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

Status:	Draft Final Amended Report for Panel Review
Release Date:	February 9, 2018
Panel Meeting Date:	March 5-6, 2018

The 2018 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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Cosmetic Ingredient Review

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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst
Date: February 9, 2018
Subject: Draft Final Amended Report on Malic Acid and Sodium Malate

Enclosed is the Draft Final Amended Report of the Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics. (It is identified as *maacid032018rep* in the pdf document).

In December 2017, the CIR Expert Panel issued a Tentative Amended Report with the conclusion that Malic Acid and Sodium Malate are safe in cosmetics in the present practices of use and concentration described in this safety assessment. This conclusion supersedes the conclusion of safety that was published in 2001.

Since the December meeting, additional data on Sodium Malate (reported as DL) from the *Food Chemicals Codex* has been incorporated into the report (designated with |brackets| in the text). No other new data have been discovered or received. Comments provided by the Council prior to the December meeting and on the tentative amended report have been addressed (*maacid032018pcpc1* and *maacid032018pcpc2*, respectively).

The Panel should carefully review the Abstract, Discussion, and Conclusion of this report. If these are satisfactory, the Panel should issue a final amended report.

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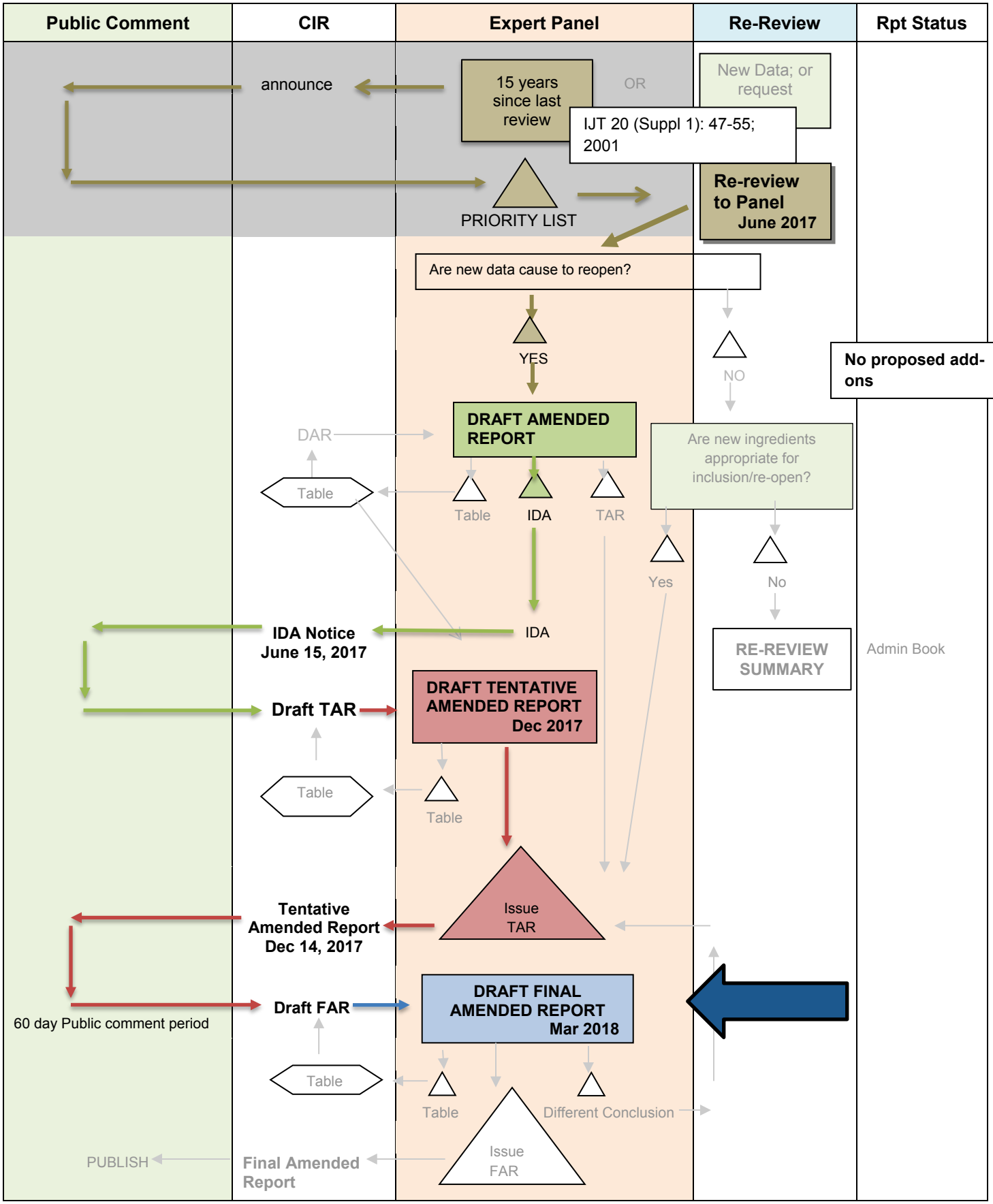
RE-REVIEW FLOW CHART

INGREDIENT/FAMILY Malic Acid and Sodium Malate

MEETING March 2018



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.

December 2017 - The Panel issued a tentative amended report for public comment with the conclusion that Malic Acid and Sodium Malate are safe in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel noted that there are no sensitization data for Malic Acid at the maximum leave-on use concentration of 2.1%. The results of a HRIPT found that Malic Acid at 1% in formulation did not induce dermal sensitization. Based on the experience of the clinicians on the Panel and the fact that Malic Acid and Sodium Malate are common chemicals in human biology, the Panel concluded that these ingredients would not induce sensitization at use concentrations. The Panel also noted that Malic Acid is an ocular irritant and use as a hair spray has been reported. The Panel thus advises consumers to minimize incidental ocular exposure to hair sprays containing Malic Acid.

Malic Acid and Sodium Malate Data Profile –March 2018 – 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 REports	Toxicokinetics
Original Report																
Malic Acid	X	X	X	X	X	X	X	X			X	X	X		X	X
Sodium Malate	1 use, no concentration				X											
Re-Review																
Malic Acid	X			X			X					X	X		X	X
Sodium Malate	X	X	X	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
PREVIOUSLY REVIEWED																			
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.

Search updated January 2018. No new relevant 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
ScfFinder (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 and
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/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions 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
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/
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/
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

Malic Acid and Sodium Malate
December 4-5, 2017

Dr. Belsito's Team

DR. BELSITO: Okay. Malic acid and sodium malate, at the June meeting we reopened the safety assessment in 2001 to revise the conclusion based upon new data that were to address the insufficient data of our original report.

And we issued an insufficient data announcement asking for an HRIPT or another suitable sensitization studies, at the maximum reported concentration in a leave-on of 2.1 percent, and information on which stereoisomer were used in cosmetic products. We did get an HRIPT on a sun protection product at one percent and on a hair product at two percent. But there was three percent dilution on product tested. There was no dermal sensitization noted in those studies that we received. We didn't get the information on the stereoisomers. I don't know if that came from you Dan, or Ron Hill or both of you?

DR. LIEBLER: That came from Ron Hill. I didn't think it was necessary for our evaluation.

DR. BELSITO: So I thought overall based upon the new data we got that safe when used when formulated be non-irritating.

DR. SNYDER: So the only issue I had was we got new data saying now the maximum concentration use was 2.1 percent not 1 percent and so that changed everything because everything prior to this was based upon maximum concentration use of 1 percent that's why we asked for sensitization at 1 percent and the article that we were supplied also stated in there the max concentration of use was one percent but we received data that now says the max concentrations of use is 2.1 percent, so does that kind of reset? I mean we didn't know that when we pressed it at one percent so if that's in fact correct, that we got new data that it's 2.1 percent now?

DR. BERGFELD: There was some additional data of insult patch test of two percent that took it up to two. That was in your wave 2…that was Malic Acid.

DR. BELSITO: That was diluted. So it wasn't two percent.

DR. SNYDER: Yes, right.

DR. BELSITO: It was probably.6.

MS. BURNETT: So when we wrote the re-review, the concentration of use survey came back with the maximum concentration of 2.1 percent.

DR. BELSITO: Yes, sorry I mean what I put here in my comment that the highest HRIPT for sensitization is one percent. Do we need the 2.1 and I said, you know, I've never seen sensitization to these products. I think irritation is the issue and if limited based when formulated to be non-irritating sensitization will not be a factor even though we don't have the data.

DR. SNYDER: Yea, I think we just have to say something because we requested it at the maximum concentration of use, we received it, but the maximum concentration of use is different now so we I think we have to have an explanation of why we previously wanted a maximum concentration of use and now we're saying we don't.

DR. BELSITO: Right.

MR. GREMILLION: So the maximum concentration of use is actually over twice as high as what the reports are based on, just confirming that it's 2.1 and the earlier conclusion is based on 1 percent.

DR. BELSITO: Right, but these are really not known at all to be sensitizers. The issue would be how it's formulated and whether it would be irritating and so that's why our conclusion is when formulated to be non-irritating because we know all acids can be irritating but you know when they're formulated they make salts which are non-irritating to the skin. So the issue with the malic acid is really more of an issue of irritation and really sensitization is not an issue.

DR. LIEBLER: Just to elaborate on that a little further because I think it's a fair question and one thing I think you might not be aware of is that most if not almost all of the molecules that are known to be sensitizing share the property of being able to modify proteins that chemically react with modified proteins that produces modified protein forms that are thought to trigger the immune response that leads to the sensitization and so one of the things that we're perhaps not articulating on our comments here is that this molecule lacks that data chemistry. Now a related issue that I thought we could bring to bare here could be whether or not there is sensitization to a higher concentration of something like succinate or fumerate.

MS. BURNETT: I do want to point out. I don't know if this makes any difference once so ever but the 2.1 use is in a hair spray

DR. SNYDER: But it's listed under leave-ons.

DR. BELSITO: Well hairsprays are leave-ons.

MS. BURNETT: Yes.

DR. KATZ: Do you need to be concerned, particularly for hairspray that at a higher concentration for ocular irritation. I understand sensitization portion but these products may actually, particularly if it's a hair spray that's sprayed into the eye, if there's no data to support that use.

DR. BELSITO: That's a good point.

DR. BERGFELD: Except would nonirritating cover that?

DR. KATZ: I'm not sure you could say that for our product, for hairspray, that you would know whether or not your irritating because it's going to get there anyway from the aerosolization and that's really my concern is that either way you got to get it into a salon if they spray your hair they tell you to put your hand there but if you're doing it at home I don't know how you're going to make sure that you're not going to get it anywhere near there. Is that portion necessary before you go on?

DR. LIEBLER: These would be irritating because of the pH. And I mean these are used as pH adjusters so if you formulated to be nonirritating you need to make the pH come out somewhere in the neutral range I guess, so it's basically the same issue as for skin irritation even though ocular is more sensitive because of the nature of the target but I guess I don't think it needs to be considered differently than we're already considering it for skin and when formulating to be nonirritating applies to all formulations.

DR. BERGFELD: You could put that in the discussion though?

DR. LIEBLER: Yeah, I think that's a good idea.

DR. SNYDER: So, Christina, clarification under ocular irritation studies, under the in vitro studies. The assays predicted in the formulation was malic acid at 3.6 so that the formulation would have a pH of 3.6 or would it be different?

MS. BURNETT: There are two different formulations tested and one had a pH of 3.6 and the other had a pH of 3.0.

DR. SNYDER: So that would go against what Dan was arguing that the formulation might not be as acidic or alkaline as - because that's the formulation.

DR. LIEBLER: That was a formulation that was tested and produced irritation. It doesn't mean that any formulation is going to be acidic.

DR. BELSITO: Yes, we just said that it could be formulated to be irritating. A pH of 3.6 would be very irritating on the skin so that would not be - I mean I don't know what the product was but -

MS. BURNETT: One says hairstyler and one says hair shampoo.

DR. BELSITO: I mean those would be diluted for use but hairstyler yes, I mean I presume that that's probably some kind of hair straightener or some type of -

DR. BERGFELD: Usually a gel. A volumizer.

MS. BURNETT: I will see if I can find but it's unpublished data I believe. I'm not sure how much detail I have.

DR. ANSELL: I think that's entirely consistent with what Dan has said is you know if it's pH dependent and if the product is very acidic then it's going to be an ocular irritant.

DR. BELSITO: (inaudible)

DR. ANSELL: So I think addressing that in the discussion is appropriate but there's nothing surprising. I know it's irritation is concentration and pH dependent for these materials.

DR. BELSITO: Okay. So safe when formulated to be non-irritating and in the discussion point out about the hairspray and the minimal ocular irritation study that we have.

MS. BURNETT: Unfortunately I don't have much detail on those ocular irritation studies, it says that test material was malic acid, 50 percent solution in hairstyler which was 2.72 percent malic acid, the pH of the test material was 3.6, and respectively 3.0 for the other one. That's all the data I have on it other than the results.

DR. BELSITO: And then we had that article on apoptosis that I found but I don't think that that changes anything.

MS. BURNETT: I did want to point out that we received the Council's comments on Thursday I believe last week and they wanted to point out that under the sodium malate it's actually a disodium not a monosodium and the monograph will be changed. Is that correct, Jay?

DR. ANSELL: Yes, we just wanted to just make the panel aware that there was an issue with the INCI ongoing to clarify whether it's the monosodium or disodium salt of the acid and the INCI monograph was going to be clarifying that.

Dr. Marks' Team

DR. MARKS: Next is malic acid and sodium malate. So we have a tentative amended report on malic acid and sodium malate. At the June Meeting the panel re-opened the assessment that was originally published in 2001 that was revised the conclusion and an insufficient data announcement was made. The data needs are listed in the memo from Christina. Can we move on to a draft final amended report?

DR. SHANK: Do you still want skin sensitization at 2.1 percent; we have them for one percent?

DR. MARKS: Yeah, these were the needs…sensitization at 2.1 percent. Ron Hill, you mentioned the isomers and then, method of manufacture and impurities. And then Don Belsito had sent a W-2 in reference to an article on some cytotoxicity and apoptotic effects. It's interesting, in the original 2001 report, we said safe as a PH-adjuster, and insufficient for other uses and their team felt we needed to re-open that conclusion.

DR. HILL: Correct.

DR. MARKS: So do we just go back to that conclusion and at this point not re-open and just have a discussion and the review? And re-review or do we go with a draft final amended report, insufficient with those three needs at 2.1 percent sensitization. Now, you said do we --

DR. EISENMANN: Could we limit it to one percent?

DR. MARKS: Or we could limit it to one percent.

DR. EISENMANN: If you wanted to.

DR. HILL: So what are the three needs again, they're listed right in the report.

DR. MARKS: Sensitization, the isomers and method of manufacture and impurities.

DR. EISENMANN: Well, the isomers appear likely to be DL because that's what's used for food.

DR. HILL: Well, my conjecture was that in food, they probably use the D produced from, from pork --

DR. EISENMANN: Well, food chemical codex listed it as DL.

DR. HILL: They do?

DR. EISENMANN: Yes. The other issue that I've discovered, in the original report the sodium malate was definitely was definitely a monosodium salt. Now the CAS number for the disodium salt has gotten in there, the unicode for disodium salt has gotten in there. So, in other words, -- and we asked the suppliers; that's the more important thing. I asked the company that reported using it, they're using disodium. They're using the food grade material. One user is using disodium and the other is using a mixture. So, it's probably -- they're using a mixture of water with malic acid and disodium malate and they gave cast numbers for both disodium and monosodium. I'm not sure that it matters for safety reasons.

DR. HILL: It doesn't.

DR. EISENMANN: But it might be good to put them both, my -- the thought was to put them both in there. Both salts.

DR. HILL: My comment last time about the toxicology data was that any simple salt with malic acid should have been captured in terms of the toxicology and then it's malic acid but, yet, I wasn't clear on -- I'm still not clear on what's the significance of the L-malic acid being in that DL mixture if there is, I doubt there is.

DR. EISENMANN: Oh, for food use, I've read a review that EHMSA, considered that they didn't matter,

DR. HILL: Yeah, I think those are actually inter- convertible in humans, more or less cremated, L converts to D. The only thing that came out of the method of manufacture is that they're making it by chewing up benzene and then hydrating it to malic acid to make the DL and then I would have expected, maybe residual benzene, except that since there's that extra reaction stuff it's probably a non-issue. Anyway, that's what I had noted down to look at. I would have thought the food grade would have been just D, but if that's not the case, then, it confirms what I thought, which is pretty well converted more in human.

DR. EISENMANN: So I don't that's a data that needs to stay.

DR. HILL: Yeah, it probably isn't.

DR. MARKS: Okay, so let's go back to, so, the isomers. How about method of manufacturing and impurities?

DR. HILL: Well, that was the benzene data that we got, is that they recalculated -- they did catalytic cleavage of benzene to get maleic acid which then they then hydrate under steam to malic acid.

DR. MARKS: So you're firm…

DR. HILL: And it makes a DL, you know. Well, you know, in principal, one should know that they're -- there's no residual benzene. But given that there is another step, I don't think that, that's a problem.

DR. MARKS: So now, we're back to, I think, the last thing is sensitization at 2.1 percent. That's what it's -- I -- you mention a limit, Carol, but I have in my notes that the HRIPT is done with.02 percent. That's a long ways from --

MS. BURNETT: There's --

DR. EISENMANN: Well, there's --

MS. BURNETT: -- there's --

DR. HILL: I have 1 percent.

MS. BURNETT: -- there's --

DR. MARK: One percent?

MS. BURNETT: Yeah, one was 1 percent. One was 2 percent with a 3 percent dilution, so.6 percent.

DR. MARKS: Yeah, so there wasn't 1 percent?

MS. BURNETT: So 1 percent was the maximum concentration.

DR. MARKS: Where did I miss that? Was that --

DR. HILL: (Inaudible)

MS. BURNETT: And it's in the notes --

DR. MARKS: Anyways, 1 percent, okay. So --

MS. BURNETT: It's in the --

DR. MARKS: -- and --

MS. BURNETT: It's in the memo.

DR. HILL: I just don't think that's a problem because there are no structural hits to suggest that they should sensitize the malic acid that's so pervasive in the human biochemistry that if we sensitize to that, none of us would live past the age of zero. That's just my thinking.

DR. MARKS: So draft final amended report safe?

DR. HILL: Yeah.

DR. MARKS: At 2.1 percent doesn't bother you. Okay?

MS. BURNETT: It needs discussion.

DR. MARKS: All right.

DR. SHANK: So if you got to defend accepting the HRIPT at 1 percent and not 2.1. And to say this in common a biochemical medium in humans.

DR. HILL: Somewhere I think there's literature that looks at that conversion of LD in humans. And we really have to capture that a little bit in biochemistry.

DR. SHANK: Okay.

DR. MARKS: And okay?

DR. SHANK: That's all.

DR. MARKS: And then what about Don's article? Is there anything that we need to mention about that in the discussion?

DR. HILL: I didn't think so, personally.

DR. SHANK: I don't have that highlighted. So what was the article?

DR. MARKS: It was an article on cytotoxiciy and apoptotic effects. It was basically a link.

DR. SHANK: Oh, really? No, that's was interesting. Then I don't make that link.

MS. BURNETT: Or, should it be --

DR. SHANK: (Inaudible) cosmetic.

MS. BURNETT: -- should it be included in the report at all?

DR. SHANK: No.

MS. BURNETT: Okay.

DR. SHANK: Doctor Belsito may not agree, since he submitted it.

MS. BURNETT: That I'm not sure. Let's -- we'll find out tomorrow.

DR. MARKS: I won't mention it. We'll wait for him.

DR. SHANK: Yes.

DR. HILL: Yes.

DR. MARKS: Okay? So tomorrow I'm going to move that a draft final amended report be issued with a conclusion of safe.

DR. EISENMANN: Okay.

DR. SHANK: (Inaudible)

DR. MARKS: Okay? Next on the -- is --

Full Panel Meeting

DR. BERGFELD: All right, the next is malic acid. Dr. Marks?

DR. MARKS: In June of this year this CIR expert panel reopened this safety assessment of malic acid and sodium malate. The original was published in 2001. We reopened to revise that conclusion. We issued an insufficient data announcement. We received data and that's detailed in the memo. So our team felt we could move forward and this is a motion that a draft final amended report be issued with a safe conclusion.

DR. BERGFELD: Belsito comment?

DR. BELSITO: Second.

DR. BERGFELD: Second. Any further discussion, comment? Editorials? Don?

DR. BELSITO: Yea, it was pointed out by Dr. Katz yesterday that this was used in hairsprays up to 2.1 percent and we should just add in the discussion that we -- you know that care when applying hairspray because we don't have the ocular it can be irritating to the eye. Although, obviously, hairsprays are not meant to be sprayed in the eye, but just have that in the discussion.

DR. BERGFELD: Just the discussion not the conclusion.

DR. BELSITO: Not the conclusion.

DR. MARKS: And the other comment I had, Don, you had sent in wave two alert us to an article on cytotoxicity and apoptotic effects. Our team discussed that and felt we didn't need to include that article, but we want to make sure that is fine with you.

DR. BELSITO: I'm fine. I was searching for something else and came across the article and noticed that it wasn't in our report and just wanted to put that out to all of you to decide whether it should be in the report or not. The concentrations, etc. are really not relevant to what we are discussing.

DR. MARKS: Thank you, Don.

DR. BERGFELD: We will call the question then on malic acid. All those in favor of a safe conclusion raise your hands. Thank you. Unanimous. And then --

(MOTION PASSED UNANIMOUSLY)

DR. HILL: I just wanted to clarify for the record that this is going out as a tentative. It will come back as a final.

DR. BERGFELD: Okay.

DR. MARKS: Thank you for clarifying that.

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The 2018 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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ABSTRACT

The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reassessed 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 that Malic Acid and Sodium Malate are safe in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

The CIR Expert 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.[1] 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. In accordance with its procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since this assessment has been issued. Because the number of uses and concentrations of use increased since the original assessment, 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.[2,3] These functions are similar to what was reported in the 2001 assessment except at that time Malic Acid was only reported to function as a pH adjuster.

Malic Acid (or malate) is an intermediate in the citric acid cycle (also known as the tricarboxylic acid (TCA) cycle or Krebs cycle) and is formed during the hydration reaction of fumarate (or fumaric acid) with the enzyme fumarase.[4] Fumarate is formed by the oxidation reaction of succinate (succinic acid) and coenzyme Q (ubiquinone) with succinic dehydrogenase. 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.[5,6]

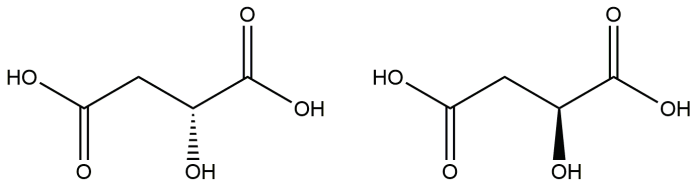
This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are 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.) The original report that was published in 2001 is available on the CIR website (http://www.cir-safety.org/ingredients).

CHEMISTRY

Definition and Structure

The *Dictionary* defines Malic Acid as an organic carboxylic acid, the molecular formula of which is $C_4H_6O_5$ and the stereoisomers of which are depicted below (Figure 1).[2]



D-Malic Acid L-Malic Acid

Figure 1. Malic Acid (D- and L-stereoisomers)

Sodium Malate is the sodium salt of Malic Acid. It conforms to the formula described below (Figure 2).[3] With two carboxylic acid functional groups, Sodium Malate is available as the mono- or di-sodium salt.

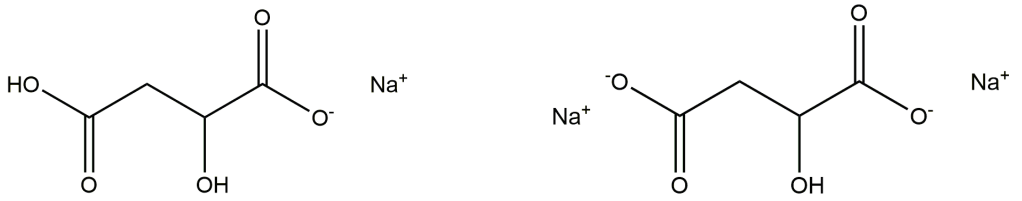


Figure 2. Sodium Malate (monosodium and disodium)

Malic Acid and Sodium Malate are α-monohydroxy succinic acid ingredients. These ingredients have one stereocenter, and thereby two stereoisomers, the configuration of which is most commonly denoted by D, L, or DL (a racemic mixture (50/50) of the D and L isomers). The *Dictionary* names as defined are ambiguous to these stereochemical details. Stereochemistry is identified when provided in the data summarized throughout this report.

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. Physical form and formula weight for Sodium Malate are also provided in Table 1. Sodium Malate (reported as DL) is freely soluble in water. No further chemical properties were found in the literature.

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.[1] L-Malic Acid is available through the [hydration] *of fumaric acid.*

Sodium Malate (reported as DL) is manufactured by reacting Malic Acid with sodium hydroxide and purifying the reaction product.[7]

Natural Occurrence

The L-isomer of Malic Acid is a naturally occurring and common metabolite of plants (most commonly found in fruits, such as unripe apples) and animals.[1]

Impurities

Maleic and fumaric acids are by-products of the manufacture of Malic Acid.[1] 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.[8]

The *Food Chemicals Codex* states Sodium Malate (disodium, DL) should have not more than 3 mg/kg arsenic, 2 mg/kg lead, 1% fumaric acid, and 0.05% maleic acid.[7] Specifications for Sodium Malate (monosodium, DL) for food use indicate that the chemical should not contain more than 0.05% maleic acid and not more than 2 mg/kg lead.[9] Purity should not be less than 99.0% on the dried basis.

USE

Cosmetic

The safety of the cosmetic ingredients 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[1] to 238 reported uses in 2017[10] (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,[1] and the results of the survey conducted by the Council in 2017 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.[11]

The frequency of use for Sodium Malate has also increased since the original review, from 1 reported use in 1998[1] to 5 reported uses in 2017[10]. 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.[1] The Council in 2017 reported that Sodium Malate (disodium) is used at 0.02% in "other" skin care preparations.[11]

Malic Acid is used in products that are used near the eye at a maximum concentration of 0.000012% (in eyeliners) and in those that can come in contact with mucous membranes at maximum concentrations up to 50% (in bath oils, tablets and salts); no concentrations of use were reported for these categories in the original assessment.[1,10] 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 μm, with propellant sprays yielding a greater fraction of droplets/particles < 10 μm compared with pump sprays.[12,13] 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.[14,15]

Malic Acid and Sodium Malate are not restricted from use in any way under the rules governing cosmetic products in the European Union (EU).[16]

Non-Cosmetic

DL- and L-Malic Acid are generally recognized as safe (GRAS) as direct food additives by the U.S. FDA for use as flavor enhancers, flavoring agents, adjuvants, and as pH control agents (21CFR184.1069, 21CFR582.60, 21CFR582.1069). DL- and L-Malic Acid are not GRAS for baby foods.

The *Merck Index* reports that Malic Acid is an intermediate in chemical synthesis.[17] 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 (DL) functions as an acidifier and a flavoring agent in food, while Sodium Malate (DL) functions as a buffer or neutralizing agent in food.[7,8] Malic Acid is listed as DL in the USP *National Formulary*.[18]

TOXICOKINETICS STUDIES

Absorption, Distribution, Metabolism, and Excretion

Most of the radioactivity from 2.5 mg/kg U-^{14}C-L-Malic Acid (specific activity 61μCi/mmol) or 4-^{14}C- DL-Malic Acid (specific activity 93 μCi/mmol) administered orally or intraperitoneally (i.p.) to male rats was excreted as carbon dioxide.[1] 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 to penetrate the skin, as used in rinse-off personal care products, was assessed in an in vitro study.[19] A shampoo with radiolabeled Malic Acid (L-(U)-[^{14}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 receptor fluid was saline. 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^2, the total absorbable dose was 0.003% and the total dose delivered was 0.000067 μg/cm^2.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The oral LD_{50} values of Malic Acid for mice, rats, and rabbits ranged from 2.66 to greater than 3.2, 1.60 - 3.5, and 3 - 5 g/kg, respectively.[1] The acute LD_{50} of Malic Acid given intravenously was 2.4 g/kg for rabbits, and the i.p. LD_{50} for mice and rats were 0.05 to 0.1 and 0.1 – 0.2 g/kg, respectively.

Chronic Toxicity Studies

In a chronic oral study in rats, Malic Acid at concentrations up to 50,000 ppm (5.0%) in feed for 104 weeks resulted in decreases in body weight gains and feed consumption, but compound-related lesions were not observed.[1] 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).[1] 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.[1] 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.[20] 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 currently or reported in the 2001 safety assessment.

DERMAL IRRITATION AND SENSITIZATION STUDIES

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).[1]

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.[1]

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. [21-23]

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).[21] 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.[1]

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.[1] *Reactions included immediate (seasonal allergic rhinitis and urticarial) and delayed (contact dermatitis) responses. 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 cumulative irritation potential of Malic Acid with other fruit acids was tested in 20 healthy volunteers.[24] The volunteers were exposed twice daily for 4 days to 2% Malic Acid (pH 2 and pH 4), either alone or in tandem with 0.5% sodium lauryl sulfate (SLS). Positive and negative controls were 0.5% 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 Malic Acid (pH 2 or pH 4) alone did not induce significant irritant reactions and were comparable to the negative control. Combined exposures to Malic Acid 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 Malic Acid. The authors of the study concluded that Malic Acid did not significantly contribute to the occurrence of irritant contact dermatitis or increase susceptibility to SLS-induced irritation.

SUMMARY

The Panel published a 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. In accordance with its procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since this assessment has been issued. Because the number of uses and concentrations of use increased since the original assessment, 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.

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 functions are similar to what was reported in the 2001 assessment except at that time Malic Acid was only reported to function as a pH adjuster.

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 report a maximum leave-on use concentration of 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. Uses of Sodium Malate include 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 $\mu g/cm^2$, the total absorbable dose was 0.003% and the total dose delivered was 0.000067 $\mu g/cm^2$.

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 in a cumulative irritation study.

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

DISCUSSION

In accordance with its procedures, the Panel evaluates the conclusions of previously-issued reports every 15 years, and it has been at least 15 years since this assessment has been issued. Because the number of uses and concentrations of use increased since the original assessment, 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.

Overall, the Panel considered that the available data, including the role of Malic Acid in normal metabolism and animal toxicity data, were adequate to assess the safety of these ingredients as used in cosmetics. The Panel noted that in formulation, a pH dependent equilibrium exists between Malic Acid and its salts, thus the safety profile between Sodium Malate would not differ from Malic Acid. The Panel also noted that there are no sensitization data for Malic Acid at the maximum leave-on use concentration of 2.1%. The results of a HRIPT found that Malic Acid at 1% in formulation did not induce dermal sensitization. Based on the experience of the clinicians on the Panel and the fact that Malic Acid and Sodium Malate are common chemicals in human biology, the Panel concluded that these ingredients would not induce sensitization at use concentrations.

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 minimized in formulated products. The Panel also noted that use of Malic Acid in a hair spray has been reported. The Panel thus advises consumers to minimize incidental ocular exposure of hair sprays containing Malic Acid.

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

The CIR Expert Panel concluded that Malic Acid and Sodium Malate are safe in cosmetics in the present practices of use and concentration described in this safety assessment. This conclusion supersedes the conclusion of safety that was published in 2001.

TABLES

Table 1. Physical and chemical properties

Property	Value	Reference
	Malic Acid	
CAS No.	6915-15-7; 636-61-3 (D-form); 97-67-6 (L-form)	[2]
Physical Form	White or colorless crystals	[25-27]
Molecular Weight (Da)	134.09	[17]
Density (g/cm^3)	1.601 (DL-form); 1.595 (D- or L-form; 20º/4ºC)	[25]
Melting Point (ºC)	126-132 (DL-form): 101 (D-form); 100 (L-form)	[17,25-27]
Boiling Point (ºC)	150 (DL-form; decomposes); 140 (D- or L- form; decomposes)	[25]
Solubility in water (g/100 g at 20 ºC)	55.8	[17]
Dissociation constant (at 20 ºC)	pKa1 = 3.51; pKa2 = 5.03	[20]
	Sodium Malate	
CAS No.	676-46-0 (disodium salt)	[3,11]
Physical Form	White powder (monosodium); white to off-white odorless crystalline powder (disodium, DL)	[7,9]
Formula Weight (Da)	156.07	[9]

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

	Malic Acid			
	# of Uses		*Max Conc of Use (%)*	
	2017[10]	**1998[1]**	**2016[11]**	**1984[1] [#]**
Totals*	**238**	**47**	**0.000012-50**	**< 0.1-1**
Leave-On	*110*	*31*	*0.000012-2.1*	*< 0.1-1*
Rinse-Off	*126*	*16*	*0.00013-4*	*<0.1-1*
Diluted for (Bath) Use	*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[a]; 22[b]	2; 3[a]; 3[b]	0.0011-2.1; 0.00013-1.9[a]	NR
Incidental Inhalation-Powder	22[b]	3[b]	0.0004-1[c]	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
	Sodium Malate			
	# of Uses		*Max Conc of Use (%)*	
	2017[10]	**1998[1]**	**2017 (disodium)[11]**	**1984[1] [#]**
Totals*	**5**	**1**	**0.02**	**NR**
Leave-On	*2*	*1*	*0.02*	*NR*
Rinse-Off	*3*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*
Eye Area	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]	1[b]	NR	NR
Incidental Inhalation-Powder	NR	1[b]	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

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays..

[b] 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

[c] 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	[21]
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	[21]
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	[22]
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	[23]

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Final Report on the Safety Assessment of Malic Acid and Sodium Malate[1]

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 Kreb's 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 irritatant 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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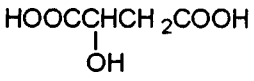
INTRODUCTION

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, Canterbery, and McEwen 2000).

CHEMISTRY

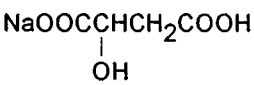
Definition and Structure

Malic Acid (CAS No. 97-67-6, Wenninger, Canterbery, and McEwen 2000; 6915-15-7, Lewis 1993a; 1993b) is the organic acid that conforms to the formula (Wenninger, Canterbery, 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, Canterbery, and McEwen 2000); Hydroxysuccinic Acid; Hydroxybutanedioic Acid (Wenninger, Canterbery, and McEwen 2000; FAO/WHO 1994; FDRL 1973a); (±)-Hydroxysuccinic Acid; Hydroxybutanedioic Acid, (±)- (US Pharmacopeial Convention, Inc. 1995); Butanedioic Acid, Hydroxy- (Wenninger, Canterbery, 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, Canterbery, and McEwen 2000):



Sodium Malate is also known as Malic Acid, Monosodium Salt (Wenninger, Canterbery, 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	Nikitakis and McEwen 1990
	128°C	Lewis 1993a; 1993b
	131–132°C	Budavari 1989
D-(+)-form	101°C	Budavari 1989
L-(−)-form	100°C	Budavari 1989
Boiling point		
DL-form	150°C (decomposes)	Lewis 1993a
D- or L-form	140°C (decomposes)	Lewis 1993a
Density		
DL-form	1.601	Lewis 1993a
D- or L-form	1.595 (20°/4°C)	Lewis 1993a
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	$[\alpha]_D - 2.3°$ (8.5 g in 100 ml water)	Budavari 1989
Ionization constants		
K_{A1}; K_{A2}	3.9×10^{-4}; 1.4×10^{-5}	Miltenberger 1989
K_1; K_2	4×10^{-4}; 9×10^{-6}	Furia 1972
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 (Wenninger, Canterbery, 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 preparations, 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)
Malic Acid		
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	
Sodium Malate		
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}C-L-Malic Acid (diluted with L-Malic Acid to a specific activity of 61 μCi/mmol) or 4-^{14}C-DL-Malic Acid (specific activity 93 μCi/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 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 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 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 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 μg, 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_{1A} litter through weaning of the F_{1B} litter, and a control group was fed untreated feed (Hazleton Laboratories, Inc. 1970). The F_{1A} 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_{1A} litter, the P_1 parents were remated to produce the F_{1B} litter, which was also culled and monitored. After 21 days, 10 male and 20 female weanlings from each group were selected for the P_2 generation. Approximately one third of the remaining pups were necropsied. The P_2 generation was

fed the appropriate diet and mated when the animals reached approximately 100 days of age to produce the F_{2A} generation, and the same procedures were followed as above. One half of the F_{2B} 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_1 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_1 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_{1A} litters, all of the necropsied pups in three of the low-dose litters had rough surfaces on the spleen. In the F_{2A} 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_1 animals died during the F_{1A} or F_{1B} phase. The P_2 test and control animals were similar throughout the study; wheezing was observed in all groups during the F_{2B} phase. In the F_{2A} 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_{2B} 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_{2B} 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_{2B} 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 μg/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^2 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 the 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^2 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 Kreb'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_{50} 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_{50} of Malic Acid given intravenously was 2.4 g/kg for rabbits, and the IP LD_{50} 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

Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

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

DATE: November 30, 2017

SUBJECT: Draft Tentative Amended Report: Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics (draft prepared for the December 4-5, 2017 CIR Expert Panel Meeting)

Identity/INCI Name Issue

At the time of the original CIR report, Sodium Malate was defined in the *Dictionary* (8th edition, 2000) as the monosodium salt. Although the structure in the current *Dictionary* monograph is still the monosodium salt, the CAS number 676-46-0 (added in 2011) is for the disodium salt. In addition, the technical name "Butanedioic acid, 2-hydroxy-, sodium salt (1:2)" has been added to the monograph and the Information Source(s) area includes the FDA Unique Ingredient Identifier (UNII) for the disodium salt, and a reference to the *Food Chemical Codex* (FCC 10;) which defines sodium DL-malate as the disodium salt (first published FCC 8).

In response to the concentration of use survey, one company reported use of Sodium Malate. After a request for clarification, the company reporting use of Sodium Malate indicates that they are using disodium malate sold for food additive purposes (updated concentration of use information attached). Among the two suppliers with trade name mixtures containing Sodium Malate registered with the Council, one reports that their mixture contains disodium malate. The other supplier, that sells a mixture that also contains Malic Acid, provided three CAS numbers that are associated with monosodium and disodium malate. The INCI Committee is still working on how the identity issue in the *Dictionary* should be resolved.

In a formulation there will be a pH dependent equilibrium between Malic Acid and its salts, and the safety profile of the two salts would not differ from Malic Acid. Therefore, we suggest that identity information (CAS, structures), and physical/chemical properties of both monosodium and disodium malate be included in the CIR report.

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Key Issues

The CIR report should state that Malic Acid included in the *Food Chemical Codex* is DL and that Malic Acid in the *USP NF* is listed as +/-.

See the 1982 JECFA specifications for information on the monosodium salt: http://www.fao.org/ag/agn/jecfa-additives/specs/Monograph1/Additive-408.pdf

CAS numbers associated with ingredients under review should be included in CIR reports.

Additional Considerations

Introduction - It is not clear to state that: "These endpoints were not included in the safety assessment...." The "endpoints" are in the safety data, the studies on fumaric acid are not included in the report.

Skin Penetration - Please state the identity of the receptor fluid.

Chronic, old report summary - Was the 50,000 ppm concentration in feed or water?

Dermal Irritation and Sensitization - Why are the HRIPTs presented before the Human Studies subheading?

Clinical Studies - What concentration of SLS was used for the positive control?

Concentration of Use by FDA Product Category – Malic Acid and Sodium Malate

Ingredient	Product Category	Maximum Concentration of Use
Malic Acid	Bath oils, tablets and salts	0.006-50%
Malic Acid	Eyeliners	0.000012%
Malic Acid	Hair conditioners	0.00025-4%
Malic Acid	Hair sprays Pump spray	 2.1%
Malic Acid	Permanent waves	0.0003%
Malic Acid	Rinses (noncoloring)	2.5%
Malic Acid	Shampoos (noncoloring)	0.00013-0.5%
Malic Acid	Tonics, dressings and other hair grooming aids	0.00013-1.9%
Malic Acid	Other hair preparations (noncoloring)	2%
Malic Acid	Hair dyes and colors	0.05%
Malic Acid	Hair rinses (coloring)	0.00015-0.01%
Malic Acid	Foundations	0.0007%
Malic Acid	Lipstick	0.0006-0.06%
Malic Acid	Nail creams and lotions	0.3%
Malic Acid	Dentifrices	0.029%
Malic Acid	Mouth washes and breath fresheners	0.55%
Malic Acid	Bath soaps and detergents	0.0085-0.95%
Malic Acid	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.005-0.15%
Malic Acid	Depilatories	1%
Malic Acid	Face and neck products Not spray	 0.001-1%
Malic Acid	Body and hand products Not spray Spray	 0.0004-0.8% 0.0011%
Malic Acid	Paste masks and mud packs	0.002-2%
Malic Acid	Skin fresheners	0.5%
Malic Acid	Other skin care preparations	0.0002-0.03%
Malic Acid	Suntan products Not spray	 0.0033-1%
Sodium Malate (disodium)	Other skin care preparations	0.02%

Information collected 2015-2016

Table prepared February 17, 2016

Updated November 27, 2017: clarification: the Sodium Malate used in other skin care preparations is disodium rather than monosodium malate

Personal Care Products Council
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Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Jay Ansell, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: January 4, 2018

SUBJECT: Tentative Amended Report: Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics

The Council respectfully submits the following comments on the tentative amended report, Safety Assessment of Malic Acid and Sodium Malate as Used in Cosmetics.

Please add the CAS numbers for these ingredients to the report. They could be added to the titles of Figures 1 and 2.

Information from the *Food Chemical Codex* for Sodium Malate (disodium salt) should be added to this report.

Chronic, old report summary - Please indicate whether the changes in body weight gain in the 104 week rat study were increases or decreases?

Clinical Studies, old report summary - What type of reactions were observed in patients with a diet high in Malic Acid?

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