Safety Assessment of Diakyl Malates as Used in Cosmetics

CIR EXPERT PANEL MEETING
SEPTEMBER 10-11, 2012
August 17, 2012

MEMORANDUM

To: CIR Expert Panel and Liaisons
From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Subject: Draft Final Report for dialkyl malates as used in cosmetics

In June, 2012, the CIR Expert Panel issued a tentative safety assessment for public comment with a safe as used conclusion for dialkyl malates.

No new data have been submitted. Industry comments have been addressed.

The Panel should review the Draft Final Report and ensure that the abstract, discussion, and conclusion reflect the Panel’s thinking.

The Panel should issue a Final Report.
SAFETY ASSESSMENT FLOW CHART

*The CIR Staff notifies 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

* Draft Priority List
* 60 day public comment period
* ANOUNCE
* 2011

Priority List INGREDIENT

Prioritized List

DRAFT PRIORITY LIST

Is new data cause to reopen?

- NO
- YES

DOES NEW DATA SUPPORT
ADDITION OF NEW INGREDIENTS?

- NO
- YES

* Draft Amended Report
  * Green Cover 1st time
  * Pink Cover 2nd time

* Draft Amended Tentative Report

* Draft Amended Final Report
  * Blue Cover

* Final Report
  * 60 day Public comment period
  * PUBLISH

* Draft Report
  * 60 day Public comment period
  * ISD Notice

* Draft TR ISD
  * 60 day Public comment period
  * TABLE

* Draft Tentative Report
  * 60 day Public comment period
  * Issue TR

* Draft Final Report
  * 60 day Public comment period
  * TABLE

* Table
  * Diff. Concl.

* Issue FR

CIR Panel Book Page 1
History of Dialkyl Malates
(formerly known as the Malates and Tartrates (dialkyl hydroxysuccinates and hydroxysuccinic acids))

June, 2011 - Added to the 2011 Priority List.

August, 2011 – SLR announced.

December, 2011 – The Panel removed the tartrates, malic acid and tartaric acid from the safety assessment (6 ingredients remaining). Data from the malic acid/sodium malate report are to be included in the new dialkyl malate report.

The Panel issued an insufficient data announcement. The Panel was looking for data on: genotoxicity, 28-day dermal toxicity, and sensitivity for dioctyldecyl malate.

June, 2012 – The Panel examined the new data and concluded that the dialkyl malates were safe.

September, 2012 - The Panel is to issue a Final Report.
### Malate aXd tartrate Data Profile for September, 2012. Writer - LilliaX Becker

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X = Xew data.
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April, 2011  

1323 hits for “L-Tartaric Acid” OR “tartaric acid” OR “d-tartaric acid”. With irritation, sensitization, phototoxicity, photoallergenicity, immunotoxicity, pharmacokinetic, tumorigenicity, carcinogenicity, genotoxicity, reproductive or developmental – 13 hits, none useful.

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April, 2011  

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Distributed for Comment - Do Not Cite or Quote

CIR Panel Book Page 7
Transcripts for Alkyl Malates
June, 2012 Meeting

Dr. Belsito's Team

DR. BELSITO: Okay. Dialkyl malates. That's Pink. Okay. In December, we issued an insufficient data announcement for the six ingredients. What we wanted was genotox 28-day dermal tox, and against my better judgment because of a couple of case reports sensitization, dermal sensitization for dioctyl dodecyl malate which that request as you may recall came from the Marks' team. Industry has submitted data and essentially we have everything we asked for except for dermal sensitization data for dioctyl dodecyl malate, which I continue to believe we do not believe. And I would go safe as used, although if the other team remains committed to what they said before, they probably will go insufficient for the dioctyl dodecyl malate based on sensitization data. So I welcome comments from my colleagues and those around the table.

DR. LIEBLER: I agree, safe as used. Let's see what they say about octyl dodecanol. Was there concern in the case report that irritation of the octyl dodecanol? I'm trying to remember where that came from.

DR. BELSITO: No, it was --

MS. BECKER: I think it was the alcohol, not the malate.

DR. LIEBLER: It's at the bottom of page 7. Panel Book page 36, the bottom of that page, case reports. I'm sorry, top of page 37. I'm trying to remember where that came from and is that significant enough to require the additional test.

DR. BELSITO: You know, I mean, there are two individual case reports without any other significant data in the literature. You know, and yet we look at compounds like quaternium-15 where there are 200,000 case reports in the literature of contact dermatitis. My clinical judgment is that octyl dodecanol is not a significant clinical issue, nor is it when it's compounded with maleic acid. So I personally don't have an issue with this. I mean, it's two case reports in the history of the world's literature but, I mean, so I thought that there was no need to delete that specific ingredient. But that's my own personal feeling.

But I guess the issue before us, besides my personal feeling, is do we have sufficient genotoxicity and dermal toxicity data, and I think we do. And then since I will be representing you tomorrow, assuming you agree with that, do you feel that sensitization data needs to be done on dioctyl dodecyl malate?

DR. LIEBLER: No.

DR. BELSITO: Paul, Curt?

DR. KLAASSEN: I'm fine with it.

DR. SNYDER: No, I'm okay with it. On page 22, the last sentence, that repeat dose study and reproductive toxicity development of toxicity, was that in rats?

MS. BECKER: I'll double-check. It's either rats or rabbits.

DR. BELSITO: Yes, Rachel.

MS. WEINTRAUB: So when I reviewed this ingredient I had three questions that I wanted the panel to address. The first is sort of strange study mentioned as the last paragraph for genotoxicity for malic acid where it seems like the mutagenicity studies, one said it was mutagenic, one said it wasn't. So I'm wondering how the panel would reconcile that.

My second question was about in the carcinogenicity section that stated products formed from treatment of malic acid with aqueous solutions of chlorine were mutagenic. So does something need to be stated in the discussion or how should the panel deal with the chlorine issue? And then third, I think we touched on it previously, but the ocular irritation seems definitely pervasive on page -- CIR Panel Book 24, you know, footnote 33, costs of ocular irritation. So I wanted the panel to address each of these issues.

DR. LIEBLER: I think I can take the first one quickly. This is the issue of under genotoxicity, this is on Panel Book page 23, halfway down the page. Malic acid. In one study, pyrolozates of malic acid were not mutagenic but in another study they were. This is malic acid that has been basically roasted to produce some other product or products. I don't think that's relevant to considering malic acid or its esters, and I'm not sure even
why that's in there. I don't think it's relevant.

MS. WEINTRAUB: So should it be included?

DR. LIEBLER: I don't think it's relevant. I think it could be excluded because it's no longer malic acid.

MS. BECKER: Which one exactly?

DR. LIEBLER: It's the last paragraph under genotoxicity. The last sentence.

MS. BECKER: Off it goes.

DR. LIEBLER: Pyrolozates.

DR. BELSITO: Are you suggesting we delete that, Dan?

DR. LIEBLER: Yeah, that sentence.

MS. BECKER: Not a problem.

DR. BELSITO: Okay. And in terms of a chlorine, I'm assuming it's hypochlorite that's formed from chlorine and it's a product of the chlorine and has nothing to do with the malic acid. But I'm not a chemist. So Dan, do you want to comment?

DR. LIEBLER: Say where you are if you could.

MS. WEINTRAUB: The second sentence in carcinogenicity.

DR. LIEBLER: Okay, hang on. Yeah, this would be if you took malic acid and you mixed it with bleach and you have some products that they were mutagenic. That may be true. I think it's irrelevant to the use of maleic acid or its esters in cosmetic products because, you know, you're not going to have bleach in them. That's a severely oxidizing environment and again, it's like paralysis -- pyrolysis, excuse me, that I just objected to earlier. It's maybe true but irrelevant.

DR. BELSITO: So should that sentence be deleted?

DR. LIEBLER: Yes.

DR. BELSITO: Okay.

MS. WEINTRAUB: Is it possible that other chemicals could cause that type of bleaching or it's really the chlorine that causes this reaction and not --

DR. LIEBLER: It's probably the chlorine oxidizing the malic acid to some product or products that's mutagenic.

MS. WEINTRAUB: So it wouldn't happen, for example, with like hydrogen peroxide which could be a bleaching agent but totally different?

DR. LIEBLER: Not in the same league with hypochlorite.

MS. WEINTRAUB: Okay.

DR. BELSITO: And then in terms of the irritation, that really was malic acid, which is really going to be more of a pH adjuster rather than salts and esters that we're looking at here. Anything else?

DR. EISENMANN: In the discussion..

DR. BELSITO: In the discussion..

DR. EISENMANN: Since you're using -- since a major use for dioctylidodecyl malate is in lipsticks, I don't think you want to say since these ingredients are not to be ingested in the discussion but I don't know exactly how you want it. I mean, you might want to say relative to -- I mean, don't know exactly how you want to word it but I just didn't think that was appropriate for the discussion.

And then my other concern in the discussion is on the next page --

DR. BELSITO: Wait a minute. Where are you?

DR. EISENMANN: I'm on page 25, the second paragraph in the discussion. Panel Book page 25.

DR. BELSITO: Okay.

DR. KLAASSEN: It said right here.

DR. BELSITO: Yeah.

DR. KLAASSEN: Not to be adjusted since they're in lipstick.

DR. BELSITO: Well --
DR. LIEBLER: How about simply saying possible ingestion of these ingredients under conditions of use would not be a reason for concern?

DR. BELSITO: Would be less than what a rat ate at 1 percent in the food product. And it wasn't toxic to dogs.

DR. EISENMANN: Well, that's a discussion about malic acid, too, versus what the ingredient is. I don't know, you might want to focus on the studies on the ingredient or on the esters versus the malic acid.

DR. BELSITO: No, I don't think we can do that. Dan, I sort of liked what you were saying, something to however. And so let's go back. You know, I really hate having these tables. I know they have to be in the back.

DR. SNYDER: The 1 percent.

DR. BELSITO: Well, it's --

MS. BECKER: It's in the discussion under cosmetic -- under use. And information is from page 2, under non-cosmetics.

DR. BELSITO: Well, we have new updated frequency of use data. And we have mucous membranes.

DR. LIEBLER: Oh, wait a minute. You have male rats fed diets containing 1 percent or more maleic acid. It's a different --

DR. SNYDER: So maleic acid is not relevant.

DR. LIEBLER: Okay, so the reason behind this research was a trace to a joint blah blah blah which expressed the need to impose a severe limitation on the content of maleic acid in malic acid due to the established nephrotoxicity of maleic acid. These are chemically very similar structures and one could be a contaminant in the other. Male rates fed diets containing 1 percent or more of maleic acid showed growth retardation, blah blah blah. So that's maleic acid.

So as long as the maleic acid is a contaminant of a malate product or a malate-containing product doesn't cross whatever that threshold would be, you're okay. Does that seem to make sense?

DR. BERGFELD: Are you putting that in the discussion?

UNIDENTIFIED SPEAKER: Yeah.

DR. BELSITO: So what's the threshold, or do we put that in the discussion or do we simply say manufacturers are to be cautioned about the potential contamination of malic acid with maleic acid?

DR. LIEBLER: Right. So I think the way to do this in the discussion, you could leave that paragraph, that second paragraph in and you could say this is due to nephrotoxicity and growth retardation due to contaminating maleic acid in feed.

DR. BELSITO: And the contamination was at 1 percent or it was -- we don't know? Where's the information on this? This was a --

DR. BERGFELD: Page 21.

DR. BELSITO: So this is 1 percent or more maleic acid.

DR. LIEBLER: Right, not malic.

DR. BELSITO: Not malic.

DR. LIEBLER: So what you could do --

DR. BELSITO: So in lipsticks, it's not even the malic acid that's used; it's the ester up to -- incident ingestion 82 percent diiososteryl malate. So let's assume 100 percent. I mean, and what do we have as a level of impurity? Do we have those listed? Ninety-nine percent pure with impurities being untreated raw materials. I mean, do we need to even say anything? The panel noted nephrotoxicity in rats due to their contamination of malic acid with maleic acid. However, given the purity of the cosmetic-grade substances and the concentrations at which this is used, we do not feel that this is an issue.

DR. LIEBLER: Right. I think that's fine. You don't need to mention the 1 percent in this case because it's confusing. And I agree with what you just said.

DR. BELSITO: So you'll craft that language and we'll get rid of the 1 percent retardation in rats at 1 percent maleic acid in feed if you include that at all. And then go on to point out the purity in the levels of use in
cosmetics does not warrant a concern for maleic acid.

MS. BECKER: Okay.

DR. BELSITO: Okay. So a few changes to the discussion.

DR. EISENMANN: I have one more.

DR. BELSITO: Okay.

DR. EISENMANN: This goes back to the aerosol boilerplates, the same sentence that I didn't like in the use section. I don't really like it in the discussion either because by now you should know what the properties are, and if you have a concern about whether or not these ingredients will cause effects in the upper respiratory tract, it's on page 26. It's in the last paragraph. It's the sentence, "Inhaled droplets, particles, deposited nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties." Well, by now you should know what the chemical properties of these ingredients are and express whether or not you have concerns rather than a general boilerplate.

DR. BELSITO: Well, we say coupled with small actual exposures in the breeding zone and concentrations at which they're used we're not concerned.

DR. EISENMANN: Right. So get rid of the sentence that says you should consider whether it's a concern.

DR. BELSITO: Well, then that goes back to readdressing the whole inhalation boilerplate and should have been raised at the time that we originally did that.

DR. EISENMANN: I didn't think it resolved where that sentence was from.

DR. LIEBLER: So the reason you need the sentence I think that you have a concern with is because of the previous sentence which says, "However, the potential for inhalation tox is not limited to respirable droplets, particles, deposited in the lungs." And then you're waiting for, okay, so now what? And then there's now what.

DR. EISENMANN: Well, actually, I'd get rid of both of those sentences.

DR. BELSITO: Well, but we don't have inhalation toxicity at all. And that was the boilerplate that we agreed to use when we didn't have toxicity data.

DR. EISENMANN: I didn't think we resolved what the actual boilerplate was going to be in the discussion.

DR. BELSITO: I thought we did at the last meeting.

DR. EISENMANN: And I've been looking on the website to read it and it hasn't been posted yet.

DR. BELSITO: Ah-ha. Maybe I was dreaming but I thought we spent a significant amount of time.

DR. EISENMANN: We did.

DR. BELSITO: At the last meeting and that we had come to a conclusion as to what would be used.

Ivan?

DR. LIEBLER: This is about the inhalation boilerplate language for a discussion section.

MS. BECKER: Carol is concerned about these two sentences.

DR. LIEBLER: Where we have no inhalation toxicity data. So the issue is the last three sentences of the discussion beginning with "however."

MR. BOYER: Yeah, those are right from the inhalation template is what we were calling it. And the question is --

DR. LIEBLER: So these sentences are part of the boilerplate that we approved last time?

MR. BOYER: Yes, they are.

DR. BELSITO: Okay.

DR. LIEBLER: That was the immediate reason we were asking you just to clarify.

DR. BELSITO: Okay.

DR. LIEBLER: And then we were discussing whether that needs to be there or not. It is part of the boilerplate. I kind of feel it should be there because we have a boilerplate for a reason.
DR. BRESLAWEC: No problem.
DR. BELSITO: Any other comments? Seeing none, we probably still have about 11 ingredients.

Dr. Marks' Team

DR. MARKS: Next is the dialkyl malates. And in December the Panel issued a formal insufficient data announcement for the six ingredients. And the needs were genotox, 28-day dermal tox, and dermal sensitization for diocetyldecyl malate. And I guess the first two are the genotox and the 28-day tox, and I doubt we'll get the dermal sensitization because diocetyldecyl isn't being used. Is that correct? So why would we get any data if it's not being used? So at any rate, how about the genotox and the 28-day dermal? Do we have enough now that we can move it forward? Well, we'll move it forward one way or another. The question is do we move it forward --

DR. SLAGA: Yeah, we have enough genotox.
DR. MARKS: So we have enough genotox now?
DR. SHANK: We do of the malates, yeah.
DR. SLAGA: Yes, we already have that. It's already in.
DR. MARKS: Oh, okay. Well, it's in this draft report. This is a draft tentative -- okay.
DR. SLAGA: We have repeated-dose toxicity in the dermis?
DR. HILL: Yes, and oral.
DR. SLAGA: Yup, and oral. So it's safe as used.
DR. SHANK: I think the conclusion's okay. I have one question. Why didn't we do a read-across for sensitization for diocetyldecyl malate?
DR. HILL: Because structurally it was very disparate from the others, the other terms of the structure of the side chain. And we had a sensitization-type hit for something that was branched in a similar fashion -- and I forget which other ingredient or ingredients. I can research what those other ingredients were, but there was a reason. It wasn't just pulled out of thin air.
DR. SHANK: Thank you.
DR. MARKS: So if we go on page 26, Panel Book page 26, you'll see that the conclusion is slightly different in that it's safe for ingredients except for insufficient data on the diocetyldecyl because of the sensitization. Do you like that conclusion? I do. We didn't get -- if we issued an insufficient data, we didn't get it on sensitization. Why should we now say it's safe?
DR. SLAGA: For that one.
DR. MARKS: Yeah, for that one.
DR. HILL: And that's what I wanted to see. So it's good with me.
DR. SHANK: Should we say in the discussion why we didn't do the read-across because structurally it isn't similar?
DR. SLAGA: It would be worthwhile to put that in the discussion.
DR. HILL: I was trying to remember -- I don't remember which report it was. I didn't have a stack of books because I don't think that particular one had been returned yet and I didn't get on the computer to find it, but somewhere along the line we had a sensitization alert for -- it was either that particular side chain or something quite close to it..
DR. SHANK: Okay, fine, but should we put that in the discussion?
DR. HILL: Yeah, I just wish I knew exactly which report we were talking about so she could write that or reference it.
MS. BECKER: Okay, or I'll just write a new one.
DR. HILL: I'll try to write something general, but it'd be nice to --
DR. MARKS: Well, I think it would also be a bit -- if we look on page 36, Panel Book and 37, the metabolite of diocetyldecyl malate -- this is in your bailiwick, Ron, you're always concerned about the
downstream. It increases dermal penetration, but when you turn the page there are two case reports -- one having a really brisk reaction is octyldodecanol.

DR. HILL: I have the book from last time and it might have been the --

DR. MARKS: And so I think if we want to include that in the discussion, we could. It's the case reports of the metabolite, the octyldodecanol was a sensitizer and that's why we wanted to see the sensitization data. And there we aren't even doing a read-across hypothesis. We actually have facts as to why we want to see them. Okay, got that, Lillian? If nothing else about the dialkyl malates, I'm going to move that we --

DR. SHANK: Page 22.

DR. MARKS: Thank you, Ron.

DR. SHANK: Book 22, report 3, right smack in the middle we have diisostearyl fumarate. Why is that included?

DR. MARKS: It's new.

DR. SHANK: Is it left over from an old report maybe, probably?

DR. HILL: I think it was intended to assist with read-across wasn't it?

MS. BECKER: Right, yes. Yes, malic acid, sodium malate, diisostearyl fumarate, and dibutyl malate were used for read-across purposes, if you look at the profile on page 3. If you think it's inappropriate, we can take it out.

DR. HILL: I think it should be removed, but thank you for supplying it. I just think it should be removed.

MS. BECKER: Well, Council supplied it.

DR. HILL: Yeah, I know. We have Council members in here.

DR. MARKS: So Ron Shank, I got the sense that you feel it should be removed also.

DR. SHANK: I do.

DR. MARKS: Okay. So, Lillian, that will be editorial. I don't know that we need to mention that tomorrow.

DR. SHANK: I do.

DR. MARKS: Page 28.

DR. SHANK: Thank you, Ron. So tomorrow I'll move that we issue a draft final report with a conclusion as stated on Panel Book page 26 that five of these ingredients are safe as used and for the dioctyldodecyl, there's insufficient information. We need dermal sensitization. Okay.

Day 2

DR. MARKS: In December of last year the panel issued an insufficient data announcement for these dialkyl malates. The data needs were geno-tox, 28-day dermal tox and dermal sensitization for the for the dialkyl dodecyl malate. We have received new data which covers the geno-tox and the 28-day dermal tox. We received no sensitization data for dialkyl dodecyl malate. So we move that we issue a draft final report as safe for five of the malates and insufficient for the dialkyl dodecyl malate as stated on page 28 of the panel book. Safe and insufficient, safe for the five, insufficient because of sensitization. That's a motion.

DR. BERGFELD: Don, do you want to respond?

DR. BELSITO: We're not seconding it because we don't feel that we have to take the dialkyl dodecyl out of that. That was all based on two case reports to dialkyl dodecanol, the alcohol, two case reports in the entire world's literature, without any other reports I haven't seen this as a significant player. If we did this on the basis of two case reports, how could we ever approve quarternium-15 that has thousands of case reports of sensitization?

DR. BERGFELD: Comments, Jim?

DR. MARKS: First of all, this is not being used so it's unlikely we're going to get the information probably. The other thing is that we don't have any safety assessment either on a guinea pig or on a human so even though there are two case reports of a metabolite of it, that to me particularly with the one case where it was a very positive patch test reaction and raised a red flag. So even though we would say safe in the same concentration in the same uses, without something that would substantiate -- we use the quarternium-15 analogy,
we have lots of RIPT and other data to support its safety even though there are case reports of sensitivity.

DR. BERGFELD: Is there any other discussion?

DR. HILL: We saw a previous instance where one of these long-chain branched in a particular way, side chains also caused clear sensitization so we felt like leaving that with insufficient given the fact that there are no uses reported wouldn't cause a big problem because if somewhere down the line wanted to come back and support the use, they would supply that sensitization data and be done with it. I know that's not a trivial request, but it's a reasonable one from where I sit.

DR. LIEBLER: I had less concern about the octyldodecanol because this case report was from testing with the alcohol as opposed to the malate ester and the malate ester of this material would arguably not produce the free alcohol in high concentration and anywhere near the concentration that was in that test. That was my logic for not reacting to that finding as you guys have.

DR. MARKS: With that reasoning and rationale I think we then could include it as safe as your team as suggested, so I withdraw my motion to have a safe and insufficient and would go all safe, but I would want that to be noted in the discussion the reason why we felt the dialkyl dodecanol malate is safe from a sensitization point, and I like your rationale.

DR. HILL: Then at that point I will disagree with Dan. I think you don't need to generate that large amount of such -- and there are lipases in the skin that potentially can do this, in reality we don't know one way or the other. A potential mechanism for sensitization can be as easy as converting to an aldehyde and linking to a sulfide and now we have a heptin. So I feel like this agent is not in use, to me there is no bad consequence of making it insufficient. I wasn't relying only on that case study. It was from a previous situation where we saw one of these long-chain branched fatty acid side chains causing a sensitization reaction with an ester and I didn't research yet to find out which one that was. So that's still the way I feel about it, and Dan's comments haven't changed my mind.

DR. BERGFELD: Thank you.

DR. BELSITO: I want Dan to comment on the maleic acid issue that we had discussed yesterday as well.

DR. LIEBLER: There was some confusing text was it pertaining to the fumarate? It was under noncosmetic use on Panel Book page 21 and it paragraph says DL malic acid are generally recognized as safe but at not for us in baby food because babies cannot digest D malic acid. The reason behind this restriction was traced to -- which expressed the need to impose a severe limitation on the content of maleic acid and malic acid due to -- toxicity of malic acid. So the problem I think comes up in the summary where it refers to maleic acid being nephrotoxic. Inadvertently I think that needed to be cleaned up because it was confusing the two. I think we explained this yesterday and covered it so I think that you've got that Lillian.

MS. BECKER: Yes, I do.

DR. BERGFELD: The motion has been made but not seconded.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? We have Ron Hill objecting. He would like to continue to have the insufficient for the one ingredient. Is there no other discussion? I'll call for the vote then. All those in favor of a safe conclusion? Abstaining? One against. Thank you. And I think we've recorded the reasons why.
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ABSTRACT

The Cosmetic Ingredient Review Expert Panel (the Panel) reviewed the safety of 6 dialkyl malate compounds used in cosmetics, including the widely used diisostearyl malate. These ingredients function mostly as skin-conditioning agents—emollients and pH adjustors. The Panel reviewed relevant animal and human data related to the ingredients along with a previous safety assessment of malic acid. The similar structure, properties, functions, and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. The Panel concluded that the available data support the safety of diisostearyl malate, dibutyloctyl malate, di-C12-13 alkyl malate, diethylhexyl malate, diisoamyl malate, and dioctyldodecyl malate.

INTRODUCTION

Dialkyl malates have a succinate core (a four-carbon, alkyl diacid ester) that is either mono- or di-hydroxy substituted.

The ingredients in this report are:
- Diisostearyl Malate
- Dibutyloctyl Malate
- Di-C12-13 Alkyl Malate
- Diethylhexyl Malate
- Diisoamyl Malate
- Dioctyldodecyl Malate

These ingredients function in cosmetics mostly as skin-conditioning agents—emollient (Table 1).

In 2001, the Cosmetic Ingredient Review Expert Panel (the Panel) reviewed and concluded that malic acid and sodium malate are safe for use as pH adjusters in cosmetic formulations. The Panel determined that the data are insufficient to determine the safety of these ingredients for any other functions. The data from that safety assessment are summarized in the appropriate sections below.

The similar chemical structures, physicochemical properties, and functions and concentrations used in cosmetics enable grouping these ingredients and reading across the available toxicological data to support the safety assessment of the entire group.

While dibutyl malate is not a cosmetic ingredient, it is a dialkyl malate and data regarding this chemical were considered relevant to the entire group. Where available, data on dibutyl malate were included in the appropriate sections.

Because these ingredients are esters, esterases in the skin may metabolize them to free acid and corresponding alcohol. For example, diisostearyl malate may result in isostearyl malate (the monoester), malic acid and isostearyl alcohol, which penetrate the skin. Accordingly, the available toxicity data on the corresponding alcohols are included in an appendix.

CHEMISTRY

Definition, Structure, and Manufacture

The core of all of these ingredients is succinic acid (a four-carbon, alkyl diacid), that is mono-hydroxy substituted. Malic acid and the malates are monohydroxy succinic acids. Except for the free acids and salts, these ingredients are esterified with an alkyl group at each end of the molecule. For instance, diisostearyl malate is monohydroxy substituted succinic acid, which is esterified at each end with a branched, eighteen carbon alkyl chain (i.e. isostearyl chain; Figures 1 and 2).

All of these ingredients have at least one stereocenter denoted by D, L, DL, meso or racemic in front of many of the names in the literature. The INCI names are defined as ambiguous to these stereochemical details. Stereochemical forms for the ingredients included in this report are identified where provided in the studies.

Malic Acid

Malic acid (monohydroxysuccinic acid), a white crystalline material, has one stereocenter, at the carbon bearing the hydroxyl group. The L-isomer is a natural constituent and common metabolite of plants (most commonly found in fruits) and animals.

DL-Malic acid is made by the catalytic oxidation of benzene to maleic acid, which is converted to malic acid by heating with steam under pressure. L-Malic acid is available through the microbiological fermentation of fumaric acid. The L-form of malic acid is the naturally occurring isomer and is found in unripe apples and other fruits.

A mixture of maleic, fumaric, rac-malic (or ±malic) acids heated with water in a closed space will cause the maleic acid to be consumed and the resulting solution to reach an equilibrium between fumaric acid and D-malic acid. Maleic and fumaric acids are by-products of the manufacture of malic acid. Malic acid is generally purified until the amounts of fumaric and maleic acid are 7.5 and <500 ppm, respectively.

Dialkyl Esters

The dialkyl esters of malic acid can be manufactured from malic acid by traditional esterification techniques, with the appropriate alcohol, and with or without acid or metal catalyst (Fischer esterification). For example, diethylhexyl malate...
can be manufactured from malic acid and ethylhexanol with a titanium catalyst.\textsuperscript{7}

### Chemical and Physical Properties

Chemical and physical properties of these ingredients are provided in Table 2.

Diethylhexyl malate was reported to be 99% pure with the impurities being unreacted raw materials.\textsuperscript{8} Diethylhexyl malate is soluble in oil, ethanol, and silicone, and insoluble in propylene glycol, water, and dimethicone.\textsuperscript{8}

### USE

#### Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) and a survey conducted by the Personal Care Products Council (Council) has collected maximum use concentrations for ingredients in this group (Table 3).\textsuperscript{9,10}

The total number of VCRP reported uses of diisostearyl malate was 694 (690 uses in leave-on products; 345 uses in lipsticks) and was reported to be used at a maximum of 0.001% - 82% (up to 0.2%-82% in leave-on products and 0.001% - 29% in rinse-off products; up to 82% in lipstick). Di-C12-13 alkyl malate was reported to be used in 27 products (24 in leave-on products; 26 with dermal exposure) and was reported to be used up to 1% - 36% in leave-on products (makeup foundation). Diethylhexyl malate was reported to be used in 12 products (11 leave-on products) and was reported to be used up to 0.4% - 2% in leave-on products and 2% in rinse-off products.

There were no reported uses for: dibutyloctyl malate, diisooamy1 malate, and dioctyldodecyl malate.

Diisostearyl malate is reported to be used in cosmetic sprays, including fragrance products, and could possibly be inhaled. These ingredients are reportedly used at concentrations up to 10% (other fragrance preparations). In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm.\textsuperscript{11-14} Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.\textsuperscript{15,13}

#### Non-Cosmetic

\textit{D}- and \textit{L}-malic acid, when meeting Food Chemicals Codex specifications, are generally recognized as safe (GRAS) as direct food additives for use as flavor enhancers, flavoring agents, and adjuvants, and as a pH control agent, but are not GRAS for use in baby foods because babies cannot digest \textit{D}-malic acid.\textsuperscript{15-17} The reasoning behind this restriction was traced to a Joint Food and Agriculture Organization of the United Nations/World/Health Organization Expert Committee on Food Additives report which expressed the need to impose a severe limitation on the content of maleic acid in malic acid due to the established nephrotoxicity of maleic acid.\textsuperscript{18} Male rats fed diets containing 1% or more maleic acid showed growth retardation, increased mortality, and changes in the renal proximal convoluted tubules.\textsuperscript{19} However, another study using dogs that were fed the same levels that showed no toxicity. Therefore, the restriction was set only for baby food (Dr. Linda Katz, USFDA, March 5, 2012). Neither \textit{D}- or \textit{DL}-malic acid should be added to food of young infants.\textsuperscript{20}

There is no set limit on the human acceptable daily intake (ADI) of \textit{L}-malic acid, and the ADI for \textit{D}-malic acid is limited only by good manufacturing practice.\textsuperscript{21,22}

\textit{L}-Malic acid is an intermediate in chemical synthesis. It is used as a chelating and buffering agent, flavoring agent, flavor enhancer, and acidulant in foods.\textsuperscript{23}

### TOXICOKINETICS

#### Absorption, Distribution, Metabolism, and Excretion

There were no absorption, distribution, metabolism or excretion studies discovered for the ingredients in this safety assessment.

#### Oral and Intraperitoneal

MALIC ACID

Malic acid plays a part in carbohydrate metabolism and is a precursor of oxalacetic and pyruvic acids.\textsuperscript{24} Most of the radioactivity from 2.5 mg/kg U\textsuperscript{14}C-\textit{L}-malic acid (sp. act. 61 µC/mmol) or 4-\textsuperscript{14}C-\textit{DL}-malic acid (sp. act. 93 µC/mmol) administered orally or intraperitoneally (i.p.) to male albino Wistar Alderly Park SPF rats was excreted as carbon dioxide.\textsuperscript{25}

Daily oral administration of 4 g/kg malic acid resulted in increased glucuronic acid excretion in the urine.\textsuperscript{26} Upon oral administration of \textsuperscript{14}C-\textit{L}-malic acid to male albino Wistar Alderly Park SPF rats, most of the radioactivity was excreted as carbon dioxide.\textsuperscript{25}

Upon i.p. administration of \textsuperscript{14}C-\textit{L}-malic acid to rats, most of the radioactivity was excreted as carbon dioxide.\textsuperscript{25}
**Acute Toxicity**

**Dermal**

Di-C12-13 ALKYL MALATE  
The acute dermal LD$_{50}$ of di-C12-13 alkyl malate for male and female Wistar rats (n = 5) was > 2000 mg/kg (2 mL/kg; 100%). There were no clinical signs during the 7-day observation period and no pathological signs at necropsy.

**Oral – Non-Human**

Di-C12-13 ALKYL MALATE  
The acute oral LD$_{50}$ of di-C12-13 alkyl malate for Wistar rats (n = 5/sex) was > 5000 mg/kg in sesame seed oil. There were no mortalities. During a 48-h observation period, 3 males exhibited intense fur erection and one male showed ant and post mortem a mycosis in one foreleg.

DIETHYLHEXYL MALATE  
The reported LD$_{50}$ for diethylhexyl malate is > 5g/kg for albino rats (strain not provided).

MALIC ACID AND SODIUM MALATE  
The oral LD$_{50}$ of malic acid for albino CD-1 outbred mice (n = 5/sex), albino Wistar rats (n = 5/sex), and Dutch-Belted rabbits (n = 5/sex) were approximately 2.66, 3.5, and 3 g/kg, respectively. Malic acid was administered as a 25% aqueous solution. Signs of toxicity included ataxia, prostration, convulsions, retraction of the abdomen, respiratory distress, cyanosis and death.  

The oral LD$_{10}$ of malic acid for rabbits was 5 g/kg. The oral “lethal dose” of L-malic acid for rabbits was 5 g/kg, and for sodium malate in dogs was 1 g/kg. The i.p. administration of 2 g/kg DL-malic acid was not lethal to rats. The i.p. LD$_{50}$ of malic acid for mice and rats ranged from 50-100 and 100-200 mg/kg, respectively.

**Other Dose Administration**

MALIC ACID  
The acute LD$_{50}$ of malic acid administered intravenously was 2.4 g/kg for rabbits, and the i.p. LD$_{50}$ values for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively. In an experiment comparing different stereocenters, the i.p. administration to rats of 1 g/kg L-malic acid was not lethal, but the same dose of D-malic acid killed rats within 20-25 min. Another experiment showed that a mixture of 1 g/kg D-malic acid and 1 g/kg L-malic acid was lethal, and death occurred sooner than it did with D-malic acid alone. The author did not have an explanation for the difference in toxicity between the two isomers.

The i.p. administration of 2 g/kg DL-malic acid was not lethal to rats. The i.p. LD$_{50}$ of malic acid for mice and rats ranged from 50-100 and 100-200 mg/kg, respectively.

**Repeated Dose Toxicity**

**Dermal**

Di-C12-13 ALKYL MALATE  
Di-C12-13 alkyl malate (10 mL/kg; 1000 mg/kg/d) was dermally applied under occlusion daily to the shaved dorsal area of male and female New Zealand White rabbits (n = 5/sex) for 28 days. Each bandage was removed after 6 h and the treatment area was not washed. There were no clinical signs observed during treatment and the two-week observation period. Necropsies, hematology, and clinical chemistry (including liver function) were unremarkable.

**Oral – Non-Human**

MALIC ACID AND SODIUM MALATE  
In a chronic oral study, feeding malic acid (500, 5000, 50,000 ppm; 0.05%, 0.5%, 5.0%) to Charles River rats (n = 30/sex) for 104 weeks resulted in no compound related lesions (types not provided). No significant changes or lesions were observed when dogs were fed malic acid (500, 5000, 50,000 ppm) for 104 weeks. DIBUTYL MALATE  
In a repeated oral dose and reproductive toxicity/developmental toxicity screening assay using rats, dibutyl malate (300 mg/kg) produced renal tubular lesions and increased liver and kidney weights. The NOEL was 95 mg/kg.

**REPRODUCTIVE AND DEVELOPMENTAL TOXICITY**

There were no reproductive or developmental studies discovered for the ingredients in this safety assessment. MALIC ACID  
Malic acid did not cause developmental toxicity in albino CD-1 outbred mice (n = 25) up to 266 mg/kg (days 6 – 15 of gestation), rats (n = 25 – 29) up to 350 mg/kg (for 10 days during gestation), or Dutch-belted rabbits (n = 15 – 23) up to 300 mg/kg (days 6 – 18 of gestation). In a multigenerational oral study of malic acid, there were no reproductive or
developmental effects to albino rats up to 10,000 ppm in feed for the P1, P2, F1, and F2 generations.\textsuperscript{44} Malic acid (10.00 mg/egg in water) was injected into the air sac or yolk of white Leghorn chicken eggs (n = 20) at the 0 or 96 h of incubation.\textsuperscript{35} There were no developmental effects observed when the chicks were examined after hatching.

**DIBUTYL MALATE**

In a repeated dose and reproductive toxicity/developmental toxicity screening assay for dibutyl malate (300 mg/kg), there were no adverse reproductive effects reported in rats.\textsuperscript{35}

**GENOTOXICITY**

**DIISOSTEARYL MALATE**

In a reverse mutation assay using *Salmonella typhimurium* (TA98, TA100, TA1535, TA1537), diisostearyl malate (312.5, 625, 1250, 2500, 5000 \textmu g/plate) was not mutagenic with or without metabolic activation.\textsuperscript{46}

**DI-C12-13 ALKYL MALATE**

In an Ames test, di-C12-13 alkyl malate (1, 10, 100, 1000, 10,000 \textmu g/plate) was not mutagenic to *S. typhimurium* (strains TA98, TA100, TA1535, TA1537, TA1538) with or without metabolic activation.\textsuperscript{47} The results of the positive controls were as expected.

In a micronucleus assay using C57BL mice (n = 5/sex), di-C12-13 alkyl malate (250 mg/ml; 12500 mg/kg in sesame seed oil) administered intraperitoneally was not mutagenic.\textsuperscript{38} Erythrocytes harvested from bone marrow were examined at 24, 48, and 72 h.

**CARCINOGENICITY**

There were no carcinogenicity studies discovered for the ingredients in this safety assessment.

**MALIC ACID**

In a chronic oral study, feeding malic acid (500, 5000, 50,000 ppm; 0.05%, 0.5%, 5.0%) to Charles River rats (n = 30/sex) for 104 weeks resulted in no compound related lesions (types not provided).\textsuperscript{39} No significant changes or lesions were observed when dogs were fed malic acid (500, 5000, 50,000 ppm) for 104 weeks.\textsuperscript{40}

**IRRITATION AND SENSITIZATION**

**Irritation**

**Dermal – Non-Human**

**DI-C12-13 ALKYL MALATE**

Di-C12-13 alkyl malate (10 mL/kg) was dermally applied under occlusion daily to the shaved dorsal area of male and female New Zealand White rabbits (n = 5) for 28 days.\textsuperscript{38} No erythema or edema was observed.

Di-C12-13 alkyl malate (500 mg in 0.5 mL sesame seed oil) was not a dermal irritant when administered to the shaved skin (20 cm\textsuperscript{2}) of New Zealand White rabbits (n = 6) for 4 h.\textsuperscript{49} No erythema or edema were observed at 1, 24, 48, and 72 h.

**DIETHYLHEXYL MALATE**

Diethylhexyl malate (100%; 0.5 ml) was applied to intact and abraded skin of New Zealand White rabbits (n = 6) under occlusion. The test sites were observed at 24 and 72 h. The primary irritation index (PII) was 1.18; diethylhexyl malate was determined not to be a primary irritant to rabbits.\textsuperscript{50}

A primary dermal irritation test of diethylhexyl malate (100%) under occlusion for 24 h was conducted using New Zealand White rabbits (n = 6).\textsuperscript{51} The PII was 3.53. The authors concluded that diethylhexyl malate was not a dermal irritant to rabbits.

**MALIC ACID**

Malic acid (500 mg/24 h) was moderately irritating to rabbit skin and was a strong irritant to guinea pigs.\textsuperscript{33}

**Dermal – Human**

**DI-C12-13 ALKYL MALATE**

In a human patch test (n = 38), di-C12-13 alkyl malate (100%; 0.5 mL) was not irritating when administered to a 1 cm\textsuperscript{2} area under occlusion for 48 h.\textsuperscript{52} No erythema or edema was observed at 15 min and 24 h.

**MALIC ACID**

In 2 human repeated insult patch tests (HRIPT) of products containing malic acid (0.022725% and 0.00375%), these products were predicted to be non to moderate irritants (Table 5).\textsuperscript{54}
**Ocular**

**DI-C12-13 ALKYL MALATE**

Di-C12-13 alkyl malate (100%; 0.1 mL) was not irritating to the eyes of New Zealand White rabbits (n = 6). In a chorio-allantoic membrane (CAM) assay, di-C12-13 alkyl malate (200 μL) was not predicted to be an ocular irritant.

**DIETHYLHEXYL MALATE**

Diethylhexyl malate (100%; 0.1 mL) was administered into 1 eye of New Zealand White rabbits (n = 6). The eyes were unwashed for 24 h. At 24 and 72 h and 4 and 7 days, the Draize score was 0. At 48 h, the score was 0.3. The authors determined that diethylhexyl malate was not an ocular irritant to rabbits.

**DIISOSTEARYL MALATE**

An HRIPT (n = 51) of diisostearyl malate (100%; 0.2 ml, 0.2 g) was performed. No adverse effects were observed during induction or challenge.

**MALIC ACID**

Malic acid caused severe ocular irritation in rabbit eyes. In chorioallantoic membrane vascular assay (CAMVA) and bovine corneal opacity and permeability tests (BCOP) of products containing malic acid (2.2725%), these products were predicted to be ocular irritants (Table 4).

**Sensitization**

**Dermal – Non-Human**

**DI-C12-13 ALKYL MALATE**

In a guinea pig sensitization assay (Buehler test) using female Hartley guinea pigs (n = 10), epicutaneous administration of di-C12-13 alkyl malate (100%) for three 6-h exposures 7 days apart under occlusion was not sensitizing.

**DIETHYLHEXYL MALATE**

In a guinea pig sensitization test (Buehler test; n = 12) of diethylhexyl malate (100%) there was slight erythema on two sites after the sixth dose. There was no sensitization observed at challenge.

**Dermal – Human**

**DIISOSTEARYL MALATE**

In predictive testing using patients with atopic dermatitis, 18 of 34 patients reacted to a diet high in malic and citric acids, and 6 reacted to a diet high in malic acid. In an in vitro study assessing the effect of malic acid on cell renewal on human skin, an 18%, 10%, and 5% increase was observed at pH 3, 5, and 7, respectively.

In two HRIPTs of products containing malic acid (0.022725% and 0.00375%), sensitization was not induced. (Table 4).

**SUMMARY**

Dialkyl malates are cosmetic ingredients that have a core of succinic acid (a four carbon, alkyl diacid), that is mono-substituted. All of these ingredients have at least one stereocenter denoted by D, L, D. The INCI names are defined as ambiguous to these stereochemical details. While not a cosmetic ingredient, dibutyl malate is a dialkyl malate and data were considered relevant.

Dialkyl malates function mostly as skin-conditioning agents-emollients and pH adjusters.

Malic acid is generally purified until the amounts of fumaric and maleic acid are 7.5 and <500 ppm, respectively.

The total number of reported uses of diisostearyl malate was 574 (572 uses in leave-on products) and was reported to be used at 0.001% - 82%. Di-C12-13 alkyl malate was reported to be used in 29 products and was reported to be used at 1% - 36% in leave-on products. Diethylhexyl malate was reported to be used in 10 products and was reported to be used at 0.4% - 2% in leave-on products and 2% in rinse-off products.

There were no reported uses for: dibutyloctyl malate, diisoamyl malate, and dioctyldodecyl malate. D- and L-malic acid, when meeting Food Chemicals Codex specifications, are generally recognized as safe (GRAS) as direct food additive for use as a flavor enhancers, flavoring agents, and adjuvants, and as pH control agent, but are not GRAS for use in baby foods.

Radio-labeled malic acid orally and intraperitoneally administered to rats was excreted mostly as carbon dioxide. The acute dermal LD₅₀ of di-C12-13 alkyl malate for rats was > 2000 mg/kg. The acute oral LD₅₀ of di-C12-13 alkyl malate for rats was > 5000 mg/kg. The reported LD₅₀ for diethylhexyl malate is > 5g/kg for rats.

The oral LD₅₀ of malic acid for mice was 2.66 g/kg, 3.5 g/kg for rats, and 3 g/kg for rabbits. The oral lethal dose of malic acid was 5 g/kg in rabbits. The oral lethal dose of sodium malate was 1 g/kg in dogs. The i.v. LD₅₀ of malic acid was 2.4 g/kg for rabbits, and the i.p. LD₅₀ values for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively. The i.p.
administration to rats of 1 g/kg L-malic acid was not lethal, but the same dose of D-malic acid killed rats within 20-25 min. The i.p. administration of 2 g/kg DL-malic acid was not lethal to rats.

There were no clinical signs observed during treatment and the two-week observation period when 10 mL/kg di-C12-13 alkyl malate was dermally applied to rabbits for 28 days.

In a chronic oral study, feeding malic acid up to 50,000 ppm to rats for 104 weeks resulted in some changes in body weight gains and feed consumption, but compound related lesions were not observed. No significant changes or lesions were observed when dogs were fed malic acid in a chronic 104-week study.

Malic acid did not cause developmental toxicity in mice up to 266 mg/kg, rats up to 350 mg/kg, or rabbits up to 300 mg/kg. In a multigenerational oral study of malic acid, there were no reproductive or developmental effects to rats up to 10,000 ppm in the P1, P2, F1, and F2 generations. Malic acid at 10.00 mg/egg in water injected into the air sac or yolk of chicken eggs at the 0 or 96 h of incubation caused no developmental effects the chicks.

In a reverse mutation assay using *S. typhimurium*, diisostearyl malate was not mutagenic with or without metabolic activation up to 5000 μg/plate. In an Ames test, di-C12-13 alkyl malate was not mutagenic to *S. typhimurium* with or without metabolic activation up to 10,000 μg/plate.

In a micronucleus assay using C57BL mice (n = 5/sex), di-C12-13 alkyl malate (250 mg/ml; 12500 mg/kg in sesame seed oil) administered intraperitoneally was not mutagenic.

Di-C12-13 alkyl malate was not a dermal irritant in rabbits at 100% when treated daily for 28 days.

Malic acid (500 mg/24 h) was moderately irritating to rabbit skin and was a strong irritant to guinea pigs. In a test determining the subjective skin irritation potential, the average irritation scores over a 15-minute period were 39.4, 37.1, and 23.1 for malic acid at pH 3, 5, and 7, respectively.

In a human patch test, di-C12-13 alkyl malate was not irritating at 100%.

Di-C12-13 alkyl malate was not irritating to the eyes of rabbits at 100%. In a chorio-allantoic membrane (CAM) assay, di-C12-13 alkyl malate was not predicted to be an ocular irritant.

Malic acid caused severe ocular irritation in rabbit eyes at 500 mg.

Di-C12-13 alkyl malate and diethylhexyl malate were not sensitizing to guinea pigs at 100%.

No adverse effects were observed during induction or challenge in an HRIPT of disostearyl malate at 100%.

In predictive testing using patients with atopic dermatitis, 18 of 34 patients reacted to a diet high in malic and citric acids, and 6 reacted to a diet high in malic acid. In assessing the effect of malic acid on cell renewal, an 18%, 10%, and 5% increase was observed at pH 3, 5, and 7, respectively. In two HRIPTs of products containing malic acid up to 0.022725%, sensitization was not induced.

**DISCUSSION**

The similar chemical structures, physicochemical properties, functions and concentrations in cosmetics allow grouping these ingredients together and extending the available toxicological data to support the safety of the entire group.

D-malic acid was considered GRAS except for use in baby food. This was due to nephrotoxicity and growth retardation in rats at 1% maleic acid in feed. However, it was not toxic to dogs. Even if there was incidental ingestion due use in lipsticks, the purity is reported to be 99% and the amount of any maleic acid would be miniscule.

The Panel noted that the previous conclusion of the malic acid/sodium malate safety assessment stated that there were insufficient data to reach a safety conclusion on the use of these ingredients as anything but pH adjusters and there was a need for dermal sensitization studies. An HRIPT of disostearyl malate at 100% did not result in irritation during induction or sensitization at challenge, and guinea pig sensitization tests of diethylhexyl malate and di-C12-13 alkyl malate, both at 100%, also did not produce sensitization in these animals. The Panel concluded that even though maleic acid/sodium maleate may be irritating, these results confirm that the dialkyl malates are not irritating or sensitizing.

Sensitization data for dioctyldodecyl malate were not available and were not provided. There was some concern expressed that the possible metabolite octyldodecanol is a penetration enhancer and dermal irritant. However, the potential concentration of use is very low; therefore, any resulting octyldodecanol would be too low for concern.

Because these ingredients can be used in products that may be aerosolized, including sprays, the Panel discussed the issue of incidental inhalation exposure. There was no inhalation toxicity data available. However, the Panel believes that the sizes of a substantial majority of the particles of spray products, as manufactured, are larger than the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. The Panel considered other data available to characterize the potential for dialkyl malates to cause systemic toxicity, irritation, or sensitization. They noted the lack of systemic toxicity at high doses in acute and subchronic oral exposure; no irritation or sensitization in multiple tests of dermal and ocular exposure; and the absence of genotoxicity in two Ames assays and a micronucleus assay. In addition, these are large molecules and di-C12-13 alkyl malate has a log Kow of > 6.4. These ingredients are reportedly used at concentrations up to 10% in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to any appreciable amount. However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Based on the properties of the dialkyl malates and on data that shows these ingredients are not irritants, these ingredients are not likely to cause any direct toxic effects in the upper respiratory tract. Coupled with the small actual exposure in the breathing zone and the concentrations at which the
ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects.

CONCLUSION

The CIR Expert Panel concluded that the following ingredients are safe for use in cosmetics in the present practices of use and concentration in this safety assessment:

- diisostearyl malate
- dibutyloctyl malate*
- di-C12-13 alkyl malate
- diethylhexyl malate
- diisoamyl malate*
- dioctyldecyl malate*

*Not in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.
### Table 1. The CAS numbers, definitions and functions of the ingredients in this safety assessment. The first definition is provided by the International Cosmetic Ingredient Dictionary and Handbook; the definition in italics was developed by the CIR staff.51

<table>
<thead>
<tr>
<th>Ingredient CAS No.</th>
<th>Definition</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monohydroxysuccinates, free acid, and salt</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diisostearyl Malate 67763-18-2 81230-05-9</td>
<td>Diisostearyl malate is the diester of isostearl alcohol and malic acid; diisostearyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, eighteen carbon alkyl chain.</td>
<td>Skin-conditioning agent – emollient</td>
</tr>
<tr>
<td>Diisostearyl Malate 399551-19-0</td>
<td>Diisostearyl malate is the diester of isostearyl alcohol and malic acid; diisostearyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, eighteen carbon alkyl chain (an eight carbon chain substituted at the two position with a four carbon alkyl chain).</td>
<td>Skin-conditioning agent – emollient</td>
</tr>
<tr>
<td>Di-C12-13 Alkyl Malate</td>
<td>Di-C12-13 alkyl malate is the diester of C12-13 alcohols and malic acid; Di-C12-13 alkyl malate is a mixture of diesters of C12 and C13 alcohols with malic acid; Di-C12-13 alkyl malate is a four carbon, hydroxy-diacid, esterified at each acid with either a twelve or thirteen carbon alkyl chain.</td>
<td>Skin-conditioning agent – emollient</td>
</tr>
<tr>
<td>Diethylhexyl Malate 56235-92-8</td>
<td>Diethylhexyl malate is the diester of malic acid and 2-ethylhexanol; diethylhexyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, eight carbon alkyl chain (a six carbon chain substituted at the two position with a two carbon alkyl chain).</td>
<td>Skin-conditioning agent – emollient</td>
</tr>
<tr>
<td>Diisooamyl Malate [1587-19-5] (per CAS)</td>
<td>Diisooamyl malate is defined structurally; diisooamyl malate is the diester of isoamyl alcohol and malic acid; diisooamyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, five carbon alkyl chain.</td>
<td>Plasticizer; skin-conditioning agent - emollient; slip modifier; solvent</td>
</tr>
<tr>
<td>Dioctyldodecyl Malate</td>
<td>Dioctyldodecyl malate is defined structurally; dioctyldodecyl malate is the diester of octyldodecyl alcohol and malic acid; dioctyldodecyl malate is a four carbon, hydroxy-diacid, esterified at each acid with a branched, twenty carbon alkyl chain (a twelve carbon chain substituted at the two position with an eight carbon alkyl chain).</td>
<td>Skin-conditioning agent – miscellaneous</td>
</tr>
</tbody>
</table>

### Table 2. Physical and chemical properties of alkyl malates.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diisostearyl malate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Form</td>
<td>Liquid</td>
<td>62</td>
</tr>
<tr>
<td>Color</td>
<td>Clear colorless to slightly yellow</td>
<td>62</td>
</tr>
<tr>
<td>Odor</td>
<td>Slight, typical</td>
<td>62</td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>639.04</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Molecular Volume m³/kmol</td>
<td>0.6944 ± 3.0 x 10⁻⁴</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20°C</td>
<td>0.920 ± 0.06 g/cm³</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Vapor pressure mmHg @ 25°C</td>
<td>3.4E-22</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>676.3 ± 35.0°C</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Water Solubility</td>
<td>Insoluble</td>
<td>64</td>
</tr>
<tr>
<td><strong>Dibutyloctyl malate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>470.73</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Molecular Volume m³/kmol</td>
<td>0.4963+/−2.0 x 10⁻⁴</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20°C</td>
<td>0.948+/−0.06</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Vapor pressure mmHg @ 25°C</td>
<td>2.8E⁻¹⁴</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>547.6+/−30.0</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Water Solubility g/L @ 25°C &amp; pH 7</td>
<td>1.0³</td>
<td>calculated 63</td>
</tr>
</tbody>
</table>
### Table 2. Physical and chemical properties of alkyl malates.

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Di-C12-13 alkyl malate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Kow @ 40°C</td>
<td>&gt;6.4</td>
<td>65</td>
</tr>
<tr>
<td><strong>Diethylhexyl malate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>358.51</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Molecular Volume m³/kmol</td>
<td>364.2 +/-3.0 cm³</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20°C</td>
<td>0.984 +/-0.06 g/cm³</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Vapor pressure mmHg@ 25°C</td>
<td>6.31 x 10⁻¹⁰</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>448.4 +/-25.0</td>
<td>calculated 63</td>
</tr>
<tr>
<td><strong>Diisoamyl malate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>274.35</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Molecular Volume m³/kmol</td>
<td>265.2 +/-3.0 cm³</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20°C</td>
<td>1.006 g/cm³</td>
<td>calculated 66</td>
</tr>
<tr>
<td>Vapor pressure mmHg@ 25°C</td>
<td>9.08E⁻⁰⁷</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>152-157</td>
<td>calculated 66</td>
</tr>
<tr>
<td><strong>Dioctyldodecyl malate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molecular Weight g/mol</td>
<td>134.09</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Density/Specific Gravity @ 20°C</td>
<td>1.641 +/-0.06 g/cm³</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Vapor pressure mmHg@ 25°C</td>
<td>7.19E⁻⁰⁵</td>
<td>calculated 63</td>
</tr>
<tr>
<td>Boiling Point °C</td>
<td>306.4 +/-27.0</td>
<td>calculated 63</td>
</tr>
</tbody>
</table>

### Table 3. Frequency of use and concentration according to duration and exposure ⁹,¹⁰

<table>
<thead>
<tr>
<th>Use type</th>
<th>Uses</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total/range</strong></td>
<td>Diisostearyl Malate</td>
<td>694</td>
</tr>
<tr>
<td><strong>Di-C12-13 Alkyl Malate</strong></td>
<td>27</td>
<td>1-36</td>
</tr>
<tr>
<td><strong>Diethylhexyl Malate</strong></td>
<td>12</td>
<td>0.4-2</td>
</tr>
</tbody>
</table>

**Duration of use**

<table>
<thead>
<tr>
<th>Use type</th>
<th>Uses</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Leave-on</strong></td>
<td>690</td>
<td>0.2-82 ¹²</td>
</tr>
<tr>
<td><strong>Rinse-off</strong></td>
<td>4</td>
<td>0.001-29</td>
</tr>
<tr>
<td><strong>Diluted for (bath) use</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

**Exposure type**

<table>
<thead>
<tr>
<th>Use type</th>
<th>Uses</th>
<th>Concentration (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eye area</strong></td>
<td>87</td>
<td>0.2-36</td>
</tr>
<tr>
<td><strong>Incidental ingestion</strong></td>
<td>345</td>
<td>5-82</td>
</tr>
<tr>
<td><strong>Incidental inhalation-sprays</strong></td>
<td>4</td>
<td>3-10</td>
</tr>
<tr>
<td><strong>Incidental inhalation-powders</strong></td>
<td>28</td>
<td>0.4-12</td>
</tr>
<tr>
<td><strong>Dermal</strong></td>
<td>346</td>
<td>0.2-49 ¹²</td>
</tr>
<tr>
<td><strong>Deodorant (underarm)</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Hair-noncoloring</strong></td>
<td>3</td>
<td>0.001-15</td>
</tr>
<tr>
<td><strong>Hair-coloring</strong></td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td><strong>Nail</strong></td>
<td>NR</td>
<td>0.4-49</td>
</tr>
<tr>
<td><strong>Mucous Membrane</strong></td>
<td>345</td>
<td>5-82</td>
</tr>
<tr>
<td><strong>Baby</strong></td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

`NR` = None reported

¹³ 3% in a body oil listed under “other fragrance preparation”.

² 10% in a lip cream.
Table 4. Dermal irritation, sensitization and ocular irritation studies of products containing malic acid.54

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Concentration of malic acid in product/actual concentration of malic acid tested/pH</th>
<th>n</th>
<th>Procedure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair styler</td>
<td>1%/0.022725%/3.6</td>
<td>101</td>
<td>Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using semi-occlusive patch.</td>
<td>Predicted not to be a significant skin irritant. Standardized cumulative irritation = 1181.5, negative control (undosed patch) = 45.6, positive control (1% SLS) = 2052.8.</td>
</tr>
<tr>
<td>Hair shampoo</td>
<td>0.5%/0.000375%/3.0</td>
<td>98</td>
<td>Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using occlusive patches.</td>
<td>Predicted to be a moderate skin irritant. Standardized cumulative irritation = 965.1, negative control (distilled water) = 33, positive control (0.1% SLS) = 1307.76.</td>
</tr>
</tbody>
</table>

Sensitization

<table>
<thead>
<tr>
<th>Test Material</th>
<th>Concentration/ pH</th>
<th>Procedure</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair styler</td>
<td>1%/0.022725%/3.6</td>
<td>Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using semi-occlusive patch.</td>
<td>Solution did not induce allergic contact dermatitis in any subject.</td>
</tr>
<tr>
<td>Hair shampoo</td>
<td>0.5%/0.000375%/3.0</td>
<td>Modified HRIPT. Induction 21 days, rest 10-24 days, challenge 4 days using occlusive patches.</td>
<td>Solution did not induce allergic contact dermatitis in any subject.</td>
</tr>
</tbody>
</table>

Ocular irritation

<table>
<thead>
<tr>
<th>Test material</th>
<th>Concentration/ pH</th>
<th>CMVA results (RC50 (95% CI))</th>
<th>BCOP Results (In vitro score/opacity score/permeability score)</th>
<th>Prediction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hair styler</td>
<td>2.275%/3.6</td>
<td>&gt;50% (NA)</td>
<td>74.3/69.9/0.296</td>
<td>Severe ocular irritant</td>
</tr>
<tr>
<td>Hair shampoo</td>
<td>2.275%/3.0</td>
<td>1.6 (0.62-3.9)</td>
<td>9.09/5.4/0.246</td>
<td>Ocular irritant</td>
</tr>
</tbody>
</table>

1 Same study as irritation study above.
2 Same study as irritation study above.

Figure 1. Diisostearyl malate.
Figure 2. Map of the ester ingredients in this assessment, and possible associated esterase metabolites.

Legend
- Ingredients which are part of this review
- Safe as used
- Result of Esterase metabolism
REFERENCES


33. Patty. Patty's Industrial Hygiene and Toxicology. 3 ed. New York: Wiley and Sons, 1981.


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37. Patty's Industrial Hygiene and Toxicology. 3 ed. New York: Wiley & Sons, 1981.


59. AMA Laboratories. 2005. 50 Human subject repeat insult patch test skin irritaiton/sensitization evaluation (occlusive patch) of PELMOL DISM (Diisostearyl Malate). AMA Ref. No.: MS05.RIPT.K75540.50.PCI. (Ingredient tested neat (100% Diisostearyl Malate)). Unpublished data submitted by the Personal Care Products Council.


63. Advanced Chemistry Development (ACD/Labs) Software V11.02. 2010. Toronto, ON:


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APPENDIX – POSSIBLE ESTERASE METABOLITE SUMMARY DATA OF ALCOHOLS

BUTYL OCTANOL – metabolite of dibutyloctyl malate
   No data was found on this alcohol.

C12-13 ALCOHOL – metabolite of di-C12-13 alkyl malate
Acute Toxicity
   The LD₅₀ of dodecanol (C12) for rats was reported to be 12,800 mg/kg.⁶⁷
   The LD₅₀ of isotridecanol (C13) for rats was reported to be 17,000 mg/kg.⁶⁷
Ocular Irritation
   Dodecanol was reported to have an ocular irritation score of 2 (out of 10) in a quantitative structure-activity relation (QSAR) analysis.⁶⁸

ISOAMYL ALCOHOL – metabolite of diisoamyl malate
Cytotoxicity
   Isoamyl alcohol had an IC₅₀ of 28 mM for human lung carcinoma epithelial cells A549.⁶⁹  In a Comet assay, isoamyl alcohol was not toxic to A549 cells and V79 Chinese hamster cells at 46 mM and human peripheral blood cells at 23 mM.
Chemical Properties
   Isoamyl alcohol is reported to have a log pKₐ of -2.00 cm/h and a log Kₒw of 1.16.⁷⁰⁻⁷²
Dermal Irritation
   Isoamyl alcohol (up to 100% in acetone; olive oil 4:1) was negative in a LLNA.⁷³
   The skin irritation potential of isostearyl alcohol was evaluated in 19 male and female subjects (18-65 years old) at a concentration of 25.0% in petrolatum.⁷⁴  The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05).  In 3 similar studies, 3 different lipstick products containing 25.0, 27.0, and 28.0% isostearyl alcohol, respectively, were tested according to the same protocol.  The 3 products did not induce skin irritation.  The irritation and sensitization potential of isostearyl alcohol (25% v/v in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21-60 years old).  Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch.  Three of 12 subjects had slight erythema during induction, and there was no evidence of sensitization.
   The sensitization potential of a pump spray antiperspirant containing 5.0% isostearyl alcohol was evaluated using 148 male and female subjects.⁷⁴  The product was applied via an occlusive patch to the upper arm for a total of 9 induction applications (3 times/week for 3 weeks).  Each patch remained for 24 h, and sites were scored immediately before subsequent applications.  During the challenge phase, a patch was applied to the induction site and to a new site on the opposite arm of each subject.  Reactions were scored 48 and 96 h after application.  Ten of the 12 subjects with reactions suggestive of sensitization were re-challenged with the product 2 months later.  Patches remained for 24 h, and sites were scored at 48 and 96 h post-application.  Six subjects had reactions during the re-challenge.  Four of the 6 subjects were then tested with 5.0% isostearyl alcohol in solution with ethanol 6 weeks after scoring of the first rechallenge; all had positive responses.  Negative responses were reported when the product (without isostearyl alcohol) and 100.0% ethanol each were tested.  In a second study, the same product was applied to 60 male and female subjects (same protocol).  Five of the subjects had positive responses after the first challenge.  One of the 5 was re-challenged with 5.0% isostearyl alcohol in ethanol solution, and a positive reaction was observed.

ISOSTEARYL ALCOHOL – metabolite of diisostearyl malate
Chemical Properties
   Physicochemical properties of isostearyl alcohol were estimated by EPISuite to be: molecular weight, 639; log Kₒw, 15.6; and water solubility, 1.5 x 10⁻¹¹ mg/ml.⁳⁵
Toxicity
   The LD₅₀ of isostearyl alcohol was reported to be > 2000 mg/kg in rats.⁵⁵
Clinical Irritation and Sensitization
   The skin irritation potential of isostearyl alcohol was evaluated in 19 male and female subjects (18-65 years old) at a concentration of 25.0% in petrolatum.⁷⁴  The test substance did not induce skin irritation in any of the subjects (Primary Irritation Index = 0.05).  In 3 similar studies, 3 different lipstick products containing 25.0, 27.0, and 28.0% isostearyl alcohol, respectively, were tested according to the same protocol.  The 3 products did not induce skin irritation.  The irritation and sensitization potential of isostearyl alcohol (25% v/v in 95.0% isopropyl alcohol) was evaluated in 12 male subjects (21-60 years old).  Challenge applications were made to original and adjacent sites 2 weeks after removal of the last induction patch.  Three of 12 subjects had slight erythema during induction, and there was no evidence of sensitization.
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OCTYLDODECANOL – metabolite of dioctyldodecyl malate
Dermal Penetration Enhancement
   Octyldodecanol (0.5, 1.00 mg/inch²) increased the dermal penetration of formoterol fumarate.⁷⁵  Octyldodecanol was not irritating to rabbit skin alone but increased the irritation of formoterol fumarate from a score of 0.21 (control) to 1.38.  No irritation was observed in guinea pigs, rats, and miniature swine.
   Octyldodecanol (5.0% w/w) increased human dermal penetration of octylmethoxycinnamate in an in vitro test.⁷⁶
Case Reports

A 37-year-old man presented with swelling of the genitalia after the use of a cream to treat “thrush.” Symptoms were treated with prednisolone and antihistamines. Patch testing revealed a 3+ reaction to 13.5% octyldodecanol in liquid paraffin at 48 and 96 h. The authors note that his particular reaction is very rare.

A 62-year-old man presented with irritation, erythema and edema after using an anti-itch cream. Patch testing revealed a + reaction to octyldodecanol at 3% in petrolatum.
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 10, 2012

SUBJECT: Comments on the Tentative Report on Dialkyl Malates

Key Issue
There are still a number of changes that need to be made to this report to completely remove malic and tartaric acids and the salts and esters of tartaric acid. Specific details are provided under additional comments.

Additional Comments
Cover - Although the Tentative report is dated June 11, 2012, this report was not posted on the CIR website until June 26, 2012. The date on the report should be the date the report was posted. The cover of Tentative Reports should indicate that there is a 60 day comment period on this draft of the report.

p.1, Abstract - In the abstract, please be more specific and use “malic acid” rather than “acid moiety”.

p.1, Introduction - As there are no longer any salts in this report, please delete “or salt” in the first sentence of the Introduction. In the first sentence of the Introduction, it is not clear what is meant by “mono-substituted”. As this report is now just about dialkyl malates, the second sentence of the Introduction should be deleted.

p.1, first paragraph of the Chemistry section - Delete “Except for the free acids and salts” as this report no longer includes any free acids or salts.

p.1, p.10 Figure 1 - The text on p.1 describes Figure 1 as showing a “mono-hydroxy substituted” compound, but the structure in Figure 1 is di-hydroxy substituted (the structure in Figure 1 is a diester of tartaric acid not malic acid). Figure 1 is not really needed as all of the relevant structures are shown in Figure 3.

p.2 - Please provide the specific FDA product category associated with the maximum leave-on concentration of Di-C12-13 Alkyl Malate.

p.2 - As indicated correctly in Table 3, the maximum concentration of these ingredients in a potential spray product is 10% in a perfume. This still needs to be corrected in the text of the Cosmetic Use section (35% needs to be changed to 10% and the specific product category should be stated).
p.2 - The following sentence in the Non-Cosmetic Use section is not complete: “However, another study using dogs that were fed the same levels that showed no toxicity.”

p.3 - The following sentence in the Other Dose Administration subsection is not complete: “The i.p. LD₅₀ of malic acid for mice and rats as 50-100 and 100-200 mg/kg, respectively.”

p.3 - Please correct the spelling of “Ayl” in the heading under Dermal in the Repeated Dose Exposure section.

p.3 - Please change “(including live function)” to “(including liver function tests)”

p.3 - Please include the route of exposure used in the repeated dose/reproductive toxicity study of dibutyl malate.

p.4 - In the last sentence of the Genotoxicity section, please change “wee” to “were”

p.4 - Please give the number of subjects used in the irritation study of malic acid (reference 59).

p.5 - If more details of the guinea pig sensitization studies are not provided, please state the type of study that was completed, e.g., the study of Diethylhexyl Malate was a Buehler test.

p.6 - In the summary, please indicate that rabbits were treated daily in the 28 day dermal study of Di-C12-13 Alkyl Malate

p.6 - The route of exposure would be clear if “In a chronic oral study...” was changed to: “In a chronic dietary study...”

p.6 - In the Discussion, it currently states that “maleic acid” is considered GRAS. This is not correct, it should be malic acid that is considered GRAS.

p.6 - Where are the data that suggest that malic acid and sodium malate are sensitzizers? These ingredients are irritants. The statement: “The Panel concluded that even though malic acid and sodium malate are sensitzizers” is not correct. In the Malic Acid report, for use other than a pH adjuster, the CIR Expert Panel requested additional dermal irritation and sensitization data.

p.6 - The Discussion should state why Dr. Hill remains concerned about the sensitzation potential of Dioctylodecyl Malate. As there is no information on the dermal penetration or metabolism of Dioctyldecoyl Malate and no information on use concentrations, the basis of the following statement is not clear: “the amount of the possible metabolite octyldecanol (a penetration enhancer and dermal irritant) produced would be too low to be of concern.”

p.6 - The maximum concentration in a product that may be a spray product needs to be changed from 35% to 10%. As the 10% concentration was for perfume use of Diisostearyl Malate, “These ingredients” needs to be changed to “Diisostearyl Malate...”

p.7 - Please correct “in his safety assessment” to “in this safety assessment”

p.8, Table 2 - Please use the same format for scientific notation throughout this table. Currently, x 10⁸ and E⁸ are being used in this table.

p.9, Table 2 - Please charge **3 to superscript 3

p.9, Table 3 - Footnote 3 is no longer needed as malic acid is not included in this table.

p.10, Figure 1 - Please delete this figure as the appropriate structures are shown in Figure 3. If the figure is left in the table, it needs to be corrected.

p.11, Figure 3 - As there are no data concerning the metabolism of these ingredients, the title of this figure should be changed to “and potential esterase metabolites”. As malic acid is not an ingredient included in this report it does not need to be shaded in this figure.