Safety Assessment of Adenosine Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	May 15, 2020
Panel Meeting Date:	June 8 - 9, 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.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.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. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety and Liaisons

From: Priya Cherian, Scientific Analyst/Writer, CIR

Date: May 15, 2020

Subject: Draft Tentative Report on Adenosine ingredients

Enclosed is the Draft Tentative Report on the Safety Assessment of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate as Used in Cosmetics (identified as *adenos062020rep* in the pdf document). At the September 2019 meeting, the Expert Panel for Cosmetic Ingredient Safety issued an Insufficient Data Announcement for this ingredient group, and requested impurities data on all ingredients. Since the September Panel meeting, unpublished data have been received and incorporated (highlighted in yellow in the report document). These data include physical and chemical properties of Adenosine (*adenos062020data1*), impurity data on Adenosine Triphosphate (*adenos062020data2*), and impurity data on a trade name mixture containing Disodium Adenosine Triphosphate (*adenos062020data3*).

Also included in this package for your review are the report history (*adenos062020hist*), flow chart (*adenos062020flow*), literature search strategy (*adenos062020strat*), updated data profile (*adenos062020prof*), and updated 2020 VCRP data (*adenos062020FDA*). No substantial differences were noted between 2019 and 2020 VCRP data. Additionally, comments on the Draft Report were received and addressed (*adenos062020pcpc*).

The Panel should carefully consider and discuss the data (or lack thereof), and the Abstract and draft Discussion presented in this report. A Tentative Report with a safe, safe with qualifications, unsafe, insufficient data, or split conclusion should then be issued.

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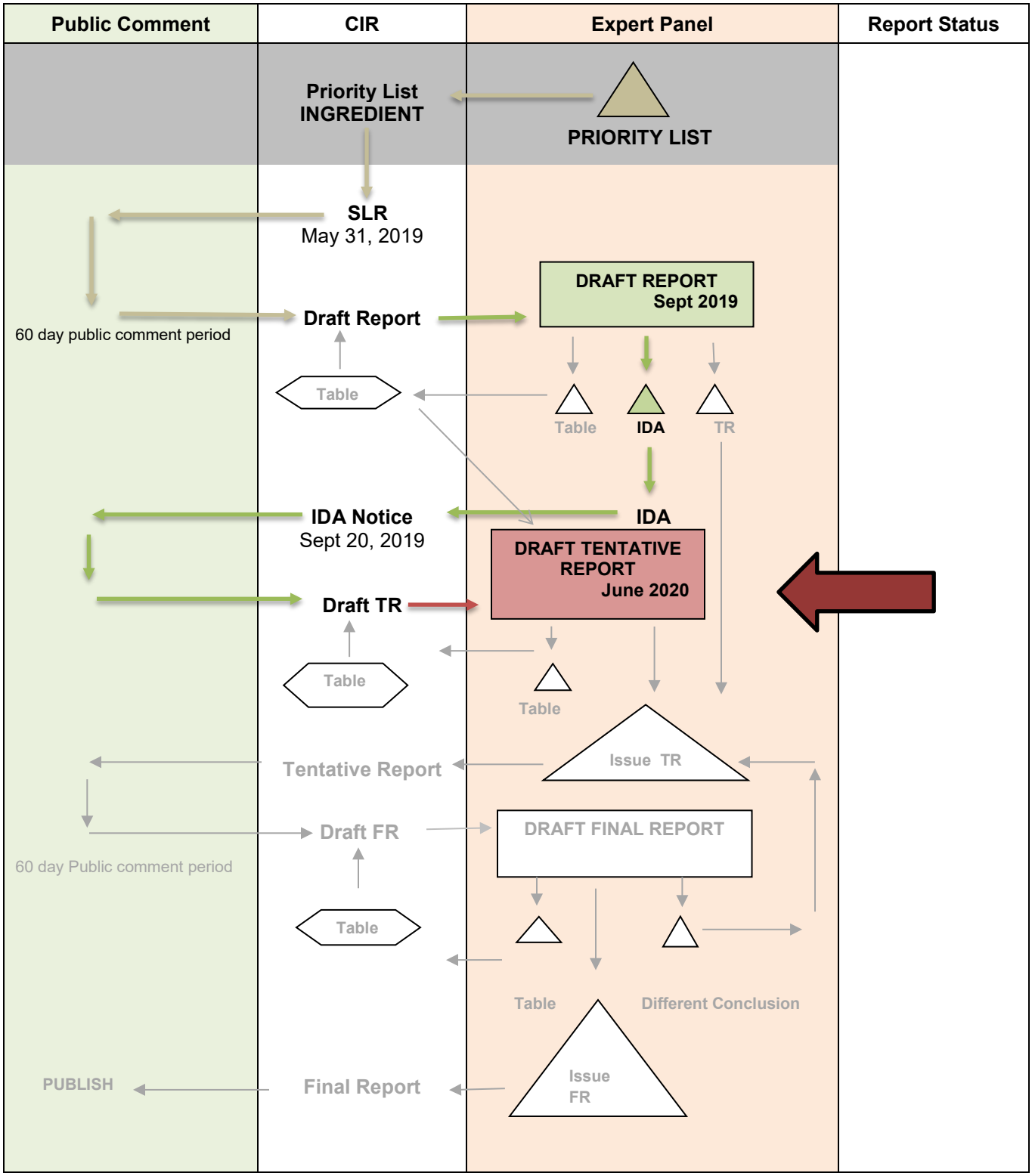
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Adenosine Ingredients

MEETING June 2020



Adenosine Ingredients History

May 2019

-SLR posted

June 2019

-Summary sensitization, phototoxicity, and photosensitization information received from Council

-Comments received on SLR

August 2019

-summary 48-hour patch test and HRIPT data on Adenosine received from Council

September 2019

-Draft report reviewed by Panel

-Insufficient data announcement issued for impurities data

-Comments by Council received on Draft Report

October 2019

-physical and chemicals properties data on Adenosine received

-impurities data on Disodium Adenosine Triphosphate received

November 2019

-impurities data on Adenosine Triphosphate received

January 2020

-FDA 2020 VCRP data received

June 2020

-Draft Tentative report reviewed by Expert Panel

Adenosine ingredients Data Profile* – June 2020 – Writer, Priya Cherian																														
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Adenosine		X		X	X			X			X				X				X	X	X	X		X		X	X	X	
Adenosine Phosphate						X																								
Adenosine Triphosphate		**X**	X			X		X			X																	X	
Disodium Adenosine Phosphate																														
Disodium Adenosine Triphosphate			X					X															X	X	X				

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

[March 2020 Meeting - Adenosine – Writer: Priya Cherian]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Adenosine	58-61-7	yes	yes	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no	no	no	yes
Adenosine Phosphate	61-19-8	yes	yes	yes	yes	yes	yes	no	no	No	No	No	No	No	No	No	No	No	No
Adenosine Triphosphate	56-65-5	yes	yes	yes	yes	yes	yes	No	No	No	No	No	No	No	No	No	No	No	No
Disodium Adenosine Phosphate	4578-31-8	yes	yes	yes	no	yes	no	no	no	no	no	no	no	no	no	No	No	No	No
Disodium Adenosine Triphosphate	987-65-5	yes	no	yes	no	Yes	No	No	No	No	No	No	No	No	No	No	No	No	no

Typical Search Terms

- Adenosine
- Adenosine Phosphate
- Adenosine Triphosphate
- ATP
- Disodium Adenosine Phosphate
- Disodium Adenosine Triphosphate
- 58-61-7
- 61-19-8
- 56-65-5
- 4578-31-8
- 987-65-5
- cosmetic, irritation, dermal, sensitization, toxicity
- medicine
- skin irritation
- genotoxicity
- carcinogenicity
- metabolism

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm
- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

SEPTEMBER 2019 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 16, 2019

DR. BELSITO: Adenosine. So this is the first time we're looking at this. We need manufacture and impurities for all.

DR. LIEBLER: I had insufficient for impurities.

DR. BELSITO: And manufacture.

DR. LIEBLER: No.

DR. BELSITO: No?

DR. LIEBLER: I think we're okay there. There's nothing for impurities.

DR. BELSITO: Right.

DR. LIEBLER: So that's why -- I mean, we don't need a lot; we need a little.

DR. BELSITO: I was just struck by these additive effects and I thought we needed epidermal. We need dermal absorption to evaluate this data where you have tumor cell promotion. I said, would this be an issue when combined with ingredients close to clinically irritant levels since chronic irritation is often a promoter for carcinogenesis? The same thing with the effect on the histamine release on page 14. So I've got impurities and absorption.

DR. SNYDER: We do have some absorption data though. For dermal penetration.

DR. LIEBLER: Don, what were you pointing to with respect to tumor promotion, tumor cell proliferation?

DR. BELSITO: Yeah.

DR. LIEBLER: Now, that's another one of these in vitro, I think irrelevant. It's noted but not relevant. I mean, tumor cell -- this isn't tumor promotion; this is just tumor cell lines that you can buy from ATC, put them in culture plates, and treat them with stuff. And they either live or die.

And they're looking at DNA synthesis and cell proliferation. It doesn't tell you anything about what would happen in vivo or particularly in the skin. So, I mean, I don't even think any of these cell lines are skin cells. So I don't think this needs to be discussed in a discussion.

DR. HELDRETH: Do you think that this study is so irrelevant that you would remove it from the report?

DR. LIEBLER: Well, historically we've kept them in. We typically kept them in. I used to say, get rid of it, but I've been trained not to say that anymore. It doesn't really need to be commented on.

DR. BELSITO: Okay. So what about this effect on histamine release? And so, if it gets absorbed into the dermis, it could cause mast cell degranulation.

DR. LIEBLER: So these are at pretty high treatment concentrations that I think are -- this is at ATP release histamine at concentrations greater than 1 mg per mil. That's a lot.

DR. SNYDER: Yeah.

DR. BELSITO: Okay.

DR. SNYDER: And we have irritation and sensitization data dermal that doesn't --

DR. BELSITO: That's fine. Yeah. It's good.

DR. SNYDER: It's fine. So I think we're okay there.

DR. BELSITO: And, if you're not concerned about that, it's safe as used, right.

DR. KLAASSEN: Yeah.

DR. SNYDER: Well the impurities I thought you said?

DR. BELSITO: Oh, yeah, impurities.

DR. LIEBLER: Right. Yeah, I said insufficient for impurities, eventually safe as used. And I had some comments. Also, Priya, with this one -- this was one of the -- it's A, it was the first one I looked at. I just said, I suggest we -- under chemistry. I suggest we begin adding the CAS number and name for each structure in parentheses. Even though it's not the same as the dictionary listing.

If there are a handful of compounds, it's easy. Then in Table 1 we list the synonyms. And we do this with the RIFM reports, and I think it just helps clear up any chemical ambiguity. And sometimes there's real big ambiguity. But, I think, it would just be a good -- Bart, I think this would be a good routine thing to start doing in our reports from now on.

DR. HELDRETH: Okay. Instead of or in addition to?

DR. LIEBLER: In addition to the information that we have.

DR. HELDRETH: In Table 1, the listing of CAS numbers there?

DR. LIEBLER: Yeah. If there's a couple of compounds you can also do it in the text under the chemistry section.

DR. HELDRETH: Okay.

DR. LIEBLER: But, if we have a long list, obviously, then we just incorporate it into Table 1.

DR. HELDRETH: Okay.

DR. LIEBLER: And you can use your discretion as to maybe just only putting it in Table 1. I wouldn't argue with that. As long as it's findable by a reader to eliminate any ambiguity on the chemistry.

DR. HELDRETH: Yeah, this one has it in the table, but it's just a handful of chemicals so it should probably go in the text as well.

DR. LIEBLER: You can -- either way is fine with me. At some point it becomes a pain. You know, if you've got 12 ingredients you put 12 CAS numbers; if you have 20, you put 20. At what point do you not? So that's up to you guys as far as I'm concerned.

DR. HELDRETH: Yeah, our current SOP, it said, if we have essentially one chemical in the document, if it's just one ingredient under review, we'll put the CAS number right in the chemistry section and there is no Table 1.

DR. LIEBLER: Yeah. That's fine.

DR. HELDRETH: But, so far, once we create a Table 1, then that information gets moved.

DR. LIEBLER: Maybe that's the most practical way to handle it. If you're going to have a Table 1, put it in a table.

DR. HELDRETH: Okay. Now, typically we've been leaving out synonyms.

DR. LIEBLER: Well, I think having the CAS numbers is most important. You don't necessarily need to put synonyms in unless there's a common usage synonym that's very common. You encounter that when you're reading and that could confuse interpretation for some reason. Then you could put it in and explain it.

DR. HELDRETH: Yeah. At one point, decades ago, CIR reports had every possible synonym listed for every ingredient in there. But I think at some point somebody decided that was confusing. So we removed them all.

DR. LIEBLER: Okay. Anyway, I would say the CAS number, synonym only if it's necessary to explain something.

DR. HELDRETH: Okay.

DR. LIEBLER: But yeah, if we could get those impurities we're safe.

MS. CHERIAN: Was there any concern for the DART study on page 13?

DR. BELSITO: I said, do we need in discussion at 1 percent topical, not an issue, although we don't have great absorption data?

DR. SNYDER: What page was it on?

DR. BELSITO: Page 13, Adenosine. It was administered IP at doses of 50, 100, 150 milligrams.

DR. SNYDER: No, no. No, no, no. Yeah, that's right. It was an IP study. That's right.

DR. BELSITO: Do we need to put it in the discussion?

DR. SNYDER: No.

DR. HELDRETH: You said the exposure was well above what you could get from cosmetics --

DR. SNYDER: Bypass everything. Bypass it. Yeah. No.

DR. BELSITO: We don't have carcinogenicity. I don't think we need that.

DR. SNYDER: No, no. We're fine.

DR. BELSITO: The effects on histamine release were very high doses. Guinea pig max was okay.

I just had one question, Priya, on page 12. The human dermal penetration you quote this Norwegian Food Safety Authority. The application of a cream containing Adenosine at low concentration, they didn't specify what that meant?

MS. CHERIAN: Those were the only details that were given.

DR. BELSITO: Pretty miserable detail. Okay. And it also didn't say the time?

MS. CHERIAN: No.

DR. BELSITO: Oh, at 30 seconds after application, there was no absorption. Okay. I think we need impurities and then safe as used.

DR. LIEBLER: Right.

DR. BELSITO: Okay. We're done.

DR. LIEBLER: Good.

DR. BELSITO: It's 12:06.

DR. LIEBLER: Lunch.

DR. BELSITO: Back at 1:00.

Marks Team – September 16, 2019

DR. MARKS: This is the first review of these five ingredients. They're naturally occurring in the human body. They have multiple functions. As I always do, Tom and Ron, are these five ingredients okay?

DR. SLAGA: Yes.

DR. MARKS: Ron, you're fine with the five ingredients? There's no outlier here?

DR. SHANK: I had some questions about the sensitization data on Adenosine. One was, can we rely on the risk profile provided by the Norwegian Food Safety Authority? I'm not familiar with that. The disodium adenosine triphosphate was negative in an HRIPT test at a concentration of 1.5 percent. In the maximum concentration, the leave-ons is only 0.1 percent. So, it's well above that. But there are no sensitization data for adenosine phosphate.

So can't we use the disodium adenosine triphosphate for read-across on that? I think we can. If so, then we wouldn't need sensitization data; and we could just say when formulated to be non-irritating to the skin and lungs would be safe.

DR. MARKS: Ron, I thought we did have some sensitization data on Adenosine. Its use is 1 percent. I thought we had an HRIPT at 0.2 percent, which was okay. Now, that's less than the use concentration but I think the read-across with the disodium adenosine triphosphate would cover that difference.

Now am I wrong in terms of having HRIPT at 0.2 percent? Let me see. I don't have a page on that.

MS. FIUME: PDF page 15, Dr. Marks.

DR. MARKS: And was that the right --

MS. FIUME: PDF page 15. Yes.

DR. MARKS: Let's see. Yeah. If you look under human adenosine an HRIPT containing 0.2 percent adenosine showed no evidence of sensitization. I think, again, with what we have for the other ingredient and with this HRIPT, I agree from a sensitization point of view it looks okay.

How about irritation? The HRIPT, the Magnusson-Kligman, there was no irritation. And we go above; there was slight erythema observed with 0.2 percent adenosine. Is that what you were basing your irritation on, that human irritation study?

DR. SHANK: Yes.

DR. MARKS: Okay. And that's, of course, less than the maximum concentration. I had flagged, do we need the impurities on page 11? No impurities data was found in the published -- and that oftentimes becomes a sticking point whether we can declare ingredients safe if we do not have the impurities.

DR. SLAGA: I didn't have any problem with the impurities. Being such a common natural product in every cell. The chemistry shouldn't be that difficult with impurities.

DR. SHANK: We have a lot of toxicology data, and I think if there was a problem with impurities those toxicology tests would have detected a problem. And they did not. So, I don't think impurities is a need.

DR. MARKS: Okay. So, I'll move that a tentative report be issued with a safe when formulated to be non-irritating.

MR. GREMILLION: There's a reference to a reproductive development that was kind of cryptic that I gather that just the abundance of the other evidence outweighs that. Sorry, I lost it as --

DR. MARKS: Page 13?

MR. GREMILLION: Yeah. The Adenosine intraperitoneal. Is that just an outlier or something?

DR. SHANK: Intraperitoneal injection provided a blood concentration much higher than would be achieved during the application of the cosmetic. So it's --

DR. BERGFELD: Microphone.

DR. SHANK: The study used the intraperitoneal route daily for five days at relatively high concentrations as compared to cosmetic use. So the blood concentrations would be much higher than would be achieved in cosmetic use. This is a known biochemical intermediate in human biochemistry. So, it would be very unlikely that this would be a reproductive toxin.

DR. MARKS: Okay. Any other comments?

MS. CHERIAN: Were there any concerns on the clinical inhalation studies?

DR. SHANK: I'm sorry. What did you say?

MS. CHERIAN: Were there any concerns on the clinical inhalation studies?

DR. SHANK: At most, they would be irritation. And we're saying this one's formulated to be non-irritating to skin and lungs.

DR. MARKS: Okay. Any other comments? Priya, did that answer your question? Good. Any other comments? If not, then tomorrow, I'll move our team wants to move forward with a tentative report of these five ingredients, safe when formulated to be non-irritating. Okay.

MR. GREMILLION: I'm sorry.

DR. MARKS: No, that's okay.

MR. GREMILLION: Is that understood to be -- that's not getting into the safe when formulated to be non-respirable kind of --

DR. SHANK: No.

DR. MARKS: Correct.

MR. GREMILLION: I mean, should there be some consideration about manufacturers inhalation hazards that goes beyond just that boilerplate?

DR. MARKS: I'll let Ron Shank answer that.

DR. SHANK: What is your question about?

MR. GREMILLION: I guess it gave me pause to hear that there's inhalation hazards. And from what I understand, you're saying that gets into the irritation. So, if there's a note that the manufacturers should formulate as to be non-irritating, then that will cover the inhalation risk.

And that brought me back to the whole discussion of whether there should be messages to formulate to be non-respirable and the decision to move away from that. So, I just wondered how that relates to -- I mean, here we've got an inhalation risk.

MR. ANSELL: I hesitate to characterize it as indicating there's a risk. I mean, these were asthmatic patients with whopping great doses delivered directly to the lung. That's not suggestive necessarily that its use as a cosmetic would present a risk.

DR. SHANK: Correct. In this case, it's just a simple irritation. We don't have a serious toxicological response that would say it cannot be inhaled. It can be inhaled as long as it's non-irritating. So it is a little different from a lot of the other compounds we've reviewed where there is a toxicological risk other than irritation.

MR. GREMILLION: Thanks. That's helpful.

DR. MARKS: Ron, from Priya's point of view, do you think we should include that in the discussion? Since you raised the question, I think, should we add a short paragraph in the discussion indicating why we're not concerned about the inhalation toxicity; one, the conduct of the study that showed some adverse effects?

MR. ANSELL: Again, they did not show adverse effects.

DR. MARKS: Oh, okay. How do you want to phrase it, Jay?

MR. ANSELL: Well, I think the studies were assessed and do not present a concern relative to its end use application. I'm not sure delivering a dose of material directly to the lung to asthmatics, which induced five coughs more quickly, is an

indication of toxicity. It's uninterpretable at best. So, I think that the studies are there. But I object to the characterization that this is an indication of toxicity.

DR. SHANK: I agree with that. I don't think it needs to be discussed.

DR. MARKS: Okay. Good. I wanted to clarify that. Since it became a discussant point here, I wanted to be sure we didn't overlook that in the final report.

DR. SHANK: Okay?

DR. MARKS: Okay. Onto Quaternium-18. And that's a re-review.

Full Panel – September 17, 2019

DR. MARKS: So, this is the first time that the panel is reviewing these five adenosine ingredients. These five ingredients are naturally occurring in the human body. They have multiple functions. After our team's review we felt we could issue a tentative report and move that the conclusion be safe when formulated to be non-irritating.

DR. BERGFELD: And that's your motion?

DR. MARKS: Yes.

DR. BERGFELD: Is there a second to that, or a comment?

DR. BELSITO: We were concerned about the lack of information about impurities, and we're requesting that.

DR. MARKS: Yeah, Ron Shank addressed this. He felt that we did not need impurities. Ron, I'll ask you to illuminate if you want. He felt, if I interpreted it correctly, that we have lots of toxicological data, which supported its safety. And, it being naturally occurring that we didn't need the usual impurities box checked.

DR. BERGFELD: Ron, do you want to make another comment?

DR. SHANK: If there were impurities at toxicologically significant levels, the toxicology testing should detect those impurities. And the toxicology data show no effect. So I don't see the reason to ask for impurities.

DR. MARKS: I think that could be handled in the discussion why, at least our team feels it. I'm not sure yet -- I can see Dan over there ready to respond to Ron Shank. Yes.

DR. LIEBLER: So, as the head box checker for impurities and chemistry, I think that it would be easy for me to accept Ron's argument in the case of adenosine in these ingredients because we know that these are metabolic intermediates, they are present in everything we eat; they're ubiquitous. And as he said, the tox data, you know, indicates that they're very safe.

I think it would not be difficult for industry to supply some reasonable -- even if minimal -- impurities data would satisfy this. But I think it's something that we just need to rigorously stick to. Particularly, when we get to other ingredient families where they don't have that trust factor hardwired into the nature of the group. That's why I feel we need to check that box.

DR. BERGFELD: Curt, any comment?

DR. KLAASSEN: Well I understand what Ron's saying. And, I guess, I'd rather go along with the idea that we tried to get some of this information, which they probably have. And then, there could be a slippery slope here of, you know, you might not need really -- if what you're saying about adenosine, and its analogs, you know, if there wasn't any great toxicity, so therefore you don't need any additional information on contaminants. But then you can say that for every chemical.

DR. LIEBLER: You can't permit impurity impunity.

DR. KLAASSEN: So, I'd rather ask for it; not that it's a big deal.

DR. BERGFELD: Tom?

DR. SLAGA: I personally agree with Ron. Adenosine is ubiquitous, period; throughout our bodies, everything we eat. I mean, it shouldn't be a difficult compound to make. On the other hand, I understand that it would be nice to double check that box. But in this case if it wasn't adenosine, I'd guess I would say, yes, we need to check the box, but I don't think we need to.

DR. MARKS: I guess I'd add, if perhaps we do issue an insufficient data announcement, and we do not get the impurities, are we going to go forward with an insufficient or are we going to come back to this reasoning and declare safe?

DR. SLAGA: That's a good point.

DR. MARKS: So any rate, I'll just bring that issue up looking down the line. Presumably, Dan, you're right, we should be able to get some impurities data from industry. But I'm thinking if we don't, are we going to change our conclusion from insufficient to safe?

DR. BERGFELD: Well, we don't have a second.

DR. SHANK: Is there an answer to that question?

DR. BERGFELD: I need a second to move forward or more comments. Jay, do you want to comment? No? Okay.

DR. MARKS: Ron, sounds like we're sticking with you.

DR. SHANK: I think it's, looking ahead when it comes time to make this a final report, and the only insufficiency is impurities data; are we going to stick to insufficient data report?

DR. LIEBLER: I'm willing to bet you a case of Maker's Mark that we would get the data.

DR. BERGFELD: Don?

DR. BELSITO: I mean, we also don't -- I mean, yes, adenosine is naturally occurring. But the adenosine that's occurring that is being used in cosmetics is not naturally occurring adenosine, it's manufactured.

And we have a very brief description of the manufacturing of adenosine and adenosine triphosphate. And it just says, you know, "include chemical synthesis, RNA degradation, and microbial fermentation" and that bacillus subtilis is used. It doesn't say anything about the solvents -- anything else. So we really don't have detailed information as to the manufacturing process here, as opposed to naturally occurring adenosine in the body, which is not synthetically made.

And we have no idea in our studies, the tox studies, what the nature of that adenosine that was used. Is it the same adenosine, adenosine triphosphate that's used in cosmetics or not. So, I think it would be nice to get a little bit more information on manufacturing and impurities.

And if we don't get it then we'll have to think about how we want to proceed. I mean, this is the first time we're looking at this, so I don't see that there's a rush to get it off our plate.

DR. BERGFELD: So, it would go out as an insufficient data announcement?

DR. BELSITO: Yeah, I mean, it's not going to be a hard re-review; we either get it or we don't get it, and then we decide, you know, how much to trust the tox data.

DR. SADRIEH: I just wanted to just mention, you know, that formaldehyde also can be naturally occurring. And so just because something is naturally occurring it doesn't mean that one does not have to look at the data. I don't know whether it's relevant here or not, but I think depending on whether something is naturally occurring to support the safety may not be the best way. One has to look at the data.

DR. BERGFELD: Thank you. Do we want to restate the motion?

DR. SHANK: The point is not that it's naturally occurring; it's that we have toxicology testing data on the ingredient. And if there were impurities at a toxicologically significant concentration in the ingredient, the toxicity test would show that. It's not an issue that it's a natural biochemical.

DR. SADRIEH: I don't know that all toxicology studies are done with characterized materials where the levels of impurities and the characterization of the impurities is done. Just assuming negative results -- I'm just speaking from a general perspective.

Because there are negative results doesn't mean that had there been any impurities, not knowing what those impurities may have been and what the levels were, that that's somehow acceptable. It's just still not supported by actual data. I don't know that because a lack of data means safety, that's just not, you know, acceptable.

DR. SHANK: It's not a lack of data; we have data on the toxicity.

DR. SADRIEH: A lack of characterization data in the presence of impurities.

DR. BERGFELD: All right. We stand with the motion that's not been seconded. Jay, did you want to say something?

DR. ANSELL: You know, I think in this particular case that you can request, you know, it's okay and we should have some information. But, the conversation has become, I think, broader.

And I have to say that the request from the panel should not be trivial. I mean, when you ask for something we really do attempt to develop that data. And if the answer to the question is going to be irrelevant, you know, we think that we would request that the request be substantive. And because that there is an impact on industry and staff to dig up these information.

DR. LIEBLER: We always document impurities in our reports, period.

DR. BERGFELD: All right, coming back to you Dr. Marks. The motion you proposed, are you changing it or sticking with it, because we're going to call the question. We need a second on your motion.

DR. SHANK: Oh, I'll second. The motion is to go insufficient.

DR. MARKS: No.

DR. BERGFELD: Safe.

DR. SHANK: Safe, yeah.

DR. SNYDER: You almost had him.

DR. BERGFELD: Are we going to call the question then?

DR. MARKS: Sure.

DR. BERGFELD: The motion is to go safe. And it's been seconded by Ron. So, all those in favor of a safe conclusion please indicate by raising your hand. So there are three. Okay. And, one, two, three, four -- four against. And so, I guess the against get it. And so we will go out as a -- or at least if we have a motion to go out as getting the impurities as an insufficient.

DR. BELSITO: Insufficient for impurities.

DR. BERGFELD: So you want to propose, again, the motion?

DR. BELSITO: Insufficient for impurities.

DR. BERGFELD: Thank you. Is there a second?

DR. SNYDER: Seconded.

DR. BERGFELD: Second. All those in favor, please indicate by raising your hand. Okay, unanimous. Thank you, very much. Interesting.

Okay, Quaternium-18, Dr. Belsito.

Safety Assessment of Adenosine Ingredients as Used in Cosmetics

Status:	Draft Tentative Report for Panel Review
Release Date:	May 15, 2020
Panel Meeting Date:	June 8 - 9, 2020

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate. These ingredients are reported to function as skin-conditioning agents – miscellaneous. The Panel considered the available data and concluded that … [to be determined].

INTRODUCTION

This is a safety assessment of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients function as skin-conditioning agents – miscellaneous.[1] (Table 1) These adenosine ingredients are being reviewed together due to their structurally similarities.

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.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[2] These summaries are available on the ECHA website, and when deemed appropriate, information from these summaries have been included in this report.

CHEMISTRY

Definition and Structure

The definitions and structures of the ingredients included in this review are provided in Table 1. All of these ingredients share Adenosine (CAS No. 58-61-7; Figure 1) as the core structure.

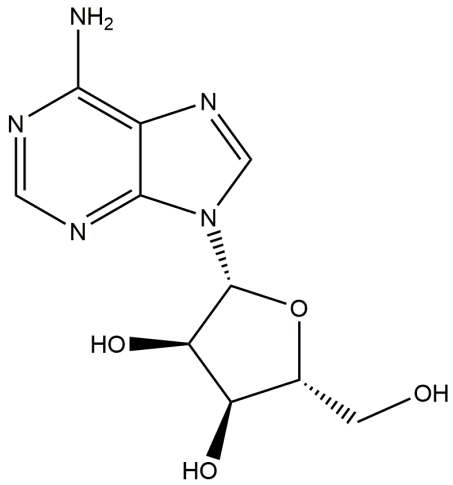


Figure 1. Adenosine

Adenosine Triphosphate (ATP; CAS No. 56-65-5) is composed of a purine nucleoside esterified with a triphosphate.[3] Adenosine Triphosphate is a ubiquitous organophosphate that connects anabolism and catabolism, but also fuels processes such as motile contraction, phosphorylations, and active transport.[4] Both Adenosine and Adenosine Phosphate (AMP; CAS No. 61-19-8) are formed when Adenosine Triphosphate is consumed in metabolic processes. Adenosine, a ribonucleoside comprising adenine and ribose, exerts pleiotropic functions throughout the body, primarily by interaction with G-protein coupled receptors.[5] Adenosine Phosphate is an ester of phosphoric acid and Adenosine. Like Adenosine Triphosphate, Adenosine Phosphate plays an important role in many cellular metabolic processes, and is an intermediate in the synthesis of nucleic acids.

Physical and Chemical Properties

The ingredients named in this report (with reported properties) are solids at room temperature and are soluble in water. Available information on the physical and chemical properties are presented in Table 2.

Method of Manufacture

These methods are general to the production of Adenosine and Adenosine Triphosphate; no methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data.

Adenosine

The main methods of manufacturing Adenosine include chemical synthesis, RNA degradation, and microbial fermentation.[6] *Bacillus subtilis* is commonly used as it is a safe and stable producer of purine nucleosides.

Adenosine Triphosphate

Adenosine Triphosphate may be produced by microbial phosphorylation of Adenosine Phosphate.[7]

Impurities

Adenosine

A supplier reported that Adenosine has a purity of ≥ 99%.[8]

Adenosine Triphosphate

A supplier reported the following impurities for Adenosine Triphosphate: < 2% Adenosine Phosphate, < 2% Adenosine diphosphate, and < 0.01% methanol.[9]

Disodium Adenosine Triphosphate

Disodium Adenosine Triphosphate used in a trade name mixture sold to the cosmetic industry was reported to be free from carcinogens, mutagens, and reproductive toxicants (CMR) as defined by European Union (EU) chemical regulations, and from phthalates, pesticides, and glycol ether.[10] Additional details 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. Use concentration 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, Adenosine has the highest frequency of use, with a total of 905 formulations (Table 3).[11] Adenosine is most commonly used in face and neck products (313 formulations) and moisturizing products (262 formulations). Disodium Adenosine Triphosphate is reported to be used in 116 formulations, 100 of which are leave-on formulations. The remaining in-use ingredients are reported to be used at 96 formulations or less. The results of the concentration of use survey conducted by the Council indicate that Adenosine has the highest concentration of use; it is used at up to 1% in body and hand products. [12] Disodium Adenosine Phosphate is not reported to be in use.

These ingredients have been reported to be used around the eyes (e.g., at up to 0.5% Adenosine Phosphate in mascara). In addition, Adenosine could result in incidental ingestion as it is used in lipstick and dentifrices (concentrations of use not reported). Some of the adenosine ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Adenosine is reported to be used at 0.041% in spray moisturizing formulations, and Adenosine Phosphate is used in aerosol hair spray formulations at up to 0.04%. 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.[13,14] 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., would not enter the lungs) to any appreciable amount.[15,16] Adenosine is reported to be used in face powders at concentrations up to 0.1% and could be incidentally inhaled. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[17-19]

All of the adenosine ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[20]

Non-Cosmetic

Adenosine

According to the US FDA, Adenosine is used for the treatment of paroxysmal supraventricular tachycardia and approved for use in nuclear stress testing in patients who cannot exercise adequately.[21] Adenosine is typically given intravenously at a dose of 3 mg/mL.[22] In 2013, the FDA issued a warning informing health care professionals of the rare but

serious risk of heart attack with the use of Adenosine-containing drugs in nuclear stress testing. Health care professionals are advised to avoid using this ingredient in patients with signs or symptoms of unstable angina or cardiovascular instability. In addition, Adenosine is used to treat surgical and nerve pain, and pulmonary hypertension.[23,24]

Adenosine Phosphate and Adenosine Triphosphate

According to 21 CFR 216.24, all drug products containing Adenosine Phosphate or Adenosine Triphosphate were withdrawn or removed from the market because the product or product components were found to be neither safe nor effective for its intended use as a vasodilator and anti-inflammatory. Adenosine Phosphate is used in the therapeutic treatment of herpes, post-herpetic neuralgia, photosensitivity, and porphyria cutanea tarda.[25-27] Adenosine Triphosphate has been previously reported to treat acute kidney failure, high blood pressure, cystic fibrosis, and lung cancer.[28,29]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Adenosine

In a dermal penetration study, human skin samples (500 µm thick) were mounted in stainless steel doubly jacketed diffusion cells.[30] The acceptor solution consisted of phosphate buffered saline and the test substance consisted of Adenosine (1.5 or 3%) in propionic acid, (0.5%) in hexanoic acid, or (1.5%) in a binary vehicle of propionic and hexanoic acid. A volume of 450 µL of the test substance was pipetted into the donor reservoir. Perfusate samples were collected after 25 or 30 min, and analyzed. The observed optimal permeability coefficients (K_p) of Adenosine from the binary vehicle, propionic acid solution, and hexanoic acid solution were 0.0004, 0.00012, and 0.00016 cm/min, respectively.

Human

According to a risk profile from the Norwegian Food Safety Authority (NFSA), it is believed that application of a cream containing a low concentration of Adenosine to skin (thickness of 2 mg/cm^2) would result in absorption of up to 2% Adenosine.[31]

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Adenosine Phosphate

Male and female Wistar rats (number of animals not stated) were given a single dose of 10 mg/kg [^{14}C]-Adenosine Phosphate dissolved in 9% aqueous sodium chloride via gavage.[32] The specific activity of the [^{14}C]-Adenosine Phosphate was reported to be 46 mCi/mmol. Within 72 hours of administration, 28% of the injected activity was excreted in the urine and 6% was recovered in the feces. Plasma levels of Adenosine Phosphate were maximal approximately 30 min after oral administration. Adenosine Phosphate was considered to be rapidly absorbed by the intestinal mucosa and quickly distributed two hours after absorption; only 20% of the maximal concentration remained in the plasma.

Human

Oral

Adenosine Triphosphate

Eight volunteers were given single doses of 5000 mg Adenosine Triphosphate or placebo via an ingested pellet targeted at release in the proximal or distal small intestine, or via a naso-duodenal tube.[33] Blood Adenosine Triphosphate and metabolite concentrations were monitored by high performance liquid chromatography (HPLC) 4.5 hours (naso-duodenal tube) or 7 hours (pellets) post-administration. Adenosine Triphosphate concentrations in the blood did not increase after supplementation of Adenosine Triphosphate via pellets or naso-duodenal tube. Concentrations of uric acid were significantly increased compared to placebo by approximately 50% after administration via proximal-release pellets and naso-duodenal tube, but not after administration via distal-release pellets. The mean time to peak uric acid concentration was shorter for naso-duodenal tube administration (75 to 195 min) as compared to the pellet administration (150 - 390 min).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Adenosine

An LD_{50} of > 2000 mg/kg bw was established for mice given Adenosine orally.[31] No other details regarding this study were provided.

An acute oral toxicity study on Adenosine was performed on female Wistar rats (3 rats/group) according to Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 423.[2] In both groups, the test substance (Adenosine in methylcellulose) was given at a dose of 2000 mg/kg bw. Animals were observed for 14 days following treatment and killed on day 15. All rats survived treatment and no treatment-related clinical symptoms were observed. Necropsy revealed pale kidneys in two animals of group 1 and all animals of group 2. The LD_{50} was reported to be > 2000 mg/kg bw.

Adenosine Triphosphate

The oral LD_{50} of Adenosine Triphosphate was reported to be > 2000 mg/kg in rats.[34] No other details regarding this study were provided. In a different study, groups of 5 male anesthetized New Zealand White rabbits were given 2 or 20 mg/kg Adenosine Triphosphate via a gastric cannula.[35] The test substance did not have an effect on diastolic aortic pressure, heart rate, central venous pressure, iliac venous blood flow, lung resistance, or the arterial partial pressure of oxygen (Pa_{O2}).

Disodium Adenosine Triphosphate

An oral LD_{50} of > 2000 mg/kg was reported for both mice and rats treated with Disodium Adenosine Triphosphate.[36] No other details regarding these studies were provided.

Short-Term Toxicity Studies

Oral

Adenosine and Adenosine Triphosphate

New Zealand White rabbits were given doses of either 3 mg/kg/d (n = 4) or 20 mg/kg/d (n = 12) Adenosine Triphosphate mixed with cellulose, or 20 mg/kg/d adenosine hemisulfate salt (n = 4) for 14 days.[35] Adenosine Triphosphate and adenosine hemisulfate, dissolved in saline, were administered daily via gastric cannula. Control rabbits received a corresponding amount of saline. No modification of electrocardiogram morphology or heart rate was detected in treated animals compared to controls. Central venous and arterial pressures were comparable in all groups. After treatment with 3 and 20 mg/kg/d, increases of 30 and 50% in the intervillous vein blood flow (IVBF) were observed, respectively. The left ventricular work index (LVWI) was significantly increased by 10% in animals given 20 mg/kg/d Adenosine Triphosphate. In addition, treatment with the higher dose level led to a 12.5% decrease of the spontaneous respiratory frequency. A 26% reduction of lung resistance was noted in all Adenosine Triphosphate-treated groups. Increases of 22 and 23% of Pa_{O2} were observed in rabbits treated with 3 mg/kg/d and 20 mg/kg/d Adenosine Triphosphate, respectively. Similar results were noticed in rabbits treated with adenosine hemisulfate; however, lung resistance and Pa_{O2} levels remained unchanged.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Intraperitoneal

Adenosine

Adenosine (50, 100, and 150 mg/kg) was administered intraperitoneally to mice and rats once a day for 5 days.[31] Decreased spermatogenesis and increased numbers of abnormal sperm were noted. No other details regarding this study were provided.

GENOTOXICITY

In Vitro

Adenosine

The potential mutagenicity of Adenosine (up to 333 µg/plate, vehicle not stated), was evaluated in *Salmonella typhimurium* (TA98, TA 100) in an Ames assay performed without metabolic activation.[37] The test material was considered to be non-genotoxic. Similarly, negative results were obtained in an Ames assay performed with and without metabolic activation on Adenosine in dimethyl sulfoxide (DMSO; up to 5000 µg/plate) using *S. typhimurium* (TA97, TA98, TA100, TA1535, TA1537, TA1538) and *Escherichia coli* (WP2 uvrA).[2]

The genotoxicity of Adenosine was also evaluated in a Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase (CHO/HGPRT) assay.[38] Adenosine in DMSO was not genotoxic when tested at up to 2000 µg/mL, with and without metabolic activation.

CARCINOGENICITY STUDIES

No data regarding the carcinogenicity of these ingredients were found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Adenosine

The cytotoxic effect of Adenosine in Swiss albino mouse embryo fibroblasts (3T3 and 3T6) and immortalized cervical cancer (HeLa) cells, cultured with and without adenosine deaminase, was studied.[39] [^{14}C]-Adenosine (0.2 - 2.5 µCi) was diluted with unlabeled Adenosine (to 10^{-5} - 10^{-3} M) in 0.3 mL of a solution containing serum-free medium, 50 mM phosphate buffer, and 10% serum. Both calf and horse serum were used; however, horse serum did not contain adenosine deaminase. Cells were exposed to Adenosine at concentrations of 0, 0.002, 0.005, 0.01, 0.02, 0.20, 1.0, and 2.0 mM, and cultures were observed over a period of 1 week. When Adenosine was added to cell cultures in a medium containing horse serum, it was found to be toxic at low concentrations. In 10% calf serum, there was no effect on cell growth at low or moderate Adenosine concentrations, while in medium containing 10% horse serum, there was definite inhibition of growth at a concentration of 0.005 mM and a killing of cells at 0.02 mM. Cell inhibition in calf serum was observed when Adenosine was used at concentrations of 1.0 mM and higher. When the same experiment was performed with horse serum with the addition of 1mM uridine to the cell culture medium, toxic effects were not observed at any concentration up to 0.2 mM.

Tumor Cell Proliferation

Adenosine

The effects of Adenosine on DNA synthesis and cell growth in human (HT-29, T84, HRT-18, Colo320HSR) and mouse (MCA-38) colorectal carcinoma cell lines were studied.[40] Cells were seeded in 24-well plates at 20,000 cells/well. Adenosine was added at final concentrations of 1 µCi/mL, 1 µM, with [methyl-[^{3}H]-thymidine. Plates were incubated for 36 - 48 hours. DNA synthesis and cell proliferation were stimulated in all cell lines tested, with a half maximal effective concentration (EC_{50}) of 2.8 - 30 µM, and a maximum stimulation being reached at 10 -100 µM.

Effect on Histamine Release

Adenosine Phosphate and Adenosine Triphosphate

Thirty-nine patients with various dermatoses were used in a study evaluating histamine release from human cutaneous mast cells following intracutaneous injection with the polycondensation product of *N*-methyl-*p*-methoxyphenethylamine with formaldehyde (compound 48/80; causes histamine degranulation from mast cells), Adenosine Triphosphate, adenosine diphosphate, or Adenosine Phosphate.[41] Solutions of Adenosine Triphosphate (60 mg/mL), adenosine diphosphate (30 mg/mL), Adenosine Phosphate (37 mg/mL), and compound 48/80 (1 mg/mL) in distilled water were prepared. The pH of these solutions was adjusted to 7.0 with sodium hydroxide. Subjects were injected with 0.02 mL of each solution. In addition, histamine dihydrochloride was also injected (1, 3, and 10 µg/mL), and used to compare the responses elicited from the test substance. Injections of approximately 6 mg/mL Adenosine Triphosphate caused a flare response similar to that of histamine at < 10 µg/mL. Adenosine Triphosphate released histamine at concentrations > 1 mg/mL, while compound 48/80 stimulated histamine release in skin at concentrations > 1 µg/mL. Adenosine diphosphate had a weaker releasing effect, and Adenosine Phosphate did not induce histamine release. In order to determine that the skin reaction was due to released histamine, the study was repeated in 17 subjects with the addition of the antihistamine chlorcyclizine. After administration of the antihistamine and Adenosine Triphosphate, the area of the flare decreased significantly.

The effects of intradermal injections of Adenosine Phosphate and Adenosine Triphosphate, as compared to intradermal injections of histamine, were evaluated.[42] The backs of subjects were injected with 50 µL isosmotic phosphate buffered saline containing Adenosine Triphosphate, Adenosine Phosphate, histamine, compound 48/80, or phosphate-buffered saline alone. Injections were carried out in 2.5-min intervals. The area of erythema induced by the injection was delineated at 30 seconds and after 4.5 min. Solutions that were extremely acidic were neutralized with sodium hydroxide prior to injection. Injection of Adenosine Triphosphate resulted in immediate erythematous reaction of the surrounding skin. This reaction faded after one min, and was replaced by slightly darker erythema that lasted for up to 2 hours. The extent of these reactions was dose-dependent. No wheals were formed after injection with Adenosine Phosphate or phosphate-buffered saline. Adenosine Triphosphate produced wheals in 5 out of 7 subjects injected with 180 nmol, and in all subjects at higher doses, in a dose-dependent manner. Wheals that resulted from 1080 nmol Adenosine Triphosphate were approximately equal to wheals due to histamine (1.63 nmol). Injections of Adenosine Triphosphate at high doses produced sensations of persistent pain which was not observed with injection of saline or histamine.

In order to evaluate the role of histamine and prostaglandins in the inflammatory response to Adenosine Triphosphate, the study was also performed with the addition of pre-treatment with an antihistamine (diphenhydramine, cimetidine, indomethacin, or doxantrazole). Erythema and wheal responses were significantly suppressed with the addition of diphenhydramine pre-treatment. Indomethacin, doxantrazole, and cimetidine did not alter the Adenosine Triphosphate reaction.

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

Adenosine

An in vitro skin irritation study was performed using reconstructed human epidermis according to OECD TG 439.[2] Ten mg of Adenosine (in powder form; concentration not provided) were applied to the epidermal surface. (The epidermal surface was first moistened with 5 µL deionized water to improve contact between the powder and the epidermis.) Phosphate buffered saline and sodium dodecyl sulfate (5%) were used as the negative and positive controls, respectively. The test substance did not significantly reduce cell viability compared to the negative control. The test substance was predicted to be non-irritating to the skin.

Animal

Adenosine

According to a risk profile from the NFSA, Adenosine was non-irritating to animal skin in multiple conventional tests.[31] No other details regarding these studies were provided.

Human

Adenosine

A 48-hour patch test was performed on 10 subjects.[43] Each subject received an occlusive patch with 15 µL of a cosmetic ingredient containing 0.2% Adenosine on the inside upper arm. Skin reactions were evaluated 1, 24, and 48 hours after patch removal. One hour after patch removal, slight erythema was observed on one volunteer. However, after 24 and 48 hours, no skin reaction was observed in any subject.

Sensitization

Animal

Adenosine

According to a risk profile from the NFSA, Adenosine was non-sensitizing in a Magnusson and Kligman maximization study.[31] No other details regarding this study were provided.

Disodium Adenosine Triphosphate

A Magnusson-Kligman test was performed on Pirbright white guinea pigs (number of animals not stated).[44] The test substance was a trade name mixture containing 15% mannitol and 15% Disodium Adenosine Triphosphate. A 0.5% aqueous dilution of the test substance (i.e., 0.075% mannitol and 0.075% Disodium Adenosine Triphosphate) was used for the intracutaneous induction, and a 10% aqueous dilution of the test substance (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate) was used for the epicutaneous induction and challenge. No signs of irritation or skin reactions indicative of an immune response were observed.

Human

Adenosine

A human repeated insult patch test (HRIPT) was completed in 205 subjects using a test material containing 0.2% Adenosine.[43] Each of the subjects received 0.2 mL of the test substance on the upper back area under a semi-occlusive patch. After a 24-hour exposure period, the patches were removed and sites were evaluated. A series of 9 test patches were applied followed by a 2-week non-treatment period. Challenge patches were applied to previously unexposed sites and allowed to remain in skin contact for 24 hours. Challenge sites were scored at 24 and 72 hours post patching. No signs of sensitization were observed.

Disodium Adenosine Triphosphate

An HRIPT was completed on 50 volunteers using a trade name material consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate.[44] A 10% aqueous dilution of the trade name material (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate) was applied to the backs of subjects under an occlusive patch for a total of 9 applications within a

3-week period. A challenge patch was applied 2 weeks later to the previously exposed area, as well as an unexposed area. Readings were taken 24, 48, and 96 hours after patch removal. No skin reactions were noted in any volunteers.

Phototoxicity/Photosensitization

Human

Disodium Adenosine Triphosphate

A phototoxicity study was conducted with a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate in 10 volunteers.[44] A 10% aqueous solution of the trade name mixture (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate; 0.2 mL) was applied under an occlusive patch to two different areas of the forearm, one irradiated and one non-irradiated. After a 24-hour exposure, one site was irradiated with long-wave ultraviolet (UVA) light (320 - 400 nm) for 15 min; the other test site served as a non-irradiated control. Skin reactions were scored immediately after light exposure as well as 24 and 48 hours later. No reactions were noted on either the irradiated or non-irradiated test site in any subject.

A photosensitization test was completed on 34 subjects with a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate .[44] For 3 weeks, six 24-hour induction patches were applied containing a 2% aqueous solution (i.e., 0.3% mannitol, 0.3% Disodium Adenosine Triphosphate) of the trade name mixture. Applications were performed in duplicate; one site was subsequently irradiated with UV light (260 - 400 nm) for 15 min each session. After 2 weeks, a challenge patch was applied at virgin sites with and without irradiation. At the challenge phase, no skin reactions were exhibited at either the irradiated site or the non-irradiated site.

OCULAR IRRITATION STUDIES

In Vitro

Adenosine

According to a risk profile from the NFSA, Adenosine was predicted to be slightly irritating to the eyes in an in vitro hen's egg test-chorioallantoic membrane (HET-CAM) assay.[31] No other details were provided for this study.

Animal

Adenosine

A Draize assay was performed on 3 Japanese White rabbits according to OECD TG 405.[2] The test substance, 100 mg undiluted Adenosine, was instilled into the left eye of each animal. The eyes, which were not rinsed, were observed for 21 days. The test substance was considered to be non-irritating to the eye.

CLINICAL STUDIES

Effects of Inhalation

Adenosine

The effect of inhaled Adenosine was studied in 8 asthmatic subjects.[45] Before administration of Adenosine, two baseline blood samples were taken, and five baseline measurements of specific airway conductance (SG_{aw}) were made. Volunteers then inhaled a single sample of Adenosine, ranging from 0.6 to 6.7 mg/mL. The test material was nebulized from a volume of 4 mL in disposable nebulizers driven by compressed air at 8 L/min. Approximately 0.5 mL of the test solution left the nebulizer as an aerosol each minute; 12.5% of this entered the lungs with a mass median particle diameter of 4.5 microns. After inhalation, SG_{aw} and blood sample measurements were taken at 1, 3, 5, 10, 15, 20, 25, and 30 min. Significant falls in SG_{aw} from a mean baseline of 0.124 ± 0.024 to 0.046 ± 0.008 and 0.066 ± 0.012 s/cm/water, were observed at 3 and 30 min, respectively. Inhalation did not produce significant changes in levels of histamine, neutrophil chemotactic factor, or cyclic adenosine phosphate in the blood.

Adenosine Phosphate and Adenosine Triphosphate

The effects of aerosolized Adenosine Triphosphate and Adenosine Phosphate on dyspnea and airway caliber were studied.[46] The perception of dyspnea quantified by a modified Borg Scale of Perceived Exertion and other symptoms was determined in 10 nonsmokers and 10 patients with asthma. Each subject attended the laboratory on three occasions. The first visit included a screening, recording of medical history, lung function assessment, and skin-prick testing of common aeroallergens. On the second and third visit, subjects were administered either Adenosine Triphosphate or Adenosine Phosphate, in aerosolized form. Before, immediately after, and 30 min after the challenge, spirometry was performed, the Borg score was determined, and symptoms other than dyspnea were recorded. In order to determine the Borg scale, subjects were asked to determine the degree of breathlessness they were experiencing on a scale of 0 - 10. For the inhalation challenge tests, Adenosine Triphosphate (0.125 - 512 mg/mL) and Adenosine Phosphate (0.048 - 400 mg/mL) were dissolved in a normal saline solution and administered via a breath-activated dosimeter with an output of 10 µL per inhalation. Participants wore a nose clip and inhaled 5 breaths of the normal saline solution, followed by sequential doubling

concentrations of either Adenosine Triphosphate or Adenosine Phosphate. Subjects who were healthy nonsmokers did experience dyspnea when given Adenosine Triphosphate or Adenosine Phosphate. All patients with asthma experienced dyspnea when given Adenosine Triphosphate, and 90% of patients with asthma experienced dyspnea when given Adenosine Phosphate. The geometric mean provocative dose (PD_{20}) in responsive subjects was 26.9 mg/mL and 39.6 mg/mL for Adenosine Triphosphate and Adenosine Phosphate, respectively. In patients with asthma, the perception of dyspnea assessed by the Borg score increased from 0.1 to 3.3 and 0.2 to 2.5 after Adenosine Triphosphate and Adenosine Phosphate, respectively. Eighty percent of subjects coughed after the Adenosine Triphosphate challenge, whereas 40% of subjects coughed after the Adenosine Phosphate challenge. Throat irritation was noted after the Adenosine Triphosphate and Adenosine Phosphate challenge in 70% and 35% of subjects, respectively.

A different study was performed to evaluate whether inhaled Adenosine Triphosphate or Adenosine Phosphate produces a tussive response, and whether chronic cough patients are hypersensitive to these ingredients compared to healthy volunteers.[47] All participants received two cumulative cough challenges, one with Adenosine Triphosphate and one with Adenosine Phosphate. Saline (0.9%) was used as the solvent for both Adenosine Phosphate and Adenosine Triphosphate. The two challenges were administered on two different days, at least 48 hours apart. Each volunteer started with a saline inhalation, followed by Adenosine Triphosphate or Adenosine Phosphate delivered in increasing concentrations on a half-log scale from 0.1 to 300 mM. The number of coughs produced in the first 15 seconds after inhalation were counted. The challenge was terminated once the volunteer coughed at least five times (C5), or the maximum concentration was inhaled. Two out of 19 healthy patients coughed with Adenosine Phosphate, none reaching C5. Eighteen out of 20 volunteers coughed after administration of Adenosine Triphosphate, with 15 reaching C5. Eight out of 20 chronic cough patients coughed with Adenosine Phosphate, two reaching C5. Eighteen of 19 chronic cough patients reached C5 after inhalation of Adenosine Triphosphate. The C5 in chronic cough patients was predominately distributed between 1 mM and 100 mM, as all patients who reached C5, did so by a concentration of 100 mM.

SUMMARY

The safety of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, these ingredients are reported to function as skin-conditioning agents – miscellaneous.

According to 2020 VCRP survey data, Adenosine, Adenosine Phosphate, Adenosine Triphosphate, and Disodium Adenosine Triphosphate are reported to be used in 905, 96, 42, and 116 formulations, respectively. The results of the concentration of use survey conducted by the Council indicate that Adenosine has the highest concentration of use; it is used at up to 1% in body and hand products. Disodium Adenosine Phosphate is not reported to be in use.

The penetration ability of Adenosine in different vehicles was evaluated in human skin. The observed optimal K_ps of Adenosine from a binary vehicle (propionic and hexanoic acid), propionic acid solution, and hexanoic acid solution were 0.004, 0.012, and 0.016 cm/min, respectively. According to a risk profile from the NFSA, a cream containing low concentrations of Adenosine would result in an absorption of up to 2% Adenosine.

Wistar rats were given 10 mg/kg [^{14}C]-Adenosine Phosphate dissolved in 9% aqueous sodium chloride via gavage. Within 72 hours of administration, 28% of the injected activity was excreted in the urine and 6% was recovered in the feces. Eight volunteers were given singles doses of 5000 mg Adenosine Triphosphate or placebo via an ingested pellet targeted at release in the proximal or distal small intestine, or via a naso-duodenal tube. Concentrations of uric acid were significantly increased compared to placebo after administration via proximal-release pellets and naso-duodenal tube, but not after administration via distal-release pellets.

No treatment-related symptoms were observed when Wistar rats were orally given 2000 mg/kg bw Adenosine in methylcellulose, however, pale kidneys were observed in all females in one group given 2000 mg/kg Adenosine. In a different study, the reported oral LD_{50} of Adenosine in mice was > 2000 mg/kg. The acute oral LD_{50} of Adenosine Triphosphate was reported to be > 2000 mg/kg in rats. No changes in diastolic aortic pressure, heart rate, central venous pressure, IVBF, lung resistance, or Pa_{O2} were observed in New Zealand White rabbits given a single dose of up to 20 mg/kg Adenosine Triphosphate orally. An oral LD_{50} of > 2000 mg/kg was reported for both mice and rats for Disodium Adenosine Triphosphate in two different studies.

In a short-term toxicity study, New Zealand White rabbits were given doses of either 3 mg/kg/d or 20 mg/kg/d Adenosine Triphosphate mixed with cellulose, or 20 mg/kg/d adenosine hemisulfate salt, for 14 days. Administrations occurred via gastric cannula. The LVWI was significantly increased by 10% in animals given 20 mg/kg/d Adenosine Triphosphate. In addition, treatment with the highest dose level led to a 12.5% decrease of the spontaneous respiratory frequency. A 26% reduction of lung resistance was noted in all Adenosine Triphosphate -treated groups. Increases of 22 and 23% of Pa_{O2} were observed in rabbits treated with 3 mg/kg/d and 20 mg/kg/d Adenosine Triphosphate, respectively.

In a reproductive study, Adenosine (50, 100, and 150 mg/kg) administered intraperitoneally in mice and rats cause decreased spermatogenesis and an increased number of abnormal sperm.

Adenosine was non-genotoxic in Ames assays performed with and without metabolic activation on *S. typhimurium* and *E. coli* at up to 5000 µg/plate. Adenosine was also non-genotoxic in a CHO/HGRPT assay at up to 2000 µg/mL, with and without metabolic activation.

The cytotoxic effects of Adenosine in Swiss albino mouse embryo 3T3 and 3T6 and in HeLa cells cultured with and without adenosine deaminase were studied. Cells were exposed to Adenosine at concentrations of 0, 0.002, 0.005, 0.01, 0.02, 0.20, 1.0, and 2.0 mM. When Adenosine was added to cell cultures in a medium containing horse serum (does not contain adenosine deaminase), it was found to be toxic at low concentrations. Cell inhibition in calf serum was observed when Adenosine was used at concentrations of 1.0 mM and higher.

The effect of Adenosine on DNA synthesis and cell growth in human HT-29, T84, HRT-18, and Colo320HSR and mouse MCA-38 cell lines was studied. Adenosine was added with methyl-[^{3}H]-thymidine (final concentrations, 1 µCi/mL, 1 µM). DNA synthesis and cell proliferation were stimulated in all cell lines tested, with an EC_{50} of 2.8 - 30 µM, and a maximum stimulation was reached at 10 - 100 µM.

The effects of intradermal injections of Adenosine Phosphate and Adenosine Triphosphate compared to intradermal injections of histamine were evaluated. The backs of volunteers were injected with 50 µL isosmotic phosphate buffered saline containing Adenosine Triphosphate, Adenosine Phosphate, histamine, compound 48/80, or saline. Adenosine Triphosphate produced wheals in 5 out of 7 subjects injected with 180 nmol, and in all subjects at higher doses, in a dose-dependent manner. Wheals that resulted from 1080 nmol Adenosine Triphosphate were approximately equal to wheals due to histamine (1.63 nmol). Injections of Adenosine Triphosphate at high doses produced sensations of persistent pain which was not observed with injection of saline or histamine.

Adenosine (10 mg) was considered to be non-irritating in an in vitro skin irritation study performed using reconstructed human epidermis, according to OECD TG 439. According to a risk profile from the NFSA, Adenosine was non-irritating to animal skin in multiple conventional tests. According to the same risk profile, Adenosine was considered to be non-sensitizing to the skin of guinea pigs. A 48-hour patch test performed using 0.2% Adenosine on 10 subjects yielded negative results. Negative results were also observed in an HRIPT performed on 205 subjects using the same test substance. A trade name material consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate was used in different aqueous dilutions in a Magnusson-Kligman maximization test (0.075% mannitol and 0.075% Disodium Adenosine Triphosphate (challenge); 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate (induction)) and HRIPT (1.5% mannitol, 1.5% Disodium Adenosine Triphosphate). No signs of sensitization were observed in either study.

A phototoxicity and photosensitization study was performed with a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate. The test substances were applied at 10% (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate and 2% (i.e., 0.3% mannitol, 0.3% Disodium Adenosine Triphosphate) aqueous dilutions in the phototoxicity and photosensitization studies, respectively. No skin reactions were noted in either study.

Adenosine was predicted to be slightly irritating to the eyes in a HET-CAM assay. It was considered to be non-irritating to rabbit eyes in a different study.

The effect of inhaled Adenosine (0.6 to 6.7 mg/mL) was studied in 8 asthmatic subjects. Significant falls in SG_{aw} from a mean baseline of 0.124 ± 0.024 to 0.046 ± 0.008 and 0.066 ± 0.012 s/cm/water were observed at 3 and 30 min, respectively. Inhalation did not produce significant changes in levels of histamine, neutrophil chemotactic factor, or cyclic adenosine phosphate in the blood.

The effects of aerosolized Adenosine Triphosphate and Adenosine Phosphate on dyspnea and airway caliber were studied. The PD_{20} was 26.9 mg/mL and 39.6 mg/mL for Adenosine Triphosphate and Adenosine Phosphate, respectively, in responsive subjects. The perception of dyspnea assessed by the Borg score increased from 0.1 to 3.3 and 0.2 to 2.5 after Adenosine Triphosphate and Adenosine Phosphate, respectively, in patients with asthma. In a different study, two out of 19 healthy patients coughed after inhalation of Adenosine Phosphate, none reaching C5. Two out of 18 volunteers coughed after administration of Adenosine Triphosphate, with 15 reaching C5. Eight out of 20 chronic cough patients coughed with Adenosine Phosphate, two reaching C5. Eighteen of 19 chronic cough patients reached C5 after inhalation of Adenosine Triphosphate.

Thirty-nine patients with various dermatoses were used in a study evaluating histamine release from human cutaneous mast cells following intracutaneous injection with 48/80 (1 mg/mL water), Adenosine Triphosphate (60 mg/mL water), adenosine diphosphate (30 mg/mL water), or Adenosine Phosphate (37 mg/mL water). In addition, 3 concentrations of histamine dihydrochloride were also injected (1, 3, and 10 µg/mL), and used to compare the responses elicited from the test substance. Injection of Adenosine Triphosphate in the skin caused a response similar to that of histamine, but only at high concentrations. Adenosine Triphosphate released histamine at concentrations > 1 mg/mL, while 48/80 stimulated histamine release in skin at concentrations > 1 µg/mL.

DRAFT DISCUSSION

The following discussion items are pending Panel approval. Additional discussion items may be added.

The ingredients reviewed in this document are naturally-occurring, ubiquitous chemicals. Because the noted, safe use of these ingredients in the diet and in therapeutics results in significantly greater systemic exposures than could be possible from cosmetic use, the concern for systemic toxicity is mitigated. The Panel noted the lack of sensitization/irritation data for these ingredients, but determined that the available sensitization/irritation data on Disodium Adenosine Triphosphate and Adenosine can be used as read-across for those ingredients lacking these data.

The Panel discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council survey results indicate that Adenosine is being used in face powders at concentrations up to 0.1%. In addition, Adenosine is used in spray moisturizing products at up to 0.041%, and Adenosine Phosphate is used at up to 0.04% in hair sprays. 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 based on the chemical and biological properties of these ingredients. 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.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions, structures, and functions of adenosine ingredients.[1, CIR Staff]

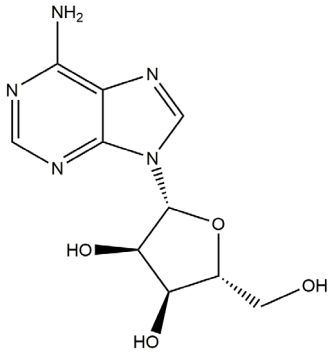
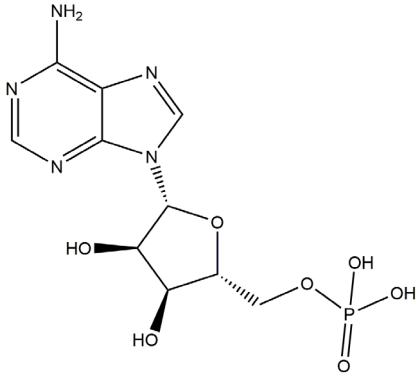
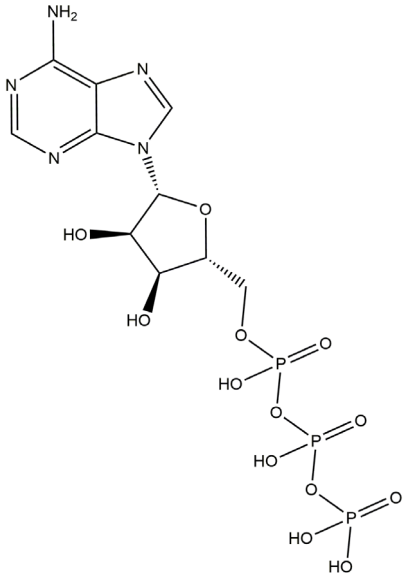
Ingredient	Definition	Function
Adenosine (58-61-7)	Adenosine is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous
Adenosine Phosphate (61-19-8)	Adenosine Phosphate is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous
Adenosine Triphosphate (56-65-5)	Adenosine Triphosphate is the organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous

Table 1. Definitions, structures, and functions of adenosine ingredients.[1, CIR Staff]

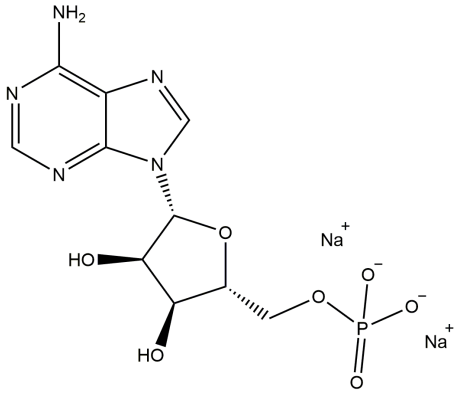
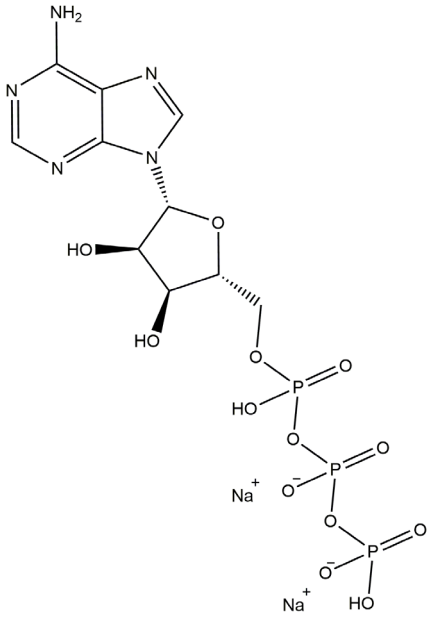
Ingredient	Definition	Function
Disodium Adenosine Phosphate (4578-31-8)	Disodium Adenosine Phosphate is the disodium salt of Adenosine Phosphate 	Skin-Conditioning Agents – Miscellaneous
Disodium Adenosine Triphosphate (987-65-5)	Disodium Adenosine Triphosphate is the disodium salt of Adenosine Triphosphate 	Skin-Conditioning Agents – Miscellaneous

Table 2. Chemical Properties of the Adenosine ingredients in this safety assessment

Property	Value	Reference
Adenosine		
Physical Form	Crystalline powder	48
Color	White	48
Odor	Odorless	49
Molecular Weight (g/mol)	267.25	50
Vapor pressure (mmHg @ 25 ºC)	6.0×10^{-15}	51
Melting Point (ºC)	235.5	52
Water Solubility (g/L @ 25 ºC)	5.1	52
log K_{ow}	-1.05	52
Λ_{max} (@ pH = 7.0; nm)	14.6 – 15.2 nm	8
Adenosine Phosphate		
Physical Form	Solid	53
Molecular Weight (g/mol)	347.22	50
Melting Point (ºC)	195	53
Water Solubility (g/L)	3.31	54
log K_{ow}	-3.1	54
Adenosine Triphosphate		
Physical Form	Solid	55
Molecular Weight (g/mol)	507.18	50
Water Solubility (g/L)	1000	56
Disodium Adenosine Phosphate		
Formula Weight (g/mol)	391.19	50
Disodium Adenosine Triphosphate		
Formula Weight (g/mol)	551.15	50

Table 3. Frequency and concentration of use[11,12]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Adenosine		Adenosine Phosphate		Adenosine Triphosphate	
Totals*	**905**	**0.04 - 1**	**96**	**0.001 – 0.5**	**42**	**NR**
Duration of Use						
Leave-On	*868*	*0.04 – 1*	*81*	*0.0048 – 0.5*	35	*NR*
Rinse-Off	*37*	*0.041*	*15*	*0.001 – 0.04*	7	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	87	0.041	12	0.04 – 0.5	2	NR
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	326[a]; 301[b]	0.04 – 0.041	1; 10[a]; 54[b]	0.04; 0.11[b]	8[a]; 17[b]	NR
Incidental Inhalation-Powder	326[a]	0.1; 0.04 – 1[c]	10[a]	0.058[c]	8[a]	NR
Dermal Contact	897	0.04 - 1	68	0.001 – 0.058	35	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	NR	27	0.0095 – 0.11	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	6	NR
Mucous Membrane	3	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Disodium Adenosine Triphosphate	
Totals*	**116**	**0.003 – 0.1**
Duration of Use		
Leave-On	*100*	*0.003 – 0.1*
Rinse Off	*16*	*0.003 – 0.005*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	11	0.003
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	41[a]; 43[b]	NR
Incidental Inhalation-Powder	41[a]	0.003[c]
Dermal Contact	116	0.003 – 0.1
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	0.005
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	3	NR
Baby Products	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – no reported use

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2020 FDA VCRP data: Adenosine ingredients

Adenosine

Eye Lotion	48
Other Eye Makeup Preparations	39
Hair Conditioner	1
Shampoos (non-coloring)	1
Tonics, Dressings, and Other Hair Grooming Aids	1
Other Hair Preparations	2
Face Powders	4
Foundations	25
Lipstick	1
Makeup Bases	2
Other Makeup Preparations	6
Dentifrices	1
Douches	1
Aftershave Lotion	1
Other Shaving Preparation Products	1
Cleansing	8
Face and Neck (exc shave)	313
Body and Hand (exc shave)	13
Moisturizing	262
Night	35
Paste Masks (mud packs)	24
Skin Fresheners	3
Other Skin Care Preps	113

TOTAL: 905

Adenosine Phosphate

Eye Lotion	8
Mascara	1
Other Eye Makeup Preparations	3
Other Fragrance Preparation	1
Hair Conditioner	6
Shampoos (non-coloring)	6
Tonics, Dressings, and Other Hair Grooming Aids	14
Other Hair Preparations	1
Other Makeup Preparations	1
Face and Neck (exc shave)	8
Body and Hand (exc shave)	2
Moisturizing	32
Night	8

Paste Masks (mud packs)	3
Other Skin Care Preps	2

TOTAL: 96

Adenosine Triphosphate

Eye Lotion	1
Other Eye Makeup Preparations	1
Tonics, Dressings, and Other Hair Grooming Aids	1
Basecoats and Undercoats	1
Nail Polish and Enamel	4
Other Manicuring Preparations	1
Cleansing	2
Face and Neck (exc shave)	6
Body and Hand (exc shave)	2
Moisturizing	10
Night	3
Paste Masks (mud packs)	5
Skin Fresheners	1
Other Skin Care Preps	2
Indoor Tanning Preparations	1
Other Suntan Preparations	1

TOTAL: 42

Disodium Adenosine Triphosphate

Eye Lotion	7
Eye Makeup Remover	2
Other Eye Makeup Preparations	2
Bath Soaps and Detergents	1
Other Personal Cleanliness Products	2
Cleansing	10
Face and Neck (exc shave)	33
Body and Hand (exc shave)	8
Moisturizing	32
Night	3
Paste Masks (mud packs)	1
Skin Fresheners	2
Other Skin Care Preps	7
Suntan Gels, Creams, and Liquids	4
Indoor Tanning Preparations	1
Other Suntan Preparations	1

TOTAL: 116

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: October 8, 2019

SUBJECT: Adenosine

Anonymous. 2019. Adenosine Specifications.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

October 2019

Adenosine Specifications

TEST	Specification
Appearance (Color)	White
Appearance (Form)	Powder
Solubility (Color)	Colorless
Solubility (Turbidity)	Clear
50 mg/mL, 1M NH_4OH	
UV/Vis absorbance	14.6 - 15.2
EmM at pH 7.0	
Wavelength	259 - 260 nm
Purity (HPLC)	≥ 99 %
Recommended Retest Period	----------
5 years	

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Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: November 19, 2019

SUBJECT: Adenosine Triphosphate

Anonymous. 2019. Adenosine Triphosphate: Impurities.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

November 2019

Adenosine Triphosphate - Impurities

A supplier reports the following impurities in Adenosine Triphosphate

Adenosine Phosphate <2%
Adenosine Diphosphate <2%
Methanol <0.010%

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Memorandum

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

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: October 15, 2019

SUBJECT: Disodium Adenosine Triphosphate

Anonymous. 2019. Disodium Adenosine Triphosphate.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

October 2019

Disodium Adenosine Triphosphate

A supplier reports that the Disodium Adenosine Triphosphate used in a trade name mixture sold to the cosmetic industry is free from CMR (carcinogens, mutagens, reproductive toxicants as defined by EU chemical regulations), phthalates, pesticides and glycol ether listed in Annex II of the EU cosmetic regulations.

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Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: September 11, 2019

SUBJECT: Draft Report: Safety Assessment of Adenosine Ingredients as Used in Cosmetics (draft prepared for the September 16-17, 2019 CIR Expert Panel meeting)

The Personal Care Products Council respectfully submits the following comments on the draft report, Safety Assessment of Adenosine Ingredients as Used in Cosmetics.

Cosmetic Use - As restrictions are not listed in the EU "inventory", it should be made clear that these ingredients are not restricted by the EU cosmetic regulations.

Summary - Please state the route of exposure used in the rat study (2000 mg/kg bw) and the mouse LD_{50} study.

In the description of the HRIPT of the mixture containing mannitol and Disodium Adenosine Phosphate, it is not clear what is meant by "different aqueous dilutions". Please state the dilutions that were used.

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