removal. Faint, minimal erythema (score = ±) was observed in 2 subjects and erythema (score = 1) was observed in a third subject. Chlorphenesin was classified as having negligible dermal irritation potential.[22]

Skin Irritation and Sensitization

Non-Human

Prior to initiation of the sensitization study below, a test was performed to determine the maximal non-irritant concentration of chlorphenesin.[23] The test involved 3 male albino Dunkin Hartley guinea pigs (ages not stated). A dorsal surface area of ~ 60 cm^2 was clipped free of hair, and, on both sides of the spinal column, 3 symmetrical intradermal injections (0.1 ml) of the following preparations were made: (1) 50% Freund's Complete Adjuvant (FCA) in distilled water, (2) distilled water, and (3) a 50/50 mixture of 1 and 2. Sites were clipped free of hair 7 days later, and the following concentrations of chlorphenesin (0.5 ml volume) were applied under an occlusive patch for 24 h: 0.1 %, 0.25 %, 0.5 %, and 1.0% in distilled water. Irritation reactions were scored at 24 h and 48 h after patch removal. Irritation was not induced by any of the concentrations tested. Test concentrations of 0.5% and 1.0% were designated for use during the challenge phase of the sensitization study.

The skin sensitization potential of chlorphenesin was evaluated in a modified guinea pig maximization test using 30 female albino Dunkin Hartley guinea pigs (ages not stated). Test and control groups consisted of 20 and 10 guinea pigs, respectively. Dorsal skin was clipped free of hair, and 3 symmetrical intradermal injections (0.1 ml) of 1% chlorphenesin (in distilled water), 1% chlorphenesin (in a mixture of Freund's complete adjuvant [FCA] and distilled water), and a mixture of FCA and distilled water, respectively, were made on both sides of the spinal column (scapular level) during induction of test animals. During induction, control animals were injected with FCA/distilled water mixtures and distilled water. Induction injections were followed by a single 48 h application of an occlusive patch (2 x 4 cm) moistened with 1% chlorphenesin in distilled water (0.5 ml, test animals) or distilled water (0.5 ml, controls). During the challenge phase, chlorphenesin (1% or 0.5% in distilled water, 0.5 ml) was applied, under occlusive patch (2 x 2 cm), to a new test site for 24 h. Reactions were evaluated at 24 h and 48 h after patch removal. Chlorphenesin did not induce sensitization in guinea pigs at a concentration of 1%, followed by challenge with 0.5% or 1.0%.[23]

Human

A human repeated insult patch test was used to evaluate the skin irritation and sensitization potential of a test material containing 5 to 9% chlorphenesin.[24] Fifty-five male and female subjects (between 27 and 67 years old) completed the study. Three of the original 58 subjects withdrew for reasons unrelated to test material application. During induction, a 1 inch x 1 inch semi-occlusive patch containing the test material (0.2 mg/cm^2) was applied to the back, between the scapulae, of each subject. Patches were removed at 24 h, and any irritation reactions scored 24 h after patch removal. The scoring of reactions was followed by application of a new patch that remained for 24 h. This cycle was repeated for a total of 9 consecutive patch applications (i.e., 3-week induction phase). The 4-day challenge phase was initiated after a 10- to 14-day non-treatment period. A new patch containing 0.2 ml or 0.2 g of the test material was applied (24 h) to a new test site on the back. Reactions were scored at 48 h and 72 h post-application. Neither irritation nor sensitization reactions were observed during the study, and it was concluded that the test material did not have dermal irritation or allergic contact sensitization potential.

The skin irritation and sensitization potential of a different test material containing 12 to 17% chlorphenesin was evaluated using 53 male and female subjects (between 18 and 66 years old).[25] Three of the original 56 subjects withdrew from the study, and it was stated that one of the subjects withdrew for reasons unrelated to test material application. The test material (0.2 ml or 0.2 g) was applied using a semi-occlusive patch according to the test procedure immediately above. In one subject, barely perceptible erythema (score = 0.5) was observed on day 19 of induction and mild erythema (score = 1) was observed on day 22. The mild erythema observed was classified as a transitory, weak response that could be considered clinically insignificant.

In a multicenter study, the prevalence of preservative allergy in 584 patients (from 111 hospital dermatology departments in Korea) with cosmetic contact dermatitis symptoms was investigated from January of 2010 to March of 2011. This study will be published in August of 2012.[26] The patients were patch-tested to identify preservative allergens. An irritancy patch test (30 normal control subjects) involving allergens at various test concentrations was also performed. Study results indicated preservative hypersensitivity in 41.1% of the patients, and the allergens with the highest rates were as follows: benzalkonium chloride (12.1%), thimerosal (9.9%), and methylchloroisothiazolinone/methylisothiazolinone

(MCI/MI) (5.5%). Results of the irritancy patch tests identified benzalkonium chloride and chlorphenesin as having the highest irritancy rate. At 4 days, 7 of the 30 normal subjects had a positive irritant patch test reading to 0.1% benzalkonium chloride, and 8 of 30 had the same reaction to 0.5% chlorphenesin in petrolatum. The authors noted that the optimum concentration of chlorphenesin for avoiding skin reactions is less than 0.5%.

Case Reports

A 38-year-old female developed widespread acute dermatitis after using a proprietary antifungal powder and cream, both containing chlorphenesin.[27] Signs included severe maceration of the toe webs, with severe eczema of the foot. A generalized rash on the legs, forearms, and hands was also observed. Patch testing of individual constituents of the products used revealed a positive response only to 1% chlorphenesin in petrolatum. No reaction to this test concentration was observed in 3 control subjects.

A 60-year old atopic female developed facial eczema within several hours after applying a foundation (cosmetic) containing chlorphenesin.[28] Patch testing revealed an allergic response (++ reaction) to 1% chlorphenesin in petrolatum. The patient was not patch tested with the foundation. In a second report, a 33-year old female who used a proprietary moisturizing cream containing chlorphenesin had a 1 –month history of facial eczema. The eczema eventually involved the entire face and spread to the neck, upper chest, and upper arms. The patient had no personal or family history of atopy. Patch test results indicated a + reaction to 1% chlorphenesin in petrolatum and a +++ reaction to the moisturizer (as is). Both reactions were observed by day 2 and persisted to day 4.

In another case report, a 24-year-old male applied an ointment containing chlorphenesin to his feet twice daily to relieve itching.[29] Following 3 days of treatment, a symmetrical vesciculo-bullous eruption was observed on the dorsa of the feet. This reaction extended to the ankles and was accompanied by extensive eczema on the trunk and arms within 24 h. Patch testing resulted in a ++++ reaction to 0.5% chlorphenesin in white soft paraffin and to the ointment.

Chronic dermatitis of the axillae was reported for a 29-year-old female who used a deodorant that contained chlorphenesin.[30] She also had a past history of allergy to metallic jewelry. Patch results for the deodorant were positive at 48 h (+ reaction) and 96 h (+ reaction), and patch test results for 1% chlorphenesin in petrolatum were positive at 48 h (+ reaction) and 96 h (++ reaction). Positive reactions were not observed in 5 control subjects patch tested with 1% Chlorphenesin in petrolatum.

A 43-year old female experienced burning discomfort and developed a florid eczema after applying a facial moisturizer containing chlorphenesin.[31] The patient had a history of hay fever, but no history of medicament or cosmetic intolerance. Patch test reactions were positive (++) for chlorphenesin on days 2 and 4. Positive patch test reactions were also reported for the product on day 2 (++) and day 4 (+).

Photoallergenicity

Eleven patients photoallergic to ketoprofen were photo patch tested with chlorphenesin.[32] Testing was initiated on day 0 and the subjects were irradiated with UVA light (5 J/cm^2) at day 2. Readings were performed on days 3 and 4 according to International Contact Dermatitis Research Group recommendations. There were no positive reactions in patients photo patch tested with chlorphenesin.

Immunosuppression

The immunosuppressive activity of chlorphenesin was evaluated using groups of 3 to 4 albino rabbits.[33] The groups were immunized with 1 ml of antigen (gram-positive bacteria (CA+) alone or antigen + chlorphenesin). A total of 3 i.v. injections (1 ml) of each was made on days 0, 3, and 7 according to the following procedure: Group 1 (control) received the mixture of one part of CA(+) antigen (final dilution of 1:100) and 9 parts of buffer. Group 2 received a mixture of one part of antigen and 9 parts of chlorphenesin at concentrations of 0.01, 0.1, 1, or 10 mg/ml. Prior to injection, these mixtures were incubated (37°C) for 30 minutes. Group 3 received the same antigen-chlorphenesin mixtures without prior incubation. The fourth group received antigen and chlorphenesin, albeit separate injections. When tested at a concentration of 1 or 10 mg/ml, but not 0.01 or 0.1 mg/ml, chlorphenesin markedly inhibited the CA (+) hemagglutinin response. It was also noted that injection of the non-incubated mixture and separate administration of the 2 materials into separate ear veins caused an undiminished immune response. The results of additional experiments indicated that chlorphenesin suppressed antibody

formation less effectively when larger amounts of antigen were used. With smaller amounts of antigen, chlorphenesin partially inhibited the antibody response, even at a concentration of 0.1 mg/ml.

The immunosuppressive activity of chlorphenesin was studied using a wide variety of *in vitro* assays for cellular immunity in both humans (25 to 40 years old) and mice (6 to 11 months old) of the following strains: BALB/c, C57Bl/6, and BDF_1 (C57Bl x DBA) F_1 mice.[34] At concentrations of 20 to 50 µg/ml, chlorphenesin inhibited mitogenic responses of B and T cells from mice and humans. Exposure to these doses for 72 h did not result in death of B or T cells. Mixed lymphocyte reactions in cells from inbred strains of mice and unrelated humans were also inhibited at concentrations of approximately 50 µg/ml. In light of these results, the generation of cytotoxic T cells in cell-mediated lympholysis assays was not inhibited to the same extent as proliferation in mixed lymphocyte reactions. Also, the cytotoxic potential of pre-sensitized mouse T cells for allogeneic targets was totally unaffected. The results of these studies suggest that chlorphenesin may have a broad spectrum of suppressive effects on both B and T lymphocytes and that the predominant inhibition of proliferative responses in these lymphocytes may reduce the expansion of clones of immunocompetent cells *in vivo*.

The effect of chlorphenesin on the immune response in mice, rabbits, and guinea pigs was studied.[35] Male Swiss Webster mice were injected with chlorphenesin mixed with sheep red blood cells (S-RBC) or chicken red blood cells (C-RBC), or penicillin conjugated to keyhole limpet hemocyanin intravenously (i.v., volume = 0.1 ml). An assay for localized hemolysis was then performed, in which the degree of hemolysis was determined after 2 h. Groups of 4 to 8 New Zealand White rabbits were used to determine the presence of circulating antibodies. The antigens were injected into the hind footpads and subcutaneously (s.c.) over each shoulder. The rabbits were bled and tested for antibody titers for up to 21 days post-immunization. Male albino guinea pigs were sensitized with bacillus Calmette-Guérin (BCG) vaccine intradermally and challenged intradermally with old tuberculin at 5 weeks post-sensitization. In the localized hemolysis assay, partial hemolysis was noted at a concentration of 10 mg/ml. The joint administration of an antigen with chlorphenesin (50 mg/kg dose) greatly reduced the number of antibody-forming cells in the spleen. The simultaneous administration of antigen with chlorphenesin also resulted in suppression of formation of humoral antibodies in mice and rabbits. Chlorphenesin was effective as an immunosuppressive agent only when administered jointly with an antigen, did not affect existing antibody levels or the secondary response, and did not increase the susceptibility of the animals to infections. If administered at the time of challenge, chlorphenesin (100 and 200 mg/kg doses) affected the BCG reaction, i.e., significantly decreased the tuberculin reaction in guinea pigs.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

The effect of chlorphenesin (suspension in 1% methylcellulose) on pregnancy and *in utero* development of the rat was evaluated using 4 groups of 25 sexually mature, Specific Pathogen Free female rats of the Crl: CD®BR VAF/Plus strain (8 to 10 weeks old).[36] Three groups received oral doses (gavage; dose volume = 10 ml/kg body weight) of 10, 50, and 100 mg/kg, respectively, once daily on days 6 to 15 post-coitum. The control group was dosed with the vehicle (1% methylcellulose) according to the same procedure. The animals were killed on day 20 and necropsy was performed to identify any congenital abnormalities or macroscopic pathological changes in maternal organs. Tissues were preserved for microscopic examination. There was no evidence of maternal toxicity at either of the 3 administered doses, and neither maternal body weight gain nor food intake was affected by treatment. Increased fur loss and transient post-dosing salivation were observed in the highest dose (100 mg/kg/day) group. Based on necropsy results, it was considered unlikely that fur loss was test substance-related. At all doses administered, chlorphenesin had no adverse effect on embryo-fetal survival, growth, or development *in utero*. The no observed effect level for selective toxicity to the developing fetus was considered to be 100 mg/kg/day.

GENOTOXICITY

The genotoxicity of chlorphenesin was evaluated in the Ames test (bacterial reverse gene mutation assay) using the following *Salmonella typhimurium* strains: TA 98, TA 100, TA 1535, TA 1537, and TA 1538.[37] Test concentrations up to 5,000 µg/plate were evaluated with and without metabolic activation . 2-Aminoanthracene served as the positive control for metabolic activation cultures and 2-nitrofluorene, 9-aminoacridine, and N-ethyl-N'-nitro-N-nitrosoguanidine served as positive controls for non-activation cultures. Chlorphenesin was not genotoxic with or without metabolic activation over the range of concentrations tested. The positive controls were genotoxic. The same conclusion was reached in another Ames test evaluating the genotoxicity of chlorphenesin in *Salmonella typhimurium* strain TA 102 and *Escherichia coli* strain WP2 uvrA over the same test concentration range (with and without metabolic activation).[38] Both positive controls (2-aminoanthracene and methyl methane sulfonate [non-activation]) were genotoxic to both strains.

Chlorphenesin was also evaluated in a forward gene mutation assay using Chinese hamster ovary cells.[39] The test substance was evaluated at concentrations up to 1500 µg/ml with and without metabolic activation. In this assay, forward mutation at the functionally hemizygous hypoxanthine-guanine phosphoribosyl transferase (HPRT) locus is detected by the ability of cells that have suffered genetic damage at this locus to form colonies in the presence of 6-thioguanine. Dimethyl sulfoxide (DMSO) served as the vehicle control and ethyl methanesulfonate (EMS, without metabolic activation) and 20-methylcholanthrene (20-Mc, with metabolic activation) served as positive controls. Without and with metabolic activation, dose-related cytotoxicity was noted at concentrations > 850 µg/ml and > 550 µg/ml, respectively. No significant correlation between mutant frequency and increasing dose levels was induced by chlorphenesin either with or without metabolic activation. Neither chlorphenesin nor the vehicle control was genotoxic either with or without metabolic activation. The positive controls (EMS and 20-Mc) were genotoxic.

CARCINOGENICITY

Antitumorigenicity

In a study involving groups of Strain A (inbred strain) female mice, immune competence during initiation-promotion carcinogenesis was determined by the length of time required to reject allografts of tail skin and by the incorporation of [^{3}H]thymidine by lymphocytes stimulated with the mitogens phytohemoagglutinin (PHA) and pokeweed mitogen (PWM).[40] During initiation-promotion carcinogenesis, mice were also treated with chlorphenesin, predicated on its reported effects to increase immunological reactivity, particularly cellular immunity. The skin grafting experiment involved 5 groups of mice. Initially, 2.5% croton oil (20 µl) was applied to the intrascapular area twice per week for 30 weeks, and mice were treated with a single application of 7,12-dimethylbenzanthracene (DMBA, 100 µg) 10 days later. The mice were then separated into 2 groups, with and without tumors, respectively. In order to study the effect of the initiating and promoting agents, DMBA (100 µg) was applied to the interscapular area of each animal in the third group at 10 days before grafting. The fourth group was treated with 2.5% croton oil (20 µl) according to the same procedure, and the fifth group served as the untreated control group.

The experiment using lymphocyte cultures also involved 5 groups of mice. Groups 1 and 2 were treated with DMBA and croton oil, respectively (same doses), and Group 3 received two 2.5 mg doses of chlorphenesin i.p. (same day). Group 4 received a dermal application of croton oil and two i.p. doses of chlorphenesin, and Group 5 served as the untreated control group. The mitogenic response of lymphocytes to PHA and PWM was determined using whole blood lymphocyte cultures. The tumor initiation-promotion experiment involved 2 groups of 30 Swiss mice. In the first group, DMBA (100 µg) was applied to the interscapular area of each animal, and, after 3 weeks, 2.5% croton oil was applied to the skin twice weekly for 20 weeks. Group 2 animals received applications of DMBA and croton oil plus two 2.5 mg injections of chlorphenesin i.p. (same day) at the same time that croton oil was applied. The animals were necropsied at 20 weeks. The carcinogen 7,12-dimethylbenzanthracene inhibited the cellular immune competence of mice, and lymphocytes from mice treated with croton oil had enhanced PWM response. Chlorphenesin inhibited tumorigenesis in initiation-promotion skin carcinogenesis when injected during promotion.[40]

Female Swiss mice were injected i.p. (day 0) with 0.2 ml of Rauscher murine leukemia virus (RMLV) or Friend murine leukemia virus (FMLV) suspension and distributed randomly into paired groups of 18 to 20 mice each.[41] Chlorphenesin in warm Hank's balanced salt solution (HBSS) was then injected i.p. (dose = 100 mg/kg in 0.5 ml) in the morning and late afternoon on each day of treatment. Chlorphenesin was injected into the RMLV mice on days 1, 2, 3, 4, 7, and 8, and FMLV mice received injections on days 1, 2, 6, 7, 9, 12, and 13. Control mice were injected with HBSS only after virus injection according to the same schedules. Injected virus routinely resulted in 80% mortality in leukemic control groups within 50 to 60 days. Chlorphenesin caused a pronounced sparing effect on mortality due to leukemia after infection with RMLV. Delayed onset of early death in chlorphenesin-treated mice was observed, but the most characteristic finding was the marked sparing effect in later stages of the disease. Mortality in mice dosed with chlorphenesin leveled off at 40%; however, controls continued to die at a nearly linear rate.

Additional experiments evaluating antiviral activity suggested that chlorphenesin was probably acting on malignant cells rather than against the transforming virus. In an effort to confirm this, Leukemia L-1210 in ascites form was implanted s.c. into B6DF1 mice, and results indicated that chlorphenesin had little effect against conventional massive i.p. doses of this highly malignant cell line. However, when the system was modified by using reduced numbers of cells implanted s.c., the

sparing effect was readily demonstrable. More than 40% of the treated mice survived until the experiment was terminated at 50 days, at which time there was no visible evidence of residual tumor.

Clinical trials involving cancer patients were conducted by the Clinical Screening Group of the European organization for Research on Treatment of Cancer. Patients (31) with a wide range of neoplasms had been treated with chlorphenesin for periods ranging from 1 to 6 weeks. Oral doses ranged from 1 to 6 g daily, with a usual dose of 4 g/day. Treatment with chlorphenesin was ineffective in 16 cases of carcinoma (cervix, uterus, tonsil, esophagus, and lung) and in 4 cases of sarcoma. However, in 9 cases of squamous cell carcinoma of the skin, complete remission was achieved in one patient and substantial, though incomplete, remission was achieved in 4 other patients. For 2 patients with basal cell carcinoma, no benefit was observed.[41]

SUMMARY

Chlorphenesin, a biocide, is produced by condensing equimolar amounts of p-chlorophenol and glycidol in the presence of a tertiary amine or a quaternary ammonium salt as a catalyst. According to information supplied to the Food and Drug Administration (FDA) by industry as part of the Voluntary Cosmetic Registration Program (VCRP) in 2012, chlorphenesin was being used in 1,386 cosmetic products. Furthermore, results from a survey of ingredient use concentrations provided by the Personal Care Products Council in 2011 indicate that chlorphenesin was being used at concentrations up to 0.32% (rinse-off products) and up to 0.3 % (leave-on products). Similarly, the maximum authorized use of this ingredient as a preservative in cosmetic products marketed in the European Union is 0.3%.

Some confusion may result in terminology because the drug chlorphenesin carbamate (CAS No. 886-74-8) also may be known as chlorphenesin. The cosmetic ingredient, chlorphenesin (CAS No. 104-29-0), is a different chemical.

The results of a toxicokinetic study involving rats and dogs indicated that chlorphenesin was rapidly absorbed and excreted mainly in the urine. Urinary end products identified included 3-p-chlorophenoxylactic acid, p-chlorophenoxyacetic acid, and unchanged chlorphenesin. In an *in vivo* percutaneous absorption study involving rats, up to 57% of the applied dose was absorbed and practically all of the absorbed dose was excreted over a period of 96 h.

In an acute oral toxicity study (rats), a mean oral LD50 of 3,000 mg/kg was reported for chlorphenesin. Repeated oral dosing of rats with chlorphenesin for 28 days caused a significant decrease in body weight gain and significantly lower hemoglobin levels in the highest dose group (1,000 mg/kg/day) when compared to controls. Significantly decreased spleen and thymus weights were also reported for this group. The only treatment-related microscopic finding in the study, renal tubular dilatation/necrosis, occurred in one male rat from the highest dose group. A badly groomed appearance and increased salivation were observed in the 100 mg/kg/day dose group. A dose of 10 mg/kg/day was considered the no adverse effect level in this study.

Chlorphenesin was classified as a weak ocular irritant when instilled into the eyes of rabbits at a concentration of 1%. The same test concentration did not induce skin irritation when applied, under an occlusive patch, to rabbits for 24 h. Negligible dermal irritation was observed in 3 of 25 subjects tested with 0.3% chlorphenesin in a 48 h occlusive patch test. In a sensory irritation test involving 16 healthy subjects, irritation induced by a formula containing methylparaben, propylparaben, and chlorphenesin was greater when compared to the same formula without chlorphenesin. In the guinea pig maximization test, chlorphenesin did not induce sensitization at a concentration of 0.5% or 1%. These 2 concentrations were classified as non-irritating in a preliminary test to determine the maximal irritant concentration.

In a human repeated insult patch test (HRIPT) involving 55 subjects, a test material containing 5 to 9% chlorphenesin did not have skin irritation or allergic contact sensitization potential. A test material containing 12 to 17% chlorphenesin induced clinically insignificant erythema in one of 53 subjects in another HRIPT. When 11 patients photoallergic to ketoprofen were photo patch tested with chlorphenesin, results were negative. In case reports, positive patch test reactions to 0.5% and 1% chlorphenesin were reported.

In a study evaluating the immunosuppressive activity of chlorphenesin in albino rabbits, marked inhibition of the CA (+) hemagglutinin response was observed at test concentrations of 1 or 10 mg/ml, but not 0.01 or 0.1 mg/ml. In other animal studies, the simultaneous administration of antigen with chlorphenesin resulted in suppression of formation of humoral antibodies in mice and rabbits. When the immunosuppressive activity of chlorphenesin was studied using a wide variety of *in vitro* assays for cellular immunity in both humans and mice, the results suggested that it may have a broad spectrum of suppressive effects on both B and T lymphocytes. However, dosing with chlorphenesin did not increase the susceptibility of animals to infections *in vivo.*

Chlorphenesin had no adverse effect on embryo-fetal survival, growth, or development *in utero* when administered orally to rats at doses up to 100 mg/kg/day on days 6 to 15 post-coitum. In the Ames test, chlorphenesin was not genotoxic to the following bacterial strains when tested at concentrations up to 5,000 µg/plate with or without metabolic activation: *S. typhimurium* strains TA 98, TA 100, TA 102, TA 1535, TA 1537, and TA 1538, and *E. coli* strain WP2 uvrA. Chlorphenesin also was not genotoxic, with or without metabolic activation, in a forward mutation assay using Chinese hamster ovary cells.

In an initiation promotion experiment, DMBA (100 µg) was applied to the interscapular area of each of 30 mice, and, after 3 weeks, 2.5% croton oil was applied to the skin twice weekly for 20 weeks. A second group of 30 mice received applications of DMBA and croton oil plus two 2.5 mg injections of chlorphenesin i.p. (same day) at the same time that croton oil was applied. Chlorphenesin inhibited tumorigenesis in initiation-promotion skin carcinogenesis when injected during promotion. In another study, mice previously injected with murine leukemia virus (RMLV or FMLV) were injected i.p. with 100 mg/kg chlorphenesin for up to 7 days. Chlorphenesin caused a pronounced sparing effect on mortality due to leukemia after infection with RMLV. Thirty-one cancer patients received chlorphenesin orally at a usual daily dose of 4 g/day for 1 to 6 weeks. Treatment was ineffective in 16 cases of carcinoma (cervix, uterus, tonsil, esophagus, and lung) and in 4 cases of sarcoma. However, in 9 cases of squamous cell carcinoma of the skin, complete remission was achieved in one patient and substantial, though incomplete, remission was achieved in 4 other patients.

DISCUSSION

The Food and Drug Administration (FDA) initially requested the review based on the agency's previous recall of a nipple cream containing chlorphenesin, based on concerns about skeletal muscle relaxation, central nervous system depression, and respiratory depression in infants. The CIR Expert Panel opined that the drug chlorphenesin carbamate (CAS No. 886-74-8, also known as chlorphenesin) is known to have muscle relaxant effects, but such effects are not expected for the cosmetic ingredient, chlorphenesin (CAS No. 104-29-0). Based on the use concentration of chlorphenesin in cosmetics and the dermal route of exposure, serum concentrations would never reach levels that are needed to cause muscle relaxation.

Chlorphenesin has no significant acute oral toxicity, a no observable adverse effect level of 10 mg/kg/day in a 28-day repeated oral toxicity study, and minimal ocular irritation. Chlorphenesin was not a dermal irritant, sensitizer, or photosensitizer. Chlorphenesin is not genotoxic in bacterial assays. Oral and other carcinogenicity studies suggested antitumor activity. The ingredient was not an oral reproductive or developmental toxicant. When applied to the skin, chlorphenesin was well-absorbed.

The Expert Panel acknowledged the potential immunosuppressive activity of chlorphenesin, based on *in vitro* assay results. However, after considering that dosing with chlorphenesin did not increase the susceptibility of animals to infections or act as a tumor promoter in *in vivo* studies, it was agreed that there would be very little to no concern relating to the immunosuppressive activity of chlorphenesin as an ingredient in cosmetic products.

The Panel considered the study in which chlorphenesin was reported to increase the sensory irritation potential of some creams, especially when used concomitantly with parabens + phenoxyethanol. The Panel had evaluated such sensory irritation potential when it considered alpha hydroxyl acid ingredients, and determined that the sensitivity of tissue around the area of the eye to sensory irritation was such that AHA-containing products intended for use near the eye be formulated in such a way to reduce stinging and burning reactions. AHA ingredients, however, were also known dermal irritants, where chlorphenesin is not. Currently, concerns about sensory irritation may be more relevant for baby products, e.g. diaper creams. Chlorphenesin, however, is not reported to be used in baby products.

CONCLUSION

The CIR Expert Panel concluded that chlorphenesin is safe in the present practices of use and concentration described in this safety assessment.

Table1. Properties of Chlorphenesin

Form	White powder with bitter taste. Almost odorless.[42]
Molecular Weight	202.63[3]
Density	0.70 to 0.75[42]
Solubility	Soluble in 200 parts water and in 5 parts alcohol (95%); soluble in ether; slightly soluble in fixed oils;[42] Solubility in water < 1%[3]
Melting Range	78 to 81°C[42]
Flash Point	100°C[42]
Assay (Dried Basis)	Contains not less than 99.0% $C_9H_{11}ClO_3$[42]
Loss on Drying	Not more than 1.0%[42]
Sulfated ash	Not more than 0.10%[42]
Chlorophenol	Complies with British Pharmacopoeia specifications[42]

Table 2. Current Frequency and Concentration of Use According to Duration and Type of Exposure Provided in 2011and 2012[6,7]

	Chlorphenesin	
	# of Uses	Conc. (%)
Exposure Type		
Eye Area	246	0.02 to 0.3
Incidental Ingestion	3	0.2 to 0.3
Incidental Inhalation-sprays	25	0.2 to 0.3
Incidental Inhalation-powders	57	0.2 to 0.3
Dermal Contact	1280	0.00004 to 0.32
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	48	0.0003 to 0.3
Hair-Coloring	NR	0.000008 to 0.003
Nail	2	0.0003 to 0.2
Mucous Membrane	24	0.00004 to 0.3
Baby Products	NR	NR
Duration of Use		
Leave-On	1224	0.0003 to 0.3
Rinse off	159	0.000008 to 0.32
Diluted for (bath) Use	3	0.0006 to 0.3
Totals*/Conc. Range**	1386	0.000008 to 0.32

NR = Not Reported; Totals = Rinse-off + Leave-on Product Uses
NOTE: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not be equal to sum total uses.

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Data

2012 FDA VCRP Data
Chlorphenesin

02D - Other Bath Preparations	3
03B - Eyeliner	2
03C - Eye Shadow	107
03D - Eye Lotion	33
03E - Eye Makeup Remover	3
03F - Mascara	53
03G - Other Eye Makeup Preparations	48
04C - Powders (dusting and talcum, excluding aftershave talc)	5
04E - Other Fragrance Preparation	9
05A - Hair Conditioner	9
05B - Hair Spray (aerosol fixatives)	2
05D - Permanent Waves	1
05E - Rinses (non-coloring)	2
05F - Shampoos (non-coloring)	11
05G - Tonics, Dressings, and Other Hair Grooming Aids	15
05I - Other Hair Preparations	8
07A - Blushers (all types)	35
07B - Face Powders	52
07C - Foundations	51
07D - Leg and Body Paints	1
07E - Lipstick	3
07F - Makeup Bases	11
07G - Rouges	1
07I - Other Makeup Preparations	7
08A - Basecoats and Undercoats	1
08G - Other Manicuring Preparations	1
10A - Bath Soaps and Detergents	6
10E - Other Personal Cleanliness Products	12
11A - Aftershave Lotion	20
11E - Shaving Cream	4
11G - Other Shaving Preparation Products	2
12A - Cleansing	70
12C - Face and Neck (exc shave)	198
12D - Body and Hand (exc shave)	97
12E - Foot Powders and Sprays	2
12F - Moisturizing	302
12G - Night	47
12H - Paste Masks (mud packs)	39
12I - Skin Fresheners	14
12J - Other Skin Care Preps	87
13A - Suntan Gels, Creams, and Liquids	5
13B - Indoor Tanning Preparations	4
13C - Other Suntan Preparations	3
Total	**1,386**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: F. Alan Andersen, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: July 9, 2012

SUBJECT: Comments on the Tentative Report on Chlorphenesin

p.1, 9, 10 - The CAS number provided for chlorphenesin carbamate (886-754-8) is not correct. CAS numbers always have two (not three) digits after the first dash.
p.3 - "92.35% dose + 3.11" needs to be changed to "92.35% dose +/-3.11"
p.4, 9 - Please include the concentration of Chlorphenesin tested in the mixture with methylparaben and propylparaben (reference 19).
p.4 - In the last sentence on this page, it would be helpful to add "at the highest concentration generally used in cosmetics".
p.8, third paragraph - Chlorphenesin at the start of the second sentence needs to be capitalized. Please correct the spelling of "chlorpehensin"
p.9 - In the Summary, it would be helpful to note that the 0.3% limit in Europe refers to use of Chlorphenesin as a preservative.
p.9 - Please remove the extra page breaks after the second paragraph.
p.10 - The dermal penetration study in rats indicated that about 57% of the dose of Chlorphenesin was absorbed. Does the CIR Expert Panel really consider a substance with this level of absorption to be "not well-absorbed?"
p.10 - In the last paragraph of the Discussion, please change: "where chlorphenesin is not" to "where chlorphenesin is not a dermal irritant at current use concentrations."
p.11, Table 2 - For reports with only one ingredient, please present the use information by FDA product category.

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