Safety Assessment of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 13, 2020
Panel Meeting Date:	December 7-8, 2020

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

© Cosmetic Ingredient Review
1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.org

Cosmetic Ingredient Review

Commitment & Credibility since 1976

Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Christina L. Burnett, Senior Scientific Writer/Analyst, CIR
Date: November 13, 2020
Subject: Safety Assessment of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate as Used in Cosmetics

Enclosed is the Draft Tentative Report of the Safety Assessment of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate as Used in Cosmetics. (It is identified as *aadiac122020rep* in the pdf document.) At the September 2020 meeting, the Panel issued a second Insufficient Data Announcement (IDA) for this report. The additional data needed to determine safety were:

- 28-day dermal toxicity on Beta-Alanine Diacetic Acid
    - If positive, DART, genotoxicity, and dermal irritation and sensitization may be needed.

Since the issuance of the IDA, CIR has not received any new data. CIR staff have included the IARC report *Nitrotriacetic Acid and Its Salts* (*aadiac122020IARC*) to this report package for the Panel to review. The staff seeks guidance on what, if any, data on this structurally similar chemical to Beta-Alanine Diacetic Acid should be included in this report.

Supporting documents for this report package include a flow chart (*aadiac122020flow*), report history (*aadiac122020hist*), transcripts from the previous meeting (*aadiac122020min*), a search strategy (*aadiac122020strat*), a data profile (*aadiac122020prof*), and 2020 VCRP data (*aadiac122020fda*).

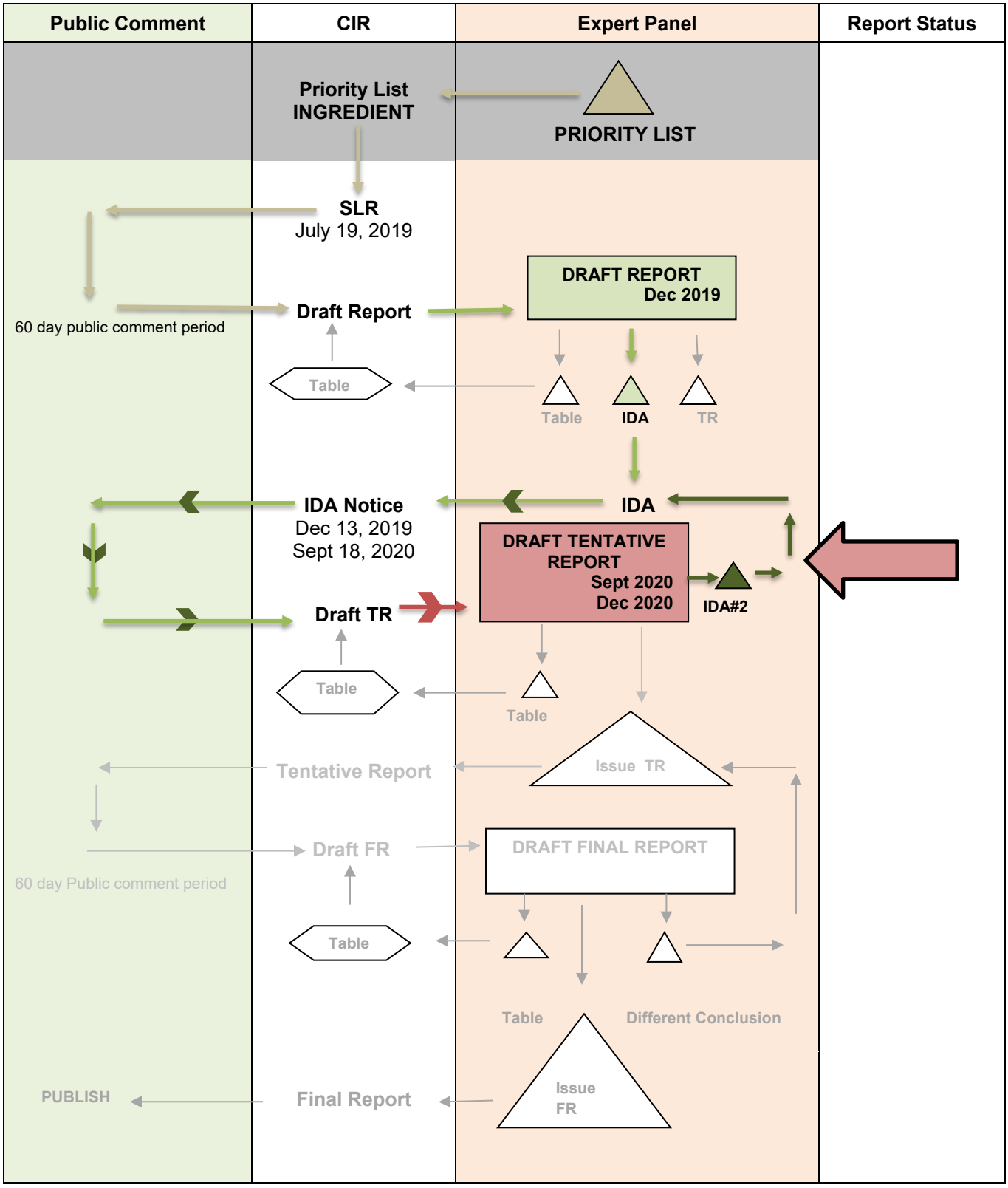
Based on the proceedings and comments from the June and September 2020 meetings, a draft Discussion has been included. The Panel should carefully consider and discuss the data (or lack thereof) and the draft Abstract and Discussion presented in this report, and issue a Tentative Report with a safe, safe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

Distributed for Comment Only -- Do Not Cite or Quote

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Amino Acid Diacetates

MEETING December 2020



Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate History

July 19, 2019 – Scientific Literature Review announced.

December 2019 - The Panel issued an Insufficient Data Announcement (IDA) for these ingredients. The additional data needed to determine safety were:

- Method of manufacturing, composition, and impurities data
- Clarification on the status of isomerization of Tetrasodium Glutamate Diacetate

February-March 2020 – CIR staff received unpublished data in response to the IDA.

September 2020 - the Panel issued a second IDA for these ingredients. The additional data needed to determine safety were:

- 28-day dermal toxicity on Beta-Alanine Diacetic Acid
  - If positive, DART, genotoxicity, and dermal irritation and sensitization may be needed.

DECEMBER 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito's Team Meeting – December 9, 2019

DR. BELSITO: Okay. Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate. We don't have method of manufacturing and impurities; however, it does not seem to be absorbed even when fed from the GI tract. We have a 90-day oral that's clean. We have a DART that's clean. We have a genotox that is clean. Can we go safe as used on this one?

DR. LIEBLER: I think we need method of manufacture and impurities.

DR. BELSITO: I just said we don't have it.

DR. LIEBLER: Oh, yeah, okay.

DR. BELSITO: We have a 90-day oral.

DR. LIEBLER: Right, right, right, right. Wait, I got that. But I thought you were saying we didn't need method of manufacture.

DR. BELSITO: I think we can go safe as used, based upon all the other information we have, is what I'm saying.

DR. EISENMANN: We don't think these two should be in the same report.

DR. BELSITO: Okay.

DR. EISENMANN: The report should just be on the material that is used, the tetrasodium glutamate, diacetate. We don't think the data on that would support the data on the other ingredients.

DR. SNYDER: We have no data on the alanines.

DR. BELSITO: Right. I understand. But I thought they were grouped because we could read across.

DR. LIEBLER: So, I think you can read across. The fact that they don't come up together in PubChem is really irrelevant.

DR. EISENMANN: But if you do that, you should add -- trisodium NTA is also in the dictionary.

DR. LIEBLER: So, this is one of the --

DR. EISENMANN: It's not used. It's a carcinogen.

DR. LIEBLER: All right. Time-out. This is one of my beefs with the way CIR works right now. And maybe with a new chemist on the panel, we can go back and fix this.

But before we sit down as a panel, or before we get reports, we should agree on the ingredients and we should agree on the read-across data sources like we do at RIFM. Because this is tremendously inefficient. I get these things -- I don't read the dictionary, so these just sprung on me at the meeting.

If that's a possibility, to include relevant members of a family -- of a plausible family in the dictionary -- then that's what we should do before we ever get a report.

DR. KLAASSEN: Yes.

DR. LIEBLER: So, if we had a way that Lisa and I, for example, could work with CIR staff, well ahead of the initial drafting of report, to agree on the families that are there, moreover, to identify the sources of data so that we can kind of prescreen what their possible read-across and data usage would be, then we can make much more efficient use of the panel's time.

Because I think that the glutamate diacetate can read across to the Beta-Alanine Diacetic Acid; and it may read across to another chemically related ingredient that's not even in this report. But I think the properties, the likely lack of absorption, likelihood of any skin effects of these would be very similar.

So, I don't know if you want to table this report, consider bringing in other ingredients that are related.

DR. EISENMANN: The thing is, trisodium NTA is not used. So, we would rather not bring it in because it not used -- it's on Annex II, because it's considered as -- with an NTP bioassay, it's considered a non-genotoxic carcinogen. It's on Annex II because they consider five percent use concentration when it's not used.

DR. LIEBLER: Um hmm.

DR. EISENMANN: And so if you lower the use concentration to one percent it would pass. They consider ten percent dermal penetration, in their opinion. It's one carbon different -- it's glycine with two acetic acid.

DR. LIEBLER: Yeah. Okay.

DR. EISENMANN: So, it's one carbon different from the beta-alanine diacetate.

So, I would hate to have you -- if you bring that in, the focus of the report will become that material. That's why I would rather just see the report on one.

DR. LIEBLER: Okay. But you just mentioned bringing it in or why -- you know, so --

DR. EISENMANN: I'd rather see the report -- our preference is just Tetrasodium Glutamate Diacetate. That's the ingredient that's used.

DR. LIEBLER: Okay, I have no objection to that. We simply get this at a point where, here are two ingredients in a report we are evaluating. And barring any other considerations, I think that you could certainly read across the safety data from the Tetrasodium Glutamate Diacetate to the beta-alanine, or vice versa, whichever one we have the data on.

And that's what is literally just presented to us. This background is not available to us.

DR. SNYDER: I agree with Dan, these are amino acid diacetates. And so the ingredients that fall underneath that should be able to be read across. A tetrasodium acetate is not a diacetate, so I don't think it's -- right, I mean, it wouldn't be appropriate to lump that one.

DR. BELSITO: We're looking at tetrasodium diacetate, glutamate diacetate.

DR. SNYDER: Triacetate, I mean. It's a trisodium, right? Triacetate is the outlier. It's not in the report, that's the carcinogen.

DR. BELSITO: Right, okay.

DR. EISENMANN: It's glycine with two -- I mean, it's -- here, this is the structures of these two. Beta-alanine, there's one carbon difference. This is nitrilotriacetic acid.

DR. SNYDER: Okay.

DR. KLAASSEN: So, going back to Dan's original comment, I would just like to second that -- and I've thought this for a long time, is that -- and especially now. It would be a good time to make this transition that the two so-called chemists, together, with the staff here help decide which chemicals should be within a report, rather than after we get the report.

But now we can go to the specific one and argue about it some more, I guess.

DR. LIEBLER: I don't care if there are two ingredients in this report or if there is one ingredient in this report for which we have data. And, I mean I really don't care. I think the rationale that was presented in the memo didn't

fully convey to me the sources of your concern. But I thought their argument what appeared together and what -- it didn't appear, I thought that was kind of not really determinative for me. So, I don't know what we do at this point.

We have two ingredients in this report. I can't exclude one ingredient based on chemical dissimilarity or any similar ground. If we want to table this report or just not review it, and have it go back and have a decision made at a level that's outside of what the expert panel is charged with, then that decision needs to be made.

DR. BELSITO: But Carol, why do you want to get rid of Beta-Alanine Diacetic Acid if you just heard from Dan that he can read across?

DR. EISENMANN: Well, you can't find any suppliers for it. It has very little use, 2); and then there's another mater- -- like I said, there is another -- and we would like the focus to be on the material that is used. Because there is another material --

DR. BELSITO: Right, that you could add in, that has potential issues with it, so you would prefer not to begin adding in and give a reason --

DR. EISENMANN: Well and it's not used. I mean, if it was used --

DR. BELSITO: Fine, then let's drop it and let's just do Tetrasodium Glutamate Diacetate. Are you okay with that, Dan?

DR. LIEBLER: Sure.

DR. BELSITO: Okay. If we do that, my question to you is, why do you feel we need manufacturing and impurities if we have data that there is no GI absorption, that the 90-day oral is fine, the DART is negative, the genotox is negative? Why do we need impurities? That would have been picked up -- any significant impurities would have been picked up with that data, no?

DR. LIEBLER: I think it's a bad precedent for us to punt on manufacture and impurities. We don't need -- we usually don't get, and we don't necessarily need in-depth descriptions. But we at least need a -- no more than cursory description of method of manufacture for this.

DR. BELSITO: Okay. So, you're just operating on protocol?

DR. LIEBLER: On protocol, plus if we start backing off on that, we're going to start having problems with a lot of other ingredients.

DR. BELSITO: Okay. So, insufficient for manufacturing and impurities.

DR. LIEBLER: Yep.

DR. BELSITO: Can we move on?

MS. FIUME: Can I please comment? I feel I'd being doing Bart a huge disservice if I don't.

DR. BELSITO: Yes.

MS. FIUME: So, as far as what we include, we so look forward to the panel members being more involved in looking at it, looking at the read-across. But Bart does develop a priority list a year --- by June it's finalized. It comes out in the first meeting of each year of what the ingredients are. And we asked for comments on that list, twice.

Because at that point, after that, then it does go into writer time of searching the ingredients, you know, preparing the report. So, the purview of the panel is fine; if you want to remove that ingredient, that's fine. As far as having zero uses or no suppliers, we've never used that as a reason before to remove an ingredient from a grouping. It either goes read-across or it is insufficient data.

So, I did just want to go on the record of stating, that we do ask for the information at least six months ahead of time before we start working on it. And I understand that the panel doesn't have the time to look at it. But that does go out twice for comments. So, whatever the panel decides is fine, but I did just want to go on the record with that.

DR. LIEBLER: So, this is the exception -- maybe the exception that proves the rule. So, most of the time the priorities translate to these reports and no problems.

But this is an example of one where I don't remember what was on the priorities list honestly. That's usually not a major focus of our bandwidth in these meetings anyhow. But I don't remember if this had three molecules or just the two.

MS. FIUME: It was just the two.

DR. LIEBLER: And, I thought that we could read across for every endpoint for the beta-alanine -- from the glutamate diacetate to the beta-alanine. Even though there are no uses, the ADME, such as it is, the --

DR. BELSITO: Well, you did your role, Dan. You know, it's PC/PC. You should have stepped in and say, no, we want this other chemical dropped for these reasons. I mean, we did what we were supposed to do.

DR. SNYDER: We use our expertise to know if there is anything in the public information to be concerned about. And number two is, we go based on concentration of use and frequency of use, and that's it. I mean, we don't really -- I never look at --

DR. BELSITO: If someone had said, there's another one we can bring in but that's going to bring in a whole lot of issues, so, ban the -- the second one, there are no uses, so why don't we just go with this chemical alone, we probably would have said yes.

But I don't think you -- I mean, quite honestly, for this, since there is no literature on it, you didn't waste a whole lot of time, it was just a computer search.

MS. FIUME: It was. But sometimes searching for ingredients that have no information is more time consuming than searching for those that do have information, to see if you're missing something.

DR. BELSITO: Yeah, I understand. Because you keep looking. Yeah. Yeah. I agree.

In the future, the panel will look, and our chemists will decide whether the groupings seem adequate. But if for some reason, the council or someone has knowledge that they don't want to -- that there are either materials that could be grouped and they want things dropped out, please do that at the stage where we are looking at priorities.

MS. FIUME: That's all we were trying to say. Thank you.

DR. SNYDER: Certainly in this instance, it would have been nice to know about the trisodium NTA issue in considering lumping these other two together.

DR. BELSITO: Right.

DR. SNYDER: Because I agree with Carol, there is some uncomfortableness with knowing that a subtle difference causes a much more significant toxicity.

DR. EISENMANN: But until I read the report, I don't know --

DR. LIEBLER: Right.

DR. EISENMANN: -- so, there's got to be some room for an interim process. Because when we were working on the priority list, I knew nothing about these materials, until I started reading this.

DR. SNYDER: Right.

DR. LIEBLER: So, we keep plenty of ingredients in our reports that have no uses. And to suddenly turn around today and drop this one because it has no uses seems, to me, to be the wrong approach.

DR. EISENMANN: Well, that wasn't the reason to drop it. The reason to drop it was because we had a -- I did get extra -- I asked CIR SSC their opinion, and they didn't think it was appropriate to read across for those two ingredients. And that was the main reason to drop it.

DR. LIEBLER: They just didn't agree with the read across?

DR. EISENMANN: Correct.

DR. LIEBLER: And it was because of the other one, that's not listed here, is a non-genotoxic carcinogen. And we thought if that structure which looks so similar to these could be a non-genotoxic carcinogen, then how can you be comfortable in reading across?

DR. EISENMANN: I think there is a --

DR. LIEBLER: Is that the reasoning?

DR. EISENMANN: I think there's a difference in kinetics. Neither one are absorbed very well, but the smaller one has a greater potential for being absorbed. And they also -- there's a difference in chirality and there's the difference in --

DR. BELSITO: Maybe we can have this discussion tomorrow morning because we are only through four materials. And if we keep this going --

DR. SNYDER: You are only through four materials.

DR. BELSITO: No, we are only through four materials. So, can we move on to the naphthalene sulfonates and see what the other team has to say?

DR. SNYDER: Sure.

Marks' Team Minutes – December 9, 2019

DR. MARKS: Amino Acid Diacetate. Let's see here. So this is the first review of these two ingredients, the Beta-Alanine Diacetate Acid and Tetrasodium Glutamate Diacetate. As I always do first, Ron, Tom, and Lisa, chemically, are these okay to group together?

DR. SLAGA: Yes.

DR. PETERSON: I think so, yeah.

DR. MARKS: Okay. And then, next is what comments that you have? As a background, the CIR issued safe for amino acids in the past. Does the diacetate portion of these molecules change the safety? There was irritation and then sensitization was okay for the Tetrasodium. Can we read across to the Beta-Alanine?

And then, needs, I didn't see either on this or -- there wasn't a Wave 2. We don't have any method of manufacture for impurities, composition. So, that alone would indicate we have an insufficient data announcement.

But Ron, you're smiling. I'll let you comment. I know if we say we don't need them, we'll have a conversation tomorrow with the other team.

DR. SHANK: Right. I don't need it. I think the only question I had was on sensitization. The guinea pig maximization test was at maximum use concentration of 1 percent, but the HRIPT was not. So, is the guinea pig enough?

DR. MARKS: I think so. I think, because that's an alert, is it a sensitizer or not? And that came up negative. And then the HRIPT just confirmed that. And actually, in the guinea pig I had, it was at 75 percent. So, it's a really big-time concentration with the Tetrasodium and the use concentration was 1 percent. So, I thought that was also very reassuring.

DR. SHANK: Okay.

DR. MARKS: You're absolutely right. The HRIPT was at one-fifth the use concentration, 0.2 percent. But I thought weighing, particularly, the guinea pig without having an alert at such a high concentration, I was fine with that. My concern was, can we read across?

DR. SHANK: Yeah, I thought we could.

DR. MARKS: Okay, that's fine.

DR. SHANK: But, I defer to the chemists.

DR. MARKS: And I guess we could do the -- what was that in the read-across document? The protein --

DR. SHANK: Protein bindings?

DR. MARKS: Yeah, protein binding alert. But we don't have that data, so we can't say --

DR. SHANK: Right.

DR. ANSELL: We have an opinion.

DR. MARKS: Okay.

DR. LORETZ: We don't like the two grouped together.

DR. MARKS: Well, see, that's why I asked that question right in the beginning. I'm sorry I didn't -- you could've spoken up right then and there.

DR. LORETZ: I think Carol had put it in a memo. But for example, one of the chemists that we consulted with called out differences in chirality -- if I'm saying that right. Different amino acids, different chelation function, and different metabolites.

DR. ANSELL: So, they don't believe that the two should be treated together. That all of the data is on the Tetrasodium Glutamate Diacetate?

DR. MARKS: Yeah.

DR. ANSELL: That there's no uses -- well, there's two uses without a concentration or suppliers for the Beta-Alanine Diacetate. And so, we're carrying it along with no data and an opinion from at least one person that the differences are too great to join together in a sense.

DR. SHANK: The difference between Alanine and Glutamate?

DR. PETERSON: There's a conditional methylene and a carboxylic acid, and they look pretty similar.

DR. ANSELL: They do.

DR. MARKS: Well, good to Lisa, because I was going to ask Bart, why'd you put these together? And then, obviously, Lisa's answered that. They look pretty similar.

DR. HELDRETH: So we, a few years back, reviewed all of the amino acids together.

DR. MARKS: Right. Yes. I had actually referred to that; and had a safe conclusion.

DR. HELDRETH: I understand if we can show that these have some different metabolism, or react differently in the body, okay, then we don't read across from one to the other. But this grouping we put together in priority lists and presented for review at least more than a year ago.

DR. ANSELL: These pictures are not the two pictures of the materials we're reviewing. These pictures do look a lot alike, but this is nitrilotriacetic acid and --

DR. HELDRETH: Those aren't the pictures that we have in our report.

DR. PETERSON: Yeah, not in the report. I think they're looking at something else.

DR. SHANK: You're looking at nitriloacetic acid?

DR. PETERSON: That would be a different one.

DR. HELDRETH: Those are read across constituents proposed by ECHA for the Glycerin Ethoxylates report.

DR. ANSELL: Oh, okay. This is not -- this was just from -- not my comment, the one that was shared with you guys.

DR. LORETZ: Well, the point was brought up that nitrilotriacetic acid was actually closer to Beta-Alanine Diacetic Acid. It's also in the dictionary.

And when we bring it in, you're going to have to bring in NTP bioassays, and it has got a positive bioassay, et cetera.

So, it just complicates the situation without adding anything to things that are -- have any real uses.

DR. SHANK: I can understand that.

MS. BURNETT: We don't have to bring them in. They're not in the report.

DR. SHANK: To me, it's using the glutamate with salt to read across to the alanine diacetate.

DR. MARKS: And you don't have a problem?

DR. SHANK: It's not a big jump for me.

DR. MARKS: Okay. So, we're back to, yes, we still like these two ingredients together, team, I gather. And Lisa, you feel the same way?

DR. PETERSON: Yep.

DR. MARKS: Then I think the key here is getting the -- it would be an insufficient data announcement if we need the method of manufacturer, impurities/composition.

DR. SHANK: Right.

DR. MARKS: And Ron, you aren't concerned with that, but I know that's going to come up tomorrow.

DR. SHANK: It will.

DR. MARKS: So, if it's okay with you, I'll move that we have an insufficient data announcement for those needs. And then, if you want to comment, you may. I know Dan Liebler is a stickler for it. I don't think that --

DR. SHANK: Yes. It'll be interesting if you say that.

DR. MARKS: If I say what?

DR. SHANK: That there's -- insufficient and a need for method of manufacture and impurity, and they say, oh, no, we don't need that. And then, I'm going to speak up.

DR. MARKS: Okay. Sounds good.

DR. PETERSON: And I would second whatever you say. I think we need to know that.

MS. BURNETT: And I already know what they want, so --

DR. MARKS: Pardon, Lisa? I didn't hear that, Lisa.

DR. PETERSON: I said I would second that. I agree that you need to know how they're made. and what the impurities are.

DR. MARKS: Okay. Okay. Good. And otherwise, everything else with these, we decided we couldn't read across. So, the sense -- and Jay duly noted in the beta-alanine spreadsheet -- well, we don't have anything up top there for that. It's all a read-across from the tetrasodium, from the glutamate. But that's fine. We feel that's okay. Okay?

Any other -- so, I'll move tomorrow insufficient data announcement, needs method of manufacture, impurities, and that's it. Anything else there? Okay.

Just a question again from me, from a toxicity point of view; since all these amino acids were found to be safe, just diacetating it, does that change anything dramatically? Or is it reassuring that all the amino acids -- you know, are these easily split?

DR. SHANK: We have a lot of toxicity data.

DR. SLAGA: Yeah, we have --

DR. MARKS: Yeah, and don't really need that.

DR. SHANK: Right.

DR. MARKS: Yeah.

DR. SHANK: It was all negative.

DR. MARKS: Yeah. Okay.

DR. PETERSON: Acetate's only activated if there's an unsaturation within the molecule that's set up appropriately next to the attributes. So, otherwise, it'd be unusual to see.

DR. MARKS: Okay. Let me save this.

Okay. Re-review summary, so we're in the Admin folder. And probably, since we're in the Admin folder, I might do these two re-reviews right at the same time, even though it's a little bit out of order.

Full Team Meeting – December 10, 2019

DR. MARKS: So, this is the first review of these two ingredients, the Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate. We actually had a lot of data, but we were missing method of manufacture and impurities. So, our team moves that we have an insufficient data announcement for those data needs.

DR. BELSITO: Second.

DR. BERGFELD: Any further discussion? Comment? Don?

DR. BELSITO: Go ahead, Jim.

DR. MARKS: No, I was just going to say we have little or nothing on the Beta-Alanine Diacetic Acid, but we thought we could read across from the tetrasodium, which we have lots of data on. Just a sort of heads-up once we get the insufficient data.

DR. LIEBLER: One question that I had that we didn't talk about yesterday during the meeting, but it occurred to me. Might have been chatting with somebody yesterday afternoon or evening.

But, the Tetrasodium Glutamate Diacetate in the structure depicted in the chemistry section on PDF 9, actually shows a structure that specifies a stereoisomer. And, what I wanted to know is this limited to one stereoisomer, or is it racemic? What is the stereochemical nature of the product?

So, we should just check and see, maybe Council can let us know just so we can be clear on that. Otherwise, if there's not an isomer specified the structure should be changed to not indicate one.

DR. BERGFELD: Don?

DR. BELSITO: There was also a discussion as to whether to drop Beta-Alanine Diacetic Acid from the report, and that was brought up by Council. And we felt that there was no need to drop it, that we could adequately read across.

DR. MARKS: Our team concurs; we also had a similar discussion whether chemically it was similar enough.

DR. BERGFELD: No other comments? Call the question on the IDA for amino acid diacetate. Okay, approved unanimously.

SEPTEMBER 2020 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito's Team Meeting – September 14, 2020

DR. BELSITO: So now we're moving on to amino acid diacetates. So these are two ingredients that we have issued an IDA for method of manufacture, composition, impurities, and clarification on isomerization of tetrasodium glutamate diacetate. And we received unpublished data on the tetrasodium for manufacture, composition, impurities, and information on racemization, and updated use information. So the question is whether that information is satisfactory.

DR. LIEBLER: Yes, it is in my opinion.

DR. SNYDER: I agree.

DR. KLAASSEN: Yes.

DR. BELSITO: Okay. I don't know what's happening with my computer here. It's extraordinarily slow. Yeah. I have safe as used. We have the Personal Care Product Councils that it's the L-isomer only and we have the information about the racemization. The only question I had to the team was this nitrilotriacetic acid as an impurity. Is that problematic? This is PDF page 20.

DR. LIEBLER: I'm not sure. I'm not sure of the amount and mode of action.

DR. BELSITO: Well, it's 0.15 percent.

DR. LIEBLER: Yeah. I understand that. But….

DR. EISENMANN: This is Carol. This is the material that we were suggesting last time you'd consider adding to the report because it's structurally very similar. It's one carbon difference from the beta-alanine diacetate. So it's another chelator. It has the same mode of action. So if you think the diacetate is safe based on the tetra-glutamate then you must also consider the NTA also safe. So it's the same -- it's -- we sort of had the discussion at the last meeting.

DR. BELSITO: Okay. I thought it was fine. I just wanted to point that out because I'm not familiar with nitrilotriacetic acid.

DR. EISENMANN: As far as I understand, it's glycine with two acetic acids on it. It's just named differently.

DR. LIEBLER: That's correct.

DR. BELSITO: Okay. So safe as used. Anything to add to the discussion? We can use the draft discussion. I had nothing to add.

DR. LIEBLER: I didn't either.

MS. BURNETT: And this is safe as used for both ingredients, correct?

DR. SNYDER: Correct.

MS. BURNETT: You're reading across to the other one?

DR. SNYDER: Yes.

Marks' Team Meeting – September 14, 2020

DR. MARKS: We'll move on to the amino acid diacetates. So Christina has sent us a draft tentative report. So recall on December of last year, the Panel issued an insufficient data announcement, and the needs were method of manufacture --

DR. SHANK: Oh, no.

DR. MARKS: I heard you say "Oh, no," Ron.

DR. SHANK: I thought I had fixed this. I'll dial in again on the telephone.

DR. MARKS: Okay. I'll hold, Ron, for a minute.

(Pause)

DR. MARKS: Good. I see Ron gave the thumbs up. I've got a comment, Lisa. You have the best -- I think your phone is close to the computer. Okay. Ron.

DR. PETERSON: He just needs to --

DR. COHEN: He has to mute his computer.

DR. HELDRETH: Yeah. I just did that. That's why it stopped. We should be good now.

DR. MARKS: I was going to say, Lisa, you have the most glamourous headphones I've ever seen.

DR. PETERSON: They're gamer headphones.

DR. MARKS: Any rate, so let's get back to the beta-alanine diacetic acid and the tetrasodium. Man, I'm having difficulty pronouncing these -- glutamate diacetate. Any rate, the two needs, method of manufacture and composition and impurities, we did get data since the insufficient data announcement was made last December -- and then clarification of the status of isomerization, and we got a memo from Alex indicating it was the L isomer. So I guess -- so Lisa, Ron, Tom, do we have enough data to move on to a safe report?

DR. PETERSON: So I had --

DR. SLAGA: That's what I had.

DR. PETERSON: Yeah. I basically do too, but I wanted to revisit something if that's possible.

DR. MARKS: Oh, even after it's finalized, it's always possible to go back and reopen an ingredient. So no problem.

DR. PETERSON: I think I agree with the recommendation by the PCPC to drop the beta-alanine diacetic. Because the more I thought about it, it actually is more -- it's also structurally similar to the chemical that is carcinogenic. And I'm looking for the name of that, and I can't find it. I guess it has -- is the triacetate.

To me, if one is going to worry about it -- and plus, there isn't -- I'm sorry. I was going to outline my rationale, and I ran out of time. There isn't a lot of -- where's the use? I guess I just felt uncomfortable with saying that it fit more -- was structurally similar to the glutamate diacetate and different from the triacetate. But actually, it's somewhat more different from the glutamate diacetate than it is from the triacetate version of the molecule. So I actually support -- if I haven't confused you completely, I support dropping the beta-alanine diacetate from this report for those reasons.

And I also think that -- I have to find the tables. You're missing a lot of information on the alanine diacetate. So I guess for that reason and then -- let me go one more place. There's only two uses for the beta-alanine acetate, too. I don't know if that plays into it, but I was a little -- the more I thought about it the more uncomfortable I got with saying, well, this is really more like this one that has four carboxylic acids than the other one that has the triacetate which has three, which is more similar to the alanine version of it.

And I ran out of time to look up the mechanism of the triacetate, but I guess I was uncomfortable saying that using the glutamate diacetate as an analog for the alanine diacetate because of the difference in the carboxylic -- an additional carboxylic acid. So I'm sorry this was muddled. I meant to --

DR. MARKS: No, so if I hear you right, Lisa, you're saying it's safe for the tetrasodium glutamate diacetate, but you're hesitant about reading across to the beta-alanine diacetic acid. Is that correct?

DR. PETERSON: Yeah. That's correct.

DR. MARKS: So then, I think the question is do we include the beta-alanine diacetic acid and say insufficient, or do we drop it? And I think that's -- oftentimes, that's why I ask are all the ingredients okay. Is this chemically so dissimilar that we shouldn't include it? We can include it, but just put an insufficient conclusion. But I'll let Tom and Ron weigh in on that.

DR. SLAGA: I would rather leave it in than put insufficient for it.

DR. SHANK: Let's see what happens.

DR. SLAGA: It's still a draft tentative report.

DR. BERGFELD: No, it's a tentative report.

DR. MARKS: Yeah. It would go out as a tentative report, and I guess we could say, well, we're now saying insufficient. Should it still go out as a draft tentative report with 60-day notice before we actually issue a tentative report, since changing the beta-alanine to insufficient -- should we give outside input another 60 days? So Bart, if we did suggest going insufficient for the beta-alanine, should it go out again as an amended -- or go out again as a draft tentative report?

DR. HELDRETH: So since this is a new report, not a rereview, the Panel has the prerogative to do one of two things. They could issue a tentative report with that conclusion, and it'll get a 60-day comment period. And it'll come back to the Panel in a future meeting, likely December or spring of 2021. And at that time, the Panel can take a look at the discussion and the conclusion and make sure it still fits what they're thinking. However, you could also -- since it seems that the data needs now are somewhat new, we're now basically wanting probably all of the information -- all of the tox information for this particular ingredient now that we're not considering it similar to the glutamate diacetate. Since it's a new data request, you could issue a new IDA.

DR. ANSELL: We would point out that it's a little more confused because, at the last meeting, you concluded that the data on one was sufficient to support both. Now, we're concluding -- correctly as the PCPC argued at the last meeting -- that they should not be in a single family. If you conclude that, then one would argue why we are looking at it since it was only included because it can rely on the first.

DR. MARKS: So that gets back to just dropping it as you suggested, Lisa. Tom, you said insufficient. Ron Shank?

DR. SHANK: Well, I based it on the read across. If we can't do read across, then it's insufficient for the beta-alanine diacetic acid. There are only two uses and no reported concentrations. So if we can't read across, then one would be insufficient: the beta-alanine diacetic acid. And the tetrasodium glutamate diacetate would be safe as used, so it would be a split conclusion.

DR. MARKS: Okay. So it looks like we're at -- at least our team, that we would issue a tentative report with a split conclusion: safe for the tetrasodium and insufficient for the beta-alanine. And we need all the tox for the beta-alanine.

DR. SHANK: Yes, yes.

DR. MARKS: Because we don't have anything at this point.

DR. SHANK: Correct.

DR. MARKS: And we've decided we can't read across. Okay. I think that's -- let me see. I'll be seconding tomorrow. We'll see what the Belsito team feels. Lisa, I'll probably ask you to comment because you really felt uncomfortable reading across because it was chemically different.

DR. PETERSON: I mean, it has the additional carboxylic acid, which could change things. And so I'll try -- I'll be more succinct and hopefully linear tomorrow.

DR. MARKS: Oh, yeah. No problem. I think you got your point across very well, Lisa, because our team now is supporting a split conclusion. Jay, I heard your comments. You wouldn't even include the beta-alanine in this report. You would have it as a single ingredient, just the tetrasodium.

DR. ANSELL: Right. I think the beta-alanine was only included because, at the last meeting, it was concluded that it was structurally similar enough to rely on the data of the TGD. But now that we've decided that it isn't supported, I think we would have to go back to first principles on it. Have we done a review on that material and related materials? What's out there? Request the industry. So I really don't want to see us vote to stop the review of the safe material while we resolve the issues on the beta-alanine diacetate.

DR. MARKS: So if we issue a tentative report with that conclusion, the split conclusion, that wouldn't delay it, Jay. That would move it forward. Okay.

DR. COHEN: Jim?

DR. MARKS: Yeah. David?

DR. COHEN: Just one quick question procedurally. You're at this impasse here. What is the committee allowed to do? Are they allowed to split the two and finalize one and put one for completely new review afterwards even though it's come to the committee as a pair?

DR. MARKS: No, the only way that would happen is if there're two separate reports, and that's why I was asking Lisa, Tom, and Ron whether or not you want to just drop the beta-alanine and do just what you suggest. Take that up again in the future versus keeping it together as a tentative report. You were going to say something, Lisa?

DR. PETERSON: Yeah. So I guess this is for my learning purposes because this is essentially -- you know, when we discussed this the last time it was the December meeting, right? And that was my first meeting, and this is

effectively my third meeting. And so that I understand -- so I would agree in some ways you could -- when you're trying to decide who to review together and who to review separate, I would say that for me I'm comfortable reviewing them together because they're structurally related. What I'm uncomfortable with is the read across because of the additional -- the structural differences.

So I don't know how this group generally thinks about these things when -- it's like with the red algae. You've got so many different things, but yet you're pulling it together. But then you determine which ones you can read across and which ones you can't. So I kind of put this in a similar category. It's like, oh, yeah. It seems like they should be grouped together, but I'm not sure I'm comfortable without some data saying that you could read across everywhere because basically in this report, you're being asked to read across everywhere because the only thing you have for this compound, I think, is method of manufacture.

You don't have anything else. You don't have any toxicity. You don't have anything. It's all -- so that's why I'm uncomfortable with the read across. I'm okay with them being together. I'm just uncomfortable with the read across.

DR. MARKS: No, that sounds good, Lisa. And that's very clear. And depending on how the discussion goes tomorrow after the Belsito team presents their motion, I may call on you, Lisa, and I think just how you summarized it then is very clear. Since December was your first meeting, we can blame the grouping of these two on Dan.

DR. PETERSON: Well, I agreed with it at the time. But again, I wasn't 100 percent sure what I was agreeing to. I was agreeing that I do think it makes sense to group them. But if you're going to read across toxicity without something that says, yeah, they're basically the same, it's also very similar to this chemical that's a carcinogen -- that's got a lot of problems. So --

DR. MARKS: Yeah. That's --

DR. PETERSON: -- I got to thinking, well, I don't know how you can -- it's so close that you can't really make a judgement. So therefore, I don't believe you can read across.

DR. MARKS: And then, Lisa, you were fine with the memo from Alex that the tetrasodium is the L-isomer because Dan brought that up at the meeting?

DR. PETERSON: Well, if she says that it's the L -- I mean, I think I agreed with her -- what was laid out in the memo that mostly it's the L-isomer. There is a circumstance under which it can undergo isomerization, but it's the L-isomer. So I think that her recommendation's for how it gets presented are appropriate.

DR. MARKS: Okay. Well, good. So tomorrow I'll second presumably a tentative report in which the Belsito team is concluding that it's safe for the tetrasodium but insufficient for the beta-alanine because we can't read across. And our needs are essentially the whole panel of toxic endpoints. Sound good, team?

DR. PETERSON: Yes.

DR. BERGFELD: Sounds good.

Full Team Meeting – September 15, 2020

DR. BELSITO: Yeah, so, at the December 2019 meeting we issued an IDA for the two ingredients. We wanted method of manufacturing, composition, impurities, and clarification on the status of isomerization of the Tetrasodium Glutamate Diacetate. We obtain those in particular from the Personal Care Products Council, and we therefore felt we could go with a safe as used for these two ingredients.

DR. BERGFELD: Thank you. Dr. Marks, do you have a comment?

DR. MARKS: Yes. Lisa yesterday threw a zinger at us, and we felt also we could go safe for the Tetrasodium. But we didn't think -- and, Lisa, I'll let you clarify -- that we could read across to the Beta-Alanine, so insufficient for the Beta-Alanine. And, we needed all the toxicity studies for that. So, Lisa, do you want to clarify or expound upon that?

DR. PETERSON: Sure. So, the issue has to do with its chemical similarity to the Tetrasodium Nitrilotriacetic, which has carcinogenic properties and the absence of any toxicity data for the Beta-Alanine Diacetate. So, if you look at it chemically, actually you could argue that the Beta-Alanine Diacetate is closer in structure to the tri-nitrilotriacetic, the carcinogenic compound. It's almost as close to that as it is to the Glutatmate Diacetate. The Glutatmate Diacetate has an extra carboxylic acid, so that it could be different.

And, the fact of the matter is, there is no toxicology data for the Beta-Alanine one, so that I am uncomfortable reading across for that compound. Because you would want at least one piece of data that shows that the Beta-Alanine is different from the NTA, the carcinogenic one. And, there's no data that says you can exclude, so I'm very uncomfortable doing a read across about the safety because there is only a methylene difference between the carcinogenic and the Beta-Alanine one. And there are two carboxylic -- you know, there's an extra carboxylic acid in the safe compound, so.

Again, if there had been some safety information that would allow you to confirm that reading across were a good idea -- you know, just being on the safe side of things, I would not be comfortable reading across. So, that's why we came up -- it belongs together because they are structurally related, but I'm uncomfortable reading across from a toxicity point of view for the reasons I stated.

DR. MARKS: So, we had a split conclusion, safe for the Trisodium, insufficient for the Beta-Alanine.

DR. BERGFELD: Dan, do you want to comment?

DR. LIEBLER: I think it's a reasonable concern, Lisa. And, I'm wondering what do we know about the mechanism of NTA carcinogenicity.

DR. PETERSON: I knew you were going to ask.

DR. LIEBLER: Any species specificities that would inform our thinking here?

DR. PETERSON: You know, I knew you were going to ask that question, and I taught two classes after we met yesterday so I did not follow up on that.

DR. LIEBLER: Carol has a hand up I see.

DR. EISENMANN: What I read is that the mechanism has to do with the chelation, that at high doses the zinc goes away and then that is why it's carcinogenic.

DR. SNYDER: It's nephrotoxic, when it loses chelating properties.

DR. LIEBLER: So, I think we can speculate about whether Beta-Alanine Diacetic Acid should or shouldn't be carcinogenic by analogy to NTA. And NTA may be one of these either nutrient depravation stories or a chronic toxicity story. Is this kidney carcinogenicity, by the way? Does anybody know?

DR. SNYDER: Yes, it's primary kidney. It does cause adrenal tumors in females and liver tumors in males also. But it's primarily the nephrotoxicity that results in renal tumors and some bladder tumors.

DR. BELSITO: And, what's the basis of that, Paul.

DR. SNYDER: I do not know. I just know that it's nephrotoxic and so therefore cause increase proliferation and turnover of the epithelium of the tubules and of the urinary bladder for the kidney.

DR. SHANK: It's not genotoxic.

DR. LIEBLER: Yeah, right. I was going to say, it looks like it's one of these sort of non-genotoxic carcinogen stories that are often mechanistically difficult to pull apart.

DR. SLAGA: Right, and generally, not a high percentage of animals get it.

DR. LIEBLER: Yeah. I think I agree with Lisa on this. And, you know, we've only got two uses for this. So, we're unlikely to get much in the way of data unfortunately to resolve this. But that doesn't prevent us from making the point and asking for it.

DR. SNYDER: I do believe that the NTA is genotoxic. We'll need to verify that, but I believe it is genotoxic.

DR. PETERSON: Yeah, I apologize. I was going to look all this up last night and I just ran out of time. And, I'm not finding it in a quick way on the internet. But, you know, I just think that it's better to error on the side of caution. I don't have a huge concern, but it's just there is no data. And, to read across on a structurally slightly different one, even though, you know, you can even argue that you're not that concerned if it was even the triacetate version. But I just --

DR. LIEBLER: This is a tentative, so it's in early stage. We go insufficient on this for tox data or carcinogenicity data for Beta-Alanine Diacetate. We'll either get it or we don't. We'll also have had a chance to do a little bit more homework collectively on this, and then come back to it next time we see the report.

DR. BELSITO: So, what would you need? I mean, looking at this from a chemist standpoint, what is the absorption likely to be? I mean, if we had a 28-day dermal and there was no absorption, would that just clear it? I mean, what do we need to clear this?

DR. SLAGA: Well, I would think that we would need Ames testing on mutagenicity. It could be genotoxic, but a lot of the non-mutagenic ones will bring about some genotoxic effects that are not really mutagenic. They're just a change in gene expression.

DR. BELSITO: Okay, so if we're going to go insufficient, I think we need to say what we need. So, we're asking for Ames, are we asking for mammalian, are we asking for 28-day dermal? Where are we with this?

DR. PETERSON: Well, I think, one of the things you want to establish is that it doesn't absorb, right?

DR. BELSITO: Right.

DR. PETERSON: So, that is one thing. And then, you know, if there is some kind of information about genotoxicity or -- you know, I guess I would like to have -- you would need to do a search on what's with a triacetate that gives it an alert. And then decide, you know, there's something in there that sort of can eliminate this concern from the chemical completely. So, maybe it's genotox.

DR. BERGFELD: Carol Eisenmann, wants to speak. Carol?

DR. EISENMANN: I was just wondering if you need to see a review of the NTA data.

DR. PETERSON: Yeah, that would be helpful, actually. Yeah, totally, that might help.

DR. BELSITO: So, are we going insufficient, or are we tabling this to look at the NTA data?

DR. HELDRETH: My suggestion would be since this is a new need that the Panel would issue an IDA.

DR. PETERSON: And just see what we get, and hope we get something.

DR. BERGFELD: So, Don, you'll have to restate your motion if you're agreeing.

DR. SNYDER: So, Don, my suggestion is we go with an insufficient data announcement. Ask for a 28-day dermal and depending upon what the dermal looks like and then ask to look -- we can also look at the profile of the NTA. And then depending upon what the absorption -- because if it's not absorbed, and it's not metabolized that's a moot

point. We don't need a genotox or anything. So, I think we just do our standard 28-day dermal. If absorbed, then we'll want the other toxicological endpoints including genotox, mammalian, Ames, etcetera.

DR. BELSITO: Yeah, that's where I would go. And a request to review the NTA report.

DR. BERGFELD: Okay. Jim, you're going to second that?

DR. MARKS: Second.

DR. BERGFELD: Yeah. Any other discussion we need to have before we vote on this? Don, you're okay?

DR. BELSITO: I'm fine.

DR. BERGFELD: Okay. We'll move the point. All those against the IDA on this ingredient, please indicate by stating your name. Hearing nothing I'll assume a unanimous support of the IDA request and statement.

Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate, December 2020 – Christina Burnett

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

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

Amino Acid Diacetates

Ingredient	CAS #	InfoBase	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	FEMA	Web
Beta-Alanine Diacetic Acid	6245-75-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√
Tetrasodium Glutamate Diacetate	51981-21-6	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√	√

Search Strategy

PubMed

"Beta-Alanine Diacetic Acid" – 8 hits, 0 relevant
"6245-75-6" – 0 hits
"N-(2-Carboxyethyl)iminodiacetic Acid" – 4 hits, 0 relevant
"Alanine, N,N-bis(carboxymethyl)" - 1 hit, 0 relevant

"Tetrasodium Glutamate Diacetate" – 0 hits
"51981-21-6" – 0 hits
"L-Glutamic acid, N,N-Bis(Carboxymethyl)-, Tetrasodium Salt" – 0 hits

Search updated October 2020.

LINKS

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

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

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

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
the Research Institute for Fragrance Materials (RIFM) should be contacted

Safety Assessment of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	November 13, 2020
Panel Meeting Date:	December 7-8, 2020

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

© Cosmetic Ingredient Review
1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢
cirinfo@cir-safety.org

DRAFT ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate, which are reported to function as chelating agents in cosmetic products. The Panel reviewed the available data to determine the safety of these ingredients. The Panel concluded that…TBD.

INTRODUCTION

Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate are reported to function in cosmetics as chelating agents, according to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*).[1] These ingredients are both *N,N*-diacetate-substituted amino acids. The Expert Panel for Cosmetic Ingredient Safety (Panel) previously reviewed the safety of the α-amino acids, including alanine, glutamic acid, and sodium glutamate.[2] The Panel concluded that these ingredients are safe in the present practices of use and concentration in cosmetics. The two ingredients under review herein, are both amino acids di-substituted at the amine functional group with acetate.

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

Much of the data included in this safety assessment was found on the European Chemicals Agency (ECHA) website on the L-isomer of Tetrasodium Glutamate Diacetate.[3] Please note that the EHCA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definitions and Structures

Beta-Alanine Diacetic Acid (CAS No. 6245-75-6) and Tetrasodium Glutamate Diacetate (CAS No. 51981-21-6; L-isomer) both function as chelating agents in cosmetic formulations.[1] The structures of these *N,N*-diacetate-substituted amino acids are depicted in Figure 1.

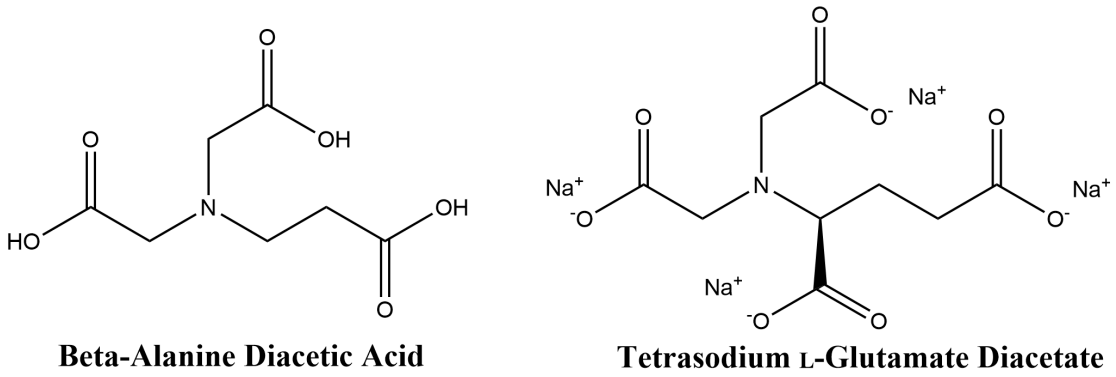


Figure 1. Amino Acid Diacetates

Chemical Properties

Available chemical properties of Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate are provided in Table 1.[3-5] Tetrasodium Glutamate Diacetate is an odorless white to off-white powder that is very soluble in water (650 g/l) and has a log $P_{o/w}$ of < 0.[3] β-Alanine has no stereocenter; however, glutamic acid does and the naturally occurring form is the L-isomer. The formula weight for Tetrasodium Glutamate Diacetate is 351.13 g/mol.[5] Beta-Alanine Diacetic Acid has a molecular weight of 205.17 g/mol and an estimated log $P_{o/w}$ of -3.32.[4,6]

A supplier reports that racemization of L-Tetrasodium Glutamate Diacetate is facilitated by low pH.[7,8] At ambient temperatures, racemization takes "a very, very long time (many months)" to occur; while at 9000.74 mm Hg and 95 - 100 ºC, it takes ≥ 70 h to get full racemization. Very high temperatures using an autoclave are needed to racemize in a few hours.

Method of Manufacture

Tetrasodium Glutamate Diacetate

Figure 2 and Figure 3 describe the manufacturing processes of Tetrasodium Glutamate Diacetate by two different suppliers. In one process, neutralized monosodium glutamate and neutralized monochloroacetic acid are reacted together to produce the ingredient, while in the second process, monosodium glutamate, hydrogen cyanide, and formaldehyde are reacted together and then saponified with sodium hydroxide to produce the ingredient.

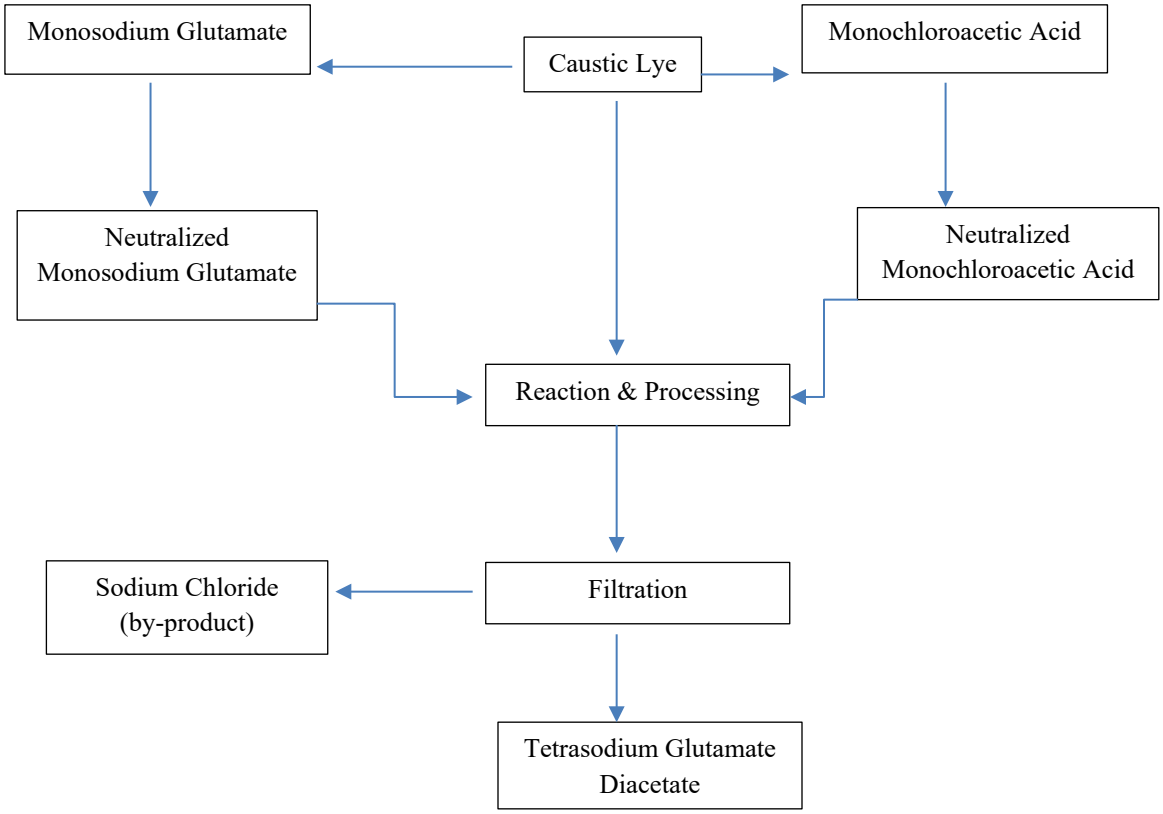


Figure 2. Manufacturing flow chart of a Tetrasodium Glutamate Diacetate tradename product.[9]

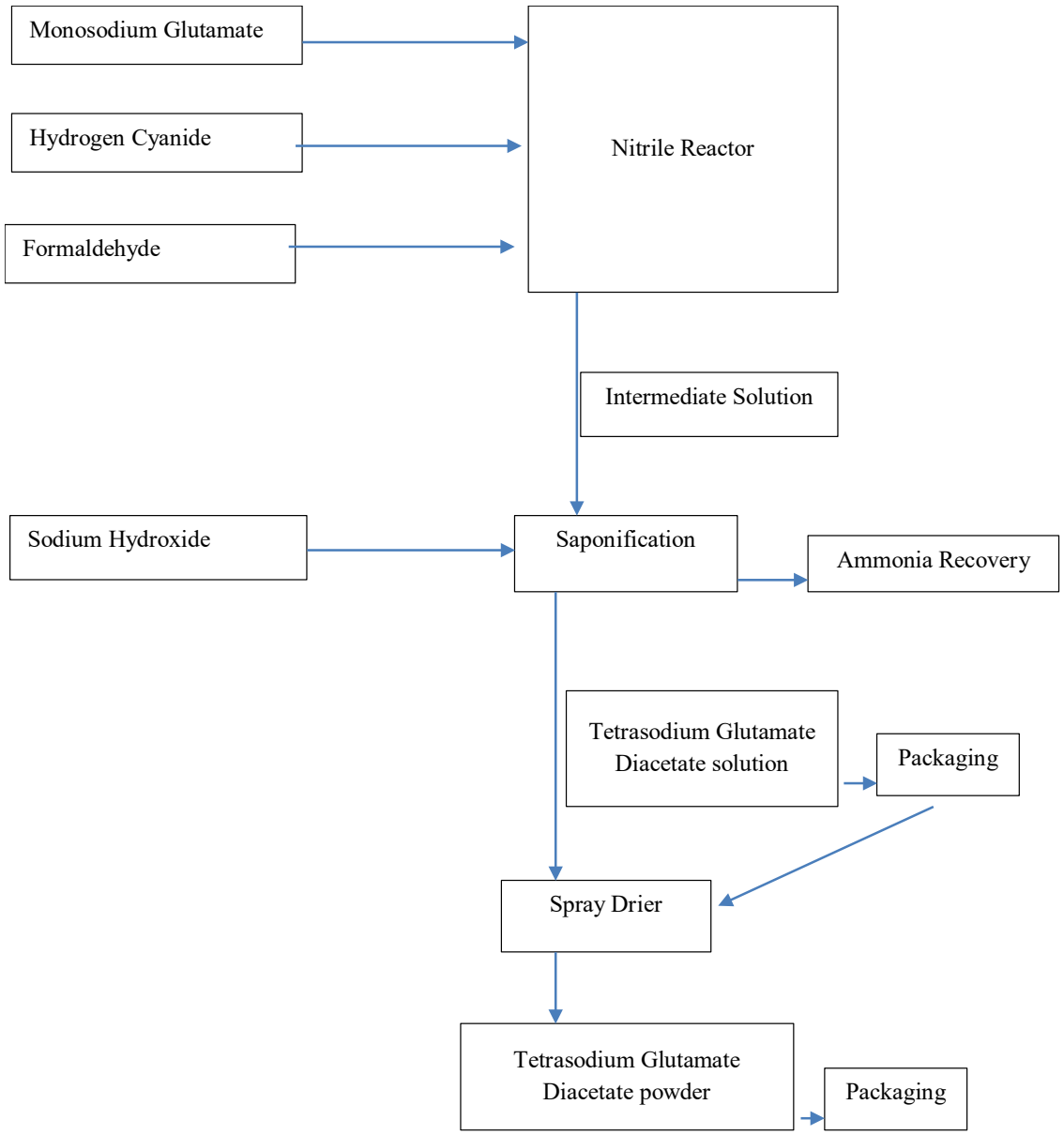


Figure 3. Manufacturing flow diagram of a Tetrasodium Glutamate Diacetate tradename solution and powder.[10]

Beta-Alanine Diacetic Acid

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

Composition/Impurities

Tetrasodium Glutamate Diacetate

A supplier of Tetrasodium Glutamate Diacetate reports that a tradename product contains 46.5% - 47.5% Tetrasodium Glutamate Diacetate, 0.00% - 0.40% sodium hydroxide, and 52.0% - 54.0% water.[11] Another supplier reports that a tradename product contains approximately 81.0% Tetrasodium Glutamate Diacetate, 1.1% sodium hydroxide (a raw material), 15.9% water, 1.7% sodium glycolate (an impurity), 0.15% sodium formate, and 0.15% nitrilotriacetic acid, trisodium salt (an impurity).[12] A trace metals report from this same supplier details the following heavy metals profile: arsenic < 5 mg/kg, cadmium < 0.5 mg/kg, chromium < 1 mg/kg, lead < 5 mg/kg, mercury < 0.05 mg/kg, and nickel < 5 mg/kg.[13]

Beta-Alanine Diacetic Acid

No composition or impurities data were found in the public literature, and unpublished data were not provided.

USE

Cosmetic

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

According to 2020 VCRP survey data, Tetrasodium Glutamate Diacetate is used in a total of 977 formulations; the majority of the uses are in bath soaps and detergents (Table 2).[14] Beta-Alanine Diacetic Acid is reported to be used in only 2 leave-on formulations: a moisturizing skin care product and "other" hair preparations. The results of the concentration of use survey conducted by the Council in 2018 indicate that Tetrasodium Glutamate Diacetate is used at up to 1%; this concentration is reported for deodorants (non-spray).[15] No concentrations of use were reported for Beta-Alanine Diacetic Acid.

Tetrasodium Glutamate Diacetate may be used in products that can come into contact with the eyes or mucous membranes; for example, it is reported to be used in eyeliner at up to 0.057% and in bath soaps and detergents at up to 0.28%.[15] Additionally, Tetrasodium Glutamate Diacetate is used in cosmetic sprays and could possibly be inhaled; for example, it is reported to be used at up to 0.029% in hair spray.[15] 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.[16,17] 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.[18,19]

Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate are not restricted from use in any way under the rules governing cosmetic products in the European Union.[20]

TOXICOKINETIC STUDIES

Dermal Penetration

No dermal penetration data were found in the public literature, and unpublished data were not provided.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Oral

Tetrasodium Glutamate Diacetate

In a single-dose elimination study, Wistar rats (4 per sex per group) received Tetrasodium Glutamate Diacetate (87.3% pure) in water via gavage at 100, 300, or 1000 mg/kg.[3] Most of the test material was found in the feces, with an overall recovery ranging from 95.8% – 103.0%. The duration of follow-up was 72 h. More than 85% of the dose was excreted in the first 24 h, unmetabolized.

In a 90-d elimination study, groups of 10 male and 10 female Wistar rats received 0, 100, 300, or 1000 mg/kg bw Tetrasodium Glutamate in water via gavage daily.[3] Concentrations of the test material in the urine were below the detection limit (< 50 mg/kg urine) in the control, low-, and mid-dose groups at the end of treatment. The researchers determined that absorption from the gastrointestinal tract was low. No further details were provided.

Intraperitoneal

Tetrasodium Glutamate Diacetate

In a single dose elimination study, Wistar rats (4 per sex per group) received Tetrasodium Glutamate Diacetate (87.3% pure) in water via intraperitoneal (i.p.) administration at 5, 15, or 50 mg/kg.[3] In 83% of the animals, the test material was mainly detected in urine, with an overall recovery ranging from 74.6% – 103.3%. (Details regarding excretion by the remaining animals were not provided.) More than 85% of the dose was excreted in the first 24 h. The results indicated that Tetrasodium Glutamate Diacetate is excreted unmetabolized.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Acute toxicity studies summarized here are described in Table 3.[3] The acute dermal and oral LD_{50}s for Tetrasodium Glutamate Diacetate (purity ranging from 70.7% to 91%) in rats were greater than 2000 mg/kg bw. The LC_{50} for an inhalation study of Tetrasodium Glutamate Diacetate was greater than 4.2 mg/l in rats.

Subchronic Toxicity Studies

The potential adverse effects of 95% Tetrasodium Glutamate Diacetate was investigated in a 90-d oral toxicity study in specific pathogen-free (SPF) Wistar rats.[3] The study was performed in accordance with Organization for Economic Co-operation and Development (OECD) test guideline (TG) 408. Groups of 10 male and 10 female rats received 0, 100, 300, or 1000 mg/kg/d of the test material via gavage. An extra 10 animals per sex were used for the control and high dose groups, to assess recovery for 14 d. No treatment-related changes were observed in clinical appearance, functional observations, body weight gains, and feed consumption at up to 1000 mg/kg/d. At 1000 mg/kg/d, an increased red blood cell count was observed in males, a reduced mean corpuscular volume and hemoglobin were observed in both males and females, and increased red blood cell distribution width and increased platelet count were observed in females. A reduced mean corpuscular hemoglobin was also observed in males and females of the 300 mg/kg/d group. Changes in clinical biochemistry parameters at 1000 mg/kg/d at the end of treatment included increased albumin and cholesterol levels (males and females, respectively), reduced creatinine levels (both males and females), and reduced inorganic phosphate and chloride levels (males and females, respectively). Changes in blood chemistry were within, or just outside, the range considered normal for rats of this age and strain, and had resolved by the end of the recovery period.

Urinalysis reported an increased sodium concentration/excretion in males and females at 300 and 1000 mg/kg/d. At 1000 mg/kg/d in females, reduced urinary volume and clarity, and increased specific gravity, protein level, and potassium concentration was observed. These changes were absent at the end of the recovery period, indicating that these were reversible in nature. Slightly increased kidney weights and kidney-to-body weight ratios were observed in males at 1000 mg/kg/d at the end of the treatment phase. At the end of the recovery phase, kidney weights were similar to control values. In females of the 1000 mg/kg/d dose group, kidney weights and kidney-to-body weight ratios were not affected at the end of the treatment period, but were increased at the end of the recovery period, indicating that the test material had an effect on kidney function. No other toxicologically significant changes were noted during macroscopic and microscopic examination. The no-observed-adverse-effect-level (NOAEL) for Tetrasodium Glutamate Diacetate in this study was 300 mg/kg/d.[3]

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Tetrasodium Glutamate Diacetate

The effects of Tetrasodium Glutamate Diacetate on reproduction were assessed in a two-generation study using groups of 24 male and 24 female Wistar Han rats.[3] Based on the results of the dose-range-finding study, dose levels for the main study were 0, 1500, 5000, and 15,000 ppm of Tetrasodium Glutamate Diacetate in feed. A second high-dose level group received the test material in feed that was supplemented with 1000 ppm zinc carbonate to compensate for potential effects from the chelating properties of the test material. The F_0 males and females were exposed to the test material from 10 wk prior to mating, and exposure was continued until euthanasia (males) or one day before euthanasia (females). F_0 females were allowed to produce and rear a litter until day 21 of lactation. On day 4 of lactation, litters were reduced in size to 8 pups (4 per sex) by random culling of F_1 pups. After weaning, one F_1 male and one F_1 female of each litter of each dose group (except the high dose zinc supplemented group) were selected for mating with a pup of another litter of the same dose group to produce an F_2 generation.

The F_1 adults were dosed in the same manner as the F_0 adults, except there was no zinc supplement group. After weaning, animals were treated for a minimum of 70 d prior to mating and continuing until euthanasia (males) or one day before euthanasia (females). F_1 females were allowed to produce and rear a litter until day 21 of lactation. On day 4 of lactation, litters were reduced in size to 8 pups by random culling of F_2 pups. During the study, the rats were evaluated for mortality, clinical signs of toxicity, body weights, feed consumption, clinical laboratory investigations (including collection of blood samples for possible future zinc analysis; females only), reproduction processes, observations on offspring, gross lesions, skeletal examination of offspring, organ weights, and histopathology.

No significant adverse effects were observed in parental animals or on reproduction or development in the 1500 ppm or 5000 ppm dose groups. At 15,000 ppm, with and without zinc, an increase in mean kidney weight was observed in F_0 and F_1 adults, and slight histopathological renal changes were observed in F_1 adults. The renal changes were minor and consisted of an increase in cortical tubular dilation in females and an increase of corticomedullary tubular basophilia in males. No significant adverse effects were observed with reproduction or development in the 15,000 ppm dose group. Based on these findings, the parental NOAEL was determined to be 5000 ppm, and the reproductive and developmental NOAELs were determined to be 15,000 ppm.[3]

In an oral developmental toxicity study of Tetrasodium Glutamate Diacetate, groups of 22 female Wistar Han rats received the test material in water via gavage at doses of 0 or 1000 mg/kg bw/d on day 6 through day 20 of gestation.[3] The animals were checked daily for clinical signs of toxicity. Body weights and water and feed consumption were determined at periodic intervals. All animals surviving to day 20 of gestation were necropsied, and external, thoracic, and abdominal macroscopic findings were recorded. The uteri and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations, and corpora lutea were recorded. Uterine weights were recorded. Viable fetuses were weighed, sexed, and examined for external, visceral, and skeletal malformations and developmental variations. No adverse effects considered to be treatment-related were observed in either the dams or the fetuses. The maternal and developmental NOAEL was considered to be 1000 mg/kg bw/d Tetrasodium Glutamate Diacetate.

In an oral developmental toxicity study, Tetrasodium Glutamate Diacetate (87.3%) in water was given to groups of 22 female New Zealand White rabbits.[3] The rabbits received the test material at 0, 20, 75, or 300 mg/kg via gavage daily from day 7 to day 28 of gestation. The animals were checked daily for clinical signs of toxicity. Body weights and water and feed consumption were determined at periodic intervals. All animals surviving to day 29 of gestation were necropsied and macroscopic findings were recorded. A laparohysterectomy was performed on each surviving female of the groups. The uteri, placenta, and ovaries were examined, and the numbers of fetuses, early and late resorptions, total implantations, and corpora lutea were recorded. Gravid uterine weights were recorded, and corrected body weights were calculated. The fetuses were weighed, sexed, and examined for malformations and developmental variations. All live fetuses were killed and examined for visceral anomalies.

One dam of the 20 mg/kg dose group died on day 22 of gestation due to gavage error. No maternal toxicity was observed in the 20 mg/kg dose group. In animals treated with 75 mg/kg bw, dark feces, diarrhea, reduced feces production, and slightly reduced feed and water intake were also observed; however, these changes were very limited and in view of the absence of more severe effects, such as changes in body weight gains, these effects were not considered to be toxicologically relevant. In dams at the 300 mg/kg dose level, clinical signs of toxicity consisted of increased incidences of dark feces, diarrhea, and reduced feces production. Feed and water consumption were reduced. Body weight gains were decreased, with several animals showing a transient body weight loss. No developmental toxicity was observed in the 20, 75, and 300 mg/kg/d groups. Based on the results of this study, the maternal no-observed-effect-level (NOEL) for Tetrasodium Glutamate Diacetate was determined to be 20 mg/kg body weight/d; the maternal NOAEL was determined to be 75 mg/kg body weight/d. The developmental NOAEL was at least 300 mg/kg body weight/d.[3]

In a similar developmental study in inseminated female New Zealand White rabbits, groups of 24 animals received 0, 30, 100, or 300 mg/kg Tetrasodium Glutamate Diacetate in water once daily by gavage from days 7 to 28 of gestation.[3] A second high-dose level group received the test material in feed that was supplemented with 1024 ppm zinc carbonate to compensate for potential effects from the chelating properties of the test material. Dose-dependent, treatment-related clinical signs that consisted of an increased incidence of dark feces and reduced feces production were observed in the 100, 300, and 300 + zinc dose groups. Body weights and/or body weight gain were reduced at 300 mg/kg (with and without zinc) throughout most of the treatment period. Feed consumption was decreased at 100 mg/kg, 300 mg/kg, and 300 mg/kg + zinc in a dose-dependent manner for the first one or two weeks of treatment. No effect on water consumption was noted. No treatment-related effects were seen in hematology parameters up to 300 mg/kg without added zinc. No treatment- related effects on clinical biochemistry and urinalysis parameters were noted. There were no treatment-related macroscopic findings. No effects were noted on the number of corpora lutea, implantation sites, viable or dead fetuses, early or late resorptions, pre- and post-implantation loss, litter size, and sex ratio. There were no significant differences in fetal body weight following treatment up to 300 mg/kg without added zinc. The addition of dietary zinc to animals treated with 300 mg/kg bw/d resulted in additional maternal toxicity (hematological changes) and in fetal toxicity (reduced fetal body weights). The maternal NOAEL for Tetrasodium Glutamate Diacetate was determined to be 30 mg/kg bw/d; the developmental NOAEL was determined to be at least 300 mg/kg bw/d.[3]

GENOTOXICITY STUDIES

Genotoxicity studies summarized here are described in Table 4. Tetrasodium Glutamate Diacetate (70.7%) was neither genotoxic with or without metabolic activation in an Ames test at up to 5000 µg/plate nor in a Chinese hamster ovary gene mutation assay at up to 3650 µg/ml; however, it was weakly clastogenic in a Chinese hamster lung cell chromosome aberration test at 1825 and 3650 µg/ml with or without metabolic activation.[3] No genotoxicity was observed with Tetrasodium Glutamate Diacetate (70.7%) in an in vivo mammalian erythrocyte micronucleus test in mice at up to 400 mg/kg bw.

CARCINOGENICITY STUDIES

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

IRRITATION AND SENSITIZATION STUDIES

Irritation

Animal

Tetrasodium Glutamate Diacetate

The dermal irritation potential of Tetrasodium Glutamate Diacetate (purity, 70.7%) in water was assessed using three New Zealand White rabbits in accordance with OECD TG 404.[3] Application of a single 4-h, semi-occluded patch (2.5 cm^2) containing 0.5 ml test material on intact skin produced very slight erythema in all rabbits. All treated skin sites appeared normal at the 24-h observation. The test material produced a primary irritation index of 0.0 and was classified as non-irritating. No corrosive effects were observed.

Human

Tetrasodium Glutamate Diacetate

The dermal irritation potential of a liquid eyeliner containing 0.2315% Tetrasodium Glutamate Diacetate was tested using 15 subjects.[21] The subjects received an occlusive patch for 24 h with the test material at full strength. No significant differences in irritancy were observed between the test material and the reference control.

Sensitization

Animal

Tetrasodium Glutamate Diacetate

In a guinea pig maximization study of a test material containing 74.33% Tetrasodium Glutamate Diacetate, 20 female Dunkin-Hartley guinea pigs received the test material in distilled water at 1% w/v during the intradermal induction, 50% w/w during the topical induction, and 50% and 25% w/w during the topical challenge.[3] Positive and negative control groups consisted of 10 animals each. No adverse skin effects were observed in the animals that received the test material. The controls yielded expected results. The test material containing 74.33% Tetrasodium Glutamate Diacetate was determined to be non-sensitizing in this study.

Human

Tetrasodium Glutamate Diacetate

The dermal sensitization potential of a liquid eyeliner containing 0.2315% Tetrasodium Glutamate Diacetate was tested in a human repeat insult patch test (HRIPT) using 104 subjects. The subjects were induced with 9 occlusive patches (2 cm^2) containing 0.2 ml of the test material for 3 consecutive weeks. Following a 2-wk rest period, the subjects were challenged in previously unexposed skin for 24 h and the test sites were observed for reactions at 24 and 48 h post patch removal. No adverse effects were observed. The test material was considered non-sensitizing.[22]

OCULAR IRRITATION STUDIES

Animal

Tetrasodium Glutamate Diacetate

The ocular irritation potential of Tetrasodium Glutamate Diacetate (purity, 70.7%) in water was assessed using three New Zealand White rabbits in accordance with OECD TG 405.[3] A single instillation of the test material (0.1 ml) to unrinsed eyes produced minimal conjunctival irritation. All treated eyes appeared normal 48 h after treatment. Tetrasodium Glutamate Diacetate was considered to be non-irritating.

SUMMARY

Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate both function as chelating agents in cosmetic formulations. According to the 2020 VCRP survey data, Tetrasodium Glutamate Diacetate is used in a total of 977 formulations; the majority of the uses are in bath soaps and detergents. Beta-Alanine Diacetic Acid is reported to be used in only 2 leave-on formulations, a moisturizing skin care product and “other” hair preparations. The results of the concentration of use survey conducted by the Council in 2018 indicate that Tetrasodium Glutamate Diacetate is used at up to 1%; this concentration is reported in deodorants (non-spray). No concentrations of use were reported for Beta-Alanine Diacetic Acid.

In an oral, single-dose elimination study with rats, Tetrasodium Glutamate Diacetate (at up to 1000 mg/kg bw) was mostly recovered unmetabolized in feces; while in an oral 90-d elimination study, concentrations of the test material in the urine were below the detection limit, and absorption from the gastrointestinal tract was low. Tetrasodium Glutamate Diacetate was mainly excreted unmetabolized in urine, in rats, in an i.p. single-dose elimination study at up to 50 mg/kg bw.

The acute dermal and oral LD_{50}s for Tetrasodium Glutamate Diacetate in rats were greater than 2000 mg/kg bw. The LC_{50} for an inhalation study of Tetrasodium Glutamate Diacetate was greater than 4.2 mg/l in rats.

The NOAEL for a 90-d oral toxicity study of 95% Tetrasodium Glutamate Diacetate was 300 mg/kg/d in rats. The rats received 0, 100, 300, or 1000 mg/kg/d daily via gavage. Slightly increased kidney weights and kidney-to-body weight ratios were observed in males with 1000 mg/kg/d at the end of the treatment phase. At the end of the recovery phase, kidney weights were similar to control levels. In females at 1000 mg/kg/d, kidney weights and kidney-to-body weight ratios were increased at the end of the recovery period, but not at the end of the treatment period.

A dietary two-generation study in rats reported no skeletal malformations at up to and including the maximum dose of 15,000 ppm. Therein, the parental NOAEL was determined to be 5000 ppm and the reproductive and developmental NOAEL was 15,000 ppm. The NOAEL for developmental and maternal toxicity in rats in a gavage study was 1000 mg/kg bw/d (only dose tested). The NOAEL for developmental toxicity in rabbits in a gavage study with Tetrasodium Glutamate Diacetate (87.3%) in water was 300 mg/kg bw/d (maximum dose tested), and the maternal NOAEL in rabbits was 75 mg/kg bw/d. In a developmental study of inseminated female rabbits that received up to 300 mg/kg Tetrasodium Glutamate Diacetate, with and without a zinc supplement, the maternal NOAEL was 30 mg/kg bw/d and the developmental NOAEL was at least 300 mg/kg bw/d.

Tetrasodium Glutamate Diacetate (70.7%) was neither genotoxic with or without metabolic activation in an Ames test at up to 5000 µg/plate nor in a Chinese hamster ovary gene mutation assay at up to 3650 µg/ml; however, it was weakly clastogenic in a Chinese hamster lung cell chromosome aberration test at 1825 and 3650 µg/ml with or without metabolic activation.[3] No genotoxicity was observed to Tetrasodium Glutamate Diacetate (70.7%) in an in vivo mammalian erythrocyte micronucleus test at up to 400 mg/kg bw.

In dermal animal studies, Tetrasodium Glutamate Diacetate was non-irritating in rabbits and non-sensitizing (at up to 50%) in guinea pigs. A liquid eyeliner containing 0.2315% Tetrasodium Glutamate Diacetate was not irritating or sensitizing in human patch studies. Tetrasodium Glutamate Diacetate was non-irritating in an ocular irritation study in rabbits.

No methods of manufacturing, composition or impurities data, toxicological data were available for Beta-Alanine Diacetic Acid. No carcinogenicity data were found in the published literature, and unpublished data were not submitted, for either Beta-Alanine Diacetic Acid or Tetrasodium Glutamate Diacetate.

DRAFT DISCUSSION

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

Beta-Alanine Diacetic Acid and Tetrasodium Glutamate Diacetate are reported to function in cosmetics as chelating agents. These ingredients are both *N,N*-diacetate-substituted amino acids. The Panel noted gaps in the available safety data for Beta-Alanine Diacetic Acid in this safety assessment.

The Panel found that the systemic toxicity data, including developmental and reproductive toxicity studies, acute and subchronic toxicity studies, and dermal irritation and sensitization studies in this report were sufficient for assessing safety for reported cosmetic uses of Tetrasodium Glutamate Diacetate. The Panel noted that Tetrasodium Glutamate Diacetate is slowly absorbed through the gastrointestinal tract due to the highly polar carboxyl substituents: dermal absorption is likely to be even slower. The Panel also noted the lack of carcinogenicity data and was concerned about the report by a supplier that Tetrasodium Glutamate Diacetate may contain a salt of nitrilotriacetic acid, a 2B carcinogen according to the International Agency for Research on Cancer, but this gap and concern was mitigated by multiple genotoxicity studies that were negative and the low concentrations of use of this ingredient in leave-on products.

Tetrasodium Glutamate Diacetate is reported to be used in spray and powder products that could possibly be inhaled. For example, this ingredient is used in hair spray at up to 0.029%. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns (e.g., limited data available from inhalation studies, including acute exposure data, suggest little potential for respiratory effects at relevant doses). 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 https://www.cir-safety.org/cir-findings.

Remaining discussion to be determined…

CONCLUSION

To be determined….

TABLES

Table 1. Chemical properties

Property	Value	Reference
Beta-Alanine Diacetic Acid		
Molecular Weight (g/mol)	205.166	[4]
log $P_{o/w}$	-3.32 (estimated)	[6]
Tetrasodium Glutamate Diacetate		
Physical Form	odorless white to off-white powder	[3]
Formula Weight (g/mol)	351.1291	[5]
Density (at 20 °C)	1.466	[3]
Vapor Pressure (mmHg; at 20 °C)	0.600	[3]
Melting Point (°C)	280 (decomposition)	[3]
Water Solubility (g/l; at 21 °C and pH 7)	650	[3]
log $P_{o/w}$ (at 27 °C and pH 7)	< 0	[3]

Table 2. Frequency (2020) and concentration of use (2018) according to duration and type of exposure for amino acid diacetates.[14,15]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Beta-Alanine Diacetic Acid		**Tetrasodium Glutamate Diacetate**	
Totals†	**2**	**NR**	**977**	**0.0013-1**
Duration of Use				
Leave-On	2	NR	118	0.0013-1
Rinse Off	NR	NR	859	0.037-0.31
Diluted for (Bath) Use	NR	NR	NR	NR
Exposure Type				
Eye Area	NR	NR	16	0.048-0.057
Incidental Ingestion	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]	NR	NR; 46[a]; 41[b]	0.029; 0.033-0.094[a]
Incidental Inhalation-Powder	NR	NR	41[b]; 1[c]	0.057[c]
Dermal Contact	1	NR	933	0.0013-1
Deodorant (underarm)	NR	NR	NR	1
Hair - Non-Coloring	1	NR	25	0.029-0.097
Hair-Coloring	NR	NR	18	NR
Nail	NR	NR	NR	NR
Mucous Membrane	NR	NR	666	0.037-0.28
Baby Products	NR	NR	4	NR

NR = Not reported

† 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.

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

[b.] Not specified that these products are sprays or powders, so this information is captured for both categories of incidental inhalation.

[c.] It is possible these products may be powders, but it is not specified whether the reported uses are powders.

Table 3. Acute toxicity

Ingredient/Concentration/Vehicle	Dose	Species	Study Protocol	Results	Reference
		Dermal			
Tetrasodium Glutamate Diacetate (91% pure); 200 mg/ml (concentration of solution); water	2000 mg/kg bw	5 male and 5 female Wistar rats	Occlusive on back; test area 25 cm^2 for males and 18 cm^2 for females; test site washed with tap water after 24 h; in accordance with OECD TG 402; observed for 14 d	LD_{50} > 2000 mg/kg bw; no mortalities; flat and/or hunched posture, piloerection, and/or slight chromodacryorrhea noted in all animals from day 1 through day 4; slight scales and/or scabs observed in treated skin of 4 females from day 3 through day 9	[3]
		Oral			
Tetrasodium Glutamate Diacetate (70.7% pure); 200 mg/ml; in water	2000 mg/kg	5 male and 5 female Sprague-Dawley rats	Gavage; observed for 14 d	LD_{50} > 2000 mg/kg bw; no mortalities; no clinical signs of toxicity; no other abnormalities	[3]
Tetrasodium Glutamate Diacetate (tradename mixture was ~78% tetra- and trisodium salt); ~35% solution in water	560 mg/kg as tradename mixture	5 male and 5 female rats; species not described	Gavage in accordance with OECD TG 401; observed for 14 d	LD_{50} > 560 mg/kg bw; no mortalities; no clinical signs of toxicity	[3]
		Inhalation			
Tetrasodium Glutamate Diacetate (90% pure); 50% (concentration in vehicle); water; particle size range 1 - 4 µm	4.2 mg/l (4.3 mg/l was technically the highest attainable concentration); mass median aerodynamic diameter) /geometric standard deviation were 2.8/2.7 µm	5 male and 5 female Wistar rats	Nose-only inhalation for 4 h in accordance with OECD TG 403; observed for 14 d	LC_{50} > 4.2 mg/l; no mortalities; slightly decreased breathing rate observed during exposure; soiled fur observed after exposure until day 2; sniffing noted in 4 animals shortly after exposure, in 7 animals on day 1, and in 1 animal on day 2; eye discharge noted in 1 animal on day 1	[3]

Table 4. Genotoxicity studies

Ingredient/Concentration	Dose	Species/Strain/Cell	Method	Results	Reference
		In Vitro			
Tetrasodium Glutamate Diacetate (70.7%) in distilled water	Up to 5000 µg/plate, with or without metabolic activation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538	Ames test	Not genotoxic	[3]
Tetrasodium Glutamate Diacetate (70.7%) in distilled water	228 - 3650 µg/ml, with or without metabolic activation	Chinese hamster ovary	HGPRT locus on X-chromosome gene mutation assay	Not genotoxic	[3]
Tetrasodium Glutamate Diacetate (70.7%) in minimal essential media (MEM)	228 - 3650 µg/ml, with or without metabolic activation	Chinese hamster lung cell line	Chromosome aberration test	Weakly clastogenic; small but statistically significant increases in the frequency of cells with aberrations were observed in cells exposed for 6-h with and without metabolic activation and in the 48-h (without metabolic activation) continuous exposure groups; test material was shown to be toxic	[3]
		In Vivo			
Tetrasodium Glutamate Diacetate (70.7%) in distilled water	0, 100, 200, or 400 mg/kg bw	Groups of 5 male and 5 female CD-1 mice	Mammalian erythrocyte micronucleus test via single intraperitoneal injection; test performed in accordance with OECD TG 474; bone marrow harvests were made at 24, 48, or 72 h post-exposure; cyclophosphamide was a positive control	Not genotoxic	[3]

REFERENCES

1. Nikitakis J, Kowcz A. Web-Based International Cosmetic Ingredient Dictionary and Handbook. http://webdictionary.personalcarecouncil.org/jsp/Home.jsp. Washington, DC: Personal Care Products Council. Last Updated: 2020. Accessed: 08/19/2020.

2. Burnett CL, Heldreth B, Bergfeld WF, et al. Safety Assessment of α-Amino Acids as Used in Cosmetics. *Int J Toxicol.* 2013;32:41S-64S.

3. European Chemicals Agency (ECHA). Tetrasodium N,N-bis(carboxylatomethyl)-L-glutamate. https://echa.europa.eu/registration-dossier/-/registered-dossier/2174/. 2019. Accessed. 07/01/2019.

4. National Center for Biotechnology Information. PubChem Database CID=535795. U.S. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/N-_2-Carboxyethyl_iminodiacetic-acid Accessed. July 12, 2019.

5. National Center for Biotechnology Information. PubChem Database CID=44630158. U.S. National Library of Medicine. https://pubchem.ncbi.nlm.nih.gov/compound/Tetrasodium-glutamate-diacetate Accessed. July 12, 2019.

6. US Environmental Protection Agency (EPA). Estimation Programs Interface Suite for Microsoft Windows, v. 4.11. Washington, DC: US EPA; 2019.

7. Nouryon. 2020. Statement regarding racemization of Tetrasodium Glutamate Diacetate. Unpublished data submitted by the Personal Care Products Council on March 27, 2020.

8. Nouryon. 2020. Clarification - Tetrasodium Glutamate Diacetate. Unpublished data submitted by the Personal Care Products Council on August 28, 2020.

9. Jarchem Industries I. 2019. Manufacturing flow chart Biopure™ GLDA (Tetrasodium Glutamate Diacetate). Unpublished data submitted by the Personal Care Products Council on February 18, 2020.

10. Nouryon. 2019. Flow diagram/production of Dissolvine GL-47-S an GL-PD-S (Tetrasodium Glutamate Diacetate). Unpublished data submitted by the Personal Care Products Council on March 27, 2020.

11. Jarchem Industries I. 2019. Composition statement Biopure™ GLDA (Tetrasodium Glutamate Diacetate). Unpublished data submitted by the Personal Care Products Council on February 18, 2020.

12. Nouryon. 2020. Dissolvine GL-PD-S (Tetrasodium Glutamate Diacetate) Composition. Unpublished data submitted by the Personal Care Products Counil on March 27, 2020.

13. Nouryon. 2020. Trace metals Dissolvine GL-PD-S (Tetrasodium Glutatmate Diacetate). Unpublished data submitted by the Personal Care Products Council on March 27, 2020.

14. US Food and Drug Administration (FDA) Center for Food Safety & Applied Nutrition (CFSAN). 2020. Voluntary Cosmetic Registration Program (VCRP) - Frequency of Use of Cosmetic Ingredients. College Park, MD Obtained under the Freedom of Information Act from CFSAN; requested as "Frequency of Use Data" January 6, 2020; received January 13, 2020

15. Personal Care Products Council. 2018. Concentration of Use by FDA Product Category: Tetrasodium Glutamate Diacetate and Beta-Alanine Diacetic Acid. Unpublished data submitted by Personal Care Products Council

16. Johnsen M. The Influence of Particle Size. *Spray Technology and Marketing.* 2004;14(11):24-27.

17. Rothe H. Special Aspects of Cosmetic Spray Evaluation. Unpublished data presented at the 26 September CIR Expert Panel meeting. Washington, D.C.

18. Bremmer H, Prud'homme de Lodder L, Engelen J. Cosmetics Fact Sheet: To assess the risks for the consumer; Updated version for ConsExpo 4. Bilthoven, Netherlands 2006. Netherlands National Institute for Public Health

and the Environment RIVM 320104001/2006. http://www.rivm.nl/bibliotheek/rapporten/320104001.pdf. Accessed 8/24/2011. Pages 1-77.

19. Rothe H, Fautz R, Gerber E, et al. Special aspects of cosmetic spray safety evaluations: Principles on inhalation risk assessment. *Toxicol Lett.* 2011;205(2):97-104.

20. European Union. 2009. Regulation (EC) No. 1223/2009 of the European Parliament and of the Council of 30 November 2009 on Cosmetic Products

21. Anonymous. 2018. Clinical evaluation report: Human patch test (eyeliner containing 0.2315% Tetrasodium Glutamate Diacetate). Unpublished data submitted by the Personal Care Products Council on August 15, 2019.

22. TKL Research. 2019. Repeated insult patch test (eyeliner containing 0.2315% Tetrasodium Glutamate Diacetate). Unpublished data submitted by the Personal Care Products Council on August 15, 2019.

2020 FDA VCRP Raw Data

TETRASODIUM GLUTAMATE DIACETATE	01A	Baby Shampoos	2
TETRASODIUM GLUTAMATE DIACETATE	01B	Baby Lotions, Oils, Powders, and Creams	1
TETRASODIUM GLUTAMATE DIACETATE	01C	Other Baby Products	1
TETRASODIUM GLUTAMATE DIACETATE	03D	Eye Lotion	9
TETRASODIUM GLUTAMATE DIACETATE	03E	Eye Makeup Remover	1
TETRASODIUM GLUTAMATE DIACETATE	03F	Mascara	1
TETRASODIUM GLUTAMATE DIACETATE	03G	Other Eye Makeup Preparations	5
TETRASODIUM GLUTAMATE DIACETATE	05A	Hair Conditioner	11
TETRASODIUM GLUTAMATE DIACETATE	05F	Shampoos (non-coloring)	8
TETRASODIUM GLUTAMATE DIACETATE	05G	Tonics, Dressings, and Other Hair Grooming Aids	3
TETRASODIUM GLUTAMATE DIACETATE	05I	Other Hair Preparations	1
TETRASODIUM GLUTAMATE DIACETATE	06C	Hair Rinses (coloring)	8
TETRASODIUM GLUTAMATE DIACETATE	06D	Hair Shampoos (coloring)	9
TETRASODIUM GLUTAMATE DIACETATE	06H	Other Hair Coloring Preparation	1
TETRASODIUM GLUTAMATE DIACETATE	07F	Makeup Bases	1
TETRASODIUM GLUTAMATE DIACETATE	10A	Bath Soaps and Detergents	647
TETRASODIUM GLUTAMATE DIACETATE	10E	Other Personal Cleanliness Products	19
TETRASODIUM GLUTAMATE DIACETATE	11A	Aftershave Lotion	1
TETRASODIUM GLUTAMATE DIACETATE	12A	Cleansing	150
TETRASODIUM GLUTAMATE DIACETATE	12C	Face and Neck (exc shave)	33
TETRASODIUM GLUTAMATE DIACETATE	12D	Body and Hand (exc shave)	8
TETRASODIUM GLUTAMATE DIACETATE	12F	Moisturizing	35
TETRASODIUM GLUTAMATE DIACETATE	12G	Night	6
TETRASODIUM GLUTAMATE DIACETATE	12H	Paste Masks (mud packs)	3
TETRASODIUM GLUTAMATE DIACETATE	12I	Skin Fresheners	2
TETRASODIUM GLUTAMATE DIACETATE	12J	Other Skin Care Preps	11
BETA-ALANINE DIACETIC ACID	05I	Other Hair Preparations	1
BETA-ALANINE DIACETIC ACID	12F	Moisturizing	1

Copyright restrictions prevented the inclusion of the following material:

IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. *Nitrilotriacetic Acid and its Salts*. Lyon: International Agency for Research on Cancer; 1990.