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# Amended Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics

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Status: Draft Tentative Amended Report for Panel Review  
Release Date: November 10, 2017  
Panel Meeting Date: December 4-5, 2017

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The 2017 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.



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Memorandum

To: CIR Expert Panel Members and Liaisons  
From: Christina L. Burnett, Senior Scientific Writer/Analyst  
Date: November 10, 2017  
Subject: Draft Tentative Amended Report on Malic Acid and Sodium Malate

Enclosed is the Draft Tentative Amended Report of the Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics. (It is identified as *maacid122017rep* in the pdf document).

In June 2017, the CIR Expert Panel reopened this safety assessment that was originally published in 2001 to revise the conclusion based on the receipt of new data that address insufficient data needs in the original report. Prior to determining the new conclusion, however, the Panel issued an Insufficient Data Announcement for Malic Acid and Sodium Malate. The data needs were an HRIPT, or other suitable sensitization studies, at the maximum reported leave-on use concentration of 2.1%. The Panel was also interested in receiving information on which stereoisomer(s) are used as cosmetic ingredients. If D- or DL-isomers are used in cosmetics, the Panel wanted additional information on impurities and method of manufacturing for these ingredients.

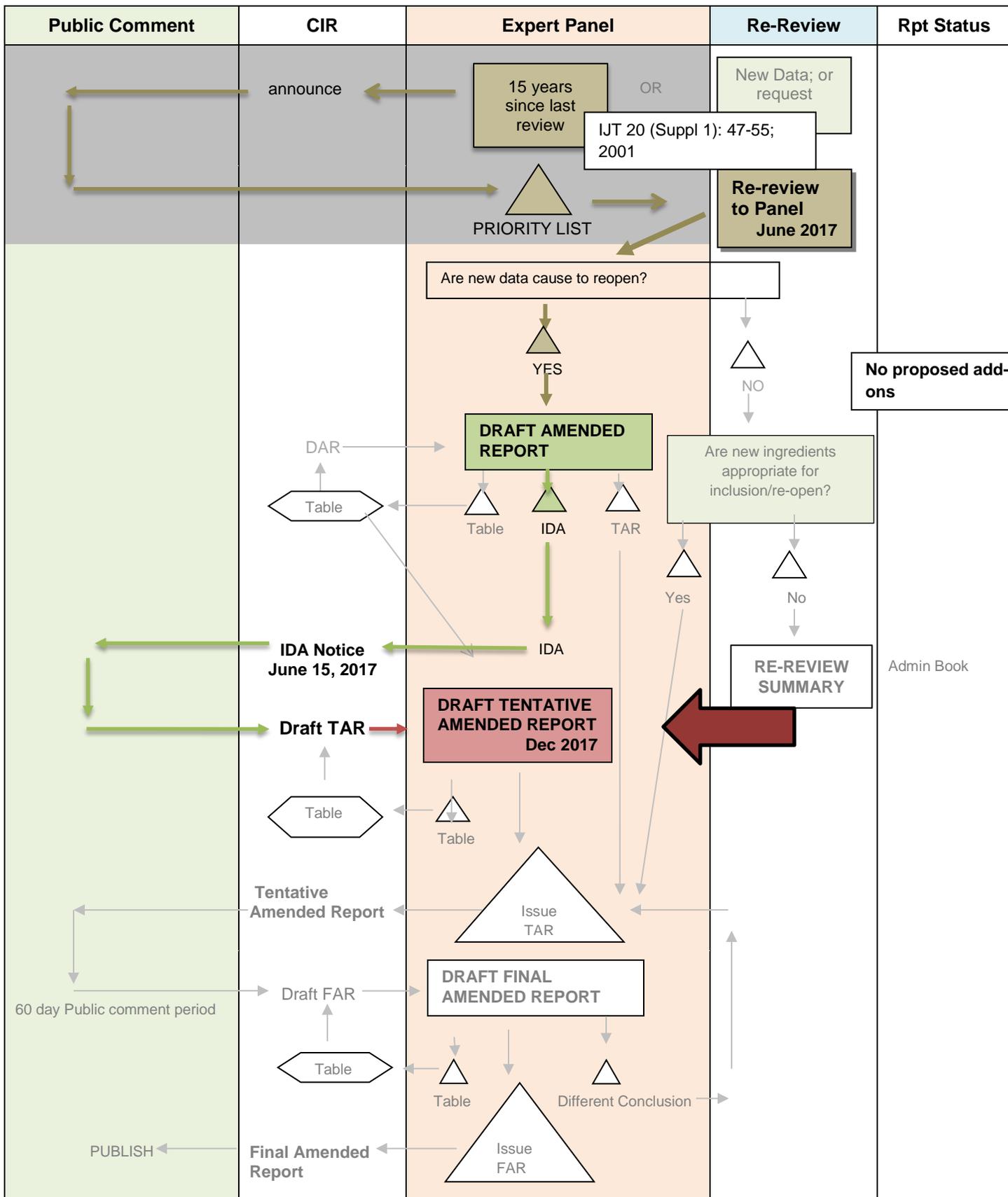
Since the June meeting, CIR has received a HRIPT of a sun protection product containing 1% Malic Acid (tested neat) and a HRIPT of a hair product containing 2% Malic Acid (3% dilution of product tested). No dermal sensitization was observed in either study. Data concerning the other data interests were not received. The new data have been incorporated in the report and have been designated with |brackets| in the text or **highlighting** in the tables (*maacid122017data1* and *maacid122017data2*). Comments provided by the Council prior to the June meeting on the re-review have been addressed (*maacid122017pcpc*).

The Panel should carefully consider and discuss the data and the draft Abstract and Discussion presented in this report and issue a Tentative Report with an amended conclusion.

# RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Malic Acid and Sodium Malate

MEETING Dec 2017



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

### **Malic Acid and Sodium Malate History**

**2001**– The CIR’s Final Report on the Safety Assessment of Malic Acid and Sodium Malate in the *IJT* after the report was finalized by the Panel in 1998. Based on the available animal and clinical data available at that time, the Panel concluded that Malic Acid and Sodium Malate are safe for use as pH adjusters in cosmetic formulations; however, the Panel determined that the data were insufficient to determine the safety of these ingredients for any other functions. The data needs, which were based on Sodium Malate’s reported function as a skin conditioning agent – humectant, were concentration of use data, dermal irritation and sensitization data, and ocular irritation data.

**April/May 2017** – Review of the available published literature since 1998 was conducted in accordance to CIR Procedure regarding re-review of ingredients after ~15 years.

**June 2017** - The Panel reopened this safety assessment to revise the conclusion based on the receipt of new data that address insufficient data needs in the original report. Prior to determining the new conclusion, however, the Panel issued an Insufficient Data Announcement for Malic Acid and Sodium Malate. The data needs were an HRIPT, or other suitable sensitization studies, at the maximum reported leave-on use concentration of 2.1%. The Panel was also interested in receiving information on which stereoisomer(s) are used as cosmetic ingredients. If D- or DL-isomers are used in cosmetics, the Panel wanted additional information on impurities and method of manufacturing for these ingredients.

Malic Acid and Sodium Malate Data Profile -December 2017 - Writer, Christina Burnett																
	In-Use	Physical/Chemical Properties	Method of Manufacturing	Composition/Impurities	Acute Toxicity	Repeated Dose Toxicity	Genotoxicity	Reproductive and Developmental Toxicity	Carcinogenicity	Other Relevant Toxicity Studies	Irritation/Sensitization - Nonhuman	Irritation/Sensitization - Human	Ocular/Mucosal	Phototoxicity	Clinical Studies/Case RE:ports	Toxicokinetics
<b>Original Report</b>																
Malic Acid	X	X	X	X	X	X	X	X			X	X	X		X	X
Sodium Malate	1 use, no concentration				X											
<b>Re-Review</b>																
Malic Acid	X						X					X	X		X	X
Sodium Malate	X															

“X” indicates that data were available in the category for that ingredient.

**Malic Acid and Sodium Malate RR****(prepared by Christina Burnett)**

Ingredient	CAS #	InfoB	SciFin	PubMed	FDA	EU	ECHA	SIDS	ECETOC	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA
<b>PREVIOUSLY REVIEWED</b>																
Malic Acid	636-61-3 (D-) 6915-15-7 97-67-6 (L-)	√	√	√	21 CFR 184.1069; 21 CFR 582.60; 21 CFR 582.1069	No	Yes; most data already in report; read across data with fumaric acid	HPV chemical, no report		No						
Sodium Malate	676-46-0	√	√	√	---	No	No	No		No						

**Search Strategy**

4/26/17 - all previously-reviewed ingredients were searched for the years 1998-2017

**Search updated October 2017, including reexamination of chemistry websites for chemical/physical properties data on Sodium Malate. No new pertinent data were found.****PubMed**

Malic Acid OR Sodium Malate AND ("1998"[Date - Publication] : "2017"[Date - Publication]) – 2263 hits. Further refinement of search detailed below:

malic acid toxicity –120 hits (including original report)/ 1 useful  
sodium malate toxicity – 32 hits (including original report)/ 0 useful  
dermal effects of malic acid –2 hits (including original report)/1 useful  
dermal effects of sodium malate – 1 hit (original report)  
irritation of malic acid – 3 hits (including original report)/1 useful  
irritation of sodium malate – 2 hits (including original report)/1 useful  
sensitization of malic acid – 5 hits (including original report)/0 useful  
sensitization of sodium malate – 1 hit (original report)  
carcinogenicity of malic acid – 1 hit/0 useful  
carcinogenicity of sodium malate – 0 hits

## LINKS

online database (self-reminder that this info has been accessed; not a public website) - <http://www.personalcarecouncil.org/science-safety/line-infobase>

wINCI (to cite publicly) - <http://webdictionary.personalcarecouncil.org>

SciFinder (usually a combined search for all ingredients in report; list # of this/# useful) - <https://scifinder.cas.org/scifinder>

PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - <http://www.ncbi.nlm.nih.gov/pubmed> ;

Also search: PubMed Dietary Supplement Subset [https://ods.od.nih.gov/Research/PubMed\\_Dietary\\_Supplement\\_Subset.aspx](https://ods.od.nih.gov/Research/PubMed_Dietary_Supplement_Subset.aspx) and  
[https://ods.od.nih.gov/Health\\_Information/IBIDS.aspx](https://ods.od.nih.gov/Health_Information/IBIDS.aspx)

Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – <https://toxnet.nlm.nih.gov/> (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases <http://www.ecfr.gov/cgi-bin/ECFR?page=browse> (CFR); then,

list of all databases: <http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm>; then,

<http://www.accessdata.fda.gov/scripts/fcn/fcnavigation.cfm?rpt=eafuslisting&displayall=true> (EAFUS);

<http://www.fda.gov/food/ingredientpackaginglabeling/gras/default.htm> (GRAS);

<http://www.fda.gov/food/ingredientpackaginglabeling/gras/scogs/ucm2006852.htm> (SCOGS database);

<http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives> (indirect food additives list);

<http://www.fda.gov/Drugs/InformationOnDrugs/default.htm> (drug approvals and database);

<http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf> (OTC ingredient list);

<http://www.accessdata.fda.gov/scripts/cder/iig/> (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions <http://ec.europa.eu/growth/tools-databases/cosing/>

and SCCS (Scientific Committee for Consumer Safety) opinions - [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/opinions/index\\_en.htm](http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm)

ECHA (European Chemicals Agency – REACH dossiers) – <http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1>

IUCLID (International Uniform Chemical Information Database) - <https://iuclid6.echa.europa.eu/search>

OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- <http://webnet.oecd.org/hpv/ui/Search.aspx>

ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - <http://www.ecetoc.org>

HPVIS (EPA High-Production Volume Info Systems) - <https://ofmext.epa.gov/hpvis/HPVISlogon>

NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- <https://www.nicnas.gov.au/>

NTIS (National Technical Information Service) - <http://www.ntis.gov/>

NTP (National Toxicology Program ) - <http://ntp.niehs.nih.gov/>

WHO (World Health Organization) technical reports - [http://www.who.int/biologicals/technical\\_report\\_series/en/](http://www.who.int/biologicals/technical_report_series/en/)

FAO (Food and Agriculture Organization of the United Nations) - <http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/>

NIOSH (National Institute for Occupational Safety and Health) - <http://www.cdc.gov/niosh/>

FEMA (Flavor & Extract Manufacturers Association) - [http://www.femaflavor.org/search/apachesolr\\_search/](http://www.femaflavor.org/search/apachesolr_search/)

Web – perform general search; may find technical data sheets, published reports, etc

**Note:** ChemPortal can be used to search several of the above databases simultaneously - [http://www.echemportal.org/echemportal/index?pageID=0&request\\_locale=en](http://www.echemportal.org/echemportal/index?pageID=0&request_locale=en)

**Malic Acid and Sodium Malate**  
**June 12-13, 2017**

**Dr. Belsito's Team**

DR. BELSITO: Okay. Its 11:57, do you think we can finish malic acid in a few minutes or?

DR. SNYDER: Yes.

DR. BELSITO: Yes, I thought so too. Good. So let's save this and go to malic acid. So a 2001 safety assessment we thought based on the available data that malic acid and sodium malate were safe as pH adjustors in cosmetic formulations insufficient for other functions. We want a concentration of use, dermal irritation, sensitization, ocular irritation. We have gotten very relevant, very few relevant new data in the published literature. Only on malic acid there was some HRIPT's that were sent in.

Frequency and concentrations of use have increased and there is now reported for sodium malate and we are essentially being asked whether we need to reopen this document. And I thought that, you know, we needed to reopen it simply because they are uses other than PH adjustors. I mean, there are new uses reported. And then if we are going to reopen it are there other ingredients that we can add and also there was a comment, I don't know if this came from council as to whether we could use fumaric acid, succinic acid and sodium succinate as read across?

MS. BURNETT: That was noted during when I was doing my literature search the ECHA database noted that they used read across data on fumaric acid for their evaluation --

DR. BELSITO: Oh that was it.

MS. BURNETT: -- for malic acid and then while we were thinking about it we were like well, if you look at the Krebs cycle, or citric acid, whatever you were raised on, succinic acids related to in terms of the biochemical relationship so the main data gap would be the carcinogenicity data.

DR. BELSITO: Right. So I guess we agree on reopening it. I guess the question so Christina can hone her studies is do we want her to bring in data on fumaric and succinic acid and sodium succinate or not?

DR. LIEBLER: Yes.

DR. BELSITO: You've got your answer.

DR. SNYDER: Well, the malic acid there was a negative two year chronic study and a negative repro study right, in the new data set? Because I have got in my notes that we have a two year chronic negative and a negative repro tox on malic acid. I mean, the insufficiency previously was based upon sensitization, concentration of use and --

DR. BELSITO: Irritation.

DR. SNYDER: Irritation sensitization. But we have now we have some HRIPT data and we know that it is irritating.

DR. BELSITO: Right.

DR. SNYDER: So we can say when formulated to be non-irritating.

DR. BELSITO: Right.

DR. SNYDER: So I think we can clear everything.

MS. BURNETT: But that's specific to malic acid. Now in the time period I don't quite understand in the past when we would discuss an acid and then the salt of an acid we have always said that the acid usually is disassociated in the solution anyway and it is the salt. When this was reviewed originally it doesn't look like that conversation took place.

DR. BELSITO: Right.

MS. BURNETT: So if you believe the HRIPT covers both ingredients then yes.

DR. BELSITO: Yes, I mean, it probably does but its, it would be nice, you know, particularly since we have very little in terms of developmental and repro tox and no carcinogenicity if Dan feels we can read across from fumaric acid it just adds to the weight of evidence of the document.

DR. LIEBLER: Right, yes. I think that's where we are.

DR. BELSITO: Yes.

MS. BURNETT: And the new conclusion would be?

DR. BELSITO: Safe as used --

DR. LIEBLER: Safe as used.

DR. BELSITO: -- when formulated to be non- irritating.

MS. BURNETT: Thank you. Any additional discussion points?

DR. BELSITO: No.

MS. BURNETT: Thank you.

Dr. Marks' Team

DR. MARKS: Malic acid is next. So this is a re- review on malic acid and sodium malate. In 2001, the CIR Expert Panel published a final report. The conclusion that these ingredients are safe for use as pH adjusters in cosmetic formulations. However, the Panel determined that the data were insufficient to determine the safety of these ingredients for any other functions. And what was needed was concentration of use, dermal irritation, sensitization ocular irritation data. Very little relevant new data were found by Christina. There is some European chemical agency input on this that, that -- there was by the Europeans, can we read across from fumaric and succinic acids. We now have use concentration. We have some irritation which it is an irritant. We have an HRIPT that was okay at 0.02 percent. So Tom, Ron, Ron, comments? Re-open, not reopen?

DR. SHANK: I think we could reopen it to change the old conclusion. I don't know why we didn't use one formulated to be a non-irritating, non-sensitizing before. That now, seems to be very common position for us. Sometime I'd like to discuss that, but not now (laughs). The -- we could include the other uses besides pH adjusters and then say, when formulated to be certainly non-irritating.

DR. SLAGA: Yeah.

DR. SHANK: Because --

DR. SLAGA: (Inaudible) non-irritating, yeah.

DR. SHANK: That is common for these absence. If you tested separately, it's an irritant. When you put it in formulation, it is no longer an irritant. It's also apparently -- it's used as an exfoliant and we could handle that by using the discussion to, you know, glycolic acid, which I think is the long discussion we have in the (inaudible) of the CIR.

MS. BURNETT: One is title, one is conclusion, one is (inaudible).

DR. SHANK: So I don't know how much that discussion would need, but we could at least refer to that because it discusses all of the issues with using the exfoliants. So I think I would recommend reopening and then adding discussions that when it's formulated, be non- irritating especially to the (inaudible) --

DR. MARKS: Yeah.

DR. SHANK: Especially to the non-sensitizing and then as far as an exfoliant is concerned, as much of the discussion from glycolic acid report is necessary or just referred to that report.

DR. MARKS: Glycolic acid, yeah. I felt it could be reopened also. I was going to -- I like how you had the non- irritating. I was just going to say maximum concentration is 0.02 percent since we have an HRIPT indicating that was safe at that concentration and I know it's -- the concentration -- the uses are up. The concentration is up. The maximum leave-on concentration is 2.1 percent, but then you -- it would leave the formulator manufacturer to come back and say, "Well, here's an HRIPT at 2.1 percent, but that was just a different way. I like the non-irritating also, but then you still have to deal with the sensitization.

DR. SHANK: Right.

MS. BURNETT: Right, I'm sorry. I'm lost on the HRIPT was for the malic acid, not the sodium malate.

MR. STEINBERG: Now, which are you talk -- what's the pH you're talking about?

DR. MARKS: Let me see.

MS. BURNETT: Because as far as I know, the --

DR. MARKS: At 2.2 percent the ocular irritation of malic acid was severe and severe, there's what you say about formulating to be non-irritating because we know at the highest use concentration, it can be a severe irritant. Now, where did I get this sensitization?

MS. BURNETT: It's right above malic acid.

DR. MARKS: Malic acid. Yeah.

MS. BURNETT: So the pH, it's about three, 3.6.

MR. STEINBERG: Okay, now, raise that pH to six and it's not -- because it's mostly the small presence.

MS. BURNETT: Right.

MR. STEINBERG: So that's on its use on the pH -- on the finished product which determines how much is present?

DR. HILL: Yeah, I was surprised that uses of pH adjuster gave people any comfort level because you could use -- you might need to use 40 percent in something to adjust pH to something.

DR. MARKS: Yeah.

DR. HILL: And do you (laughs) know, so --

DR. MARKS: Just based on that.

DR. HILL: No, I would not reopen because for me there's a lot of open questions here that need to be answered if we reopen this sucker. For me, I mean, that's probably no good reason not to open it, but yeah, do we have anything going on in the world that suggest that there are problems with this? Do we have anybody stumping for these uses that -- other than the pH adjuster obviously is being used.

DR. MARKS: Well, the uses are going up (inaudible).

DR. HILL: And I guess if you don't reopen, we've already talked about this before, there is nothing equivalent to the two-year clock when things having ever been cleared for safety for some uses now in common use, but -- so without reopening it, I guess you don't get that, but I have no real toxicological concerns with this guy at all, but I have a lot of unanswered questions if you reopen it.

MS. BURNETT: So what -- some of those questions be covered and the question I pose because like, ECHA it as read across because of its relationship in the citric acids cycle. Same thing with succinic acid, it's related in a citric acid, so we have reviewed both. We have found both to be safe as used. With that help cover bridging you the

(crosstalk) acid --

DR. HILL: No --

MS. BURNETT: -- especially, I think there's a data gap in like, carcinogenicity data.

DR. HILL: You know, for me, number one, that's only appropriate read across for irritant. But number two, because it is malic acid, at least D-malic acid, there should be no concern. This is pervasive in human biochemistry and I can't even stretch in my imagination, come up with a concern. I would be looking for information if the commercial product happens to be DL. Do we know that the L, which is the unnatural -- I wish that system would

be abandoned for this? Chemists don't want to see that system used anymore except for sugars and amino acids, which is two separate systems. So we really should try to go towards plus and minus and get rid of this lower case -- it's small cap D and small cap L because the confusion is small italic D and small italic L are not equivalent to small cap D and small cap L. And so there's this confusion that it's pervasive out there in the literature of using that.

But anyway, there's lots of legacy. The point is, what do we really know about the unnatural -- the uppers in stereoisomers that freely interconverted in human biochemistry. If we have toxicity studies being done with D malic, excuse me, L malic, does that create across to the D? So there are a number of open questions along those lines and even your search strategy if we reopen, we need to revisit that because with sodium malate, is that the monosodium or the disodium, have we captured that in the search? Have we also captured monopotassium and dipotassium, ammonium and diammonium? In other words, all the simple alkaloid salt and I was going to ask, we do have structure based searching capability with scifinder, right? We are paying for that and have it because the easy way to search this and make sure you get everything is to put in that structure and leave ions unspecified --

MS. BURNETT: right.

DR. HILL: -- to be sure that we've captured everything.

MS. BURNETT: I did check to make sure it was monosodium malate when I search.

DR. HILL: But the point is, the toxicology could be done with any of the above and would be relevant.

MS. BURNETT: Right, okay because I did note that there were some disodium malate. Toxicity papers, since this is monosodium, I did not --

DR. HILL: So there should be at least another six or eight CAS numbers that would be included in the search and then none of that would get into PubMed because in general, the CAS numbers don't show up in PubMed when you search PubMed that way.

MS. BURNETT: Okay.

MR. STEINBERG: Ron?

DR. HILL: Yeah.

MR. STEINBERG: Just one problem. How do you have pure mono?

DR. HILL: You don't.

MR. STEINBERG: You can't. It's always a mixture.

DR. HILL: That's what -- and my point.

MR. STEINBERG: Yeah.

DR. HILL: That's exactly my point, so if you search it by structure in scifinder and find out all the associated CAS numbers and then make sure we've captured the stereoisomer issue, then you got everything.

MR. STEINBERG: Yeah, I mean, a high enough pH, you'll have all di-, but --

DR. HILL: Well, you don't --

MR. STEINBERG: You don't want to have a mixture of mono in time (crosstalk) --

DR. HILL: But in solution, it's no longer salt anyway. Once it's dissolved, you've got the conjugate base which is either monoamine or diamine and you've got the sodium amine, similarly with potassium. It's --

MR. STEINBERG: Or whatever --

DR. HILL: So once it's dissolved, it's not the salt anymore. It's conjugate base and ions, but you're right and then it'll be a mixture thereof and -- but in biology -- in human biology, once you get out of the stomach or (inaudible), everything is pH 7.4 pretty much. So --

DR. MARKS: Okay, so with your concern about reopening and this long discussion and the chemistry here, Ron Shank, you want to reopen and -- you said formulate to be non-irritating, does that cover the sensitization, do you feel with that? We know it's a severe irritant ocular, so I think that covers that easily.

DR. HILL: Do we have any reason to believe that this should sensitize because I can't come up with the mechanism for that either? I mean, only some farfetched ones.

DR. MARKS: I guess, there you come back to the lack of case reports.

DR. HILL: Right.

MS. FIUME: Well, if I could just jump in --

DR. MARKS: Sure.

MS. FIUME: -- for a second.

DR. MARKS: Absolutely.

MS. FIUME: So if you're going to reopen this, we're not adding ingredients, so we're not worrying about a no-brainer or anything else.

DR. MARKS: Uh-uh.

MS. FIUME: It's becomes like, essentially a new draft report, so there are questions you have if you would like to see sensitization at maximum concentration of use.

DR. MARKS: (Inaudible)

MS. FIUME: You're free to go ahead and issue an IDA for any data concerns you have. I also want to say, so I was looking at the concentration of use sent to us and the true on skin highest concentration that I see, I believe is 1 percent in face and neck products. The 2.1 percent that is a leave-on is a hairspray.

DR. MARKS: Yeah, which I noted that, but I think that means --

MS. FIUME: It still could have --

DR. MARKS: -- yeah, the skin contact is going to be 2.1 percent, you just don't spray your hands or your hair. The scalp gets it too.

DR. SLAGA: Could we do that for irritation or something that --

DR. MARKS: Well, I think irritation we're going to -- I don't -- we already have a lot of --

DR. SLAGA: Yeah. Well, we could ask for more data

(crosstalk) --

DR. MARKS: -- irritants, yeah.

DR. SLAGA: -- (crosstalk)

MR. FIUME: Right, essentially as if it's the first time you're seeing --

DR. SLAGA: Right.

DR. MARKS: Right.

MS. FIUME: -- once you reopen it. So you can ask for whatever you feel that you need.

DR. MARKS: Well, I think we can have direction though. I like the idea of formulation of being non-irritating because I can't imagine we're going to get any data that's going to sway that.

MS. FIUME: It seems like that would be kind of --

DR. MARKS: Yeah, but to me --

DR. SLAGA: Yeah.

DR. MARKS: -- the main question is --

DR. SHANK: Sensitization.

DR. MARKS: Sensitization at 2.1 percent if we reopen it. And then you have a lot of other questions --

DR. SLAGA: Most of which I --

DR. MARKS: -- but does that sound like a reasonable direction at this point? I like the insufficient data announcement and let's get sensitization HRIPT. That's our concern. We would aim towards formerly to be non-irritating and then we deal with the sensitization. Tom, Ron, Ron, does that sound like a reasonable -- we'll be seconding it so the -- I have a feeling that the Belsito team will have a different approach, but who knows? Maybe not. So reopen, I like that insufficient data announcement. Does that sound good? I know Ron Hill you were real -- announcement -- I don't think we need the irritation -- anymore irritation. We have enough. And need sensitization at -- I'm going to put HRIPT. Could be a guinea pig, but HRIPT at 2.1 percent. Sound good? And then an alternative -- and then I'm going to put in parentheses formulate to the non-irritating -- I don't like in non-sensitizing. I know we've done that with the botanicals. We've slipped into that with botanicals, but with this, I think we need. And the other would be, the conclusion could be formulate to be non-irritating and maximum concentration is 0.02 percent since we have an HRIPT that supports that. Does that sound reasonable?

DR. HILL: When you were looking at --

DR. SHANK: Go ahead --

DR. MARKS: Okay.

DR. HILL: Is exfoliant a listed used of this and if so, what kind of concentration?

MS. BURNETT: It's -- Bart will go on his little tangent, but it's -- if by -- I got to remember this correctly. Too many reports -- I think that was listed as a function, but I don't think we actually have it --

DR. MARKS: Before you -- in that use, yeah.

DR. EISENMANN: But we don't report --

MS. BURNETT: We don't report --

DR. EISENMANN: -- as it was --

MR. BURNETT: Yeah.

DR. HILL: No. So you have VCRP that reports uses and then you have concentration from the survey.

DR. EISENMANN: Right and then we'll product categories. We don't tell -- they don't tell me what function.

DR. HILL: Yeah.

DR. EISENMANN: They don't tell if (inaudible) what function it is. You have to read the -- look at the product label and --

MR. STEINBERG: And guess.

DR. EISENMANN: Mm-hmm.

DR. MARKS: Well --

DR. EISENMANN: Right, you still wouldn't know.

DR. MARKS: I guess we'll be getting that information would be all but impossible, but --

DR. EISENMANN: Yes.

DR. MARKS: -- it sure would be --

DR. SHANK: I like to say, reopen it and then set the concentration to 0.02 percent for sensitization and if that's too low, then data will have to be submitted.

DR. EISENMANN: Well, why don't you just add an insufficient data and I'll put like Monice suggested and we'll see if we can get the data and then come up with a conclusion --

DR. MARKS: Yeah, I kind of like that. Gives a little heads up to industry to find -- send that in and support it. Usually, we don't -- when we look at things first -- this isn't exactly the first time at it, but first time we often don't get a right to a tentative report. We'll have an insufficient data now announcement, but --

DR. SHANK: Well, we read in the report said it could be used only as a pH Adjustment.

DR. MARKS: Right.

DR. SHANK: But now, we see it's used for other purposes.

DR. MARKS: Exactly.

DR. HILL: Well, then again, if -- depending on what you're adjusting, you could end up using 40 percent in a formulation to adjust the pH to something useful and I'm sure that's not happening, but I don't think there should be any particular comfort level with expecting that to be the use because I can't imagine.02 percent would adjust anybody's pH to anything, quite frankly. So I would think all the uses as pH adjusters are probably in excess of.02 --.02 percent

(laughs) and probably more like a few percent, but for sure one (inaudible), if I had to make an educated guess.

DR. MARKS: Well, I don't think we have any question that we're going to reopen it and then I think if it's okay, Ron Shank, maybe just do the insufficient data announcement. We like the sensitization at 2.1 percent, but it may end up being -- we end up with a conclusion that it's going to be formulated to be on the irritating maximum concentration of 0. -- well, we don't even have to put formulated to be non- irritating --

DR. HILL: No.

DR. MARKS: -- (inaudible), but I guess that's -- you know, that raises what you're saying is if it's a pH -- the maximum concentration after it's diluted is 0.02 percent as a pH adjuster.

DR. HILL: That doesn't -- I find that difficult to believe --

DR. MARKS: Yeah.

DR. HILL: -- but yeah, we do have concentration surveys, so we do on by whatever pops out of that, which is obvious it was 1 percent, except for -- what was it 2 percent?

MS. FIUME: There were several -- 2.1 percent was in the hairspray.

DR. HILL: Hairspray, yes. It does with hairspray, so that's --

MS. BURNETT: So I just double checked, so I'm not sure how the word exfoliant was brought in, but the two uses for malic acid functions are the pH adjuster and a fragrance. For a sodium malate, it's only the humectant-skin conditioning.

DR. HILL: Yeah.

MS. FIUME: I was wondering, the inferred exfoliant came from as well as it's in the previous minutes that it was discussed that there's possible use as an exfoliant and that's how it got into the original report.

DR. HILL: Possible use.

MS. BURNETT: Right.

DR. MARKS: So what you're saying is it was in the minutes, but not actually in the (inaudible).

MS. FIUME: But it was in the discussion because that must have come up.

DR. MARKS: That's where you probably picked it up wrong.

MS. FIUME: Yeah, it was in the discussion.

DR. MARKS: So it sounds like we don't have --

DR. HILL: I read the transcripts of the previous report. I remember hearing it.

DR. MARKS: Yeah, so I guess what you're willing to believe at this point, can we just drop the issue with the exfoliant?

MS. FIUME: Well, if I was speaking for Bart, I'm sure he would say his request would be not to determine safety based on proposed functions because those can change and they're just --

DR. MARKS: Right.

MS. FIUME: -- propositions for the dictionary --

DR. MARKS: Yeah.

MS. FIUME: -- just to base safety on the ingredient itself regardless of functions.

DR. HILL: Well, what would be the mechanism guys and ladies for exfoliant? I mean, I'm pretty sure if I take malic acid and make a paste in water and smear it on my skin, I'm going to exfoliate and do a lot of other things too and have a nice big red mark. (Laughter) But if it's more like the alpha hydroxyl acid exfoliant type, then there's biochemistry associated with that, so I guess -- I mean, I'm just raising that.

On the -- to return to a couple of questions --

DR. MARKS: No, I want to finish up with the exfoliant --

DR. HILL: Okay, great.

DR. MARKS: Ron, what do you want to do with that now at this point? Do you want to include that in the discussion using the glycolic acid as a basis or just ignore the exfoliant at this point?

DR. SHANK: We can ignore -- I just said it now --

DR. MARKS: Right.

DR. SHANK: -- we should consider this and we have - -

DR. MARKS: Okay.

DR. SHANK: And since it's not listed as a function -- as a use --

DR. MARKS: Okay.

DR. SHANK: Then we won't have to a --

DR. MARKS: Okay. Okay, Ron, Tom, I'm sorry, I'm --

DR. HILL: No, I -- no, thank you.

DR. MARKS: -- you reach that, make sure we close the loop on that. Okay. I'll agree.

DR. HILL: Okay.

MR. STEINBERG: Can -- just a comment that it is used, not per se as an exfoliating agent, but in combination with several others for the people who want to have fruit-based exfoliating agents and not use lactic and glycolic acid. And it's a hodgepodge or mishmash mixture of God's know what, but it's really geared to the people who want an exfoliating agent without glycolic or lactic with the concept that they're safer.

DR. HILL: Which is nothing more than folklore.

DR. MARKS: Which is -- yeah, absolutely.

DR. HILL: Wives tail actually.

DR. MARKS: Yeah.

DR. HILL: Not even folklore.

DR. MARKS: That's on the concentration. There are or they can -- I think that would be covered in the conclusion anyway. Some way either we're going to be in such a low concentration that it's not going to be a significant irritant or in the conclusion, it's going to be formulated as non-irritating, so even if it's added in that, I would think --

DR. SHANK: It wouldn't --

DR. MARKS: -- as an exfoliant, it's going to be covered. To me, it's also like a (inaudible). Is that okay, Ron and then --

DR. SHANK: Okay.

DR. MARKS: If not, we can --

DR. SHANK: No.

DR. MARKS: -- we're going to see it again.

DR. SHANK: I just wanted to bring it up.

DR. MARKS: Yeah. No, I --

DR. SHANK: (Inaudible)

DR. MARKS: Ron Hill, you had a --

DR. HILL: Yeah, so if in the searching we could add to the task a little bit about what's known about D malic acid in human biochemistry. That's the -- not the natural sensitization. My sense is that it ought to be more or less freely interconverted and from -- if we have that information and it's known, that's pretty much all we would need. A little bit of information about that. You'll have to find a way of searching specifically the D isomer. There will be a CAS number associated with that, would be one way and probably the easiest way and then use side finder as the starting point and it should probably pick up everything you need to find.

DR. MARKS: You want to mention that to Margo (phonetic) during discussion.

DR. HILL: I don't see any reason to do that.

DR. MARKS: Christina has it, so okay.

MS. BURNETT: And just to make sure with the reopening, you don't want the (inaudible) that signifies that --

DR. HILL: The other comment I was going to make is to me, they're perfectly good read across for irritation, but if you're leaning towards ending that, but non-irritating -- I mean, I agree with what they're saying about the biochemistry and the Krebs cycle --

DR. SHANK: How about for sensitization?

DR. MARKS: No, not at all.

DR. SHANK: Would it read across?

DR. MARKS: No, no read across for sensitization if that's of issue.

DR. SHANK: Well, that's the issue.

DR. MARKS: All right. If that's the issue, then no, no read across.

MS. BURNETT: Should I mention that they even exist in the intro?

DR. MARKS: ECHA has got it. I don't see how you just ignore them.

MS. BURNETT: Okay, so I can just say we have -- we reviewed chemicals of the citric acid cycle --

DR. SLAGA: Relation, yeah.

MS. BURNETT: Okay.

DR. SLAGA: That would read across for carcinogenicity if you were referring to (inaudible).

DR. SHANK: Pardon?

MS. BURNETT: Yep, that's the main data gap.

DR. SLAGA: That probably (inaudible).

DR. SHANK: I think that's fair.

DR. MARKS: Well, you can put that in too. Yeah, I'm comfortable with that. I -- again, there's the bringing in the D if we have commercially synthetic -- the Apple people, by the way, wouldn't like that. (Laughter) You have (inaudible) commercially, but anyway. We don't need to put that in lights. I don't see any point to that.

DR. HILL: I didn't know any irritating (inaudible), did you want to mention that so the rest of the

MS. FIUME: I did go back to look at the alpha hydroxy acids discussion to see what it may have said about exfoliation and I haven't found anything about that yet. But there was specific talk about alpha hydroxyl acids could be general irritants and that the interdependence on pH. And I didn't know that mattered for the discussion and once we said formulated to be non-irritating, that that would be sufficient.

DR. SHANK: I think so.

DR. HILL: Yeah, absolutely.

DR. MARKS: Okay, so that was a real positive discussion. A little malic acid and sodium malate. So presumably -- well, tomorrow be seconding a motion. We'll see what that motion is, but our team feels, let's reopen it. We do an insufficient data announcement and we need an HRIPT at 2.1 percent or another sensitization study to support the data at this use concentration. Going forward in the conclusion, we'll have formulate to be non-irritating and then decide on the maximum concentration at point -- and then you wanted the D malic data acid, but I'm not sure I'll bring that up tomorrow.

DR. HILL: There was one other thing which it'd be nice to put to bed and my question here was, was there ever a resolution concerning why this was not regarded as GRAS in baby food? My educated guess would be that this would be a source of Oxaloacetate by simple oxidation which could then be freely transaminated to aspartate which is an excitatory amino acid in an excitotoxin. You would really have to have -- then should be totally irrelevant to any cosmetic and personal care product use because we're just talking about incidental oral exposure. There's no way you get near enough in -- by any other route for this to become at all a concern. But because it was raised in our document, it would not necessarily have to be included in what we end up with finally, but we need to be sure that if this comes up, hey, you all raised this. It was an FDA issue, not our issue, but do we need to even mention it.

MS. BURNETT: You mean like --

DR. HILL: No, it came off that it's not GRAS, specifically not GRAS --

MS. BURNETT: Right.

DR. HILL: -- for baby food.

MS. BURNETT: As far as I understand, babies can't digest it; can't be digested currently. They can't metabolize it correctly or something.

DR. HILL: Yeah, I doubt that.

MS. BURNETT: All right, I --

DR. HILL: This -- if this takes us to the '70s when all this stuff about MSGs in baby food was showing up, it could be --

MS. BURNETT: Let me check. I'm --

DR. HILL: -- pressing back to that.

MS. BURNETT: -- pretty sure that said an original of why.

DR. HILL: I don't think it did because I think I went out and looked, but maybe it does.

MS. BURNETT: I know I read about it, but I can't find where I read about it.

DR. HILL: Okay, we can research that data.

MS. BURNETT: Yea.

DR. HILL: We can resolve that.

DR. MARKS: Ron Hill and Christina, I'll let you guys settle that issue and then if it's important, bring it up tomorrow.

DR. HILL: If it's not reopened it goes away (laughs). If it's reopened, it might need to be at least mentioned somewhere --

DR. MARKS: Okay.

**Full Panel Meeting**

DR. BERGFELD: All right. Moving on then to malic acid. Dr. Belsito?

DR. BELSITO: Okay. So in 2001, we looked at this based on the available animal and clinical data. At that time we concluded that malic acid, sodium malate were safe as used as pH adjusters in cosmetic formulations but the data were insufficient to determine safety of use for these ingredients in other functions. And the data needs for those were concentration of use, dermal irritation, sensitization, ocular irritation. We've now been told that these materials are being used other than as pH adjusters and also that there are other ingredients that could be added to this re-review. So we thought that based upon the information that there were uses that we had at least considered in 2001 to have insufficient data to support, and given the fact that it's time to reopen and we can add other ingredients we would reopen.

MS. BURNETT: I want to clarify, there are no add-ons for this.

DR. BELSITO: Okay.

MS. BURNETT: It's just malic acid and sodium malate.

DR. BELSITO: Okay.

MS. BURNETT: Which were both together in the original.

DR. BELSITO: Okay. But we would reopen to look at safety for non-leave on or for non-pH adjuster use. I see. We thought we could add in the data for fumaric acid and succinic acid and sodium succinic as read-across, particularly for repro and carcinogenicity, which had very limited data.

MS. BURNETT: Right.

DR. BERGFELD: Comments from the Marks' team?

DR. MARKS: We second the motion to reopen and with reopening, we agree Don would have an insufficient data announcement. Our team felt we needed an HRIPT at 2.1 percent to support the safety at its use concentration now and leave-ons at that high concentration. Or potentially -- we aren't going to do that now -- could be formulate to be nonirritating with a maximum concentration of 0.02 percent. That's the HRIPT we have now for malic acid. Our team -- Tom, Rons, we weren't as convinced that we could read-across from fumaric and succinic acids. Do you want to clarify on that? Did I interpret our team correctly with that?

DR. SLAGA: I didn't say that.

DR. MARKS: Okay. You didn't, Tom. Go ahead, Ron Hill.

DR. HILL: I guess it was my assertion that, one, there's really no reason to do that except for irritation, and to me the irritation issue is that it's an acid which in a cosmetic or personal care formulation would be a nonissue anyway because it won't exist as malic acid at that point. It will be the conjugate base, mono and di-conjugate base of malic acid. And while I agree with the interrelatedness in the Krebs cycle, why you even need that information, I mean, it's malic acid, for god's sake. So the only concern I had was the fuzziness related to the stereochemistry that malate is a naturally occurring molecule and I'm not sure that I have a good handle if it's synthetically produced racemate, the DL-malate, whether we have a good handle on that. But that doesn't relate to succinic or fumaric, and I think the issues with malic might even be less than either of those. And I guess the question is why we even need it for read-across. And I realize the ECHA used that but I'm not sure why they felt the need to do that. I just -- I don't see why. We've got a compound that will be extensively ionized not all that well absorbed through the skin. If it's absorbed in the gut, we get that in our diet pervasively. I just -- I don't see the issue.

DR. MARKS: Dan?

DR. BERGFELD: Dan?

DR. LIEBLER: Yeah, I think you're right about the main point. I'm not sure we need read-across materials here. So it was raised in the memo and I was responding to that, but if you actually look, there are data on chronic toxicity and developmental repro. So, I mean, I think we're probably in the clear. We don't need it.

DR. HILL: And I can't even dream up a mechanism by which that would cause a problem in our wildest imagination, and I have a pretty good one as you know.

DR. LIEBLER: No, no, no.

DR. HILL: And I have a pretty good one, as you know.

DR. LIEBLER: Yes, that's true. We all do. So anyway, I think it's kind of a moot point. It's not a major issue for us.

DR. BERGFELD: So the motion has been made to reopen. It's been agreeable. I guess seconded. And we have a list of things that have needs. Do we need to relist those? The original needs?

MS. BURNETT: Is there a conclusion? Is it an IDA?

DR. BERGFELD: Well, we're getting there. We're just going to reopen first.

MS. BURNETT: Right.

DR. BERGFELD: All those in favor of reopening?

(The motion passed unanimously.) Okay. Can we move forward with an insufficient data announcement?

DR. MARKS: Yes.

DR. BERGFELD: Okay. So we'll do that. So general agreement. All right. Moving on to the next item them.

DR. HILL: Did we list needs?

DR. BELSITO: Yes.

DR. BERGFELD: They were the same they said.

DR. BELSITO: Yes. The needs were from the original report. You just specified concentration.

DR. HILL: Well, I wanted to add -- at least at an inquiry because the information we have on impurities, or for that matter, production processes, but impurities is what we're really interested in, is essentially not informative. And if it is being produced as a synthetic racemase, in other words, a DL mixture, I would like to see a little more information about that.

DR. BERGFELD: We can add that.

MS. BURNETT: Okay. So to make sure I have the right list.

DR. BERGFELD: All right. Will you repeat it then, Christina?

MS. BURNETT: Impurities.

DR. BERGFELD: Methods of manufacturing with that.

DR. HILL: I really just am interested in impurities if, in fact, it is being produced and used by the industry as a synthetic racemase.

MS. BURNETT: Okay. And then HRIPT at 2.1 percent for leave-ons?

DR. HILL: Correct.

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## Amended Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics

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Status: Draft Tentative Amended Report for Panel Review  
Release Date: November 10, 2017  
Panel Meeting Date: December 4-5, 2017

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The 2017 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Christina L. Burnett, Senior Scientific Analyst/Writer.

## DRAFT ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) assessed the safety of Malic Acid and Sodium Malate in cosmetics. Malic Acid is reported to function in cosmetics as a fragrance ingredient and a pH adjuster and Sodium Malate functions as a skin-conditioning agent - humectant. The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded [to be determined].

## INTRODUCTION

The CIR Panel published the Final Report on the Safety Assessment of Malic Acid and Sodium Malate in 2001 and concluded that Malic Acid and Sodium Malate are safe for use as pH adjusters in cosmetic formulations; however, the Panel determined that the data were insufficient to determine the safety of these ingredients for any other functions.<sup>1</sup> The data needs, based on the reported function of Sodium Malate (skin conditioning agent – humectant), were concentration of use data, dermal irritation and sensitization data, and ocular irritation data. Based on the receipt of data that addressed the data insufficiencies in the original report, the Panel reopened the Safety Assessment of Malic Acid and Sodium Malate in 2017 to amend the original conclusion. The conclusion of this report supersedes the one found in the 2001 report.

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook (Dictionary)*, Malic Acid is reported to function in cosmetics as a fragrance ingredient and a pH adjuster, while Sodium Malate is reported to function in cosmetics as a skin-conditioning agent – humectant.<sup>2,3</sup> These reported functions are the same as those indicated in the 2001 assessment, although fragrance ingredient is a new function for Malic Acid.

Malic Acid (or malate) is an intermediate in the citric acid cycle (also known as the tricarboxylic acid (TCA) cycle or Krebs cycle) formed during the hydration reaction of fumarate (or fumaric acid) with the enzyme fumarase.<sup>4</sup> Fumarate is formed by the oxidation reaction of succinate (succinic acid) and coenzyme Q (ubiquinone) with succinic dehydrogenase. Because of the chemical relationship for fumaric acid and Malic Acid, the entities submitting data to the European Chemicals Agency (ECHA) have used safety test data on fumaric acid as read across to support the safety of Malic Acid.<sup>5</sup> The toxicological endpoints to support the safety using fumaric acid included in the registration dossier were acute oral, inhalation, and dermal toxicity, dermal an ocular irritation, dermal sensitization, repeated dose oral toxicity, and in vitro genotoxicity. These endpoints were not included in this safety assessment as the Panel felt the systemic data on Malic Acid were sufficient. The Panel published the safety assessments of Fumaric Acid (with related salts and esters) in 2009 and Succinic Acid and Sodium Succinate (as part of the report on dicarboxylic acids) in 2012 and concluded that these ingredients, which have the same functions as Malic Acid, are safe as used in cosmetics.<sup>6,7</sup>

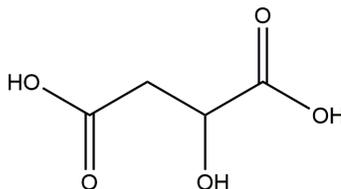
This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Excerpts from the summary of the 2001 report on are disseminated throughout the text of this re-review document, as appropriate, and are identified by *italicized text*. (This information, except for chemical and physical properties, is not included in the tables or the summary section.) Additionally, the Discussion from the original report (available at <http://www.cir-safety.org/ingredients>) is also included in this document.

## CHEMISTRY

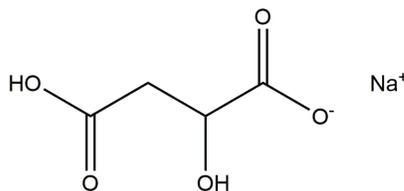
### Definition and Structure

The *Dictionary* defines Malic Acid as the organic acid whose molecular formula is C<sub>4</sub>H<sub>6</sub>O<sub>5</sub> and whose structure is depicted below (Figure 1).<sup>2</sup>



**Figure 1.** Malic Acid

Sodium Malate is the monosodium salt of Malic Acid. It conforms to the formula described below (Figure 2).<sup>3</sup>



**Figure 2.** Sodium Malate

Malic Acid and Sodium Malate are monohydroxy succinic acid ingredients. Malic Acid has a stereocenter denoted by D, L, DL, or meso. The *Dictionary* name as defined is ambiguous to these stereochemical details. Stereochemistry is identified where provided in the data.

### Physical and Chemical Properties

Physical and chemical properties of Malic Acid were previously reported in the 2001 safety assessment and the pertinent information from that document along with additional properties are provided in Table 1. No physical or chemical properties for Sodium Malate were reported previously nor found in the updated literature search.

### Methods of Manufacture

*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.*<sup>1</sup> *L-Malic Acid is available through the ~~microbiological fermentation~~ [hydration] of fumaric acid.*

### Natural Occurrence

*The L-isomer of Malic Acid is naturally occurring and common metabolite of plants (most commonly found in fruits, such as unripe apples) and animals.*<sup>1</sup>

### Impurities

*Maleic and fumaric acids are by-products of the manufacture of Malic Acid.*<sup>1</sup> *Malic Acid is generally purified until the amounts of fumaric and maleic acid are 7.5 and <500 ppm, respectively.*

The *Food Chemicals Codex*, a compendium of internationally recognized standards published by the United States Pharmacopeia (USP) for the purity and identity of food ingredients, states Malic Acid for food use should be 99-100.5% pure with no more than 1% fumaric acid and no more than 0.05% maleic acid.<sup>8</sup>

## USE

### Cosmetic

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetics industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

The frequency of use of Malic Acid has increased since safety was originally reviewed, from 47 reported uses in 1998<sup>1</sup> to 238 reported uses in 2017<sup>9</sup> (Table 2). Notably, the number of uses near the eye area and mucous membranes increased from no reported uses to 4 and 19, respectively. The reported maximum concentration of use has increased; the maximum leave-on concentration of use reported was 1% (in multiple formulation types) in 1984,<sup>1</sup> and the results of the survey conducted by the Council in 2016 now indicate that the maximum leave-on use concentration is 2.1% (in a hair spray).<sup>10</sup> It is used at up to 50% in products diluted for baths.

The frequency of use for Sodium Malate has also increased since the original review, from 1 reported use in 1998<sup>1</sup> to 5 reported uses in 2017<sup>9</sup>. Current uses of Sodium Malate are reported in coloring hair care products and skin care preparations. No concentration of use for Sodium Malate was reported in the 2001 safety assessment.<sup>1</sup> The Council in 2016 reported that Sodium Malate is used at 0.02% in "other" skin care preparations.<sup>10</sup>

Malic Acid is used in products that are used near the eye at a maximum concentration of 0.00012% (in eyeliners; no maximum use concentration was reported in 1984 for this category) and in those that can come in contact with mucous membranes at maximum concentrations up to 50% (in bath oils, tablets and salts; again, no previously reported concentrations in this category).<sup>1,10</sup> Additionally, Malic Acid is used in body and hand products and pump hair spray formulations at concentrations up to 2.1%; these product-types could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters > 10  $\mu\text{m}$ , with propellant sprays yielding a greater fraction of droplets/particles < 10  $\mu\text{m}$  compared with pump sprays.<sup>11,12</sup> Therefore, most droplets/particles

incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.<sup>13,14</sup>

Malic Acid and Sodium Malate are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).<sup>15</sup>

### **Non-Cosmetic**

*DL- and L-Malic Acid are generally recognized as safe (GRAS) as direct food additives for use as flavor enhancers, flavoring agents, adjuvants, and as pH control agents.<sup>1</sup> DL- and L-Malic Acid are not GRAS for baby foods.*

The *Merck Index* reports that Malic Acid is an intermediate in chemical synthesis.<sup>16</sup> It is a chelating and buffering agent. In foods, it is a flavoring agent, a flavor enhancer, and an acidulant (a substance that gives food a tart, sour, or acidic flavor). The *Food Chemicals Codex* reports that Malic Acid functions as an acidifier and a flavoring agent in food.<sup>8</sup>

## **TOXICOKINETICS STUDIES**

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

*Most of the radioactivity from 2.5 mg/kg U-<sup>14</sup>C-L-Malic Acid (specific activity 61 μCi/mmol) or 4-<sup>14</sup>C-DL-Malic Acid (specific activity 93 μCi/mmol) administered orally or intraperitoneally (i.p.) to male rats was excreted as carbon dioxide.<sup>1</sup> Daily oral administration of 4 g/kg Malic Acid resulted in increased glucuronic acid excretion in the urine.*

### **Skin Penetration**

The ability for Malic Acid in rinse-off personal care products to penetrate the skin was assessed in an in vitro study.<sup>17</sup> A shampoo with radiolabeled Malic Acid (L-(U)-[<sup>14</sup>C-Malic Acid; <1%; pH 5.0-7.0) was applied as a single dose to human epidermal membranes mounted in static diffusion cells. The membranes were not occluded. The exposures were 1 min in duration. Epidermal penetration of Malic Acid from the shampoo was considered negligible, with > 99% removed by rinsing. The actual skin dose for Malic Acid was 2.69 μg/cm<sup>2</sup>, the total absorbable dose was 0.003% and the total dose delivered was 0.000067 μg/cm<sup>2</sup>.

## **TOXICOLOGICAL STUDIES**

### **Acute Toxicity Studies**

*The oral LD<sub>50</sub> values of Malic Acid for mice, rats, and rabbits ranged from 2.66 to greater than 3.2, 1.60 to 3.5, and 3 to 5 g/kg, respectively.<sup>1</sup> The acute LD<sub>50</sub> of Malic Acid given intravenously was 2.4 g/kg for rabbits, and the i.p. LD<sub>50</sub> for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively.*

### **Chronic Toxicity Studies**

*In a chronic oral study in rats, Malic Acid at concentrations up to 50,000 ppm (5.0%) for 104 weeks resulted in some changes in body weight gains and feed consumption, but compound-related lesions were not observed.<sup>1</sup> No significant changes or lesions were observed when dogs were fed Malic Acid at concentrations up to 50,000 ppm for 104 weeks.*

## **DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES**

*Oral dosing of Malic Acid did not cause developmental toxicity in mice (at up to 266 mg/kg), rats (at up to 350 mg/kg), or rabbits (at up to 300 mg/kg).<sup>1</sup> In a multigenerational oral DART study, no significant adverse effects were observed in rats that received up to 10,000 ppm Malic Acid.*

## **GENOTOXICITY STUDIES**

### **In Vitro**

*Malic Acid was not mutagenic in Ames tests or a mammalian cell chromosomal assay.<sup>1</sup> In one bacterial cell study, pyrolyzates of Malic Acid were not mutagenic, but in another bacterial cell study they were. Products formed from treatment of Malic Acid with aqueous solutions of chlorine were considered mutagenic.*

DL-Malic Acid was not mutagenic in an Ames test in *Salmonella typhimurium* strains TA97 and TA102 when tested with and without metabolic activation.<sup>5</sup> The material was tested at up to 10 mg/plate in distilled water.

## **CARCINOGENICITY STUDIES**

No published carcinogenicity studies on Malic Acid or Sodium Malate were discovered and no unpublished data were submitted either currently or in the 2001 safety assessment.

## **DERMAL IRRITATION AND SENSITIZATION STUDIES**

The findings of human repeat insult patch tests (HRIPTs) are summarized in Table 3. Malic Acid at up to 1% in formulation was not a significant skin irritant and did not induce allergic contact dermatitis.<sup>18-20</sup>

### **Animal Studies**

*Malic Acid was moderately irritating to rabbit skin (500 mg for 24 h) and was a strong irritant to guinea pigs (concentration not reported).<sup>1</sup>*

### **Human Studies**

*In a test determining subjective skin irritation potential, the average irritation scores over a 15-minute period were 39.4, 37.1, and 23.1 for 1 M Malic Acid at pH 3, 5, and 7, respectively.<sup>1</sup>*

## **OCULAR IRRITATION STUDIES**

### **In Vitro Studies**

The ocular irritation potential of Malic Acid was tested in formulation in chorioallantoic membrane vascular assays (CAMVA) and bovine corneal opacity and permeability tests (BCOP).<sup>18</sup> Malic Acid at 2.2725% was tested in a hair styler and a hair shampoo at pH 3.6 and pH 3.0, respectively. The assays predicted that the formulation with Malic Acid at pH 3.6 would be a severe ocular irritant and the formulation with Malic Acid at pH 3.0 would be an ocular irritant.

### **Animal Studies**

*Malic Acid (750 µg) caused severe ocular irritation in rabbit eyes.<sup>1</sup>*

## **CLINICAL STUDIES**

*In predictive testing using patients with atopic dermatitis, 18 of 34 patients reacted to a diet high in Malic Acid and citric acid, and 6 reacted to a diet high in Malic Acid.<sup>1</sup> 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. Malic Acid (200 mg) was not toxic in a clinical efficacy and safety test.*

The occupational cumulative irritation potential of Malic Acid with other fruit acids was tested in 20 healthy volunteers.<sup>21</sup> The volunteers were exposed twice daily for 4 days to 2% Malic Acid (pH 2 and pH 4), citric acid, or lactic acid, either alone or in tandem with 0.5% sodium lauryl sulfate (SLS). Positive and negative controls were SLS and distilled water, respectively. Approximately 50 µl of the test materials were applied to each test area on the paravertebral mid back by occlusive patches (Finn Chambers on Scanpor, 12 mm diameter). The patches were removed after 30 min, rinsed with ~10 ml of tap water, and dried with tissue paper without rubbing. Irritant cutaneous reactions were quantified by visual scoring, transepidermal water loss, and skin color reflectance. The twice daily application of either Malic Acid (pH 2 or pH 4) or citric acid alone did not induce significant irritant reactions and were comparable to the negative control. Combined exposures to one of the acids and SLS caused marked barrier disruption, but the effect was less than that observed from combined exposure to SLS and water, which indicated a protective effect by the fruit acids. The authors of the study concluded that Malic Acid, citric acid, and lactic acid did not significantly contribute to the occurrence of irritant contact dermatitis or increase susceptibility to SLS-induced irritation.

## **SUMMARY**

The CIR Panel published the Final Report on the Safety Assessment of Malic Acid and Sodium Malate in 2001 and concluded that Malic Acid and Sodium Malate are safe for use as pH adjusters in cosmetic formulations; however, the Panel determined that the data were insufficient to determine the safety of these ingredients for any other functions. Based on the receipt of data that addressed the data insufficiencies in the original report, the Panel reopened the Safety Assessment of Malic Acid and Sodium Malate in 2017 to amend the original conclusion. The conclusion of this report supersedes the one found in the 2001 report.

In 2017, Malic Acid is reported to function in cosmetics as a fragrance ingredient and a pH adjuster, while Sodium Malate is reported to function in cosmetics as a skin-conditioning agent – humectant. These reported functions are the same as those indicated in the 2001 assessment, although fragrance ingredient is a new function for Malic Acid.

Malic Acid (or malate) is an intermediate in the citric acid cycle (also known as TCA cycle or Krebs cycle) formed during the hydration reaction of fumarate (or fumaric acid) with the enzyme fumarase.

The frequency of use of Malic Acid has increased since safety was originally reviewed, from 47 reported uses in 1998 to 238 reported uses in 2017. Notably, the number of uses near the eye area and mucous membranes increased from no reported uses to 4 and 19, respectively. The reported maximum concentration of use has increased; the maximum leave-on concentration of use reported was 1% (in multiple formulation types) in 1984, and the results of the survey conducted by the Council in 2016 now indicate that the maximum leave-on use concentration is 2.1% (in a hair spray). It is used at up to 50% in products diluted for baths.

The frequency of use for Sodium Malate has also increased since the original review, from 1 reported use in 1998 to 5 reported uses in 2017. Current uses of Sodium Malate are reported in coloring hair care products and skin care

preparations. No concentration of use for Sodium Malate was reported in the 2001 safety assessment. The Council in 2016 reported that Sodium Malate is used at 0.02% in “other” skin care preparations.

Malic Acid is an intermediate in chemical synthesis. It is a chelating and buffering agent. In foods, it is a flavoring agent, a flavor enhancer, and an acidulant.

In an in vitro study, epidermal penetration of < 1% radiolabeled Malic Acid (pH 5.0 - 7.0) in a shampoo was considered negligible, with > 99% removed by rinsing. The actual skin dose for Malic Acid was 2.69  $\mu\text{g}/\text{cm}^2$ , the total absorbable dose was 0.003% and the total dose delivered was 0.000067  $\mu\text{g}/\text{cm}^2$ .

DL-Malic Acid at up to 10 mg/plate was not mutagenic in an Ames test.

Malic Acid at up to 1% in formulation was not a significant skin irritant and did not induce allergic contact dermatitis in HRIPTs.

Malic Acid in formulations at 2.2725% was predicted to be an ocular irritant was tested in vitro.

Malic Acid (2%, pH 2 and pH 4) did not significantly contribute to the occurrence of irritant contact dermatitis or increase susceptibility to SLS-induced irritation

No published carcinogenicity studies on Malic Acid or Sodium Malate were discovered and no unpublished data were submitted.

## **DISCUSSION FROM THE ORIGINAL FINAL SAFETY ASSESSMENT OF MALIC ACID AND SODIUM MALATE**

*The Expert Panel considered separately the ways in which Malic Acid and Sodium Malate are used. As a pH adjuster, Malic Acid historically has been used at concentrations less than 1%. The available data demonstrate that what toxicity has been demonstrated for Malic Acid and Sodium Malate is related to concentration. Accordingly, the Expert Panel concluded that Malic Acid and Sodium Malate are safe for use as pH adjusters (even though Sodium Malate is not currently used for that purpose).*

*The data included in this report, however, were insufficient to determine the safety of these ingredients when used in cosmetics as other than pH adjusters. Specifically, the data are insufficient to determine the safety of Sodium Malate when used as a skin conditioning agent – humectant. The types of data required for the Expert Panel to determine the safety of Sodium Malate as a skin conditioning agent are:*

- 1. concentration of use data;*
- 2. dermal irritation and sensitization data; and*
- 3. ocular irritation data, if available.*

*The data needed to assess the safety of Malic Acid or Sodium Malate for some function other than as a skin conditioning agent – humectant cannot be specified without knowing the intended function. Were these ingredients to be used as exfoliants, for example, data similar to that included in the report on Glycolic and Lactic Acid (i.e. the Alpha Hydroxy Acid report)<sup>22</sup> would be needed.*

## **DRAFT DISCUSSION**

In June 2017, the CIR Expert Panel reopened this safety assessment that was originally published in 2001 to revise the conclusion based on the receipt of new data that address insufficient data needs in the original report. Prior to determining the new conclusion, however, the Panel issued an Insufficient Data Announcement for Malic Acid and Sodium Malate. The data needs were an HRIPT, or other suitable sensitization studies, at the maximum reported leave-on use concentration of 2.1% (this concentration is greater than that reported in the original safety assessment, which was 1%). The Panel was also interested in receiving information on which stereoisomer(s) are used as cosmetic ingredients. If D- or DL-isomers are used in cosmetics, the Panel wanted additional information on impurities and method of manufacturing for these ingredients. The Panel received HRIPT data of Malic Acid in formulation at 1%. No other data needs were met.

Overall, the Panel considered that the available data, including the role of Malic Acid in normal metabolism, animal toxicity data, and human sensitization studies, were adequate to assess the safety of these ingredients as used in cosmetics. The Panel noted that the only significant toxic effect of Malic Acid was irritation to the skin and eyes, which would be expected for acids. Since Malic Acid is used as a pH adjuster in cosmetics, the irritating property of the acid would be lost.

The Panel discussed the issue of incidental inhalation exposure in body and hand products and in pump hair sprays. There were no inhalation toxicity data available. The Panel considered other pertinent data indicating that incidental inhalation exposures to Malic Acid and Sodium Malate in such cosmetic products would not cause adverse health effects, including data characterizing the potential for these ingredients to cause acute and chronic toxicity, developmental and reproductive toxicity, genotoxicity, and ocular or dermal irritation or sensitization. These ingredients are reportedly used at concentrations up to 2.1% 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. The potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other

properties. However, 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. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <http://www.cir-safety.org/cir-findings>.

### **CONCLUSION**

To be determined...

**TABLES****Table 1.** Physical and chemical properties of Malic Acid.

<b>Property</b>	<b>Value</b>	<b>Reference</b>
Physical Form	White or colorless crystals	<sup>23-25</sup>
Molecular Weight (Da)	134.09	<sup>16</sup>
Density (g/cm <sup>3</sup> )	1.601 (DL-form); 1.595 (D- or L-form; 20°/4°C)	<sup>23</sup>
Melting Point (°C)	126-132 (DL-form); 101 (D-form); 100 (L-form)	<sup>16,23-25</sup>
Boiling Point (°C)	150 (DL-form; decomposes); 140 (D- or L- form; decomposes)	<sup>23</sup>
Solubility in water (g/100 g at 20 °C)	55.8	<sup>16</sup>
Dissociation constant (at 20 °C)	pKa1 = 3.51; pKa2 = 5.03	<sup>5</sup>

**Table 2.** Current and historical frequency and concentration of use of Malic Acid and Sodium Malate according to duration and exposure.

	<b>Malic Acid</b>			
	<i># of Uses</i>		<i>Max Conc of Use (%)</i>	
	<b>2017<sup>9</sup></b>	<b>1998<sup>1</sup></b>	<b>2016<sup>10</sup></b>	<b>1984<sup>1</sup> #</b>
<b>Totals*</b>	<b>238</b>	<b>47</b>	<b>0.000012-50</b>	<b>&lt; 0.1-1</b>
<i>Leave-On</i>	110	31	0.000012-2.1	< 0.1-1
<i>Rinse-Off</i>	126	16	0.00013-4	<0.1-1
<i>Diluted for (Bath) Use</i>	2	NR	0.006-50	NR
Eye Area	4	NR	0.000012	NR
Incidental Ingestion	4	NR	0.0006-0.55	NR
Incidental Inhalation-Spray	3; 26 <sup>a</sup> ; 22 <sup>b</sup>	2; 3 <sup>a</sup> ; 3 <sup>b</sup>	0.0011-2.1; 0.00013-1.9 <sup>a</sup>	NR
Incidental Inhalation-Powder	22 <sup>b</sup>	3 <sup>b</sup>	0.0004-1 <sup>c</sup>	NR
Dermal Contact	106	7	0.000012-50	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	100	18	0.00013-4	0.1-1
Hair-Coloring	13	NR	0.00015-0.05	< 0.1-1
Nail	15	22	0.3	< 0.1-1
Mucous Membrane	19	NR	0.0006-50	NR
Baby Products	8	1	NR	NR
	<b>Sodium Malate</b>			
	<i># of Uses</i>		<i>Max Conc of Use (%)</i>	
	<b>2017<sup>9</sup></b>	<b>1998<sup>1</sup></b>	<b>2016<sup>10</sup></b>	<b>1984<sup>1</sup> #</b>
<b>Totals*</b>	<b>5</b>	<b>1</b>	<b>0.02</b>	<b>NR</b>
<i>Leave-On</i>	2	1	0.02	NR
<i>Rinse-Off</i>	3	NR	NR	NR
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	1 <sup>a</sup>	1 <sup>b</sup>	NR	NR
Incidental Inhalation-Powder	NR	1 <sup>b</sup>	NR	NR
Dermal Contact	3	1	0.02	NR
Deodorant (underarm)	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR
Hair-Coloring	2	NR	NR	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR

\*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

# At the time of the original safety assessment, concentration of use data were not reported by the FDA; however, the FDA provided historic data

<sup>a</sup> It is possible these products are sprays, but it is not specified whether the reported uses are sprays..

<sup>b</sup> Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories

<sup>c</sup> It is possible these products are powders, but it is not specified whether the reported uses are powders

NR – no reported use

**Table 3.** Human repeat insult patch tests.

Ingredient	Concentration	Method	Results	Reference
Malic Acid	0.0227% in a hair styler formulation at pH 3.6	Modified HRIPT in 101 subjects; semi-occlusive patch	Not a significant skin irritant; did not induce allergic contact dermatitis	<sup>18</sup>
Malic Acid	0.00375% in a hair shampoo at pH 3.0	HRIPT in 98 subjects; occlusive patch	Not a significant skin irritant; did not induce allergic contact dermatitis	<sup>18</sup>
Malic Acid	1% in a sun protection formulation	HRIPT in 106 subjects; 0.2 g applied with semi-occlusive patch on infrascapular back or on upper arm	Not sensitizing	<sup>19</sup>
Malic Acid	2% in a hair product; 3% dilution of product tested	Modified HRIPT in 105 subjects; semi-occlusive patch	Not a significant skin irritant; did not induce allergic contact dermatitis	<sup>20</sup>

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# Final Report on the Safety Assessment of Malic Acid and Sodium Malate<sup>1</sup>

Malic Acid functions in cosmetic formulations as a pH adjuster, and Sodium Malate functions as a skin conditioning agent-humectant. Malic Acid is reportedly used in almost 50 cosmetic formulations across a range of product types at low concentrations, whereas Sodium Malate is used in only one. As a pH adjuster, Malic Acid is used at low concentrations. One commercial method of preparing Malic Acid is hydration of fumaric acid or maleic acid, and then purified to limit the amount of the starting material present. Because Malic Acid is a component of the Krebs cycle, another method is fermentation. Malic Acid was relatively nontoxic in acute toxicity studies using animals. In a chronic oral study, feeding Malic Acid to rats resulted only in weight gain changes and changes in feed consumption. Malic Acid did not cause reproductive toxicity in mice, rats, or rabbits. Malic Acid was a moderate to strong skin irritant in animal tests, and was a strong ocular irritant. Malic Acid was not mutagenic across a range of genotoxicity tests. Malic Acid was irritating in clinical tests, with less irritation seen as pH of the applied material increased. Patients patch tested with Malic Acid, placed on a diet that avoided foods containing Malic or citric acid, and then challenged with a diet high in Malic and citric acid had both immediate urticarial and delayed contact dermatitis reactions. These data were considered sufficient to determine that Malic Acid and Sodium Malate would be safe at the low concentrations at which these ingredients would be used to adjust pH (even though Sodium Malate is not currently used for that purpose). The data, however, were insufficient to determine the safety of these ingredients when used in cosmetics as other than pH adjusters and specifically, the data are insufficient to determine the safety of Sodium Malate when used as a skin conditioning agent-humectant. The types of data required for the Expert Panel to determine the safety of Sodium Malate as a skin-conditioning agent are: concentration of use data; dermal irritation and sensitization data; and ocular irritation data, if available. The data needed to assess the safety of Malic Acid or Sodium Malate for some function other than as a skin-conditioning agent cannot be specified without knowing the intended function. Were these ingredients to be used as exfoliants, for example, data similar to that included in the Cosmetic Ingredient Review safety assessment of Glycolic Acid would be needed. Until these data are available, it is concluded that the available data are insufficient to support the safety of these ingredients in cosmetic formulations for functions other than use as a pH adjuster.

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<sup>1</sup>Reviewed by the Cosmetic Ingredient Review Expert Panel. Monice Zondlo Fiume, former Scientific Analyst/Report Management Coordinator, prepared this report. Address correspondence to Director, Cosmetic Ingredient Review, 1101 17th Street, NW, Suite 310, Washington, DC 20036, USA.

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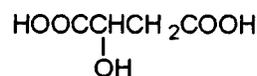
## INTRODUCTION

The safety of Malic Acid and Sodium Malate as used in cosmetic formulations is reviewed in this report. Malic Acid functions in cosmetics as a pH adjuster and Sodium Malate functions as a skin conditioning agent-humectant (Wenninger, Canterbury, and McEwen 2000).

## CHEMISTRY

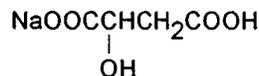
### Definition and Structure

Malic Acid (CAS No. 97-67-6, Wenninger, Canterbury, and McEwen 2000; 6915-15-7, Lewis 1993a; 1993b) is the organic acid that conforms to the formula (Wenninger, Canterbury, and McEwen 2000):



Malic Acid is also known as (±)-Malic Acid (US Pharmacopeial Convention, Inc. 1995); D,L-Malic Acid (Food and Agriculture Organization of the United Nations/World Health Organization [FAO/WHO] 1994; Food and Drug Research Labs, Inc. [FDRL] 1973a); DL-Malic Acid (Wenninger, Canterbury, and McEwen 2000); Hydroxysuccinic Acid; Hydroxybutanedioic Acid (Wenninger, Canterbury, and McEwen 2000; FAO/WHO 1994; FDRL 1973a); (±)-Hydroxysuccinic Acid; Hydroxybutanedioic Acid, (±)- (US Pharmacopeial Convention, Inc. 1995); Butanedioic Acid, Hydroxy- (Wenninger, Canterbury, and McEwen 2000); Succinic Acid, Hydroxy-; alpha-Hydroxysuccinic Acid; Deoxytetraric Acid (Registry of Toxic Effects of Chemical Substances [RTECS] 1997); 1-Hydroxy-1,2-Ethanedicarboxylic Acid; Methyl Tartronic Acid (FDRL 1973a); Oxyethylenesuccinic Acid (Grant 1972); Pomalous Acid (FAO/WHO 1994); and Apple Acid (Lewis 1993b).

Sodium Malate (CAS No. not available) is the sodium salt of Malic Acid (q.v.) that conforms to the formula (Wenninger, Canterbury, and McEwen 2000):



Sodium Malate is also known as Malic Acid, Monosodium Salt (Wenninger, Canterbury, and McEwen 2000).

**TABLE 1**  
Physical and chemical properties of Malic Acid

Property	Description	Reference
Physical characteristics	White crystals	Nikitakis and McEwen 1990
	White or nearly white crystalline powder or granules with a strongly acidic taste	National Academy of Sciences (NAS) 1996
	Colorless crystals with a sour taste	Lewis 1993a
	White or colorless crystals with an acid taste	Lewis 1993b
	White odorless triclinic crystals with a smoothly tart taste	Furia 1972
Molecular weight	134.09 Da	NAS 1996; Budavari 1989
Grades	Technical, active, and inactive	Lewis 1993a
Melting point	DL-form	126–132°C
		128°C
		131–132°C
	D-(+)-form	101°C
	L(-)-form	100°C
Boiling point	DL-form	150°C (decomposes)
	D- or L-form	140°C (decomposes)
Density	DL-form	1.601
	D- or L-form	1.595 (20°/4°C)
Solubility	Soluble in water; slightly soluble in alcohol and ether	Nikitakis and McEwen 1990
	Very soluble in water and alcohol; slightly soluble in ether	Lewis 1993a; 1993b
	Soluble in water, methanol, ethanol, acetone, diethyl ether, and dioxane; practically insoluble in benzene	Budavari 1989
Optical rotation	L(-)-form	$[\alpha]_D - 2.3^\circ$ (8.5 g in 100 ml water)
Ionization constants	$K_{A1}; K_{A2}$	$3.9 \times 10^{-4}; 1.4 \times 10^{-5}$
	$K_1; K_2$	$4 \times 10^{-4}; 9 \times 10^{-6}$
Reactivity	Combustible	Lewis 1993a

### Physical and Chemical Properties

The physical and chemical properties of Malic Acid are described in Table 1.

### Manufacture and Production

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 (Lewis 1993b). Malic Acid can be prepared by fermentation from sugars (Anonymous 1975). L-Malic Acid is available through the microbiological fermentation of fumaric acid (Miltenberger 1989). The L-form of Malic Acid is the naturally occurring isomer and is found in unripe apples and other fruits (Lewis 1993b).

### Analytical Methods

Malic Acid has been detected and quantitated in biological fluids using gas chromatography (GC), enzymatic methods, and fluorometry; in general foods and in fruits and fruit

derivatives using fluorometry, GC, gas-liquid chromatography, thin-layer chromatography (TLC), paper chromatography, polarimetry, manometry, and ion exchange plus ultraviolet (UV); and in synthetic mixtures of food acids using TLC, thin-layer electrophoresis plus chromatography, and fluorometry (FDRL 1973a). Liquid chromatography (Agarwal 1988; Eisele 1996), GC (Agarwal 1988), and ligand-exchange photometric ion chromatography (Yamamoto, Matsunaga, and Mizukami 1991) have been used to determine Malic Acid in apple juice. A spectrophotometric method with use of a malic enzyme was used to determine Malic Acid in other liquids (Suye, Yoshihara, and Inuta 1992).

### Impurities

Maleic and fumaric acids are by-products of the manufacture of Malic Acid (Miltenberger 1989). Malic Acid is generally purified until the amounts of fumaric and maleic acid are 7.5 and <500 ppm, respectively.

**USE****Cosmetic**

Malic Acid functions as a pH adjuster and Sodium Malate functions as a skin conditioning agent—humectant in cosmetic formulations (Weninger, Canterbury, and McEwen 2000). The product formulation data submitted to the FDA in 1998 stated that Malic Acid was contained in 47 cosmetic product formulations and that Sodium Malate was contained in one cosmetic formulation (FDA 1998). Concentration of use values are no longer reported to the FDA by the cosmetics industry (FDA 1992) and no current concentration of use data were provided by industry; however, historical product formulation data submitted to the FDA in 1984 stated that Malic Acid was used at concentrations of  $\leq 1\%$  (FDA 1984). Such low concentrations are expected to correspond to use as a pH adjuster. Sodium Malate was not reported to be used in 1984. This information is summarized in Table 2.

**International**

Malic Acid is listed in the *Japanese Comprehensive Licensing Standards of Cosmetics by Category (CLS)* as DL-Malic Acid (Rempe and Santucci 1997). DL-Malic Acid, which conforms to the specifications of the *Japanese Cosmetic Ingredients Codex* or *Japanese Standards of Food Additives*, has precedent for use without restriction in all *CLS* categories except eyeliner prepa-

rations, for which there is no precedent for use. Malic Acid does not appear in Annex II (list of substances which must not form part of the composition of cosmetic products) or Annex III (list of substances which cosmetic products must not contain except subject to restrictions and conditions) of the Cosmetics Directive of the European Union (European Economic Community 1995).

**Noncosmetic**

DL- 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 (FDA 1997). Using good manufacturing practices, the following maximum concentrations are allowed in foods as served: hard candy, 6.9%; processed fruits and fruit juices, 3.5%; nonalcoholic beverages, 3.4%; soft candy, 3.0%; chewing gum, 3.0%; jams and jellies, 2.6%; gelatins, puddings, and fillings, 0.8%; and all other food categories, 0.7%. Malic Acid can be used as an acidifying ingredient in milk and cream, and can be used in French dressing, mayonnaise, and salad dressing. There is no set limit on the human acceptable daily intake (ADI) of L-Malic Acid, and the ADI for D-Malic Acid is limited only by good manufacturing practice (FAO/WHO 1967; 1969). Neither D- or DL-Malic Acid should be added to food of young infants.

**TABLE 2**  
Product formulation and concentration of use data

Product category (number of formulations reported to FDA) (FDA 1984)	Number of formulations containing ingredient (FDA 1998)	Historical concentration of use (FDA 1984)
<b>Malic Acid</b>		
Other baby products (29)	1	
Hair conditioners (636)	8	
Hair sprays (aerosol fixatives) (261)	2	
Shampoos (noncoloring) (860)	7	
Tonics, dressings, and other hair-grooming aids (549)	1	
Wave sets (55)	—	0.1–1.0%
Hair rinses (coloring) (33)	—	<0.1–1.0%
Basecoats and undercoats (48)	9	<0.1%
Nail polish and enamel (80)	9	<0.1–1.0%
Other manicuring preparations (61)	4	<0.1–1.0%
Face and neck preparations (excluding shaving preparations) (263)	2	
Body and hand preparations (excluding shaving preparations) (796)	1	
Moisturizing preparations (769)	1	
Night preparations (188)	1	
Paste masks (mud packs) (255)	1	
1998 total for Malic Acid	47	
<b>Sodium Malate</b>		
Body and hand preparations (excluding shaving preparations) (796)	1	
1998 total for Sodium Malate	1	

Malic Acid is used in foods as an acidifier and flavoring agent (National Academy of Sciences [NAS] 1996). It can also be used as a discoloration inhibitor and a synergist with antioxidants (Furia 1972). It is used in the manufacture of various esters and salts, in wine manufacturing, and as a chelating agent (Lewis 1993a). Malic Acid is also used in medicine and in the preparation of esters and salts (Patty 1981-2).

## GENERAL BIOLOGY

### Absorption, Distribution, Metabolism, and Excretion

Male albino Wistar Alderly Park SPF rats were given 2.5 mg/kg  $^{14}\text{C}$ -L-Malic Acid (diluted with L-Malic Acid to a specific activity of 61  $\mu\text{Ci}/\text{mmol}$ ) or 4- $^{14}\text{C}$ -DL-Malic Acid (specific activity 93  $\mu\text{Ci}/\text{mmol}$ ) in an aqueous solution by gavage or by intraperitoneal (IP) injection (Daniel 1969). (The number of animals per group was not specified.) Urine, feces, and expired carbon dioxide were collected. Most of the radioactivity was excreted as carbon dioxide; after 24 hours, 91.6% and 83.4% of orally and intraperitoneally administered DL-Malic Acid, respectively, and 88.0% and 86.6% of orally and intraperitoneally administered L-Malic Acid, respectively, was found in expired air. The amount of radioactivity recovered after oral and IP administration of DL-Malic Acid was 3.1% and 8.8% in the urine and 0.6% and 0.3% in the feces, respectively, and the amount recovered after oral and IP administration of L-Malic Acid was 3.2% and 3.1% in the urine and 1.4% and 1.4% in the feces, respectively. After 24 hours, the total amount of radioactivity recovered was 95.3% and 92.5% after oral and IP administration of DL-Malic Acid, respectively, and 92.6% and 91.1% after oral and IP administration of L-Malic Acid, respectively.

Daily oral administration of 4 g/kg Malic Acid resulted in increased glucuronic acid excretion in the urine (Martin and Stenzel 1944).

### Biochemistry

Malic Acid is an intermediate in the tricarboxylic acid (Kreb's) cycle (Taylor 1988). It is formed from fumaric acid and is oxidized to oxaloacetic acid (Patty 1981-2). Malic Acid plays an essential role in carbohydrate metabolism (Liebrand 1992).

## ANIMAL TOXICOLOGY

### Acute Toxicity

#### Oral

The oral  $\text{LD}_{50}$  values of Malic Acid for albino CD-1 outbred mice, albino Wistar rats, and Dutch-Belted rabbits were approximately 2.66 (FDRL 1973b), 3.5 (FDRL 1973c), and 3 g/kg (FDRL 1973d) respectively. Each study used 50 animals, consisting of five groups of 5 males and 5 females, and Malic Acid was administered as a 25% aqueous solution. Mortality was observed for 14 days. Signs of toxicity included ataxia, prostration, convulsions, and death.

In a review of studies done in the 1920s, FAO/WHO (1967) stated that the oral lethal dose of L-Malic Acid for rabbits was 5 g/kg, and for Sodium Malate in dogs was 1 g/kg. In a more recent review, the oral  $\text{LD}_{50}$  of Malic Acid for rabbits was 5 g/kg (Sax 1979). In a review of industrial chemicals, Patty (1981-2) stated that the oral  $\text{LD}_{50}$  values of Malic Acid for mice and rats were reported to be 1.6 to 3.2 and  $>3.2$  g/kg, respectively. The signs of acute poisoning in rats and mice were weakness, retraction of the abdomen, respiratory distress, and cyanosis.

#### Parenteral

The acute toxicity of intravenously administered 0.25 N Malic Acid aqueous solution to four rabbits was 2.4 g/kg (FDRL 1973a).

The IP 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 to 25 minutes (Brookdale Dental Center of New York University 1973). The vehicle was not reported. 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 IP administration of 2 g/kg DL-Malic Acid was not lethal to rats.

In a review of hazardous substances, Patty (1981-2) reported that the IP  $\text{LD}_{50}$  of Malic Acid for mice and rats as 50 to 100 and 100 to 200 mg/kg, respectively.

### Chronic Toxicity

#### Oral

Groups of 30 male and 30 female Charles River rats were fed 500, 5000, or 50,000 ppm (0.05%, 0.5%, and 5.0%, respectively) Malic Acid for 104 weeks, and a control group of 60 male and 60 female rats was given untreated feed (TRW/Hazleton Laboratories 1971a). Animals were observed daily for mortality. Clinical observations were made and body weights and feed consumption were determined weekly for the first 26 weeks, biweekly for the second 26 weeks, and monthly thereafter. Clinical pathology studies were performed on five males and five females per group prior to study initiation and at 13, 26, 52, and 104 weeks. After 26 and 52 weeks, 5 male and 5 female test animals per group and 10 male and 10 female control animals were killed; the remaining animals were killed at study termination.

Physical appearance, behavior, and survival were similar for test and control animals. Body weight gains were significantly decreased for males and females of the high-dose group during weeks 0 to 52. Feed consumption was statistically significantly decreased for males of the high-dose group during this period. For females of the high-dose group, feed consumption was significantly decreased during weeks 0 to 26 and decreased, but not to a significant degree, during weeks 27 to 52, as compared to controls. These differences were less distinct during the second year; terminal body weights of the high-dose group were similar to controls for male animals and decreased, but not significantly, for female animals. Significant changes were not observed in hematological, blood, or urine parameters. Significant lesions were not found at gross and microscopic examination. For males

of the high-dose group, relative thyroid weights were significantly decreased at week 26, relative testes weights were significantly increased and liver weights were significantly decreased at week 52, and spleen weights were significantly increased and relative kidney weights were significantly decreased at study termination as compared to control animals. For females of the high-dose group, heart and body weights were significantly decreased at week 26, body weights were significantly decreased at week 52, and thyroid gland weights were significantly decreased at study termination. These differences were considered incidental.

Groups of four male and female beagle dogs were fed 500, 5000, or 50,000 ppm Malic Acid for 104 weeks, and a control group was given untreated feed (TRW/Hazleton Laboratories 1971b). Clinical observations were made daily. Body weights and feed consumption were determined weekly for the first 26 weeks, biweekly for the second 26 weeks, and monthly thereafter. Clinical pathology studies were performed prior to study initiation and at 4, 13, 26, 52, 78, and 104 weeks. One male and one female from each group was killed after 52 weeks, and the remaining animals were killed at study termination.

Body weight gains were normal for all animals. Significant changes were not observed in hematological, blood, or urine parameters. Significant lesions were not observed at necropsy or at microscopic examination, and dose-related differences in absolute and relative organ weights were not found.

### Dermal Irritation

In a review of industrial chemicals, Patty (1981–2) stated that Malic Acid was moderately irritating to rabbit skin (500 mg/24 h) and was a strong irritant to guinea pigs.

### Ocular Irritation

In a review of industrial chemicals, Patty (1981–2) stated that application of Malic Acid, 750  $\mu$ g, to the conjunctival sac of rabbits caused severe ocular irritation.

## REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Groups of 25 albino CD-1 outbred mice were mated and dosed orally with 2.66, 12.4, 57.3, or 266 mg/kg Malic Acid on days 6 through 15 of gestation (FDRL 1974a). A negative-control group was given vehicle (water) and a positive-control group was given 150 mg/kg aspirin. All animals were observed daily. Body weights were determined on days 0, 6, 11, 15, and 17 of gestation. On day 17 of gestation, the number of implantation sites, resorption sites, and live and dead neonates were determined. The body weights of live pups were recorded, and all neonates were examined grossly.

At gross examination, 19, 22, 21, and 21 animals of the 2.66, 12.4, 57.3, and 266 mg/kg dose groups, respectively, were gravid. All animals except one of the 12.4 mg/kg test group survived until study termination. The researchers concluded that “the administration of up to 266 mg/kg (body weight) of the test

material to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls.”

A study following a similar procedure was conducted using groups of 25 to 29 Wistar albino rats dosed orally with 3.5, 16.2, 75.4, or 350 mg/kg Malic Acid (FDRL 1974b). The number of implantation sites, resorption sites, and live and dead neonates were determined on day 20 of gestation. At gross examination, 20/25, 21/29, 22/25, and 26/28 animals of the 3.5, 16.2, 75.4, and 350 mg/kg dose groups, respectively, were gravid. All animals except three of the 350-mg/kg test group (two were gravid) survived until study termination. The researchers concluded that “the administration of up to 350 mg/kg (body weight) of the test material to pregnant rats for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls.”

A study was also conducted using groups of 15 to 23 Dutch-belted rabbits that were inseminated artificially and dosed orally with 3, 14, 65, or 300 mg/kg Malic Acid on days 6 to 18 of gestation (FDRL 1974c). A negative-control group was given water and a positive-control group was dosed with 6-aminonicotinamide. All animals were observed daily and body weights were determined on days 0, 6, 12, 18, and 29 of gestation. On day 29 of gestation, the number of corpora lutea, implantation sites, resorption sites, and live and dead fetuses were determined.

At gross examination, 12/15, 10/20, 13/15, and 13/23 animals of the 3, 14, 65, and 300 mg/kg dose groups, respectively, were gravid. All animals of the negative and positive control groups and the 3 and 14 mg/kg dose groups, 12/15 of the 65-mg/kg dose group (two were gravid), and 15/23 of the 300-mg/kg dose group (four were gravid) survived until study termination. The researchers concluded that “the administration of up to 300 mg/kg (body weight) of the test material to pregnant rabbits for 13 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival. The number of abnormalities seen in either soft or skeletal tissues of the test groups did not differ from the number occurring spontaneously in sham-treated controls.”

Groups of 10 male and 20 female weanling albino rats were fed 1000 or 10,000 ppm Malic Acid for 9 weeks prior to mating for the F<sub>1A</sub> litter through weaning of the F<sub>1B</sub> litter, and a control group was fed untreated feed (Hazleton Laboratories, Inc. 1970). The F<sub>1A</sub> litters were culled to a maximum of eight pups, reproductive indices were monitored, and after 21 days, approximately one third of the pups were necropsied. One week after weaning of the last F<sub>1A</sub> litter, the P<sub>1</sub> parents were remated to produce the F<sub>1B</sub> litter, which was also culled and monitored. After 21 days, 10 male and 20 female weanlings from each group were selected for the P<sub>2</sub> generation. Approximately one third of the remaining pups were necropsied. The P<sub>2</sub> generation was

fed the appropriate diet and mated when the animals reached approximately 100 days of age to produce the F<sub>2A</sub> generation, and the same procedures were followed as above. One half of the F<sub>2B</sub> litters were delivered naturally and held until weaning, whereas the other half were delivered by caesarean section on day 19 of gestation.

Prior to mating of the P<sub>1</sub> generation, body weight gains of males of the test groups were slightly decreased compared to control animals; female body weights were comparable. Feed consumption and survival were similar for test and control animals. Appearance and behavior were similar for P<sub>1</sub> test and control rats. For all litters, the various indices, litter sizes, and pup body weights were comparable among test and control animals. In the F<sub>1A</sub> litters, all of the necropsied pups in three of the low-dose litters had rough surfaces on the spleen. In the F<sub>2A</sub> litters, the number of pups that were weak or had labored respiration during lactation was increased in the high-dose group. Abnormal findings were not reported at necropsy. None of the P<sub>1</sub> animals died during the F<sub>1A</sub> or F<sub>1B</sub> phase. The P<sub>2</sub> test and control animals were similar throughout the study; wheezing was observed in all groups during the F<sub>2B</sub> phase. In the F<sub>2A</sub> litters, renal discoloration (two animals), dark renal medullas (four animals), rough surfaces on the spleen (four animals), and white foci on the spleen (three animals) were found in low-dose weanling animals. Renal discoloration (three animals), dark red corticomedullary zones (three animals), dark renal medullas (three animals), rough surfaces on the spleen (two animals), and a firm, enlarged, irregularly-shaped cecum with a hole penetrating it (one animal) were found in high-dose weanling animals at necropsy. In the F<sub>2B</sub> litters, weakness and labored respiration were reported for a few low-dose pups, and the renal pelvis of one high-dose pup was dilated at necropsy. The animals of the F<sub>2B</sub> generation delivered by caesarean section had no "meaningful differences" between test and control animals in the number and placement of implantation and resorption sites or in the number, weight, or length of live neonates, and none of the neonates died. The skeletal development of the F<sub>2B</sub> neonates was similar between test and control animals. Slight differences in developmental indices were "considered to be within the range of normal variations in fetal development. No trends toward lesser or greater skeletal development were observed."

## GENOTOXICITY

The mutagenic potential of 0.001% Malic Acid was determined in a plate test using *Salmonella typhimurium* strains TA1535, TA1537, and TA1538 without and with metabolic activation (Litton Bionetics, Inc. 1974). Negative and positive controls were used, and duplicate testing was done. Malic Acid was not mutagenic.

An Ames test was performed to determine the mutagenic potential of Malic Acid in phosphate buffer,  $\leq 10.0$  mg/plate, using *S. typhimurium* strains TA92, TA1535, TA100, TA1537, TA94, and TA98 with metabolic activation (Ishidate et al. 1984). Testing was done in duplicate. Malic Acid was not mutagenic.

The mutagenic potential of 1100 to 2000  $\mu\text{g}/\text{plate}$  Malic Acid in distilled water was determined in a plate test using *S. typhimurium* TA97, TA98, TA100, and TA104 with and without metabolic activation (Al-Ani and Al-Lami 1988). Distilled water was used as a negative control and 2-aminoanthracene was used as a positive control. Testing was done in triplicate. Malic Acid was not mutagenic.

The mutagenic potential of Malic Acid was examined in a suspension test using *S. typhimurium* strains TA1535, TA1537, and TA1538 and *Saccharomyces cerevisiae* strain D4 without and with metabolic activation (Litton Bionetics, Inc. 1974). Malic Acid was tested at concentrations of 0.0005% and 0.001% using *S. typhimurium* and 0.05% and 0.1% using *S. cerevisiae*. Negative and positive controls were used. Malic Acid was not mutagenic for either *S. typhimurium* or *S. cerevisiae*.

A chromosomal aberration test was performed without metabolic activation using a Chinese hamster fibroblast cell line to determine the mutagenic potential of  $\leq 1.0$  mg/ml Malic Acid in physiological saline (Ishidate et al. 1984). The incidence of polyploid cells and cells with structural chromosomal aberrations was 0% and 1%, respectively, after 48 hours. Malic Acid was not mutagenic.

The effect of pyrolysis on the mutagenic potential of Malic Acid was first determined using *S. typhimurium* TA98 and TA100 with and without metabolic activation (Yoshida and Okamoto 1982). In this study, pyrolyzates of Malic Acid were not mutagenic. In a study by Kuroda, Yoshida, and Mizusaki (1985), pyrolyzates of Malic Acid were mutagenic when tested using *S. typhimurium* TA97 with and without metabolic activation. The pyrolyzates of Malic Acid were fractionated into neutral, acidic, phenolic, and basic fractions, and the mutagenicity of each fraction was determined using TA97 and TA98. Most of the mutagenicity was found in the neutral fraction, with TA97 being more sensitive, and weak activity was found in the acidic and phenolic fractions. No activity was found in the basic fractions with either strain.

Malic Acid was treated with aqueous solutions of chlorine, pH 2.5, 4, and 7 (Chang et al. 1988). Diethyl ether extraction followed by gas chromatography/mass spectrometry (GC/MS) was performed and the results indicated that "large amounts" of trichloroacetaldehyde were present in the treated Malic Acid. Methyl esters of dichloro- and trichloroacetic acid were detected by GC/MS analysis when comparably treated Malic Acid was reacted with diazomethane. The products that are formed are considered mutagenic.

## CARCINOGENICITY

Published data on the carcinogenic potential of Malic Acid and Sodium Malate were not found.

## CLINICAL ASSESSMENT OF SAFETY

### Irritation

The subjective skin irritation potential of Malic Acid was evaluated by applying 2 mg/cm<sup>2</sup> of 1 M Malic Acid in vehicle

(15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol) to the nasal fold area of at least 10 subjects (Smith 1996). Irritation was graded on a scale of 0 to 4 every minute for 15 minutes. The irritation scores, as an average of the summation of each individual irritation score over the 15-minute test period, were 39.4, 37.1, and 23.1 for pH 3, 5, and 7, respectively.

## Sensitization

### *Predictive Testing*

Thirty-four patients with atopic dermatitis were tested to determine their sensitivity to foods containing Malic (and citric) Acid (Walsh 1979). The patients were first patch tested with Malic (and citric) Acid applied as a 10% aqueous solution under occlusive patches for 48 hours. For 2 weeks, the patients followed a diet that avoided processed foods in which Malic (and citric) Acid were used, and then challenged themselves with a diet high in Malic (and citric) Acid during the third week. Eighteen patients reacted to both Malic and citric Acid and 6 patients reacted to only Malic Acid. Both immediate reactions (seasonal allergic rhinitis and urticaria) and delayed reactions (contact dermatitis) were present. Patch-test results were reliable in predicting results of the challenge with diet.

### *Skin Effects*

The effect of Malic Acid on cell renewal was assessed using the dansyl chloride method (Smith 1996). Two mg/cm<sup>2</sup> of 1 M Malic Acid in a simple liquid vehicle (15% ethanol [SD 40], 5% ethoxydiglycol, and 5% butylene glycol) was applied to the volar forearm which was stained with dansyl chloride twice daily until all the stain was removed. An 18%, 10%, and 5% increase in cell renewal was observed at pH 3, 5, and 7, respectively.

## Medical/Therapeutic

The data from clinical use of Malic Acid are included here to provide a complete record of reported dermal effects. Information included in this section represents the opinions of researchers; such information is only included in order to provide the full scope of information available. Inclusion is not an endorsement of validity.

Fourteen patients, 11 males and 3 females, with various forms of ichthyosiform dermatoses were used to evaluate the therapeutic potential of more than 60 chemicals, including Malic Acid (Van Scott and Yu 1974). Malic Acid was dissolved in either water or ethanol and incorporated into a hydrophilic ointment of plain petrolatum. The ointment, containing 5% Malic Acid (pH not specified), was applied twice daily to the appropriate test site for 2 weeks. Daily to weekly observations were made. Malic Acid provided 3+ (disappearance of scales from lesions) or 4+ (restoration to normal looking skin) improvement in all patients except one with epidermolytic hyperkeratosis.

An efficacy and safety test of a tablet containing 200 mg Malic Acid (and 50 mg magnesium) was conducted using patients with

primary fibromyalgia syndrome (Russell et al. 1995). In the first part of the test, 24 patients were given three tablets twice daily (bid) for 4 weeks. In the second part, 16 patients started with three tablets bid and increased the dosage every 3 to 5 days as necessary; at month 6, the average dose was 8.8 tablets per day. (For a 50-kg person, ingestion of six tablets would be equivalent to 24 mg of malate/kg of body weight.) In the first part of the study, one test patient reported diarrhea, one reported nausea, and one reported dyspepsia. (In the placebo group, two patients reported diarrhea and one reported dyspepsia.) In the second part of the study, five test patients reported diarrhea, one reported nausea, one reported dyspepsia, one reported panic attacks, and one reported dizziness.

## SUMMARY

Malic Acid, an intermediate in the Krebs's cycle, is an organic acid that functions as a pH adjuster and Sodium Malate is an organic salt that functions as a chemical additive. In 1998, it was reported to the Food and Drug Administration (FDA) that Malic Acid was used in 47 cosmetic formulations and that Sodium Malate was used in 1 formulation. In 1984, Malic Acid was reported to be used at concentrations of  $\leq 1\%$ ; Sodium Malate was not reported to be used in 1984.

Malic Acid is generally purified until the amounts of the by-products fumaric and maleic acid are 7.5 and <500 ppm, respectively. Malic Acid is a direct food additive.

Upon oral and IP administration of radioactive Malic Acid to rats, most of the radioactivity was excreted as carbon dioxide.

The oral LD<sub>50</sub> values of Malic Acid for mice, rats, and rabbits ranged from 2.66 to >3.2, 1.60 to 3.5, and 3 to 5 g/kg, respectively. The acute LD<sub>50</sub> of Malic Acid given intravenously was 2.4 g/kg for rabbits, and the IP LD<sub>50</sub> values for mice and rats were 50 to 100 and 100 to 200 mg/kg, respectively. In a chronic oral study, feeding Malic Acid to rats 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 study. Malic Acid did not cause reproductive toxicity in mice, rats, or rabbits.

Malic Acid was moderately irritating to rabbit skin and was a strong irritant to guinea pigs. Malic Acid caused severe ocular irritation in rabbit eyes.

Malic Acid was not mutagenic in plate tests, an Ames test, a suspension test, or a chromosomal aberration assay. In one study, pyrolyzates of Malic Acid were not mutagenic, but in another study they were. Products formed from treatment of Malic Acid with aqueous solutions of chlorine were mutagenic.

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 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.

Malic Acid was not toxic in a clinical efficacy and safety test.

## DISCUSSION

The Expert Panel considered separately the ways in which Malic Acid and Sodium Malate are used. As a pH adjuster, Malic Acid historically has been used at concentrations less than 1%. The available data demonstrate that what toxicity has been demonstrated for Malic Acid and Sodium Malate is related to concentration. Accordingly, the Expert Panel concluded that Malic Acid and Sodium Malate are safe for use as pH adjusters (even though Sodium Malate is not currently used for that purpose).

The data included in this report, however, were insufficient to determine the safety of these ingredients when used in cosmetics as other than pH adjusters. Specifically, the data are insufficient to determine the safety of Sodium Malate when used as a skin conditioning agent—humectant. The types of data required for the Expert Panel to determine the safety of Sodium Malate as a skin conditioning agent are:

1. concentration of use data;
2. dermal irritation and sensitization data; and
3. ocular irritation data, if available.

The data needed to assess the safety of Malic Acid or Sodium Malate for some function other than as a skin conditioning agent—humectant cannot be specified without knowing the intended function. Were these ingredients to be used as exfoliants, for example, data similar to that included in the report on Glycolic and Lactic Acid (i.e., the Alpha Hydroxy Acid report) (Andersen 1998) would be needed.

## CONCLUSION

On the basis of the animal and clinical data included in this report, the Cosmetic Ingredient Review (CIR) Expert Panel concludes that Malic Acid and Sodium Malate are safe for use as pH adjusters in cosmetic formulations. The Expert Panel determined that the data are insufficient to determine the safety of these ingredients for any other functions.

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**2017 FDA VCRP RAW DATA**

01C - Other Baby Products	MALIC ACID	8
02A - Bath Oils, Tablets, and Salts	MALIC ACID	2
03B - Eyeliner	MALIC ACID	3
03E - Eye Makeup Remover	MALIC ACID	1
04E - Other Fragrance Preparation	MALIC ACID	1
05A - Hair Conditioner	MALIC ACID	45
05B - Hair Spray (aerosol fixatives)	MALIC ACID	2
05E - Rinses (non-coloring)	MALIC ACID	1
05F - Shampoos (non-coloring)	MALIC ACID	35
05G - Tonics, Dressings, and Other Hair Grooming Aids	MALIC ACID	5
05I - Other Hair Preparations	MALIC ACID	12
06C - Hair Rinses (coloring)	MALIC ACID	9
06D - Hair Shampoos (coloring)	MALIC ACID	4
07E - Lipstick	MALIC ACID	4
07I - Other Makeup Preparations	MALIC ACID	1
08A - Basecoats and Undercoats	MALIC ACID	1
08B - Cuticle Softeners	MALIC ACID	2
08E - Nail Polish and Enamel	MALIC ACID	9
08G - Other Manicuring Preparations	MALIC ACID	3
10A - Bath Soaps and Detergents	MALIC ACID	5
10E - Other Personal Cleanliness Products	MALIC ACID	8
12A - Cleansing	MALIC ACID	13
12C - Face and Neck (exc shave)	MALIC ACID	13
12D - Body and Hand (exc shave)	MALIC ACID	9
12F - Moisturizing	MALIC ACID	17
12G - Night	MALIC ACID	4
12H - Paste Masks (mud packs)	MALIC ACID	5
12J - Other Skin Care Preps	MALIC ACID	16
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	SODIUM MALATE	1
06G - Hair Bleaches	SODIUM MALATE	1
12A - Cleansing	SODIUM MALATE	1
12F - Moisturizing	SODIUM MALATE	1
12J - Other Skin Care Preps	SODIUM MALATE	1



**Memorandum**

**TO:** COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** June 20, 2017

**SUBJECT:** Malic Acid

TKL Research Inc. 2004. Repeated insult patch test of an SPF product containing 1% Malic Acid.



**REPEATED INSULT PATCH STUDY**

**TKL STUDY NO. DS101904-7**

*1% malic acid SPF*

**CONDUCTED FOR:**



**DATE OF REPORT:**

May 12, 2004

1% maleic acid SPF

TKL Study No. DS101904-7

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**APPENDICES**

- I SUMMARY TABLES
- II DATA LISTINGS
- III CLINICAL MATERIAL RECORD
- IV INFORMED CONSENT DOCUMENT

1% malic acid SPF

**SIGNATURES**

Kathleen Georgeian  
Kathleen Georgeian, Clinical Research Coordinator  
and Manager, Dermatologic Safety Testing

5/12/04  
Date

Jonathan S. Dosik  
Jonathan S. Dosik, MD  
Principal Investigator

5/11/04  
Date

**STATEMENT OF QUALITY ASSURANCE**

This report has been reviewed by the TKL Research, Inc. (TKL) Corporate Quality Assurance Department and the report accurately reflects the raw data for this study.

Clinical research studies are performed by TKL in accordance with all applicable federal regulations and proposed guidelines for Good Clinical Practices, which include:

- 21 CFR Part 312,      Investigational New Drug Application
- 21 CFR Part 50,      Protection of Human Subjects
- 21 CFR Part 56,      Institutional Review Boards

Henry Brewer  
Quality Assurance

5/12/04  
Date

1% malic acid SPF

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TKL Study No. DS101904-7

**TITLE OF STUDY**

Repeated Insult Patch Study

**SPONSOR****STUDY MATERIAL**

PRODUCT	FORMULA	DILUTION
1% malic acid Day SPF 15		Neat, Semi-occlusive

**DATE STUDY INITIATED**

March 10, 2004

**DATE STUDY COMPLETED**

April 16, 2004

**DATE OF REPORT**

May 12, 2004

1% malic acid SPF

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TKL Study No. DS101904-7

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#### **INVESTIGATIVE PERSONNEL**

Jonathan S. Dosik, MD  
Principal Investigator

Kathleen Georgeian  
Clinical Research Coordinator  
and Manager, Dermatologic Safety Testing

Tina Kelly  
Assistant Manager, Dermatologic Safety Testing

#### **CLINICAL SITE**

TKL RESEARCH, INC.  
1099 Wall Street West  
Lyndhurst, NJ 07071

1% malic acid SPF

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TKL Study No. DS101904-7

**SUMMARY**

One study material, Formula No. <sup>1% malic acid</sup> 5PF was evaluated neat to determine its ability to sensitize the skin of normal volunteer subjects using a semi-occlusive repeated insult patch study. One hundred six subjects completed the study.

Under the conditions employed in this study, there was no evidence of sensitization to Formula No.

1% malic acid  
5PF

1/8 malic acid SPF

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TKL Study No. DS101904-7

## 1.0 OBJECTIVE

The objective of this study was to determine the ability of the study material to cause sensitization by repeated applications to the skin of humans under controlled patch study conditions.

## 2.0 RATIONALE

Substances that come into contact with human skin need to be evaluated for their propensity to irritate and/or sensitize. Once an appropriate pre-clinical safety evaluation has been performed, a reproducible, standardized, quantitative patch evaluation procedure must be used to demonstrate that a particular material can be applied safely to human skin without significant risk of adverse reactions. The method herein employed is generally accepted for such a purpose.

Repeated insult patch evaluation is a modified predictive patch study that can detect weak sensitizers that require multiple applications to induce a cell-mediated (Type IV) immune response sufficient to cause an allergic reaction. Irritant reactions may also be detected using this evaluation method, although this is not the primary purpose of this procedure. Results are interpreted according to interpretive criteria based upon published works, as well as the clinical experience of TKL Research, Inc. These interpretive criteria are periodically reviewed and amended as new information becomes available.

## 3.0 STUDY DESIGN

### 3.1 STUDY POPULATION

A sufficient number of subjects were enrolled to provide 100 completed subjects.

#### 3.1.1 Inclusion Criteria

Individuals eligible for inclusion in the study were those who:

1. were males or females, 18 years of age or older, in general good health;
2. were free of any systemic or dermatologic disorder which, in the opinion of the investigative personnel, would have interfered with the study results or increased the risk of adverse events;
3. were of any skin type or race, providing the skin pigmentation would allow discernment of erythema;
4. had completed a medical screening procedure; and
5. had read, understood, and signed an informed consent agreement.

1% malic acid SPF

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TKL Study No. DS 101904-7

### 3.1.2 Exclusion Criteria

Individuals excluded from participation in the study were those who:

1. had any visible skin disease at the study site which, in the opinion of the investigative personnel, would have interfered with the evaluation;
2. were receiving systemic or topical drugs or medication which, in the opinion of the investigative personnel, would have interfered with the study results;
3. had psoriasis and/or active atopic dermatitis/eczema;
4. were females who were pregnant, planning to become pregnant during the study, or breast-feeding; and/or
5. had a known sensitivity to cosmetics, skin care products, or topical drugs as related to the material being evaluated.

### 3.1.3 Informed Consent

A properly executed informed consent document in compliance with FDA regulations (21 CFR Part 50) was obtained from each subject prior to entering the study. The signed informed consent document is maintained in the study file. In addition, the subject was provided with a copy of the informed consent document (see Appendix IV).

## 3.2 DESCRIPTION OF STUDY

### 3.2.1 Outline of Study Procedures

Subjects participated in the study over a 6-week period involving 3 phases: (1) Induction, (2) Rest, and (3) Challenge. Prior to study entry, the subjects were screened to assure that they met the inclusion/exclusion criteria. Informed consent was obtained. Each subject was provided with a schedule of the study activities. All subjects were told to avoid wetting the patches and were asked not to engage in activities that caused excessive perspiration. They were instructed to notify the staff if they experienced any discomfort beyond mild itching or observed any adverse changes at the patch sites, while on the study or within 2 weeks of completing the study.

The Induction Phase consisted of 9 consecutive applications of the study material and subsequent evaluations of the patch sites. Prior to application of the patches, the sites were outlined with a skin marker, eg, gentian violet. The subjects were required to remove the patches approximately 24 hours after application. They returned to the facility at 48-hour intervals to have the sites evaluated and identical patches applied to the same sites. Patches applied on Friday were removed by subjects after 24 hours. The sites were evaluated on the following Monday, ie, 72 hours after patch application.\*

Following the ninth evaluation, the subjects were dismissed for a rest period of approximately 10-15 days.

\* A Monday or Friday holiday could result in evaluation at 96 hours after patch application.

1% malic acid SPF

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TKL Study No. DS101904-7

Subjects who were absent once during the induction phase received a make-up (MU) patch at the last induction visit. The MU applications were graded 48 hours later at the MU visit, or were recorded as N9G (no ninth grading).

The Challenge Phase was initiated during the sixth week of the study. Identical patches were applied to sites previously unexposed to the study material. The patches were removed by subjects after 24 hours and the sites graded after additional 24-hour and 48-hour periods (ie, 48 and 72 hours after application). Rechallenge was performed whenever there was evidence of possible sensitization.

To be considered a completed case, a subject must have had 9 applications and no fewer than 8 subsequent readings during induction, and a single application and 2 readings during challenge. Only completed cases were used to assess sensitization.

### 3.2.2 Definitions Used for Grading Responses

The symbols found in the scoring scale below were used to express the response observed at the time of examination:

- = No reaction
- ? = Minimal or doubtful response, slightly different from surrounding normal skin
- + = Definite erythema, no edema
- ++ = Definite erythema, definite edema
- +++ = Definite erythema, definite edema and vesiculation

### SPECIAL NOTATIONS

- E = Marked/severe erythema
- S = Spreading of reaction beyond patch site (ie, reaction where material did not contact skin)
- p = Papular response > 50%
- pv = Papulovesicular response > 50%
- D = Damage to epidermis: oozing, crusting and/or superficial erosions
- I = Itching
- X = Subject absent
- PD = Patch dislodged
- NA = Not applied
- NP = Not patched (due to reaction achieved)
- N9G = No ninth grading

1% malic acid SPF

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TKL Study No. DS101904-7

### 3.2.3 Evaluation of Responses

All responses were graded by a trained dermatologic evaluator meeting TKL's strict certification requirements to standardize the assignment of response grades.

## 4.0 NATURE OF STUDY MATERIAL

### 4.1 STUDY MATERIAL SPECIFICATIONS

Identification	:	1% malic acid	Day SPF 15
Amount Applied	:	0.2 g	

### 4.2 STORAGE, HANDLING, AND DOCUMENTATION OF STUDY MATERIAL

Receipt of the material used in this study was documented in a general logbook, which serves as a permanent record of the receipt, storage, and disposition of all study material received by TKL. On the basis of information provided by the sponsor, the study material was considered reasonably safe for evaluation on human subjects. A sample of the study material was reserved and will be stored for a period of 6 months. At the conclusion of the clinical study, the remaining study material was discarded or returned to the sponsor and the disposition documented in the logbook. All information regarding the receipt, storage, and disposition of the study material was also recorded on a Clinical Material Record form (see Appendix III), which is incorporated in this study report. All study material is kept in a locked product storage room accessible to clinical staff members only.

### 4.3 APPLICATION OF STUDY MATERIAL

Study material was applied to the patch as instructed. The patch was applied to the infrascapular area of the back, either to the right or left of the midline, or to the upper arm.

### 4.4 DESCRIPTION OF PATCH CONDITIONS

Material evaluated under occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad attached to a non-porous, plastic film adhesive bandage (3M medical tape). The patch was secured with hypoallergenic tape (Micropore), as needed.

Material evaluated under semi-occlusive patch conditions was applied to a 2-cm x 2-cm Webril pad. The pad was affixed to the skin with hypoallergenic tape (Micropore).

## 5.0 INTERPRETATION

Sensitization is characterized by an acute allergic contact dermatitis. Typical sensitization reactions begin with an immunologic response in the dermis resulting in erythema, edema formation, and secondary epidermal damage (vesiculation), sometimes extending beyond the patch site and often accompanied by itching. Sensitization reactions tend to be delayed. The reaction typically becomes evident between 24 and 48 hours, peaks at 48-72 hours and subsequently subsides. The reaction is

1% malic acid SPF

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TKL Study No. DS101904-7

often greater at 72 hours than at 48 hours. The severity of the reaction is generally greater during the challenge phase of a Repeated Insult Patch Test (RIPT) than that seen during induction.

Irritant reactions are characterized as a non-immunologic, localized, superficial, exudative, inflammatory response of the skin due to an externally applied material. The typical initial reaction does not develop much edema or vesiculation but results in scaling, drying, cracking, oozing, crusting, and erosions. The reaction is usually sharply delineated, not spreading beyond the patch site. Irritant reactions are typically evident by 24 hours and diminish over the next 48-72 hours. Removal of the offending agent results in gradual improvement of the epidermal damage. The reaction seen at 72 hours is, therefore, less severe than that seen at 48 hours. Finally, the severity of the reaction experienced in the challenge phase is generally similar to that seen during induction.

If the results of the study indicate the likelihood of sensitization, the recommended practice is to rechallenge the subjects who have demonstrated sensitization-like reactions to confirm that these reactions are, indeed, associated with the product. Our preferred rechallenge procedure involves the application of the product to naïve sites, under both occlusive and semi-occlusive patch conditions. Use of the semi-occlusive patch condition helps to differentiate irritant and sensitization reactions. Generally speaking, if a product is a sensitizer it will produce a similar reaction under both occlusion and semi-occlusion. Whereas, if the product has caused an irritant reaction, the reactions will be less pronounced under the semi-occlusive condition.

## 6.0 DOCUMENTATION AND RETENTION OF DATA

The case report forms (CRFs) are designed to identify each subject by subject number and initials, and to record demographics, examination results, adverse events, and end of study status. Originals or copies of all CRFs, correspondence, study reports, and all source data will be kept on hard-copy file for a minimum of 5 years from completion of the study. Storage is maintained either at a TKL facility in a secured room accessible only to TKL employees, or at an offsite location which provides a secure environment with burglar/fire alarm systems, camera detection and controlled temperature and humidity. Documentation will be available for the sponsor's review on the premises of TKL.

## 7.0 RESULTS AND DISCUSSION

One hundred fifteen subjects between the ages of 19 and 75 were enrolled and 106 completed the study (see Tables 1 and 2 in Appendix I and Data Listings 1 and 2 in Appendix II).

The following table summarizes subject enrollment and disposition.

Number enrolled:	115
Number discontinued:	9
Lost to follow-up:	7
Voluntary withdrawal:	2
Number completed:	106

Source: Table 1, Appendix I

1% malic acid SPF

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TKL Study No. DS101904-7

There were no adverse events reported.

A summary of response data is provided in Table 3, Appendix I. Individual dermatological response grades are provided in Data Listing 3, Appendix II.

## 8.0 CONCLUSION

Under the conditions employed in this study, there was no evidence of sensitization to Formula No.

1% malic acid SPF

## 9.0 REFERENCES

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**APPENDIX I**

**SUMMARY TABLES**

TKL STUDY NO. 09101904  
TABLE 1: SUMMARY OF SUBJECT ENROLLMENT AND DISPOSITION

---

	n (%)
Subjects enrolled	115
Subjects completed induction phase	108 ( 93.9)
Subjects completed all phases	108 ( 92.2)
Total subjects discontinued	9 ( 7.8)
Lost to follow-up	7 ( 6.1)
Voluntary withdrawal	2 ( 1.7)

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Note: All percentages are relative to total subjects enrolled

See Data Listing 1 for further detail

Program: DISPSMY.SAS/USES: FINAL/26APR04:10:32:15

TKL STUDY NO. DS101804  
TABLE 2: SUMMARY OF SUBJECT DEMOGRAPHICS  
ALL ENROLLED SUBJECTS

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Age

n (%) 18 to 44	42 ( 36.5)
n (%) 45 to 64	51 ( 44.3)
n (%) 65 and up	22 ( 19.1)
Mean (SD)	50.7 (13.8)
Median	50.8
Range	19.8 to 75.7

Gender

n (%) Male	24 ( 20.9)
n (%) Female	91 ( 79.1)

Race

n (%) Amer Indian	2 ( 1.7)
n (%) Black	1 ( 0.9)
n (%) Cauoasian	81 ( 70.4)
n (%) Hispanic	31 ( 27.0)

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See Data Listing 2 for further detail

Program: DEMOSMY.SAS/USES: DEMOGS/26APR04:16:32:15

TKL STUDY NO. DS101804  
 TABLE 3: SUMMARY OF DERMATOLOGIC RESPONSE GRADES  
 NUMBER OF SUBJECTS BY PRODUCT

PRODUCT = 1% malic acid SPF

Response	-----Induction Reading-----									Make- Up	Challenge Phase		
	1	2	3	4	5	6	7	8	9		48hr	72hr	96hr(*)
-	113	111	107	109	108	104	104	103	108	23	106	106	
?	0	0	0	0	0	1	1	0	0	0	0	0	
Total available	113	111	107	109	108	105	105	103	108	23	106	106	
Number absent	2	2	5	2	3	4	4	5	0		0	0	
Number discontinued	0	2	3	4	4	6	6	7	7		9	9	

MAXIMUM ELICITED RESPONSE DURING INDUCTION  
 ALL SUBJECTS COMPLETING INDUCTION (N=108)

Response	n(%) Subjects
-	106 ( 98.1%)
?	2 ( 1.9%)

(\*) when required

Key to Symbols:

- = No reaction
- + = Definite erythema, no edema
- ++ = Definite erythema, definite edema
- +++ = Definite erythema, definite edema and vesiculation
- D = Damage to epidermis: cozing, crusting and/or superficial erosions
- p = Papular response >50%
- ? = Minimal or doubtful response, slightly different from surrounding normal skin

Program: SUMMARY.SAS/USES: RESPONSE, PRODLIST, FINAL/28APR04:16:32:19

**APPENDIX II**

**DATA LISTINGS**

TKL STUDY NO. DS101904  
 DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION  
 Page 1 of 3

Subject No.	Screened	Study Dates 1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
1	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
2	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
3	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
4	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
5	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
6	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
7	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
8	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
9	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
10	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
11	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
12	03/10/04	03/10/04		03/19/04	I2	L	10
13	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
14	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
15	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
16	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
17	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
18	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
19	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
20	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
21	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
22	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
23	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
24	03/10/04	03/10/04		03/15/04	I1	L	6
25	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
26	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
27	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
28	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
29	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
30	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
31	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
32	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
33	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
34	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
36	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
36	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
37	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
38	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
39	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38

Key: Last Reading # (I=Induction Phase, C=Challenge Phase)  
 Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal  
 V=Protocol violation, AE=Adverse event, O=Other)

Program: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/26APR04:16:32:08

TKL STUDY NO. DS101804  
 DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION  
 Page 2 of 3

Subject No.	Screened	Study Dates 1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
40	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
41	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
42	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
43	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
44	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
45	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
46	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
47	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
48	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
49	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
50	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
51	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
52	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
53	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
54	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
55	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
56	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
57	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
58	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
59	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
60	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
61	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
62	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
63	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
64	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
65	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
66	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
67	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
68	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
69	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
70	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
71	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
72	03/10/04	03/10/04		03/29/04	I7	L	20
73	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
74	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
75	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
76	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
77	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
78	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38

Key: Last Reading # (I=Induction Phase, C=Challenge Phase)  
 Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal  
 V=Protocol violation, AE=Adverse event, O=Other)

Program: DISPLIST.SAS/USE: DEMOGS, RESPONSE, FINAL/26APR04:18:32:08

TKL STUDY NO. DS101804  
 DATA LISTING 1: SUBJECT ENROLLMENT AND DISPOSITION  
 Page 3 of 3

Subject No.	Screened	Study Dates 1st Applic	Chall Applic	Ended	Last Reading #	Completion Status	Days on Study
79	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
80	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
81	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
82	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
83	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
84	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
85	03/10/04	03/10/04		03/26/04	I5	L	17
86	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
87	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
88	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
89	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
90	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
91	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
92	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
93	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
94	03/10/04	03/10/04		03/15/04	I1	L	8
95	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
96	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
97	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
98	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
99	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
100	03/10/04	03/10/04		03/22/04	I3	L	13
101	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
102	03/10/04	03/10/04		04/13/04	I9	S	35
103	03/10/04	03/10/04		04/13/04	I9	S	35
104	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
105	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
106	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
107	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
108	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
109	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
110	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
111	03/10/04	03/10/04		03/24/04	I5	L	16
112	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
113	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
114	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38
115	03/10/04	03/10/04	04/13/04	04/16/04	C2	C	38

Key: Last Reading # (I=Induction Phase, C=Challenge Phase)  
 Completion Status (C=Completed, L=Lost to follow-up, S=Voluntary withdrawal  
 V=Protocol violation, AE=Adverse event, O=Other)

Program: DISPLIST.SAS/USES: DEMOGS, RESPONSE, FINAL/26APR04:16:32:08

TKL STUDY NO. DS101904  
 DATA LISTING 2: SUBJECT DEMOGRAPHICS  
 Page 1 of 3

Subject No.	Age	Gender	Race
1	44.4	Male	Caucasian
2	44.7	Female	Caucasian
3	68.1	Female	Caucasian
4	53.5	Female	Caucasian
5	54.8	Female	Caucasian
6	48.0	Male	Caucasian
7	72.8	Female	Caucasian
8	52.0	Female	Caucasian
9	24.1	Female	Hispanic
10	45.4	Female	Hispanic
11	69.3	Female	Caucasian
12	22.7	Male	Caucasian
13	71.1	Female	Caucasian
14	38.7	Female	Caucasian
15	63.4	Female	Caucasian
16	54.8	Female	Caucasian
17	60.8	Female	Caucasian
18	67.7	Male	Caucasian
19	37.3	Female	Hispanic
20	62.3	Female	Caucasian
21	42.4	Female	Hispanic
22	49.9	Male	Hispanic
23	65.5	Male	Caucasian
24	52.7	Female	Caucasian
25	70.2	Female	Caucasian
26	65.9	Female	Caucasian
27	72.8	Female	Caucasian
28	37.0	Female	Hispanic
29	40.7	Female	Caucasian
30	51.1	Female	Hispanic
31	62.7	Female	Caucasian
32	69.5	Female	Caucasian
33	50.8	Female	Black
34	30.1	Female	Caucasian
35	63.5	Male	Caucasian
36	39.3	Female	Caucasian
37	58.1	Female	Caucasian
38	52.9	Female	Caucasian
39	44.1	Male	Caucasian
40	52.5	Female	Caucasian

Program: DEMOLIST.SAS/USES; DEMOGS/26APR04:18:32:08

TKL STUDY NO. DS101904  
 DATA LISTING 2: SUBJECT DEMOGRAPHICS  
 Page 2 of 3

Subject No.	Age	Gender	Race
41	58.7	Female	Caucasian
42	67.8	Female	Caucasian
43	40.0	Female	Caucasian
44	35.1	Female	Caucasian
45	48.8	Female	Caucasian
46	63.5	Female	Caucasian
47	56.2	Female	Caucasian
48	64.9	Female	Caucasian
49	60.8	Female	Caucasian
50	66.6	Male	Caucasian
51	30.1	Female	Caucasian
52	61.8	Male	Hispanic
53	48.4	Female	Caucasian
54	75.7	Female	Caucasian
55	57.4	Female	Caucasian
56	35.8	Female	Hispanic
57	47.8	Male	Hispanic
58	50.4	Female	Hispanic
59	27.7	Female	Hispanic
60	28.8	Female	Hispanic
61	41.7	Female	Hispanic
62	68.6	Female	Hispanic
63	72.2	Male	Caucasian
64	42.9	Female	Caucasian
65	59.0	Female	Caucasian
66	32.5	Female	Caucasian
67	69.1	Female	Caucasian
68	65.1	Male	Hispanic
69	30.1	Male	Caucasian
70	38.0	Male	Caucasian
71	34.5	Male	Hispanic
72	32.8	Female	Hispanic
73	68.7	Female	Caucasian
74	42.0	Female	Hispanic
75	47.2	Female	Hispanic
76	51.7	Female	Hispanic
77	37.1	Female	Caucasian
78	32.8	Female	Caucasian
79	48.0	Female	Amer Ind
80	64.0	Female	Caucasian

TKL STUDY NO. DS101904  
 DATA LISTING 2: SUBJECT DEMOGRAPHICS  
 Page 3 of 3

Subject No.	Age	Gender	Race
81	45.1	Female	Hispanic
82	57.1	Male	Hispanic
83	31.5	Female	Caucasian
84	38.0	Female	Hispanic
85	71.1	Male	Caucasian
86	31.5	Female	Caucasian
87	54.8	Female	Caucasian
88	41.8	Female	Hispanic
89	31.0	Female	Hispanic
90	38.2	Female	Caucasian
91	47.0	Female	Caucasian
92	40.5	Female	Caucasian
93	62.0	Female	Caucasian
94	37.3	Female	Caucasian
95	60.4	Female	Caucasian
96	55.7	Female	Caucasian
97	56.0	Male	Hispanic
98	48.8	Female	Caucasian
99	37.3	Female	Caucasian
100	44.5	Female	Caucasian
101	52.5	Male	Caucasian
102	34.8	Male	Caucasian
103	39.2	Female	Caucasian
104	61.3	Male	Caucasian
105	63.9	Female	Caucasian
106	73.4	Female	Hispanic
107	71.5	Female	Hispanic
108	46.4	Female	Hispanic
109	72.3	Female	Caucasian
110	53.0	Male	Amer Ind
111	50.3	Female	Caucasian
112	53.5	Male	Caucasian
113	46.0	Female	Caucasian
114	29.1	Female	Hispanic
115	19.8	Female	Caucasian

NEUTROGENA CORP  
 TKL STUDY NO. DB101804  
 DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES  
 BY PRODUCT AND SUBJECT

PRODUCT= 1% malic acid SPF  
 Page 1 of 4

Subject No.	-----Induction Reading-----									Challenge Phase			
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
1	-	-	X	-	-	-	-	-	-	-	-	-	-
2	-	-	-	-	-	-	-	-	-	-	-	-	-
3	-	-	-	-	-	-	-	-	-	-	-	-	-
4	-	-	-	-	-	-	-	-	-	-	-	-	-
5	-	-	X	-	-	-	-	-	-	-	-	-	-
6	-	-	-	-	-	-	-	-	-	-	-	-	-
7	-	-	-	-	-	-	-	-	-	-	-	-	-
8	-	-	-	-	-	-	-	-	-	-	-	-	-
9	-	-	-	-	-	-	-	-	-	-	-	-	-
10	X	-	-	-	-	-	-	-	-	-	-	-	-
11	-	-	-	-	-	-	-	-	-	-	-	-	-
12	-	-	X	X	X	X	X	X	X	-	X	X	-
13	-	-	-	-	-	-	-	-	-	-	-	-	-
14	-	-	-	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-	-	-	-
16	-	-	-	-	-	-	-	-	-	-	-	-	-
17	-	-	-	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	X	-	-	-	-	-	-	-	-
19	-	-	-	-	-	X	-	-	-	-	-	-	-
20	-	-	-	-	-	X	-	-	-	-	-	-	-

Key to Symbols:

- = No reaction
- ? = Minimal or doubtful response, slightly different from surrounding normal skin
- + = Definite erythema, no edema
- ++ = Definite erythema, definite edema
- +++ = Definite erythema, definite edema and vesiculation
- NSG = No ninth grading
- NA=Not applied
- NP=Not patched due to reaction achieved
- X = Reading not performed due to missed visit or subject discontinuation
- D = Damage to epidermis: oozing, crusting and/or superficial erosions
- p = Papular response >50%
- NR=Data not recorded
- MU = Make-up reading for missed induction visit

(\*) when required

NEUTROGENA CORP  
 TKL STUDY NO. D8101904  
 DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES  
 BY PRODUCT AND SUBJECT

PRODUCT= 1% malic acid SPF  
 Page 2 of 4

Subject No.	-----Induction Reading-----									Challenge Phase			
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
21	.	.	.	.	X	.	.	.	.	.	.	.	.
22	.	.	.	.	.	.	.	.	.	.	.	.	.
23	.	.	.	.	.	.	.	.	.	.	.	.	.
24	.	X	X	X	X	X	X	X	X	.	X	X	.
25	.	.	.	.	.	.	.	X	.	.	.	.	.
26	.	.	.	.	.	.	.	.	.	.	.	.	.
27	.	.	.	.	.	.	.	.	.	.	.	.	.
28	.	.	.	.	.	.	X	.	.	.	.	.	.
29	.	.	.	.	.	.	.	.	.	.	.	.	.
30	.	.	.	.	.	.	.	.	.	.	.	.	.
31	.	.	.	.	.	.	.	.	.	.	.	.	.
32	.	.	.	.	.	.	.	.	.	.	.	.	.
33	.	.	.	.	.	.	.	.	.	.	.	.	.
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50	.	.	.	.	.	.	.	.	.	.	.	.	.
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52	.	.	.	.	.	.	.	.	.	.	.	.	.

(\*) when required

Program: DETAIL.SAS/U8ES: RESPONSE, PRODLIST/26APR04:16:32:09

NEUTROGENA CORP  
 TKL STUDY NO. DS101904  
 DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES  
 BY PRODUCT AND SUBJECT

PRODUCT= 1% malic acid SPF  
 Page 3 of 4

Subject No.	-----Induction Reading-----									MU	Challenge Phase		
	1	2	3	4	5	6	7	8	9		48hr	72hr	96hr(*)
53	.	.	.	.	.	.	.	.	.	.	.	.	.
54	.	.	.	.	.	.	.	.	.	.	.	.	.
55	.	.	X	.	.	.	.	.	.	.	.	.	.
56	.	.	.	.	.	.	.	.	.	.	.	.	.
57	.	.	.	.	.	.	.	.	.	.	.	.	.
58	.	.	.	.	.	.	.	.	.	.	.	.	.
59	.	.	.	.	.	.	.	X	.	N9G	.	.	.
60	.	.	.	.	.	.	.	.	.	.	.	.	.
61	.	X	.	.	.	.	.	.	.	.	.	.	.
62	.	.	.	.	.	.	.	.	.	.	.	.	.
63	.	.	.	.	.	.	.	.	.	.	.	.	.
64	.	.	.	.	X	.	.	.	.	.	.	.	.
65	.	.	.	.	.	.	.	.	.	.	.	.	.
66	.	.	.	.	.	.	.	.	.	.	.	.	.
67	.	.	.	.	.	.	.	.	.	.	.	.	.
68	.	.	.	.	.	.	.	.	.	.	.	.	.
69	.	.	.	.	.	.	.	.	.	.	.	.	.
70	.	.	.	.	.	.	X	.	.	.	.	.	.
71	.	.	.	.	.	.	.	.	.	.	.	.	.
72	.	X	.	.	.	.	.	X	X	.	X	X	.
73	.	.	.	.	.	.	.	.	.	.	.	.	.
74	.	.	.	.	.	.	.	.	.	.	.	.	.
75	.	.	.	.	.	.	.	.	.	.	.	.	.
76	.	.	.	.	.	X	.	.	.	N9G	.	.	.
77	.	.	.	.	.	.	.	X	.	.	.	.	.
78	X	.	.	.	.	.	.	.	.	.	.	.	.
79	.	.	.	.	.	.	.	.	.	.	.	.	.
80	.	.	.	.	.	.	.	.	.	.	.	.	.
81	.	.	.	X	.	.	.	.	.	.	.	.	.
82	.	.	.	.	.	.	.	.	.	.	.	.	.
83	.	.	.	.	.	.	.	.	.	.	.	.	.
84	.	.	.	X	.	.	.	.	.	.	.	.	.

(\*) when required

Program: DETAIL.SAS/USES; RESPONSE, PRODLIST/28APR04:16:32:09

NEUTROGENA CORP  
 TKL STUDY NO. DS101904  
 DATA LISTING 3: DERMATOLOGIC RESPONSE GRADES  
 BY PRODUCT AND SUBJECT

PRODUCT: 1% malic acid SPF  
 Page 4 of 4

Subject No.	-----Induction Reading-----									Challenge Phase			
	1	2	3	4	5	6	7	8	9	MU	48hr	72hr	96hr(*)
85	.	.	.	.	.	X	X	X	X		X	X	
86	.	.	.	.	.	.	.	.	.		.	.	.
87	.	.	.	.	.	.	.	.	.		.	.	.
88	.	.	.	.	.	.	.	.	.		.	.	.
89	.	.	.	.	.	.	.	.	.		.	.	.
90	.	.	.	.	.	.	.	.	.		.	.	.
91	.	.	.	.	.	.	?	.	.		.	.	.
92	.	.	.	.	.	.	.	.	.		.	.	.
93	.	.	.	.	.	.	.	.	.		.	.	.
94	.	X	X	X	X	X	X	X	X		X	X	
95	.	.	.	.	.	.	.	.	.		.	.	.
96	.	.	.	.	.	.	.	.	.		.	.	.
97	.	.	.	.	.	.	.	.	.		.	.	.
98	.	.	.	.	.	.	.	.	.		.	.	.
99	.	.	.	.	.	.	.	.	.		.	.	.
100	.	.	.	X	X	X	X	X	X		X	X	
101	.	.	.	.	.	.	.	.	.		.	.	.
102	.	.	.	.	.	.	.	X	.		X	X	
103	.	.	.	.	.	.	.	X	.		X	X	
104	.	.	.	.	.	.	.	.	.		.	.	.
105	.	.	.	.	.	X	.	.	.		.	.	.
106	.	.	.	.	.	.	.	.	.		.	.	.
107	.	.	.	.	.	.	.	.	.		.	.	.
108	.	.	.	.	.	.	.	.	.		.	.	.
109	.	.	.	.	.	.	.	.	.		.	.	.
110	.	.	.	.	.	.	X	.	.		.	.	.
111	.	.	X	.	.	X	X	X	X		X	X	
112	.	.	.	.	.	.	.	.	.		.	.	.
113	.	.	X	.	.	.	.	.	.		.	.	.
114	.	.	.	.	.	.	.	.	.		.	.	.
115	.	.	.	.	.	.	X	.	.		.	.	.

(\*) when required

Program: DETAIL.SAS/USES: RESPONSE, PRODLIST/26APR04:16:32:09



**Memorandum**

**TO:** Bart Heldreth, Ph.D., Interim Director  
COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** August 1, 2017

**SUBJECT:** Malic Acid

Anonymous. 2015. Summary of a repeated insult patch test of a hair product containing 2% Malic Acid (3% dilution of product tested).

## **Malic Acid**

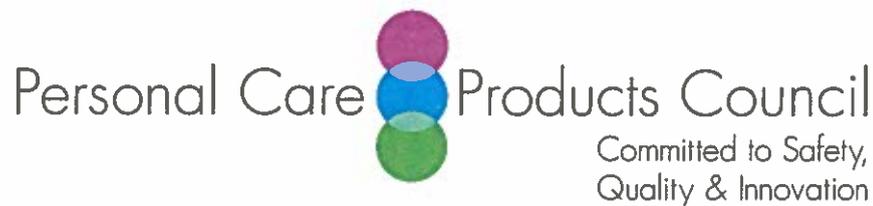
### **Summary of HRIPT**

A hair clarifying rinse-off treatment (used as a pre- and post-hair chemical service) containing 2.0% Malic Acid was tested using Modified Draize Human Repeated Insult Patch Test (HRIPT) procedure to determine the potential of this product to induce irritation and contact sensitization. The product was tested as a 3% dilution under semi-occlusive conditions.

The HRIPT consists of three phases: induction phase, rest phase and challenge phase. During the induction phase, patches were applied on the subject's back and were removed 24 hours after each application. A trained examiner scored skin responses when subjects returned to the testing facility for next patch application. Patches were applied at the same site 3 times a week (Monday, Wednesday and Friday) for 3 consecutive weeks. Around 2 weeks (rest phase) after application of the last induction patch, challenge patches were applied to adjacent virgin sites. Patches were removed after 24 hours. Test sites were scored at 24 and 72 hours after application.

One hundred and five (105) subjects satisfactorily completed the study. Under the conditions of a Modified Draize HRIPT procedure, the test material did not indicate a clinically significant potential for dermal irritation or allergic contact sensitization. There was no evidence of induced allergic contact sensitization.

The study was conducted by Bio Screen Testing Services, Inc., from March 16, 2015 through April 24, 2015 in accordance with the spirit of Good Clinical Practice regulations described in CFR 21, Part 50 (Protection of Human Subjects-Informed Consent) and Part 56 (Institutional Review Boards).



## Memorandum

**TO:** COSMETIC INGREDIENT REVIEW (CIR)

**FROM:** Beth A. Jonas, Ph.D.  
Industry Liaison to the CIR Expert Panel

**DATE:** June 7, 2017

**SUBJECT:** Re-review: Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics (draft prepared for the June 12-13, 2017 CIR Expert Panel Meeting)

**Introduction** - It should not be implied that ECHA completed the "read-across". The company submitting the data used read-across to support Malic Acid. It would be helpful to state the endpoints for which data on fumaric acid were used to support the safety of Malic Acid.

**Chemistry** - The *Food Chemical Codex* acceptance criteria (99-100.5% pure; fumaric acid NMT 1%; maleic acid NMT 0.05%) should be added to the Chemistry section.

**Non-Cosmetic Use** - The *Food Chemical Codex* says that in food Malic Acid functions as an acidifier and a flavoring agent.

**Genotoxicity, old report summary** - Please state the type of cells used in the chromosomal assay (it is helpful to distinguish assays done in bacterial versus mammalian cells).

**Summary** - It would be helpful if the normal physiological role of Malic Acid was also mentioned in the Summary.