Safety Assessment of Diacetone Alcohol as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	November 10, 2021
Panel Meeting Date:	December 6 – 7, 2021

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 Priya Cherian, Scientific Analyst/Writer, CIR.

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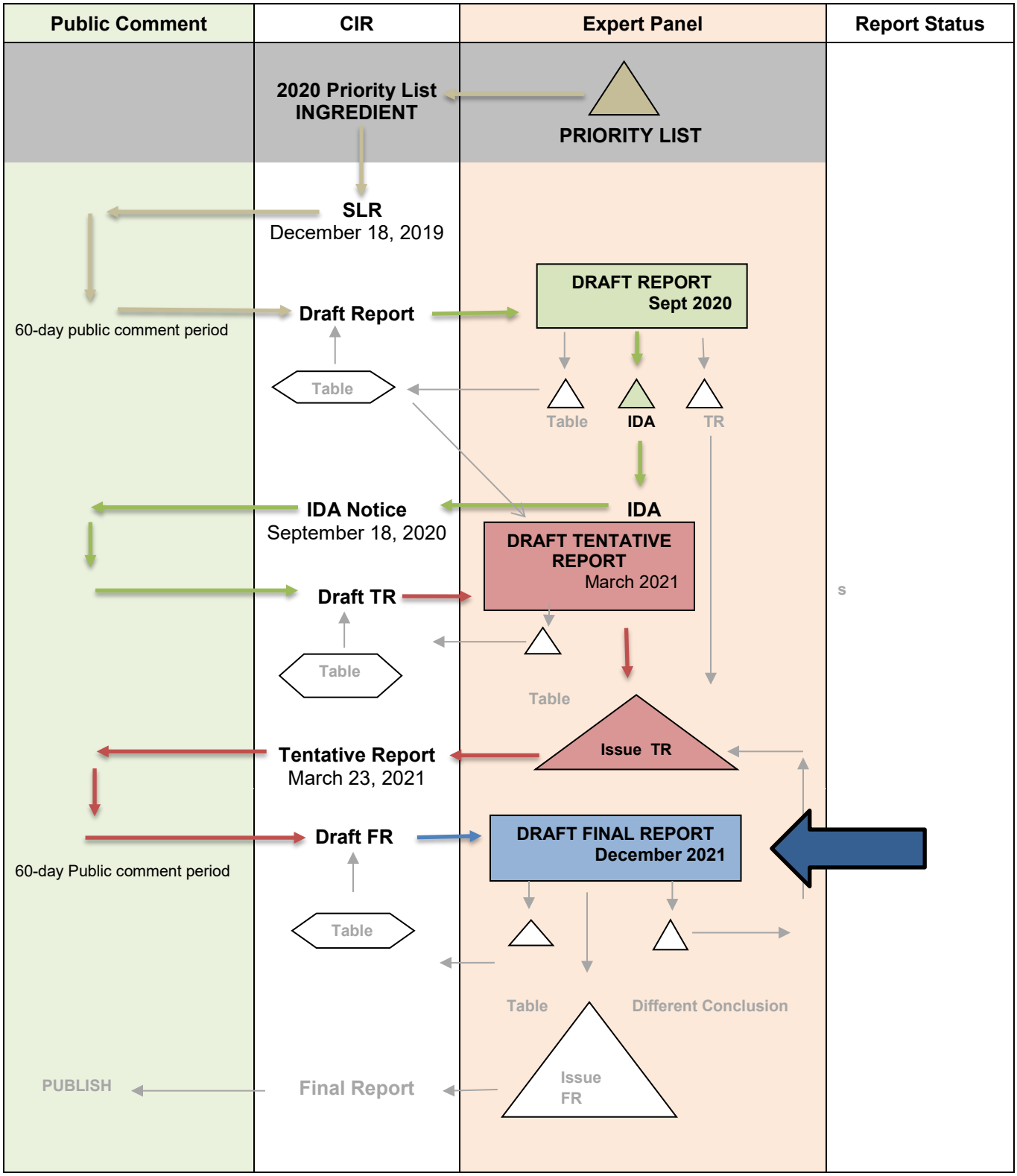
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Diacetone Alcohol

MEETING December 2021



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Priya Cherian, Scientific Analyst/Writer, CIR
Date: November 10, 2021
Subject: Safety Assessment of Diacetone Alcohol as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Diacetone Alcohol as Used in Cosmetics (*report_DiacetoneAlcohol_122021*). At the March 2021 meeting, the Expert Panel for Cosmetic Ingredient Review Safety (Panel) issued a Tentative Report for public comment with the conclusion that Diacetone Alcohol is safe in the present practices of use and concentration.

The attached comments on the Tentative Report were received from the Council (*PCPCcomments_DiacetoneAlcohol_122021*) were addressed; responses to the comments follow (*response-PCPCcomments_Diacetone Alcohol_122021*). Also included in this package for your review are the report history (*history_DiacetoneAlcohol_122021)*, flow chart (*flow_DiacetoneAlcohol_122021*), transcripts (transcripts_*DiacetoneAlcohol_122021*), 2021 FDA VCRP data (VCRP_*DiacetoneAlcohol_122021),* literature search strategy (*search_DiacetoneAlcohol_122021),* and data profile (*dataprofile_DiacetoneAlcohol_122021*).

The Panel should carefully consider the Abstract, Discussion, and Conclusion presented in this report. If these are satisfactory, the Panel should issue a Final Report.

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Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: April 2, 2021

SUBJECT: Tentative Report: Safety Assessment of Diacetone Alcohol as Used in Cosmetics (release date: March 23, 2021)

The Personal Care Products Council respectfully submits the following comments on the tentative report, Safety Assessment of Diacetone Alcohol as Used in Cosmetics.

Acute; Summary – The statement "The lowest LD_{50}s reported for mice, rats, and rabbits were…" implies that there was more than one study completed for each species. Although this is true for rats, there was only one study in mice, and only one study in rabbits so the values stated are the only LD_{50}s in mice and rabbits.

Occupational Exposure – Please change this heading to "Occupational Exposure Limits" as the limits, not actual occupational exposure are described in this section.

Summary – Please correct: "Rats up to 4500 mg/m^3 of the test substance…."

Please correct: "The possible reproductive effects on Diactone Alcohol…"

Please correct: "was placed in the eyes of 3 rabbits (strain not stated) to observed potential eye irritation"

Diacetone Alcohol - December 2021 – Priya Cherian	
Comment Submitter: Council **Date of Submission: April 2, 2021**	
Comment	**Response/Action**
Acute; Summary – The statement "The lowest LD50s reported for mice, rats, and rabbits were…" implies that there was more than one study completed for each species. Although this is true for rats, there was only one study in mice, and only one study in rabbits so the values stated are the only LD50s in mice and rabbits.	addressed
Occupational Exposure – Please change this heading to "Occupational Exposure Limits" as the limits, not actual occupational exposure are described in this section.	addressed
Summary – Please correct: "Rats up to 4500 mg/m3 of the test substance…."	addressed
Please correct: "The possible reproductive effects on Diactone Alcohol…"	addressed
Please correct: "was placed in the eyes of 3 rabbits (strain not stated) to observed potential eye irritation"	addressed

Diacetone Alcohol History

December 2019

-SLR posted

January 2020

-comments on the SLR received from Council

-updated 2020 VCRP data received

-2020 concentration of use data received

September 2020

-Panel reviews Draft Report and issues an IDA for impurities data

-Comments received from council on Draft Report

January 2021

-Updated 2021 FDA VCRP data received

March 2021

-Panel reviews Draft Tentative Report

Diacetone Alcohol Data Profile – December 2021 – 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
Diacetone Alcohol	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

Diacetone Alcohol

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Diacetone Alcohol	123-42-2	yes	yes	yes	yes	yes	yes	no	yes	no	no	yes	yes	yes	no	no	no	no	yes

Typical Search Terms

- INCI name (Diacetone Alcohol)
- CAS number (123-42-2)
- 4-hydroxy-4-methylpentan-2-one
- 2-hydroxy-2-methyl-4-pentanone
- 4-hydroxy-4-methyl-2-pentanone
- 2-pentanone,4-hydroxy-4-methyl-
- Cosmetic
- Irritation
- Dermal
- Sensitization
- Toxicity
- Medicine
- Pharmaceutical
- Industrial
- Genotoxicty
- Carcinogenicity
- Cancer
- 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

Fragrance Websites, if applicable

- IFRA (International Fragrance Association) – http://www.ifraorg.org/
- Research Institute for Fragrance Materials (RIFM)

SEPTEMBER 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 14, 2020

DR. BELSITO: Okay. This is the first time we're looking at this ingredient. It's a fragrance ingredient and a solvent, so we need to look at it and determine where we are with it. So one of the question that I had are there other beta-hydroxy ketones that could be added to this report?

MS. FIUME: I'd defer that to Bart and Dan because I don't have that answer.

DR. BELSITO: Okay. Oh, that would be just one thing to look into. We don't have impurities, but, based on manufacturing, Dan and Curt and Paul, do you feel we need them?

DR. LIEBLER: I think what we really need is not so much an explicit composition because it's very clear from the method of manufacture, but we do need a typical purity level of the cosmetic ingredient. The method of manufacture concludes by saying, "The crude Diacetone Alcohol is then purified via distillation." But the purity level should be indicated. That could be even the sentence under, you know, impurity is reported to be X percent. I think that that's not going to be a problem, but it should be indicated and that, I doubt, would be anybody's secret sauce.

MS. KOWCZ: So impurities.

DR. BELSITO: Okay. So you want in method of manufacture, you want the purities stated?

DR. LIEBLER: Yeah or put it under impurities.

DR. BELSITO: So it's insufficient for purity.

DR. LIEBLER: Yes. And I do have a comment on method of manufacture where it says it's an ingredient in sleepy grass. Unless it's commercially -- they can (audio skip) the commercial ingredient is purified from sleepy grass, we could just take that phrase out. And just say that it's typically manufactured synthetically via dimerize- if that's true.

MS. CHERIAN: Okay.

DR. BELSITO: Okay. Now, I just want to point out that leave-on concentration is extremely low except in nail works -- 0.25 percent -- which is still very low.

DR. LIEBLER: Yeah.

DR. BELSITO: So does that impurities still bother you, Dan? We're talking about leave ons of 0.0009 as the highest.

DR. LIEBLER: Right. No, I get your point. I think at this stage for the report, it's very reasonable to ask for that.

DR. BELSITO: Okay.

DR. LIEBLER: And I feel that we're heading towards safe as used.

DR. BELSITO: Okay.

DR. SNYDER: Yeah. Tox profile's pretty good. It's a very large NOAEL.

DR. BELSITO: Right. I had a question for you, Paul, on page 12 of the PDF. It says, no observed adverse effect level for parental toxicity -- this is in the first paragraph -- was a hundred milligram per kilogram. But then it says that at a hundred milligram per kilogram, there were hyaline droplets in the proximal tubular epithelium in males. Is that not an adverse effect?

DR. SNYDER: No. It's a common male rat thing.

DR. BELSITO: Okay. Good.

DR. KLAASSEN: I would like to suggest in the chemical properties section, while it's in the table below, I think we should give in chemicals properties in the text what the molecular weight is and what the octanol water partition is. That is just such an important chemical property, and I think we should have it always listed in chemical property.

DR. BELSITO: Okay.

DR. HELDRETH: Will do.

DR. KLAASSEN: What?

DR. HELDRETH: Will do.

DR. KLAASSEN: Oh, will do. Thank you.

DR. BELSITO: Okay. Paul, another question for you on page 13 of the PDF, the top paragraph, it says, "Unossified or incomplete ossification of various parts of the skeleton were noted... These findings were associated with the presence of cartilage and considered non-adverse effects." Is that true?

DR. SNYDER: Yes, it's again -- those skeletal ossifications centers, they -- if that's the -- basically, the paper that I sent to the staff was a good paper because it said that, in the absence of any other skeletal defects, that you don't want to over-interpret those because they're so common and they're so variable throughout the study.

So when I see a study like that, if I don't see any other skeletal abnormalities -- you know, deformed limbs or anything like that -- and that's the only thing that they saw -- and that's also what these guys concluded -- that it was a non-adverse finding. It occurred, but it was considered to be non-adverse because of the absence of any other findings.

DR. BELSITO: Okay. And then just one last question for Dan. Given the negative DART findings and all the other data, do we still the impurities?

DR. LIEBLER: I wasn't saying we need impurities, but I would like to have the purity level --

DR. BELSITO: Okay.

DR. LIEBLER: -- the purity of the product that's typically used in cosmetics, and it sounded like from a quick comment Alex made that that shouldn't be hard to get.

DR. BELSITO: Okay. So we're basically going insufficient for purity level.

DR. LIEBLER: Yep. Piece of cake.

DR. BELSITO: And then, Monice, you all search and see whether there are other ketones that would be appropriate for this?

MS. FIUME: Yes, we'll take a look to it.

DR. HELDRETH: I actually took a look to see if there was anything remotely close. I only came up with one, and I hesitate to even say that it's closest to dihydroxy acetone. I think it itself is also pretty different, and it's by far the closest thing to this ingredient.

DR. BELSITO: Okay.

DR. HELDRETH: I wouldn't suggest any addons, but I'll leave that up to Dan and Lisa.

DR. LIEBLER: Does it have different uses, Bart?

DR. HELDRETH: Uh, let's see. Its reported functions are colorant and skin conditioning agent miscellaneous.

DR. LIEBLER: I see.

DR. HELDRETH: So it's an approved colorant in the U.S.

DR. LIEBLER: Yeah. Dihydroxy acetone, interesting. I don't know. I mean, if it appeared in this report in the first place, I'd probably wouldn't really bat an eye. But, if there's no driving programmatic reason to review it right now, it doesn't need to go anywhere. We got a pretty good thing going as it.

DR. BELSITO: Okay. Anything else? Okay. So the next is Red Algae. Before we go on to that, do you want to take a bio break because I think this is going to potentially be longer than a half hour?

DR. LIEBLER: Sounds good.

DR. BELSITO: Yeah. So let's take a ten-minute break. It's 2:27. Try and be back around 2:37/2:40.

DR. LIEBLER: Sounds good. Thanks.

DR. BELSITO: Okay.

Marks Team – September 14, 2020

DR. MARKS: We're going to go to the diacetone alcohol, and this is a draft report. It's the first time that we've seen this single ingredient. And as Wilma mentioned earlier, this has two uses: as a fragrance and a solvent. And normally, if an ingredient -- and Bart, clarify this or modify it -- if it's only used as a fragrance, then we defer to RIFM to do the safety assessment, but this is also being used as a solvent. So that's why I assume that we're reviewing it in the CIR.

DR. HELDRETH: That's correct. If something is only used as a fragrance ingredient and we're of the understanding that RIFM either has or plans to review the safety of it, we'll defer the safety to them so that we're not redundant. But if there are

other uses, like solvent, or if RIFM makes it clear to us they have no plans to look at the safety of this ingredient, then the Panel may choose to review the ingredient anyway.

DR. MARKS: So I'll call on Lisa, Ron, and Tom now. If there are multiple ingredients I would ask them, "Are all these ingredients okay?" Look at it from a chemistry point of view or whatever. Since there's only one ingredient, for Lisa, Ron, and Tom, do you have needs?

I was particularly interested in whether or not we could proceed with the impurities and then also about respiratory irritation. But again, Lisa, Ron, Tom, pipe in. What needs do we have? And at this point we either issue an insufficient data announcement -- so that gives the public time to respond to our questions -- our insufficiencies -- or we can move with a tentative report. So Lisa, Ron, Tom, comments, needs?

DR. SHANK: We have extensive toxicity data, and there are no concerns for use in cosmetics at the concentrations that are used. Sensitization doesn't seem to be a concern. I think the chemistry data is sufficient, but that's what Dr. Lisa -- or Dr. Peterson can comment on that. So I think it's safe as used.

DR. MARKS: And you weren't concerned about the respiratory irritation on page 14, Ron, because the concentration issue was --

DR. SHANK: Yes. And if the Panel feels that's a concern, I think that could be handled with the boilerplate.

DR. SLAGA: I agree with Ron, and to add, it's really a food additive, too. And it's been used for a long time for that purpose.

DR. PETERSON: So I -- there is no impurity information, and I was reading all of the previous reports and noting that Dan always asks for impurities if it's not there. And I agree that it's probably not a big issue, but I think basically trying to get some information on the impurities I think is a good idea to know what they are, if there are any.

DR. MARKS: Okay. Lisa, I highlighted the same thing and for the same reason. I would say our direction is this ingredient is safe, but we should probably issue an insufficient data announcement for impurities. What do you feel, Lisa?

DR. PETERSON: Yeah. I agree with that.

DR. SHANK: Okay.

DR. SLAGA: Okay here too.

DR. PETERSON: Besides, Dan is going to say the same thing, so it's going to get hung up anyway. But I do believe the best practice is to ask for the impurities.

DR. SHANK: I keep losing the sound. Does anybody else have a sound problem?

DR. SLAGA: I don't.

DR. MARKS: I guess one of the things might be if somebody's not speaking. I'm keeping my mic on all the time, but if you aren't speaking, maybe, like, David, you can mute your mic. I hesitate, Priya, to tell you to mute your mic, but at the same time, you're so adept you probably have no difficulty. So Ron, is the sound a little better now?

DR. SHANK: Yes. Every once in a while, especially when you talk Jim --

DR. MARKS: Oh, boy.

DR. SHANK: -- I loose maybe five seconds of the sound, and it's usually when you're asking the question or saying what you're going to say tomorrow at the Panel meeting. I don't understand why. It may be that every time somebody signs on as a guest my sound cuts out. I think that's what's happening, but it's only on you, Jim.

DR. MARKS: Lisa, are you having the same problem -- Tom or Wilma, hearing me?

DR. BERGFELD: No, I hear a lot of background noise, but other than that I'm not having trouble. And I hope everybody's having an okay time hearing me.

DR. SHANK: No, I hear you fine.

DR. SLAGA: I don't --

DR. COHEN: I can hear everybody.

DR. SLAGA: I don't have any trouble hearing you, Jim.

DR. MARKS: Okay.

DR. SHANK: Yeah. It's just me.

DR. MARKS: Maybe I've got a bottle of Aldo's Zinfandel. It may come in clearer. So tomorrow I will second a motion presumably that's going to be insufficient in data announcement for impurities. In the future, we will expect that there's going to be a safe conclusion as sort of a headline what's coming up. But the only unmet need is impurities at this point. Sound good, Ron? Could you hear all that?

DR. SHANK: I did. Thank you.

DR. MARKS: All right. Okay. We'll move on to the next ingredient in a minute. Oh. Don't you laugh, Wilma. I don't even have to look at you to see that. So welcome to the CIR, David, and to red algae.

Full Panel – September 15, 2020

DR. BELSITO: Okay, so, we looked at this material, one question was whether other materials could be added to the report. We decided there were none. And, after looking at all the data we thought that it was insufficient for impurity of the final product.

DR. BERGFELD: Okay. So it's a motion, insufficient for impurities?

DR. BELSITO: Right.

DR. MARKS: Second.

DR. BERGFELD: Okay.

DR. LIEBLER: You know, I hate to hold up the whole report just for impurity, but you know how I am about these things.

DR. MARKS: Listen Dan, we agreed with you; there was no hesitation. The preview is in the future it'll go out as a safe, but we agree with you; we want impurities.

DR. BERGFELD: Any other discussion? I'm going to call the question. All those voting against this motion of insufficient, please indicate by stating your name. Hearing none, this is a unanimous decision to go forward as insufficient.

MARCH 2021 MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – March 11, 2021

DR. BELSITO: Okay. So then we move to diacetone alcohol. Okay. So at the September meeting, we issued an insufficient data announcement and that we wanted impurities data. We haven't gotten it. So what are we doing?

DR. SNYDER: Safe as used.

DR. BELSITO: Yeah. I said, based upon the manufacturing, are there specific impurities that we might restrict and find as safe? The highest concentration is a nail product and then leave-on 0.2 in the eye product and 9.2 in a wash off.

DR. EISENMANN: Regarding the impurities, I looked at the ECHA dossier again, and it gives the purity as 99 to 100 percent. And it says impurity is acetone, but it doesn't give a concentration.

DR. SNYDER: That's actually what Dan wanted was purity, not impurities.

DR. LIEBLER: That's all we need.

DR. SNYDER: Yep. I think we're good.

DR. EISENMANN: It's in the dossier. And I think she'll also be able to find a little bit more after she reviews these studies. And some of the studies, I think, say it's purity of the material tested. That could be added to the report.

DR. LIEBLER: Yeah. That's all we need. That's great.

DR. BELSITO: Okay. Then safe as used?

DR. SNYDER: Yes.

DR. LIEBLER: Yes.

DR. BELSITO: Okay. Discussion?

DR. SNYDER: I didn't think there was much to discuss.

DR. BELSITO: Yeah. Okay.

DR. SNYDER: The good toxicity profile, low, poorly absorbed, lowest concentration of use, no issues.

DR. BELSITO: Okay. So do we need to add anything to Priya's existing discussion? I think it's fine, right? It's not used in anything that's aerosolized, right? Not reported.

DR. SNYDER: Yeah. Again, I would just --

DR. BELSITO: Inhalation as a powder, 0.0031, so we need to add the inhalation boilerplate.

DR. SNYDER: Yeah. Again, I would just have that statement like I wanted before that the panel found the data for evaluation of safety in cosmetic use to be adequate. I wouldn't put in here all this acute, chronic, developmental, reproductive, dermal, irritation. I'd just say that the data were adequate to support safety -- done with it.

DR. LIEBLER: Yep. It can be very short discussion.

DR. SNYDER: Yeah. And just the inhalation boilerplate.

MS. CHERIAN: So I didn't have the inhalation boilerplate in there because I wasn't sure if it was a powder. But it's possible that the product is a powder. So I don't think, when we have that, we don't normally include it. I don't think. We usually include it if it's a for-sure use as a powder.

DR. BELSITO: I don't know. Is that right, Bart?

MR. HELDRETH: Yes. That's correct. But you're welcome to include it if you feel that it's a possibility and a potential risk. There might be --

DR. BELSITO: I would because we list it as incidental inhalation powder.

MR. HELDRETH: Yeah. The caveat there is that it's possible that it was used in a powder, but we don't know for sure. The classifications that we received don't make it clear.

DR. BELSITO: Right.

MR. HELDRETH: That's why we're kind of on the edge there. But if you wanted to be very conservative about it and put the boilerplate in there, that's no problem.

DR. BELSITO: Oh. So we could simply say that the information received was that this could potentially be present in a powder. But even if so, we weren't concerned and put in the usual respiratory boilerplate.

DR. SNYDER: Yeah. I think the way we have it footnoted is fine. We clearly state we don't know and because we don't know, well, we got to put in the boilerplate.

MR. HELDRETH: We can do that.

Marks Team – March 11, 2021

DR. COHEN: Okay. Okay. All right. We'll move on to diacetone alcohol. This is Priya's. It's a draft tentative report, last seen in September and issued insufficient data announcement for this ingredient asking for impurities data. In Bart's March 9th memo, he indicated that the ECHA dossier states the impurity -- that the degree of purity of the diacetone alcohol is greater than 99 to 100 percent. Any comments from the team now?

DR. PETERSON: I thought it was fine. I mean, the report. I didn't have any edits or anything to the report.

DR. SHANK: Right. This can go final.

DR. COHEN: I just have one question. Lisa, so we have very little human data on dihydroxyacetone, I don't know how similar those would be, but that's been reported as a contact sensitizer. Is there enough --

DR. PETERSON: Oh, I'm sorry. I was looking at the wrong report. I need to get to the right report.

DR. COHEN: Oh, we're on diacetone --

DR. PETERSON: I thought I had these in order, and I looked at the wrong thing. Sorry.

DR. COHEN: Diacetone alcohol.

DR. PETERSON: Oh. So we didn't get the purity and --

DR. COHEN: In the March 9th memo, Bart gave us a little further information.

DR. PETERSON: Yeah. And I guess I felt that at the concentration used and given that the compound was safe -- and the impurities would be very low in a leave-on concentration, so I was okay with saying safe. I have the right report now.

DR. COHEN: And I just -- I guess one question I had was, just from my own clinical activities, dihydroxyacetone has been reported as a sensitizer. Do you think that this is sufficiently different not to draw any conclusions that way or any analogies? The max use is 0.84 percent. Lisa, any thought on that or not really?

DR. PETERSON: Okay. I'm sorry. Because I've been scrambling and all over to try to get -- to make sure I am on the same page as you, you're worried about the impurity?

DR. COHEN: No. No. I wasn't worried about the impurities. No, no. I was just asking, from a clinical perspective, dihydroxyacetone is a known sensitizer. We don't have a lot of human sensitization data in this report. Is there any reason to think there's anything to connect the two from a chemistry perspective? If not, we can move on.

DR. SHANK: That's a good point.

DR. PETERSON: There -- dihydroxyacetone -- yeah. I think that the structures are different enough that I'm not sure I would worry about it because -- especially if we have sufficient data for the cosmetic ingredient, which is diacetone alcohol. I mean, that -- the thing is is that the dihydroxyacetone, it has two alcohols on the end, and then there's a ketone in the middle. And the hydroxyl groups will make that ketone more reactive because it's pulling electrons away, so the carbonyl will have a more positive charge and make it more susceptible to react with nucleophiles.

So I actually think structurally it's quite different because the alcohols are also on the carbons adjacent, right next door to the carbonyl, with the dihydroxy. And in the diacetone alcohol, the hydroxyl group is a carbon yet step away so that the carbonyl in our -- that we're reviewing is going to be less reactive most likely. So I don't think that dihydroxyacetone's structure, while it's similar, shouldn't cause concern for this compound unless there's some reason this compound leads you to think that there's a concern.

DR. COHEN: No. You addressed it exactly as I was hoping your conclusion would come out. But I felt I needed to raise the issue.

DR. PETERSON: Okay. Yeah. I don't have a concern. Chemically, I would say that the dihydroxyacetone would be more reactive and that it's a sensitizer is not surprising. And I think the structure of diacetone alcohol is sufficiently different that I wouldn't worry about it, unless there were data to support that you should worry about it.

DR. COHEN: No.

DR. PETERSON: But it doesn't look like that in the data.

DR. COHEN: Other than the similarities in name and size. All right.

DR. PETERSON: Yeah.

DR. COHEN: Thank you. So we're going to go out as we're going to advance this at this point, right? Are we going out as safe as used because this is a draft tentative report? Do we skip the draft report on this? Do we just go right to the end?

MS. FIUME: So this is the second time that you're seeing the document. So the last time was an IDA. This time it will go out as a tentative report, and we ask for public comment. And then the next time you see it is when it will go final.

DR. COHEN: Okay. And one other just general comment from this, you know, I see razor lube strips listed as wash-off products. And they're a funny thing clinically how people use them. They're not quite a leave-on product, but they're not quite fully rinse-off product sometimes.

It's not like you're sort of leaving soap behind. People will shave and maybe just wipe their face instead of wash their face afterwards. It's not for adjudication in this particular circumstance, but I don't know when that kind of thing comes up in our conversations.

MS. FIUME: So David --

DR. COHEN: Who --

MS. FIUME: -- to ask that -- so when we look at how we classify ingredients as leave-on, rinse-off, we try to consider it as expected use or intended use versus --

DR. BERGFELD: Actual.

MS. FIUME: -- I think the panel always takes into consideration that not everyone uses the cosmetics as they're supposed to. Like, people will put lipstick on and actually eat it, but we -- I don't think the panel generally reviews -- and Dr. Bergfeld, correct me if I'm wrong -- the ingestion to that point. So is that a personal usage-type thing? And I don't know if Jay is still on and wants to respond on how industry looks at that, or is it something that does need to be taken further?

Because that concentration is a lot higher than the other uses, or is it at least diluted? You know, when we look at rinse-off, I believe a lot of times if something's put on and is diluted down, that's also considered a rinse-off. So I don't know if that's something that needs to be addressed or not. But I'm just curious as how you see it.

DR. ANSELL: I mean, I think that's very interesting. And we would have to consider whether it would require a modification. But the material applied to the glide isn't actually a cosmetic in and of itself, applied directly.

It's the amount that would leach off while it's used and then only partially wiped off. The distinction between leave-on and rinse-off itself is just kind of an arbitrary definition. So I would just put this in my back pocket and look at the actual data as opposed to postulating how this specific application might be treated.

Full Panel – March 12, 2021

DR. BELSITO: So, at the September 2020 meeting we issued an insufficient data announcement. In order to come to a conclusion of safety we requested impurities data. Since the issue, CIR has not received any new data.

And, so we looked at this and we thought that based upon the manufacturing that we have there were really no specific impurities that we would see that we would be concerned about. Particularly, because the highest use, .84, was in a nail product and so that would mitigate absorption of that. The highest leave-on was 0.2 percent, except for they called the leave-on in a shaving strip -- well, not, I'm sorry they called a wash-off in a shaving strip that contained 9.2.

And, we thought that looking at that information that the data were adequate and we could go with a safe as used conclusion.

DR. BERGFELD: Is that a motion?

DR. BELSITO: That is a motion.

DR. BERGFELD: Is there a second or discussion?

DR. COHEN: We'll second that.

DR. BERGFELD: Okay. Any further discussion regarding the motion? All right, seeing none, those opposed? Abstaining? The motion pass. Are there some discussions now, please?

DR. BELSITO: Yeah, we need to add the inhalation boilerplate.

DR. BERGFELD: Anything else? Do you need to discuss why it was insufficient first and now it is not, in the discussion?

DR. BELSITO: Of course.

DR. BERGFELD: Yeah.

DR. BELSITO: Which is the exact -- what I said.

DR. BERGFELD: Yeah.

DR. BELSITO: Manufacturing, there were no specific impurities (audio distorted), max leave-on .2 percent.

DR. COHEN: (Audio skip).

DR. BELSITO: Max leave-on .84 in a nail product, .2 on skin.

DR. BERGFELD: David did you have something to say?

DR. COHEN: No, no. We sort of went through the same iteration about how we came to the safe as used conclusion.

DR. BERGFELD: Okay. I don't see any other discussion, so we'll move on to the Silicates, Dr. Cohen.

Safety Assessment of Diacetone Alcohol as Used in Cosmetics

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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 Priya Cherian, Scientific Analyst/Writer, CIR.

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Diacetone Alcohol as used in cosmetic formulations. This ingredient is reported to function as a fragrance ingredient and solvent. The Panel considered the available data and concluded that Diacetone Alcohol is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This is a safety assessment of Diacetone Alcohol as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), this ingredient is reported to function in cosmetics as a fragrance ingredient and solvent.[1]

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 Expert Panel for Cosmetic Ingredient Safety (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) database[2] or was available from the Organisation for Economic Cooperation and Development (OECD) Screening Information Dataset (SIDS) reports.[3] Please note that the ECHA website and OECD SIDS document provides summaries of information generated by industry, and when cited herein, it is those summary data that are incorporated into this safety assessment.

CHEMISTRY

Definition and Structure

Diacetone Alcohol (CAS No. 123-42-2; molecular weight = 116.16 g/mol; log K_{ow} = 1.03) is a beta-hydroxy ketone formed by hydroxylation of 4-methylpentan-2-one at the 4-position.[4] According to the *Dictionary*, this ingredient is a ketone that conforms to the structure:

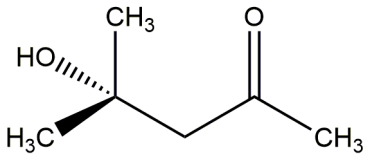

Figure 1. Diacetone Alcohol

Chemical Properties

Diacetone Alcohol is a clear, colorless liquid with a faint, minty odor.[5] This ingredient is miscible in water, alcohol, ether, and other solvents.[6] A list of chemical properties for Diacetone Alcohol is provided in Table 1.

Method of Manufacture

The following methods of manufacturing are general to the production of Diacetone Alcohol, and it is unknown whether they are used in the manufacture of Diacetone Alcohol for use in cosmetics.

Diacetone Alcohol is typically manufactured synthetically via the dimerization of acetone.[7,8] Diacetone Alcohol may be prepared by the action of alkali metal hydroxides (calcium hydroxide or barium hydroxide).[9] Acetone is first placed in a round-bottom flask with a Soxhlet extractor fitted with a reflux condenser. Two thimbles are placed in the extractor, each containing barium hydroxide and glass wool. The flask is then heated until the reaction is complete (approximately 95 to 120 h). The crude Diacetone Alcohol is then purified via distillation.

Impurities

According to an ECHA dossier, Diacetone Alcohol is reported to have a 99 - < 100% degree of purity.[2] In addition, acetone is reported to be a possible impurity of Diacetone Alcohol.

USE

Cosmetic

The safety of the cosmetic ingredient 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 this ingredient 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 2021 VCRP survey data, Diacetone Alcohol is reported to be used in 107 nail formulations; uses were not reported in any other product category in the VCRP (Table 2).[10] However, the results of a concentration of use survey conducted by Council in 2019 indicate that Diacetone Alcohol is used in several different product categories. The highest maximum concentration of use reported is 9.2% in rinse-off shaving products (a "razor lube strip"); all other uses are at 0.84% or below. Diacetone Alcohol is used at up to 0.84% in nail polish and enamel formulations, and the highest concentration resulting in leave-on dermal exposure is 0.25% in "other" eye makeup preparations.[11] In many cases, reports of uses in certain categories were not reported in the VCRP, but concentration of use data were reported in the industry survey. Therefore, it should be presumed there is at least one use in every category for which a concentration is reported.

Diacetone Alcohol is reported to be used in formulations near the eye (e.g., other eye makeup preparations) at concentrations of up to 0.25%. It is also reported to be used in baby shampoos at up to 0.0011%.

Diacetone Alcohol is not restricted from use in any way under the rules governing cosmetic products in the European Union.[12]

Non-Cosmetic

Diacetone Alcohol is used as a solvent for cellulose acetate, nitrocellulose, celluloid, fats, oils, waxes, and resins.[6] It is also used in industrial coatings, household cleaners, inks, paints, paint removers, paint thinners, sealants, primers pesticides, antifreeze solutions, and hydraulic fluids.[13] Diacetone Alcohol is approved as an indirect food additive for the use of adhesives as a component (monomer) of articles intended for use in packaging, transporting, or holding food in accordance with the conditions prescribed in 21 CFR 175.105.[14]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

The in vitro dermal penetration rate of radiolabeled Diacetone Alcohol spiked with non-radiolabeled Diacetone Alcohol was studied in human cadaver skin taken from the abdominal region.[15] A minimum of 6 replicates represented by at least three donors were used. A standard in vitro diffusion cell model was used for this procedure. The test substance, in water, was applied to skin samples at a dose of 25 mg/cm^2 for either 10 min, 1 h, or 24 h. Total recovery (amount of test substance recovered in receptor solution), based on liquid scintillation count data for total radioactivity, was between 89.6 and 91.7% of the applied dose. Skin penetration (amount of test substance found in the skin) was 0.04, 0.15, and 5.71% of the dose after 10 min, 60 min, and 24 h, respectively.

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

An evaluation of the plasma pharmacokinetic profile of Diacetone Alcohol was performed in 9 male Sprague-Dawley rats according to OECD Test Guideline (TG) 417.[2] Diacetone Alcohol (5.81 g) was weighed and mixed with 18.25 g corn oil, and administered to the animals via gavage. Blood samples were sampled from animals at 0.25, 0.5, 1, 2, 3, 6, 9, 12, and 24 h post-dosing. Diacetone Alcohol was quantifiable in the plasma via a gas chromatography-mass spectrometry method from 0.25 h to 24 h post-dosing. An initial plasma concentration peak at 4.40 mmol/l was reached 1 h post-dosing, but the maximum concentration was observed 6 h post-dosing, indicating a prolonged absorption phase. The terminal half-life was determined to be 2.3 h. The plasma levels of the potential metabolites, methyl isobutyl carbinol (MIBC) and methyl isobutyl ketone (MIBK), were below the lower limit of quantification at all time-points.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Details regarding the acute toxicity studies summarized below are provided in Table 3.

The dermal LD_{50} in Wistar rats was >1875 mg/kg bw; this dose was applied for 24 h using an occlusive patch.[2] In rabbits, the dermal LD_{50} was reported to be 14.5 ml/kg in one study (occlusive 24-h patch), and > 13,630 mg/kg bw in another study (details not provided).[3] Several acute oral toxicity studies were performed with Diacetone Alcohol. LD_{50}s reported for mice and rabbits were 3950 and 4653 mg/kg bw, respectively. The lowest LD_{50} reported for rats was 2520 mg/kg bw.[16] An acute inhalation toxicity study was performed in Wistar rats exposed to aerosolized Diacetone Alcohol (7.6 mg/l) for 4 h.[2] The inhalation maximum tolerable concentration (LC_0) of Diacetone Alcohol was reported to be greater than 7.6 mg/l.

Short-Term Toxicity Studies

Oral

Groups of 10 albino rats (sex not specified) were given Diacetone Alcohol in drinking water for 30 d in concentrations resulting in doses of 0, 10, 40, or 130 mg/kg bw/d.[17] No deaths occurred throughout the study. In one rat dosed with 40 mg/kg bw/d, cloudy swelling and degeneration of renal tubular epithelium was noted. No adverse effects were reported in any rats at the 10 mg/kg bw/d dose level. No other details regarding this study were provided.

A combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was performed using SD(Crj:CD(SD)) SPF rats (10/sex/group) according to OECD TG 422.[2] Rats were treated with Diacetone Alcohol (purity: 99.8%) in water via gavage at doses of 30, 100, 300, or 1000 mg/kg bw/d. Males were treated for 44 d while females were treated for 41 - 45 d. Treated males and females were mated, and the F1 and parent generations were evaluated. Findings in parental animals included decreased locomotion and decreased response to stimulation in 300 and 1000 mg/kg bw/d males. Increases in platelet count, glutamic oxaloacetic transaminase, choline esterase, total protein, total cholesterol, total bilirubin, blood urea nitrogen, creatinine, and calcium, as well as a decrease in glucose at 1000 mg/kg bw/d was observed in males and females. Increased kidney weights were noted at 300 and 1000 mg/kg bw/d in males, and increased liver and adrenal weights were noted in males treated with 1000 mg/kg bw/d. Histological evaluation of kidney tissues confirmed the presence of hyaline droplets in the proximal tubular epithelium in males dosed with 100 mg/kg bw/d or higher, and basophilic tubules in males dosed with 300 and 1000 mg/kg bw/d. Hepatocellular hypertrophy was noted in the livers of male rats treated with 1000 mg/kg bw/d, and vacuolization of the cells of the zona fasciculata were noted in the adrenals of males treated with 300 and 1000 mg/kg bw/d. In females, a reduction of premating body weight gain, histopathological changes of the liver and adrenals, and an increase in liver weight was observed in high-dose females. Dilation of the distal tubules and fatty degeneration of the proximal tubule epithelium in the kidneys were noted in female rats dosed with 300 and 1000 mg/kg bw/d. The NOAEL for parental systemic toxicity was considered to be 100 mg/kg/d. Results regarding the reproductive effects evaluated in this study are presented in the Developmental and Reproductive Toxicity section of this report.

Inhalation

The potential inhalation toxicity of undiluted Diacetone Alcohol (purity: 99.44%) vapor was evaluated in Wistar rats (12/sex/group) exposed to 0, 230, 1040, and 4500 mg/m^3 (analytical concentrations of 0, 233, 1041, and 4685 mg/m^3) of the test substance for 6 h/d, 5 d/wk, for 6 wk.[18] Rats were exposed in 1-m^3 chambers with a flow rate of approximately 0.45 m^3/min. No deaths occurred throughout the duration of the experiment. No clinical signs of toxicity were noted up until wk 4 of exposure, however, during w 4 and 5, slight lethargy was noted in several of the animals exposed to the medium and high concentrations when they were examined 30 min after cessation of exposure. Body weights of females exposed to high concentrations were significantly lower than control animals at wk 6. No significant differences were noted in any other group. Blood was taken from each rat 17 h after the last exposure session. Lactase dehydrogenase levels were significantly higher in females exposed to high concentrations compared to controls. In males, plasma protein levels were increased in the high concentration group, plasma chloride levels were reduced in animals of the medium and high concentration groups, and plasma sodium levels were reduced in animals at all test concentrations. Examination of animals post-mortem showed male liver weights to be significantly higher than controls in the medium and high concentration groups, and male kidney weights were significantly higher than controls in the high concentration group. The kidneys of all males, excluding one, exposed to the high concentration showed eosinophilic hyaline droplets in the proximal tubular cells. Other abnormalities included alveolar wall thickening and minor inflammatory infiltrates in the lungs, and similar infiltrates in the nasal cavities and trachea.

Subchronic Toxicity Studies

Oral

A subchronic toxicity study was performed according to OECD TG 408.[2] Sprague-Dawley rats were given Diacetone Alcohol in corn oil via gavage in doses of 0, 25, 150, or 600 mg/kg bw/d. Fifteen animals/sex were used in the 0 and 600 mg/kg bw/d test groups, and 10 animals/sex were used in the 25 and 150 mg/kg bw/d test groups. Animals were treated once daily for 13 wk. On completion of the treatment period, animals in each group were sacrificed, with the exception of the recovery animals (5 animals/sex in the control and high-dose groups), which were kept for a 6-wk treatment-free period. Non-adverse, slightly lower body weights were recorded from wk 10 in males treated with the highest dose. When compared with controls, a slightly higher neutrophil count was noted in males treated with 600 mg/kg bw/d. In females, mean red blood cell count was statistically significantly decreased at 150 and 600 mg/kg bw/d when compared with controls, and was associated with lower hemoglobin and packed cell volume at the highest dose level. Lower total white blood cell and lymphocyte counts were also noted at the highest dose in females. Moderately higher cholesterol concentration was noted at 600 mg/kg bw/d in both males and females. In addition, in both sexes, administration of 600 mg/kg bw/d induced minimal to slight non-adverse centrilobular hepatocellular hypertrophy that correlated with increases in liver weights and with an increase in the incidence of macroscopically accentuated lobular pattern. In the kidneys of male rats, at the 25, 150, and 600 mg/kg bw/d dose levels, there were increased incidences and severity of tubular hyaline droplets, tubular basophilia, and

granular casts, which correlated with increased kidney weights. Results regarding sperm analysis and estrous cycle monitoring can be found in the Developmental and Reproductive Toxicity Studies section of this report.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

A prenatal developmental toxicity study was performed in mated female Sprague-Dawley rats (24/group) according to OECD TG 414.[2] Diacetone Alcohol in corn oil was administered via gavage at doses of 100, 300, and 1000 mg/kg bw/d from day 6 to day 20 of gestation. A group of mated females received the vehicle only under the same experimental conditions and served as the control group. Animals were checked at least once daily for mortality and clinical signs. On day 21 post-coitum, animals were killed and submitted for a macroscopic post-mortem examination. All pregnant females had viable fetuses and there were no unscheduled deaths. Excessive salivation and tremors were observed in dams treated with 1000 mg/kg bw/d. No effect on body weight, body weight change, or food consumption was observed at any dose-level compared to controls. No test article-related effects were reported regarding uterus and carcass weights. A statistically significant increase was noted in mean relative liver and kidney weight values in dams treated with 1000 mg/kg bw/d when compared with controls. There were no effects on mean fetal body weight and sex ratio. In addition, there were no treatment-related effects at external examination and soft tissue examination of fetuses. Unossified or incomplete ossification of various parts of the skeleton were noted in all litters from mothers dosed with 1000 mg/kg bw/d. These findings were associated with presence of cartilage and were considered to be non-adverse effects of the test item treatment. A no-observed-adverse-effect level (NOAEL) for maternal parameters was considered to be 1000 mg/kg bw/d. The NOAEL for embryo-fetal development was considered to be 1000 mg/kg/d.

As described earlier in this report, a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test was performed using SD(Crj:CD(SD)) SPF rats (10/sex/group) according to OECD TG 422.[2] Rats were treated with Diacetone Alcohol in water via gavage at doses of 30, 100, 300, or 1000 mg/kg bw/d. Males were treated for 44 d while females were treated for 41 - 45 d (before and throughout pregnancy). Treated males and females were mated, and the F1 and parent generations were evaluated. A decrease in fertilization rate, number of implantations, and implantation rate was observed at the 1000 mg/kg bw/d dose level. Reduced birth rate, delivery rate, and number of live pups at day 4 of lactation was observed in pups at the 1000 mg/kg bw/d dose level. In one 1000 mg/kg bw/d litter, no pups survived due to death or cannibalism. The NOAEL for reproductive function in males and females, as well as for development of offspring, was considered to be 300 mg/kg bw/d. Findings regarding other toxicity parameters evaluated in this study are provided in the Short-Term Toxicity Studies section of this report.

The possible reproductive effects of Diacetone Alcohol were evaluated in Sprague-Dawley rats, according to OECD TG 408.[2] As described previously in the Subchronic Toxicity Study section, rats were given Diacetone Alcohol in corn oil via gavage at doses of either 0, 25, 150, or 600 mg/kg bw/d. Fifteen animals/sex were used in the 0 and 600 mg/kg bw/d test groups, and 10 animals/sex were used in the 25 and 150 mg/kg bw/d test groups. On completion of the treatment period, animals in each group were sacrificed, with the exception of the recovery animals (5 animals/sex in the control and high-dose groups), which were kept for a 6-wk treatment-free period. At the end of the treatment period, the number of cycles measured in female animals during a period of 21 d in the high-dose group was slightly lower than in the control group. At the end of the treatment-free period, this effect was no longer observed. There were no test article-related effects on mean epididymal sperm motility and morphology, mean testicular sperm head, and daily production rate. At the highest dose level, lower mean epididymal sperm counts were observed compared to controls; however, a relationship to the test article was considered to be unlikely in view of the low magnitude, the large standard deviations, the absence of microscopic finding in the testis and epididymis, and because individual values are comparable to what can typically be observed when Sprague-Dawley rats are used in laboratory conditions.

GENOTOXICITY

Details of the genotoxicity studies summarized below are provided in Table 4**.**

Diacetone Alcohol was not mutagenic in multiple Ames tests performed at up to 10,000 µg/plate, with and without metabolic activation.[2,19,20] Diacetone Alcohol was also evaluated in a yeast mitotic conversion assay (up to 5 mg/ml), and a chromosome assay (up to 4000 µg/ml).[2,20] Metabolic activation was used in the yeast mitotic assay. The test substance did not induce reverse gene mutation in bacteria or mitotic gene conversion in yeast; however, in the rat liver chromosome assay, a small increase in chromatid damage was observed within the concentration range of 2000 - 4000 µg/ml. No chromosomal damage was observed in the chromosomal aberration assay. Mouse lymphoma assays performed on Diacetone Alcohol at up to 10,000 µg/plate with and without metabolic activation yielded negative results.[2,21]

CARCINOGENICITY STUDIES

Carcinogenicity studies were not found in the published literature, and unpublished data were not submitted.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Animal

A dermal irritation assay was performed according to OECD TG 404.[2] Undiluted Diacetone Alcohol (0.5 ml) was applied to the shaved skin of New Zealand white rabbits (3/sex) under an occlusive patch. Two test sites were evaluated per animal, one intact, and one abraded. Patches remained on the skin for 24 h. The intact and abraded test sites were examined and scored for erythema and edema at 24 h, 72 h, and 7 d after application. Very slight, transient erythema was observed in 3 animals with abraded skin, which was fully reversible by day 3 in all animals. No irritation was observed in animals with intact skin.

Irritation was also evaluated by brushing the inside of the right ear of rabbits with Diacetone Alcohol, once per day, for 10 successive days.[22] No skin irritation was reported. Similarly, no irritation was observed when guinea pigs were exposed to Diacetone Alcohol on the back, once per day, for 10 consecutive days. Details regarding dosing and number/strain of animals were not reported in either study.

Human

No itching or irritation was reported when a coin-sized amount of Diacetone Alcohol was placed on the back of the hands of human volunteers.[22] The substance evaporated, and the spots on the skin remained healthy thereafter. No details regarding this study were provided.

Sensitization

Animal

A guinea pig maximization test was performed according to OECD TG 406.[2,23] Thirty Dunkin-Hartley guinea pigs were allocated into two groups: a control group (5 animals/sex) and a treated group (10 animals/sex). On day 1, intradermal injections of an adjuvant mixed with the test substance (25% Diacetone Alcohol (purity: 99.72%) in sterile isotonic saline solution) or the vehicle were performed in the dorsal region between the shoulders. On day 7, sodium lauryl sulfate was topically applied to the previously injected site to induce local irritation. On day 8, the same test site was treated with undiluted Diacetone Alcohol or vehicle, and was covered by an occlusive dressing for 48 h. After a 12-d non-treatment period, all animals were challenged with a 24-h occlusive patch of undiluted Diacetone Alcohol that was applied to the right flank. The left flank served as a control and received the vehicle only. Skin reactions were evaluated 24 and 48 h after application. No cutaneous reactions were observed after the challenge application. The test substance was considered to be non-sensitizing.

OCULAR IRRITATION STUDIES

Animal

Undiluted Diacetone Alcohol (0.1 ml) was placed in the eyes of 3 rabbits (strain not stated).[2] Animals were observed 1 h and 1, 2, 3, 4, 7, and 14 d post-treatment, and irritation was scored via a Draize scale (maximum score of 4). Slight to moderate conjunctival irritation, slight iritis, and slight to mild corneal opacity was observed. All effects were fully reversible. The mean individual scores over 24, 48, and 72 h were 1.3, 1.7, and 1.7 for chemosis, 1.7, 2.3, and 2.0 for conjunctival redness, 0.3, 1.0, and 0.7 for iritis, and 1.3, 1.0, and 1.7 for corneal opacity. It was concluded that Diacetone Alcohol is irritating to the eyes of rabbits.

In a different study, albino rabbit eyes were treated with 0.005 ml of undiluted Diacetone Alcohol, with the lids retracted.[24] The number of test animals were not stated. After approximately 1 min, the lids were released. Eighteen to 24 h later, the eyes were examined in strong diffuse daylight, then stained with fluorescein to assess injury on a scale of 1 - 10. Diacetone Alcohol was reported to cause grade 5 injury (on a scale of 1 – 10).

Human

Ocular irritation was apparent in 12 male and 12 female subjects exposed to vaporized Diacetone Alcohol at a concentration of 100 ppm for 15 min.[25] No other details regarding this study were provided.

CLINICAL STUDIES

Inhalation Exposure

Potential respiratory irritation from Diacetone Alcohol was evaluated in humans (12/sex).[25] Subjects were exposed to vaporized Diacetone Alcohol in a concentration of 100 ppm for 15 min. The majority of the subjects found the odor unpleasant at 100 ppm, complained of an unpleasant taste, and irritation to nose and throat. Although the majority of the subjects indicated that they could work an 8-h day in 100 ppm, 50 ppm appeared to be a more reliable limit. It was concluded that Diacetone Alcohol is irritating to the respiratory tract.

OCCUPATIONAL EXPOSURE LIMITS

The National Institute for Occupational Health and Safety (NIOSH) established a recommended inhalation exposure limit of 50 ppm for Diacetone Alcohol over a 10-h work day.[5] Similarly, the permissible exposure level for Diacetone Alcohol exposure over a 8-h work day was determined to be 50 ppm, according to Occupational Safety and Health Administration (OSHA).[26]

SUMMARY

This assessment addresses the safety of Diacetone Alcohol as used in cosmetics. According to the *Dictionary*, this ingredient is reported to function as a fragrance ingredient and solvent in cosmetic formulations.

According to 2021 VCRP data, Diacetone Alcohol is reported to be used in 107 nail formulations, uses were not reported in any other product category; however, according to the concentration of use survey conducted by Council in 2019, concentrations have been reported for nail formulations, as well as other categories. The highest concentration of use reported for Diacetone Alcohol in leave-on products is 0.84% in nail polish and enamel, and the highest concentration resulting in leave-on dermal exposure is 0.25% in "other" eye makeup preparations.

The in vitro dermal penetration rate of Diacetone Alcohol (25 mg/cm^2) was studied in human cadaver skin. Skin penetration (amount of test substance found in the skin) was 0.04, 0.15, and 5.71% of the dose after 10 min, 60 min, and 24 h, respectively. The plasma pharmacokinetic profile was studied in 9 male Sprague-Dawley rats given Diacetone Alcohol (5.81 g) mixed with corn oil (18.25 g) via gavage. An initial plasma concentration peak at 4.40 mmol/l was reached 1 h post-dosing, but the maximum concentration was observed 6 h after post-dosing, indicating a prolonged absorption phase.

The dermal LD_{50} in Wistar rats was > 1875 mg/kg bw; this dose was applied for 24 h using an occlusive patch. In rabbits, the dermal LD_{50} was reported to be 14.5 ml/kg in one study (occlusive 24-h patch), and > 13,630 mg/kg bw in another study (details not provided). Several acute oral toxicity studies were performed with Diacetone Alcohol. The lowest LD_{50}s reported for mice, rats, and rabbits were 3950, 2520, and 4653 mg/kg bw, respectively. An acute inhalation toxicity study was performed in Wistar rats exposed to aerosolized Diacetone Alcohol (7.6 mg/l) for 4 h.[2] The inhalation maximum tolerable concentration (LC_0) of Diacetone Alcohol was reported to be greater than 7.6 mg/l.

In a 30-d oral toxicity study, 10 albino rats were given Diacetone Alcohol in drinking water at doses of 0, 10, 40 or 130 mg/kg bw/d. No deaths occurred throughout the study. In one rat dosed with 40 mg/kg bw/d, cloudy swelling and degeneration of renal tubular epithelium was noted. No adverse effects were reported in any rats at the 10 mg/kg bw/d dose level. In a combined repeated dose toxicity study with a reproduction/developmental toxicity screening test performed in SD(Crj:CD(SD)) SPF rats, groups of 10 rats/sex were treated with Diacetone Alcohol in water via gavage at doses of 30, 100, 300, or 1000 mg/kg bw/d. Males were treated for 44 d while females were treated for 41 - 45 d. Treated males and females were mated, and the F1 and parent generations were evaluated. Signs of toxicity, such as increases in organ weights and abnormalities in kidney tissues, were observed in animals given high doses of the test substance. In a 13-wk oral toxicity study, Sprague-Dawley rats were given Diacetone Alcohol in corn oil via gavage once daily. Fifteen animals/sex were given 0 or 600 mg/kg bw/d, and 10 animals/sex were given 25 or 150 mg/kg bw/d. In females, mean red blood cell counts were statistically significantly decreased at 150 and 600 mg/kg bw/d when compared with controls. Lower total white blood cell and lymphocyte counts were also noted at the highest dose in females. In the kidneys of male rats in the 25, 150, and 600 mg/kg bw/d dose levels, there were increased incidences and severity of tubular hyaline droplets, tubular basophilia, and granular casts, which correlated with increased kidney weights.

The potential inhalation toxicity of undiluted Diacetone Alcohol was evaluated in Wistar rats (12/sex/group). Rats were exposed to up to 4500 mg/m^3 of the test substance for 6 h/d, 5 d/wk, for 6 wk. No clinical signs of toxicity were noted during the first 4 wk of exposure. Decreases in body weight and abnormalities in the kidneys were observed in animals treated with a high concentration of the test substance.

A prenatal developmental toxicity study was performed in mated female Sprague-Dawley rats (24/group). Diacetone Alcohol in corn oil was given to the test animals at doses of up to 1000 mg/kg/d on days 6 - 20 post-coitum. No toxic effects were noted in offspring. The NOAEL for maternal parameters was considered to be 1000 mg/kg/d, and the NOAEL for embryo-fetal development was considered to be 1000 mg/kg/d. A different study was performed in order to evaluate the reproductive/developmental toxicity of Diacetone Alcohol (up to 1000 mg/kg bw/d) in SD(Crj:CD(SD)) SPF rats (10/sex/group). Males were treated for 44 d while females were treated for 41 - 45 d (before and throughout pregnancy). Treated males and females were mated, and the F1 and parent generations were evaluated. The NOAEL for parental systemic toxicity was considered to be 100 mg/kg/d and the NOAEL for reproductive function in males and females, as well as for development of offspring, was considered to be 300 mg/kg bw/d. The possible reproductive effects of Diacetone Alcohol (up to 600 mg/kg/d) were evaluated in Sprague-Dawley rats via a sperm analysis and monitoring of estrous cycles. At the end of the treatment period, the number of cycles measured in female animals during a period of 21 d in the high dose group was slightly lower than in the control group. At the highest dose level, lower mean epididymal sperm counts were observed compared to controls, however, a relationship with the test item was considered to be unlikely in view of the low magnitude,

the large standard deviations, the absence of microscopic finding in the testis and epididymis, and because individual values are comparable to what can be observed in Sprague-Dawley rat laboratory conditions.

Diacetone Alcohol was negative in multiple Ames tests performed at up to 10,000 µg/plate, with and without metabolic activation. Diacetone Alcohol was also evaluated in a yeast mitotic conversion assay (up to 5 mg/ml), and a chromosome assays (up to 4000 µg/ml). Metabolic activation was used in yeast mitotic assay, but was not used in the chromosome assay. The test substance did not induce reverse gene mutation in bacteria or mitotic gene conversion in yeast, however, in the rat liver chromosome assay, a small increase in chromatid damage was observed within the concentration range of 2000 - 4000 µg/ml. A mouse lymphoma assay performed on Diacetone Alcohol at up to 10,000 µg/plate with and without metabolic activation yielded negative results.

The irritation potential of undiluted Diacetone Alcohol to intact and abraded skin was evaluated in New Zealand white rabbits (3/sex). After a 24-h application under an occlusive patch, slight, transient erythema was observed in 3 animals with abraded skin, and no irritation was observed in animals with intact skin. In a different study, Diacetone Alcohol was brushed on the ears of rabbits, once per day, for 10 d. No irritation was observed. Similarly, no irritation was reported when guinea pigs were exposed to Diacetone Alcohol on the back, once per day, for 10 d. In a human study, no itching or irritation was reported when a coin-sized amount of Diacetone Alcohol was placed on the back of the hands of volunteers.

A guinea pig maximization test was performed using Dunkin-Hartley guinea pigs (10/sex). Undiluted Diacetone Alcohol was used during the epicutaneous induction and challenge exposure. No cutaneous reactions attributable to the sensitization potential of Diacetone Alcohol were observed in the test animals.

Undiluted Diacetone Alcohol (0.1 ml) was placed in the eyes of 3 rabbits (strain not stated) to observe potential eye irritation. Slight to moderate conjunctival irritation, slight iritis, and slight to mild corneal opacity was observed. All effects were fully reversible. In a different study, albino rabbit eyes were treated with 0.005 ml of undiluted Diacetone Alcohol. On a scale of 1 - 10, Diacetone Alcohol was reported to cause grade 5 injury. Ocular irritation was apparent in twelve male and twelve females exposed to vaporized Diacetone Alcohol in a concentration of 100 ppm for 15 min.

Potential respiratory irritation from Diacetone Alcohol was evaluated in humans (12/sex). Subjects were exposed to vaporized Diacetone Alcohol in a concentration of 100 ppm for 15 min. The majority of the subjects found the odor unpleasant at 100 ppm, complained of an unpleasant taste, and irritation to nose and throat. It was concluded that Diacetone Alcohol is irritating to the respiratory tract.

NIOSH has established a recommended inhalation exposure limit of 50 ppm for Diacetone Alcohol over a 10-h work day. Similarly, OSHA established a permissible exposure level of 50 ppm over an 8-h work day.

DISCUSSION

Diacetone Alcohol is a beta-hydroxy ketone that is reported to function as a fragrance ingredient and solvent in cosmetic ingredients. The Panel found that the systemic toxicity, dermal irritation, and sensitization data in this report were sufficient, and determined Diacetone Alcohol is safe in cosmetics in the present practices of use and concentration. The need for carcinogenicity data was mitigated by multiple negative genotoxicity assays. Safety of this ingredient was further supported by low concentrations of use in leave-on products. Also, because Diacetone Alcohol is used at low concentrations of use, expected amounts of exposure to possible impurities would be extremely low, mitigating the need for further Diacetone Alcohol impurities data.

The Panel discussed the issue of potential incidental inhalation exposure from powders. The Council survey results indicate that Diacetone Alcohol is used in face, neck, and night products, which may be formulated as powders, at up to 0.0031%. Furthermore, particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of this ingredient. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredient is 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. In addition, the Panel noted the available acute and short-term inhalation studies, and determined that inhalation exposure to Diacetone Alcohol via cosmetic use would not be of concern.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Diacetone Alcohol is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

TABLES

Table 1. Chemical Properties

Property	Value	Reference
Physical Form	Liquid	5
Color	Colorless	5
Odor	Faint, minty odor	5
Molecular Weight (g/mol)	116.16	27
Density (g/ml @ 25 ºC)	0.94	26
Vapor pressure (mmHg @ 25 ºC)	0.97	28
Vapor Density (mmHg)	4	29
Melting Point (ºC)	-43.89	26
Boiling Point (ºC)	167.78	5
Water Solubility	Miscible	6
log K_{ow}	1.03	30

Table 2. Frequency (2021) and concentration (2019) of use of Diacetone Alcohol[10,11]

	# of Uses	Conc of Use (%)
Totals*	**107**	**0.00029 – 9.2**
Duration of Use		
Leave-On	*106*	*0.00029 – 0.84*
Rinse-Off	*1*	*0.00076 – 9.2*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	NR	0.00099 – 0.25
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	NR	NR
Incidental Inhalation-Powder	NR	0.0031[a]
Dermal Contact	NR	0.00094 – 0.25; 9.2[#]
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	0.00029 – 0.0011
Hair-Coloring	NR	0.014
Nail	107	0.1 – 0.84
Mucous Membrane	NR	NR
Baby Products	NR	0.00094 – 0.0011

*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.

[#] "razor lubricant strip"

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

NR – no reported use

Table 3. Acute toxicity studies of Diacetone Alcohol

Animals	No./Group	Concentration/Dose/Protocol	LD_{50}/Results	Reference
		DERMAL		
Wistar rats	6/sex	1875 mg/kg bw undiluted Diacetone Alcohol placed on skin under occlusive patch for 24 h; animals observed for 14-21 d post-dosing, in accordance with OECD TG 402	No reactions or clinical signs of toxicity observed; LD_0 was reported to be greater than 1875 mg/kg bw	[2]
rabbits (strain not reported)	6/sex	Draize assay; undiluted Diacetone Alcohol was placed on the skin, under an occlusive patch, for 24 h; amount placed on skin not stated	LD_{50} was reported to be 14.5 ml/kg bw; there was no skin injury beyond erythema followed by shallow scaling	[2]
rabbits (strain not reported)	NR	Up to 13,630 mg/kg bw; no other details reported	LD_{50} reported to be greater than 13,630 mg/kg bw	[3]
		ORAL		
mice (strain not specified)	NR	NR	LD_{50} reported to be 3950 mg/kg bw	[3]
Wistar rats	6/sex/group	1880, 2369, 3002, 3760, 5969 mg/kg bw administration via gavage; animals observed for 14 d after dosing, in accordance with OECD TG 401	Two out of the 12 animals administered 2369 mg/kg bw of the test substance died over a period of 14 d. All animals given 1880 mg/kg bw of the test substance survived the test period. Within a few hours of dosing, the rats were lethargic and displayed piloerection. One d after administration, animals were ataxic, and at high dose levels, comatose. The oral LD_{50} value of Diacetone Alcohol was determined to be 3002 mg/kg bw.	[2]
Sherman rats (male)	6/sex/group	Animals were dosed via gavage; in accordance with OECD TG 401; specific dosing not stated	LD_{50} reported to be 4000 mg/kg bw; death was prompt and due to narcosis; survivors gained weight well	[2]
rats (strain not specified)	NR	NR	LD_{50} reported to be 2520 mg/kg	[16]
rats (strain not specified)	NR	NR	LD_{50} reported to be 4000 mg/kg bw	[3]
rabbits (strain not specified)	NR	NR	LD_{50} reported to be 4653 mg/kg bw	[3]
		INHALATION		
Wistar rats	5/sex	Rats exposed to test substance in an amount of 7.6 mg/l for 4 h; whole body exposure. Animals were observed for 14 d following exposure. Performed in accordance with OECD TG 402.	No animals died and no symptoms of toxicity were noted during the duration of the study or 14-d observation period. The inhalation maximum tolerable concentration (LC_0) of Diacetone Alcohol was reported to be greater than 7.6 mg/l.	[2]

NR = Not Reported

Table 4. Genotoxicity studies of Diacetone Alcohol

Test Substance	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
Diacetone Alcohol (purity: 99.8%)	0, 313, 625, 1250, 2500, and 5000 µg/plate	Water	*S. typhimurium* TA98, TA100, TA1535, TA1537 and *E. coli* strain WP2 uvr A	Ames test performed with and without metabolic activation	Non-mutagenic	[2]
Diacetone Alcohol (purity not stated)	100 – 10,000 µg/plate	Water	*S. typhimurium* TA98, TA100, TA1535, TA1537, and TA1538	Ames test performed with and without metabolic activation	Non-mutagenic	[19]
Diacetone Alcohol (purity not stated)	Up to 4000 µg/plate	Water	*S. typhimurium* strains TA1538, TA98, and TA100	Ames test performed with metabolic activation	Non-mutagenic	[20]
Diacetone Alcohol (purity: 99.70%)	0, 156.3, 312.5, 625, 1250, 2500, and 5000 µg/mL	Culture medium	Mouse lymphoma L5178Y (tk+/tk-) cells	Mouse lymphoma assay performed with and without metabolic activation	Non-mutagenic	[2]
Diacetone Alcohol (purity not stated)	100 – 10,000 µg/plate	NR	Mouse lymphoma L5178Y (tk+/tk-) cells	Mouse lymphoma assay performed with and without metabolic activation	Non-mutagenic	[21]
Diacetone Alcohol (purity not stated)	Up to 5 mg/ml	Water	*Sacc. cerevisiae* JD1	Yeast mitotic assay performed with metabolic activation	Non-mutagenic	[20]
Diacetone Alcohol (purity not stated)	Up to 4000 µg/ml	Water	Rat liver (RL_4) cells	Chromosome assay performed without metabolic activation	A small increase in chromatid damage was observed within the concentration range of 2000 – 4000 µg/ml.	[20]

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2021 FDA VCRP – Diacetone Alcohol

Basecoats and Undercoats	6
Nail Polish and Enamel	94
Nail Polish and Enamel Removers	1
Other Manicuring Preparations	6

Total Uses: 107