Safety Assessment of Hydroxyacetophenone as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	September 1, 2022
Panel Meeting Date:	September 26-27, 2022

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.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D.
This safety assessment was prepared by Preethi Raj, Senior Scientific Analyst/Writer, CIR.

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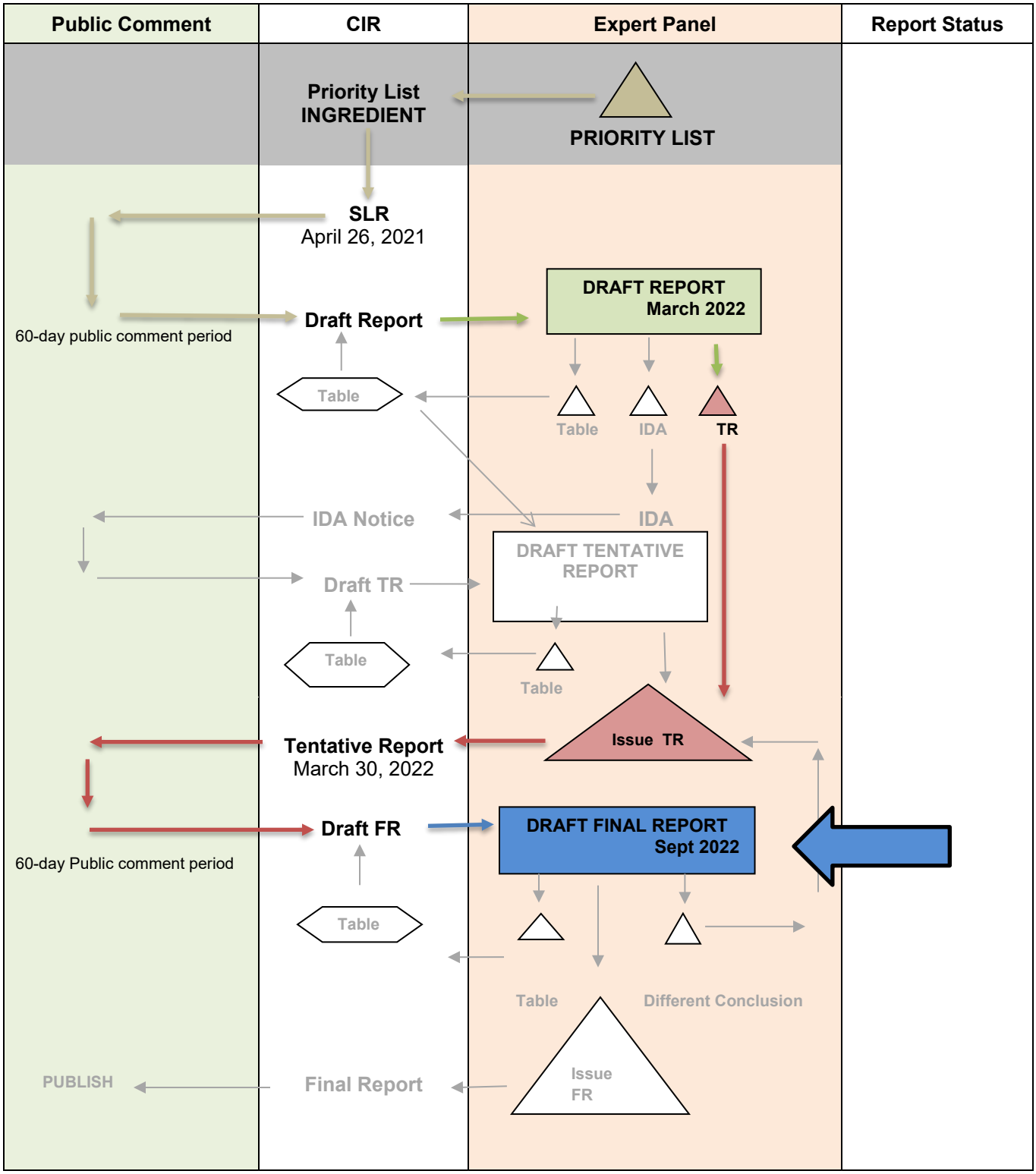
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Hydroxyacetophenone

MEETING September 2022



Cosmetic Ingredient Review

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons
From: Preethi S. Raj, M.Sc.
Senior Scientific Analyst/Writer, CIR
Date: September 1, 2022
Subject: Safety Assessment of Hydroxyacetophenone as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Hydroxyacetophenone as Used in Cosmetics (identified as *report_Hydroxyacetophenone_092022* in the pdf). This is the second time the Expert Panel for Cosmetic Ingredient Safety (Panel) is seeing a safety assessment of this cosmetic ingredient. At the March 2022 meeting, the Panel issued a Tentative Report for public comment with the conclusion that Hydroxyacetophenone is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

Comments on the Tentative Report that were received from the Council have been addressed, and follow this memo (*PCPCcomments_Hydroxyacetophenone_092022*). A comments response checklist is also included (*response-PCPCcomments_Hydroxyacetophenone_092022*).

Also included in this package, for your review, are:

- a flow chart (*flow_Hydroxyacetophenone_092022*)
- literature search strategy (*search_Hydroxyacetophenone_092022*)
- data profile (*dataprofile_Hydroxyacetophenone_092022*)
- transcripts from the previous meeting (*transcripts_Hydroxyacetophenone_092022*)
- ingredient history (*history_Hydroxyacetophenone_092022*)
- 2022 FDA VCRP data (*VCRP_Hydroxyacetophenone_092022*)

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.

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 4, 2022

SUBJECT: Tentative Report: Safety Assessment of Hydroxyacetophenone as Used in Cosmetics (release date: March 30, 2022)

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

Short-Term, Inhalation; Summary – Please state the endpoints (hematology, clinical chemistry, histopathologic examination of kidneys, liver, lungs, spleen and testes/epididymis) that were examined in the 4-week inhalation study of Hydroxyacetophenone in rats.

Dermal Irritation and Sensitization – In the description of the guinea pig maximization study, please state that one of the induction exposures was by intradermal injection.

Summary – Please revise: "mortality in 7 animals across the dose groups (number not specified) was considered accidental deaths" (delete "deaths")

Discussion – It is not clear what is meant by "biological properties" of Hydroxyacetophenone. Perhaps this should be "biological activity".

Table 3 – In the Concentration/Dose row of the fifth study, "with metabolic activation" appears to be missing after "31.5-500 µg/ml".

Table 4 – In the Concentration/Dose row of the third study, either something needs to be added after the last 0.5 ml (perhaps "vehicles alone"), or the last 0.5 ml needs to be deleted.

Hydroxyacetophenone - September 26-27th, 2022 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: April 4, 2022 (comments received on TR, posted March 30, 2022)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Short-Term, Inhalation; Summary- State endpoints that were examined in 4-wk inhalation study in rats	revised	
2	Dermal Irr and Sens – in guinea pig maximization study, state that one of the induction exposures was by intradermal injection	revised	
3	Summary – Revise sentence: number of animals was not specified and delete deaths	revised	
4	Discussion: revise: change 'biological properties' to 'biologic activity'		
5	Table 3, Conc/dose column – with metabolic activation seems to be missing after conc/dose in fifth study row	added	
6	Table 4, Conc/dose column – vehicles alone needs to be added or the last 0.5 ml needs to be deleted	deleted	

CIR History of:

Hydroxyacetophenone

January 2021

-Concentration of use data submitted by Council (survey conducted in 2020)

January 2021

-FDA frequency of use data obtained

April 2021

- SLR posted on the CIR website; received SLR comments in May

Data received, by date:

May 3, 2021:

- single occlusive patch test of a SPF product containing 0.05% Hydroxyacetophenone
- 21-d cumulative irritation assay using a SPF 70 cream containing 0.05% Hydroxyacetophenone
- HRIPT of a SPF 70 cream containing 0.5% Hydroxyacetophenone

June 21, 2021:

- Buehler test of guinea pigs (20% aqueous Hydroxyacetophenone)
- Single occlusive patch test of rabbits (1%, 10%, 50% aqueous Hydroxyacetophenone)

June 22, 2021:

- Certificate of analysis, production flow chart, dermal irritation study summary, and HRIPT summary data

January 2022

-Updated FDA frequency of use data obtained

March 2022

-A Draft Report was presented to the Panel. The Panel issued a Tentative report with conclusion that Hydroxyacetophenone is safe as used in cosmetics in the present practices of use and concentration described in the safety assessment. The Panel was reassured of this ingredient having no systemic toxicity concerns by its FEMA GRAS status as a food flavoring substance, as well by a high reported purity of 99.5%, low concentration of use in cosmetics, favorable toxicological profile, and a lack of chemical structure alerts.

April 2022

-Comments on the Tentative Report were received from Council

September 2022

-A Draft Final Report is being presented to the Panel.

Hydroxyacetophenone Data Profile* – September 26-27, 2022 – Preethi Raj																															
				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/log K_{ow}	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
Hydroxyacetophenone	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

Hydroxyacetophenone – 1 ingredient

Ingredient	CAS #	PubMed	FDA	HPVIS	NIOSH	NTIS	NTP	FEMA	EU	ECHA	ECETOC	SIDS	SCCS	AICIS	FAO	WHO	Web
Hydroxyacetophenone	99-93-4	✓*	NR	NR	NR	✓	✓*	✓	✓*	✓	NR	NR	NR	NR	✓	✓	

✓- data available
✓*- mentioned but relevant data not available
NR – not reported

Search Strategy (PubMed) [*total # of hits / # hits that were useful*]

Updated search on 07/21/22: (((((hydroxyacetophenone) OR (Ethanone, 1-(4-hydroxyphenyl)-)) OR (p-hydroxyacetophenone)) OR (parahydroxyacetophenone)) OR (4-Hydroxyacetophenone)) AND (toxicity)- 53 hits/ 0 useful

Ethanone, 1-(4-hydroxyphenyl) + toxicity- 10- 27 hits/0 useful
p-Hydroxyacetophenone toxicity – 137 hits/0 useful
4-Hydroxyacetophenone- 313 hits/ 0 useful
Piceol – 325 hits/ 0 useful
(((((Hydroxyacetophenone) OR (Ethanone, 1-(4-hydroxyphenyl))) OR (p-Hydroxyacetophenone)) OR (4-Hydroxyacetophenone)) OR (piceol))
AND (cosmetic toxicity) – 1 hit/0 useful
AND (method of manufacture) – 2 hits/ 0 useful
AND (impurities) – 5 hits/ 0 useful
AND (dermal penetration) – 0 hits
AND (toxicokinetics) – 20 results/ 1 useful
AND (dermal toxicity) – 14 results/ 1 useful
AND (oral toxicity) – 92 results /0 useful
AND (inhalation toxicity) – 11 results/ 0 useful
AND (repeated dose toxicity)- 43 results/ 0 useful
AND (repeated dose oral toxicity)- 22 results/0 useful
AND (repeated dose dermal toxicity)- 4 hits/ 1 useful
AND (repeated dose inhalation toxicity) – 2 hits/0 useful
AND (developmental toxicity) – 29 hits/0 useful
AND (reproductive toxicity) – 24 hits/ 0 useful
AND (genotoxicity/ mutagenicity) – 21-22 hits/ 0 useful
AND (carcinogenicity) – 22 hits/0 useful
AND (dermal irritation) – 5 hits/ 1 useful
AND (dermal sensitization) – 4 hits/ 0 useful
AND (phototoxicity) – 6 hits/ 0 useful
AND (ocular irritation) – 2 hits/ 0 useful
AND (clinical studies) – 38 hits/ 0 useful

General Web Search (Google)

Hydroxyacetophenone Australian industrial chemicals introduction scheme risk assessment – 27300 hits/ 0 useful
Ethanone, 1-(4-hydroxyphenyl) safety assessment- 20,300 hits/ 0 useful
p-Hydroxyacetophenone dermal irritation– 46 hits/ 0 useful
p-hydroxyacteophenone EU risk assessment – 25 hits/ 0 useful
p-hydroxyacetophenone European medical assessment – 143,000 hits/ 0 useful; 4-Hydroxyacetophenone dermal sensitization – 38,500 hits/ 5 useful
Where is piceol found – 6,60 hits/ 4 useful; CAS 99-93-4 toxicity – 82 hits/ 1 useful

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Connected Papers (https://www.connectedpapers.com)

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;,
- Substances Added to Food (formerly, EAFUS): https://www.fda.gov/food/food-additives-petitions/substances-added-food-formerly-eafus
- 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
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/
- HPVIS (EPA High-Production Volume Info Systems) - https://iaspub.epa.gov/oppthpv/public_search.html_page
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
  - technical reports search page: https://ntrl.ntis.gov/NTRL/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) GRAS: https://www.femaflavor.org/fema-gras
- 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/
- 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
- AICIS (Australian Industrial Chemicals Introduction Scheme)- https://www.industrialchemicals.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

MARCH 2022 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – March 7, 2022

DR. DONALD BELSITO: OK. So, then we're moving onto Hydroxyacetophenone. This is the first time that we're seeing this and Monice. If I send you something here come [inaudible]. Where did I put this, OK, can you show it up on the screen?
MONICE FIUME (CIR): Yes, I can.
DR. DONALD BELSITO: And let me let me send you the UV absorption spectrum for this. OK, you should be getting it shortly. So, we have an issue with this in it. It's an issue that really sort of brought up to me. And our writers should be aware when we're looking at things with ring structures like this, we should really always be trying to look for UV absorption data, this molecule absorbs in the UV range, which is going to create an issue for us because I believe we have photo tox. That phototox study, but we don't have any photo allergies studies. To support its use. Did it come through Monice?
MONICE FIUME (CIR): Yeah, I'm putting it up now. You should be able to see it.
DR. DONALD BELSITO: So, that's the UV absorption spectra for it and you can see that at pH 8, it really goes through the UVA range now. Now, you know, as Dan and I know, I don't know about the rest of you, I actually found out that pH can significantly change the UV absorption of fragrance materials and you're seeing that here at pH 7. It's already moving away from the UV absorption. So, I would imagine most cosmetic products aren't going to be formulated at a pH of 8, since the skin pH is 5.5, which probably would put that out of the absorbance range, but I don't really know how to handle this.
DR. DAN LIEBLER: Well, if you look at the, if you look at the spectrum the blue one, which is the pH 7 version. First of all, if you think about the structure, it's got a ring with a hydroxyl group on it and the pH is affecting essentially the protonation of that hydroxyl. In other words, there's a 0h or 0 minus at pH 8, some of its deprotonated. You got 0 minus, which is a different chromophore in a different UV absorbance. And that's what shifts the absorbance spectrum from the band around 270 to the shoulder band between 300 and 350. So, you see that somebody is getting an amber alert. I don't know if that's the American Chemical Society doing an amber alert on my photochemistry commentary anyway. So, I think the relevant spectrum to consider is the one in blue.
DR. CURTIS KLAASSEN: There we go.
DR. DAN LIEBLER: Now because of the formulation reasons, reasons Don just mentioned, but that represents really what we can anticipate being the behavior of the chromophore under in physiological. OK, so and anyway I don't. I did not have a concern about this one and I'm not sure what phototox data referring to Don. Is it in the report or is it in a wave? Two or?
PREETHI RAJ (CIR): I don't believe there's that tox data.
DR. DONALD BELSITO: No, I think there was a photo tox study, right?
DR. DAN LIEBLER: I missed it.
PREETHI RAJ (CIR): I don't think there is any photo tox data in this report, Dr Belsito.
DR. DONALD BELSITO: OK, maybe I was thinking of another report anyway, so we're not even going to.
DR. DAN LIEBLER: Just mute your phone there, Curt, I think would be fine.
DR. CURTIS KLAASSEN: Hello.
DR. DONALD BELSITO: So, we're not even going to bring this issue up then.
DR. DAN LIEBLER: No, I don't think it's an issue.
DR. PAUL SNYDER: So, you don't even think we need to put it in the discussion as we acknowledge it in the final formulations should not approach that pH.
DR. DAN LIEBLER: No, I mean, I mean I don't we have looked at so many molecules that have this kind of structure in him [inaudible] and we never mentioned it.
DR. PAUL SNYDER: OK.
DR. DAN LIEBLER: And in the absence of data, I don't think it makes any sense to mention it, otherwise we sort of handcuff ourselves for the future, for anything that's got a phenol structure in it.
DR. DONALD BELSITO: Right. OK.
DR. DAN LIEBLER: So many flavonoids, for example, look like this and behave like this. And then we put ourselves in a box with respect to lots of botanical naturals.
DR. CURTIS KLAASSEN: Yeah.
DR. DONALD BELSITO: Going to the comments PCPC that were submitted in May of 2021. On this is PDF page 6. The last one, table three and about the study of Balb C mice, it says. It seems like the objective was to evaluate cellular transforming potential. Hydroxy acids are from their own in cells that were exposed to carcinogens. So, to me it seems like they were looking at the promotion of fact of this material is that what you all assumed?
DR. PAUL SNYDER: Yes, that's not a carcinogenicity study that would be under the. The promoter initiator category we had sometimes in these reports.

DR. DONALD BELSITO: Right.
PREETHI RAJ (CIR): Dr Snyder, do you mean tumor promotion?
DR. PAUL SNYDER: That's correct.
DR. DONALD BELSITO: Right.
DR. PAUL SNYDER: The ocular irritancy of this Don?
DR. DONALD BELSITO: What PDF page you on, Paul?
DR. PAUL SNYDER: 2nd.
PREETHI RAJ (CIR): PDF page 16, I believe.
DR. PAUL SNYDER: Thank you. It's a pretty severe irritant.
DR. DONALD BELSITO: Yeah, but it was applied neat, right?
DR. PAUL SNYDER: True, but we can we do have a 1 use of .23. So that's why I just wanted to make sure we acknowledge that we considered it.
DR. DONALD BELSITO: Yeah. So that can go in the discussion now.
DR. PAUL SNYDER: OK.
DR. DONALD BELSITO: So, this is GRAS.
DR. DONALD BELSITO: There's good respiratory data on it and we have the boilerplate. We have normal irritation and sensitization, I think we pretty much have everything we need on this no?
DR. DAN LIEBLER: I agree, I agree. I think that this is going to be safe as used. All the chemistry related stuff looks great. The you know the only we don't have any genotox. I don't know carcinogenicity. So, given the broad range of the negative genotox and the lack of any structure alerts, I think we're OK.
DR. DONALD BELSITO: And its GRAS.
DR. DAN LIEBLER: It's just. It it's GRAS, right? This rate [inaudible]?
DR. PAUL SNYDER: No, we do have genotox. We do have Table 3 genotoxicity.
DR. DAN LIEBLER: I know I misspoke, Paul. I meant no carcinogenicity.
DR. PAUL SNYDER: I'm sorry. OK.
DR. DAN LIEBLER: And one of the things that that I thought of when I was reading this report -- or was that we can just, you know, make a potential consideration using structure alert prediction software tool for discrete small molecules in the future and there would be particularly useful where we either have no genotox and no carcinogenicity now in this case we've got it's you know it's a GRAS substance and we don't need to worry about any of that but I emailed Bart. Think I copied Don and David on this and I also can't talk to my colleague at RIFM Terry Schultz to ask for a recommendation on what might be the optimum software package to use. And I forwarded his recommendation on to Bart. So, I think in the future would be nice to start bringing in a sort of an in silico screen for structure alerts for genotox or carcinogenicity in cases where we don't have. It's not in this case, but in future cases. So that's I just wanted to mention that.
DR. DONALD BELSITO: OK. We have GRAS, we have good respiratory data.
DR. PAUL SNYDER: Now I'm going back to my comment on the ocular irritant it I was looking at my notes again and it was queried will be partly because we have baby use with no concentration of use.
DR. DONALD BELSITO: Yeah.
DR. PAUL SNYDER: Wouldn't again [inaudible]--. Probably that could be wrapped up into discussion, but we have reported baby use has been no concentration of use.
DR. DONALD BELSITO: So, we have ocular irritation. Or how do you want to phrase that? I mean we --The dermal area [inaudible] there really wasn't good. I mean the dermal irritation was good, right?
DR. PAUL SNYDER: Right. It was just that ocular was the one that just stuck me there. It was a severe irritant, granted it was neat, but we don't know. We don't have any. But to what level it goes down to.
DR. DONALD BELSITO: Right. OK.
DR. PAUL SNYDER: I mean those are pretty high scores, I mean.
DR. DONALD BELSITO: So, basically something in the discussion that formulated should be aware of the ocular attention when. How do you want to put it up? Where of ocular irritation when? Used in products that may be applied close to the eyes or?--
DR. PAUL SNYDER: I mean that seems reasonable to me. I mean, it's just that it was severe ocular irritant and then we have these baby uses with no concentration. So, what if the concentration and the baby product is much higher than that 5% we have? Here because we don't have that.
DR. DONALD BELSITO: We say as used, meaning 5% would be the higher limit of concentration, right Monice?
MONICE FIUME (CIR): Or it wasn't here. Yeah, as used, I mean, generally we assume those concentrations, you could put it in. I was looking at this study and it says finally ground so. When it's something like that, where says finely ground and not

like that it's in a solvent. How do you know if the ocular irritation-- and this is just my curiosity-- is because it's a ground substance versus the material itself?
DR. DONALD BELSITO: Good point.
DR. PAUL SNYDER: Yeah, true.
MONICE FIUME (CIR): I mean, I think it's something that can be handled in the discussion. If you don't feel that there's dermal irritation or, I mean I think the max use is 5% so assuming 100% in a baby product seems like a big leap, so I don't know if you need to put non irritating in the conclusion. I think it seems to be something that could be handled in the discussion with the assumption that the concentration is similar to what's recorded.
DR. PAUL SNYDER: Correct, yes, 5%. Yeah, that's why I was raising and just make sure it gets incorporated into discussion because the discussion isn't developed yet.
DR. DONALD BELSITO: Right.
DR. PAUL SNYDER: That's appropriate.
THOMAS GREMILLION (CFA): Is it common to have a use with no concentration?
DR. DONALD BELSITO: All the time.
THOMAS GREMILLION (CFA): OK. Is that I mean it seems like that would be the use would babies would be the one you'd want the concentration for more than any other. I don't know if there's. I mean, I don't know what the implications are for how you write the article that. It's concerning to think that that maybe that they use for the babies is higher than the max reported concentration.
DR. DAN LIEBLER: We encountered this situation all the time, Thomas.
DR. PAUL SNYDER: Well, it's it might extend stated and we it's covered in our use, you know-- as used statement [inaudible]--
MONICE FIUME (CIR): It is the prerogative of the Panel to include a definitive paragraph in the discussion stating that we noted that there are baby uses. We know that there's ocular irritation of the undiluted chemical. So, it it's assumed that the use in baby products is no higher than the max reported use. Or something to that effect.
DR. DONALD BELSITO: Yeah. So, I just sort of typed up something quickly, said aware of ocular irritation. And, you know, given the ocular toxicity data of the neat granular substance formulated should be aware of the potential for irritation in products that may be used close to the eye.
DR. PAUL SNYDER: That sounds fine.
DR. DONALD BELSITO: And then elsewhere in the discussion, basically it's GRAS. Not a sensitizer, not a dermal irritant at concentrations of use who's good respiratory data [inaudible], but we're going to use the inhalation boilerplate.
I couldn't think of anything else to discuss with this. Team help me out here.
DR. DAN LIEBLER: I know I agree with you. I think our data needs are met.
DR. PAUL SNYDER: I agree.
DR. DONALD BELSITO: So, then we're going to move on to the acrylamide acrylate copolymers.
PREETHI RAJ (CIR): Thank you.

Cohen Team – March 7. 2022

DR. DAVID COHEN: Yeah. Yeah. I really mulled over that one just I thought there was there was a lot of information online about it and not --and in peer-reviewed articles about it, it's just wasn't, it wasn't something trivial, OK? If we may. Go on. Alright, hydroxyacetophenone, this is the first time we're reviewing this. It's used as an antioxidant. And skin conditioning agent and we're evaluating one ingredient. We have reported use, which is considerable. And we have a max, you said 5% in a non-spray night product. It's also used in paste masks and mud masks. It's used also around the eye, in an eye lotion. And we saw a case of contact dermatitis from a face cream, perhaps from that. And we have a lot of data on this. I was going to ask for some comments about the clastogenic effects in the mouse lymphoma model. And some irritancy in rabbit eyes. So, I'll just open it up for you all--
DR. RON SHANK: OK, I think that's it.
DR. DAVID COHEN: Tom, go ahead--
DR. RON SHANK: The tox data are complete. And the only concern I have is possible ocular irritation-- as you mentioned. Now, presumably these night products are, solids. Yeah. So, they may be applied to the face, so there may be a risk to the eyes.--Could that be handled by when formulated to be non-irritating?
DR. DAVID COHEN: Now was my conclusion but--
DR. WILMA BERGFELD: They were-- They were an undiluted, the first one.
DR. DAVID COHEN: Ah, I think there was a severe irritant under the study conditions-- 21 day cumulative irritancy with 0.05% SPF had some signal PDF 42 and 43. I have to go to that. Tom. What did you have?

DR. THOMAS SLAGA: If I had to say it, like Ron -- I had no concerns other than ocular irritation, the clastogenic fact by itself. It's not that useful. It has to be with other data to help support, you know genotoxicity or carcinogenicity, there has to be other data with it because there's a lot of positive compounds that have no effect as a carcinogen or as a mutagen.
DR. DAVID COHEN: So, Wilma. You know, your point is it's important that you know when if you look at the daily cumulative irritancy scores, it's a .05% SPF. So, I mean, there's a lot of other stuff in there that might be causing it, but there are, sorta signals during induction.
DR. WILMA BERGFELD: Well, I don't mind it, except that you know the first paragraph, undiluted, did not do much, and the second one was seven day application which did something. It had erythema process--
DR. DAVID COHEN: Yeah. So, my inclination was safe as used when formulated to be non-irritating.
DR. WILMA BERGFELD: It's fine.
DR. DAVID COHEN: OK, I think I present-- I think I present that one tomorrow, OK.
DR. RON SHANK: OK.
DR. WILMA BERGFELD: Is your ocular --is your ocular in the table?
DR. RON SHANK: It was good. What table?
DR. WILMA BERGFELD: Yeah, Table 4 which is dealing with the irritation and sensitization.
PREETHI RAJ (CIR): I don't believe so.
DR. WILMA BERGFELD: Don't you think we ought to put it there if we're going to use that?
DR. RON SHANK: Yes.
DR. BART HELDRETH: Do you want to a separate table for ocular or do you want us to just change the title of Table 4 to dermal or ocular?
DR. WILMA BERGFELD: Yeah. Why don't you do that?
DR. BART HELDRETH: Yeah.
DR. DAVID COHEN: Yeah. We don't need another table.
DR. BART HELDRETH: Yeah.
DR. WILMA BERGFELD: Well, it's really raining here.
PREETHI RAJ (CIR): Yes. So, any particular boilerplate or language in the discussion since the Panel is going with a tentative report?
DR. DAVID COHEN: I didn't have anything special that I needed in there but. Tom, Ron, Wilma?
DR. RON SHANK: No.
DR. WILMA BERGFELD: I was just trying to figure out chemically, why is it an irritant? Is there something of that chemistry? I mean it it's used in antioxidants in skin conditions and not a pH adjuster anything. I don't know the chemistry so. But it looks like it's a liquid. Strictly due to concentration and frequency of testing--
DR. DAVID COHEN: I--
DR. WILMA BERGFELD: I don't know--
DR. DAVID COHEN: Now I-- Your vitamin C can be irritating as an antioxidant.
DR. WILMA BERGFELD: That's an acid-- ascorbic acid.
DR. DAVID COHEN: Right, but that is an acid. I can't look at that and know exactly how it's going to metabolize in the skin.
DR. WILMA BERGFELD: Maybe Ron can, or Tom?
DR. RON SHANK: Could be -- could be demethylated. To form a para- hydroxybenzoic acid.
DR. WILMA BERGFELD: Oh, I wasn't here.
DR. DAVID COHEN: No.
DR. WILMA BERGFELD: Yeah.
DR. BART HELDRETH: Additionally, whenever you have a hydroxyl group right on a benzene ring like this, especially para to an unsaturated system, that proton that's on the O-H there, is rather acidic. So, that it can be acidic because of that proton.
DR. DAVID COHEN: Ah.
DR. BART HELDRETH: Is. It's got, it's got, you know, those electrons can be stabilized across the ring and even into the ketone on the other side.
DR. DAVID COHEN: Ah, so the proton just pops off--
DR. BART HELDRETH: Yeah-- And then the electrons that remain can be stabilized through the benzene ring and through the ketone.

DR. DAVID COHEN: Right, like some sunscreens do, right?
DR. BART HELDRETH: You have. You know you have a kind of enol kind of structure--
DR. DAVID COHEN: OK.
DR. WILMA BERGFELD: Thank you.
DR. BART HELDRETH: Mmhmm.
DR. COHEN: That was good. OK, so acrylamide acrylate polymers --

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DR. DAVID COHEN: Yeah. So, hydroxyacetophenone. This is the first time we're reviewing this, and this assessment is for one ingredient. It's used as an antioxidant and skin conditioning agent. We have many reported uses. We have max use of 5% in a non-spray night product and it's in paste masks and mud masks. It's also used in about 1/4 percent in eye lotions and eye makeup removers. We felt this was a rather comprehensive package, having a lot of necessary material. We saw a case of contact dermatitis described and we have an HRIPT at a much higher than —at max concentration. So, we would go out with a motion as safe as used.
DR. DON BELSITO: 2nd.
DR. WILMA BERGFELD: Second, any further comment?
DR. DON BELSITO: Yes, in the ocular data. Granted, it was applied neat and as a powder, but there was some severe irritation and we just wanted in the discussion that formulators should be aware of this ocular irritation in products that may be used close to the eye, since we don't have a NOAEL for that.
DR. DAVID COHEN: Yeah. So, Don, we waffled back and forth with safe as used or safe as used when formulated to be non-irritating, but I think--
DR. DON BELSITO: No. It's safe, as used is fine, it should just go conclusion.
DR. DAVID COHEN: Yeah. Yeah, we, concur.
DR. DON BELSITO: I mean in the discussion, rather.
DR. WILMA BERGFELD: I could I interrupt by saying there was some discussion to put the ocular into the skin irritation table.
DR. DON BELSITO: There was no skin irritation, it was simply ocular.
DR. WILMA BERGFELD: I know, I know, but I meant. Did the studies, the tables?
DR. DAVID COHEN: Oh yeah, we to include this study in the table and just generalize the title of the table-- just so people their eyes would go to it, so to speak. In the.
DR. RON SHANK: Or make a separate table.
DR. DON BELSITO: Yeah, I mean it's a separate table-- we never make—
DR. DAVID COHEN: Or make a separate table--
DR. DON BELSITO: --to put ocular in with skin.
DR. WILMA BERGFELD: No, but your depending on it and your conclusion and your discussion.
DR. DON BELSITO: It's in the document [inaudible] and it's not like it's seven, eight, nine, ten studies…
DR. RON SHANK: Right.
DR. DAVID COHEN: I think having it clearly articulated in discussion will do the job.
DR. WILMA BERGFELD: Everyone agreed to that.
DR. DON BELSITO: I think it's fine creating a table for. I forget what it's a one or two.
DR. RON SHANK: Yes.
PREETHI RAJ (CIR): There are two ocular irritation studies.
DR. DON BELSITO: What 2 studies? Yeah.
PREETHI RAJ (CIR): So, is the Panel in agreement to add those to the existing dermal table?
DR. DON BELSITO: No, you should never mix.
DR. DAVID COHEN: No.
DR. WILMA BERGFELD: No, they appear not to be. Yep.
DR. DAVID COHEN: No, but if it if there's two of them, Don.
DR. DON BELSITO: I mean, fine. If you want to make a table for two, please.
DR. DAVID COHEN: Yeah, it's, going to be highlighted, but when we're not changing the conclusion so-- I think it's a good compromise.
DR. WILMA BERGFELD: So, they're adding a separate table for ocular.

PREETHI RAJ (CIR): OK. Thank you.
DR. DAVID COHEN: Yes.
DR. WILMA BERGFELD: OK. Are we ready to vote then?
DR. RON SHANK: Yeah.
DR. WILMA BERGFELD: Alright, all those opposed? Abstaining? This ingredient is approved as safe --moving on to the next ingredient, Dr. Belsito, glucosamine.

Safety Assessment of Hydroxyacetophenone 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.; Allan E. Rettie, Ph.D.; David Ross, Ph.D.; Thomas J. Slaga, Ph.D.; Paul W. Snyder, D.V.M., Ph.D.; and Susan C. Tilton, Ph.D. Previous Panel member involved in this assessment: Ronald C. Shank, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D.
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ABBREVIATIONS

CAS	Chemical Abstracts Service
CII	cumulative irritation index
CIR	Cosmetic Ingredient Review
Council	Personal Care Products Council
CPSC	Consumer Product Safety Commission
Dictionary	*International Cosmetic Ingredient Dictionary and Handbook*
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
FCA	Freund's complete adjuvant
FDA	Food and Drug Administration
FEMA	Flavor and Extract Manufacturing Association
GRAS	generally recognized as safe
HRIPT	human repeated insult patch test
ICDRG	International Contact Dermatitis Research Group
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LD	lethal dose
MMAD	mass median aerodynamic diameter
MeOH	methanol
MW	molecular weight
N/A	not applicable
NOAEC	no-observed-adverse-effect-concentration
NOAEL	no-observed-adverse-effect-level
NOEL	no-observed-effect-level
NR	not reported/none reported
OECD	Organisation for Economic Co-operation and Development
Panel	Expert Panel for Cosmetic Ingredient Safety
PDII	primary dermal irritation index
PII	primary irritation index
SIOPT	single insult occlusive patch test
SLS	sodium lauryl sulfate
TG	test guideline
THF	tetrahydrofuran
US	United States
VCRP	Voluntary Cosmetic Registration Program

ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Hydroxyacetophenone as used in cosmetic formulations. This ingredient is reported to function in cosmetics as an antioxidant and skin-conditioning agent. The Panel reviewed relevant data related to the safety of this ingredient in cosmetic formulations, and concluded that Hydroxyacetophenone is safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This assessment reviews the safety of Hydroxyacetophenone 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 an antioxidant and skin-conditioning agent - miscellaneous.[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 were found on the European Chemicals Agency (ECHA) website.[2] Please note that the ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited.

CHEMISTRY

Definition and Structure

Hydroxyacetophenone (CAS No. 99-93-4) is the organic compound that conforms to the structure depicted in Figure 1.

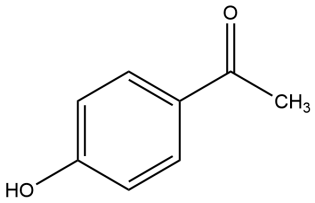

Figure 1. Hydroxyacetophenone

Chemical Properties

Hydroxyacetophenone has a molecular weight (MW) of 136.15 g/mol and an estimated log K_{ow} of 1.65.[2,3] The chemical properties of Hydroxyacetophenone are further outlined in Table 1.

Natural Occurrence

Hydroxyacetophenone, also known as piceol, and its glucoside, picein, have been found at concentrations of 0.4% - 1.1% and 1.8 - 2.2%, dry weight, respectively, in Norway spruce (*Picea abies*) needles.[4]

Method of Manufacture

According to a supplier, Hydroxyacetophenone is manufactured by first combining phenol and acetic anhydride to produce phenylacetate.[5] The phenylacetate is then converted to Hydroxyacetophenone via a Fries rearrangement, after which it is purified.

Impurities

According to a supplier-provided certificate of analysis, gas liquid chromatography of a Hydroxyacetophenone sample confirmed up to 100% purity.[6] The chromatography results also indicate that the sample contained < 10 mg/kg phenol/ 1,2dichlorobenzene.

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, and does not cover their use in airbrush delivery systems. Data are submitted by the cosmetic industry via the FDA's Voluntary

Cosmetic Registration Program (VCRP) database (frequency of use) and in response to a survey conducted by the Personal Care Products Council (Council) (maximum use concentrations). The data are provided by cosmetic product categories, based on 21CFR Part 720. For most cosmetic product categories, 21CFR Part 720 does not indicate type of application and, therefore, airbrush application is not considered. Airbrush delivery systems are within the purview of the US Consumer Product Safety Commission (CPSC), while ingredients, as used in airbrush delivery systems, are within the jurisdiction of the FDA. Airbrush delivery system use for cosmetic application has not been evaluated by the CPSC, nor has the use of cosmetic ingredients in airbrush technology been evaluated by the FDA. Moreover, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety.

According to 2022 VCRP survey data, Hydroxyacetophenone is reported to be used in 791 formulations, of which 671 are leave-on products; there are 236 reported uses in moisturizing products and 202 reported uses in face and neck products (Table 2).[7] Results from the 2020 concentration of use survey conducted by the Council indicate that the highest maximum concentration of use reported for Hydroxyacetophenone is 5%, in non-spray night products, in paste masks, and in mud packs; the night product use represents the greatest maximum concentration of use for leave-on dermal exposure.[8]

This ingredient has been reported to be used in products that may come into contact with the eyes; for example, Hydroxyacetophenone is reported to be used at up to 0.23% in eye lotions and eye makeup removers. Reported use of Hydroxyacetophenone in lipsticks also indicates the possibility for incidental ingestion. Hydroxyacetophenone is also reported to be used at up to 0.6% in formulations that could come in contact with mucous membranes, such as bath soaps and detergents. Hydroxyacetophenone is reported to be used in 7 baby products; concentration of use data were not provided for this type of exposure.

Hydroxyacetophenone is reported to be used in cosmetic formulations that could be incidentally inhaled. For example, it is reported to be used in aerosol hair sprays (at up to 0.5%) and in moisturizing spray (at up to 0.3%), and in face powders (concentration of use not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions of the respiratory tract and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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.

Although products containing some of these ingredients may be marketed for use with airbrush delivery systems, this information is not available from the VCRP or the Council survey. Without information regarding the frequency and concentrations of use of these ingredients, and without consumer habits and practices data or particle size data related to this use technology, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

Hydroxyacetophenone is not restricted from use in any way under the rules governing cosmetic products in the European Union.[9]

Non-Cosmetic

In 2011, the Joint Expert Committee on Food Additives (JECFA) mentioned Hydroxyacetophenone as a flavoring agent, and that it posed no safety concerns.[10] In Europe, Hydroxyacetophenone dietary exposure was estimated as 0.0002 µg/kg bw/d, while in Japan, Hydroxyacetophenone dietary exposure was estimated as 0.0059 µg/kg bw/d. Hydroxyacetophenone also has a Flavoring, Extract, and Manufacturing Association (FEMA) generally recognized as safe (GRAS) designation, under FEMA No. 4330.[11]

TOXICOKINETIC STUDIES

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

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

The acute dermal toxicity of Hydroxyacetophenone (99.97% pure) was investigated following a single, occlusive application to New Zealand white rabbits.[2] Five male and 5 female New Zealand white rabbits (no controls used) were exposed to a single, undiluted dose of 2000 mg/kg Hydroxyacetophenone for 24 h, and were observed for mortality and clinical abnormalities for 14 d. No animals died during the observation period. All animals exhibited abnormal stools, ocular discharge, erythema, and edema at the test site; by day 13, all external abnormalities had resolved. Upon necropsy, no visible lesions were observed. The acute dermal LD_{50} in rabbits was > 2000 mg/kg bw.

Oral

The acute oral toxicity of Hydroxyacetophenone (99.97% pure) was determined in groups of 5 male and 5 female Sprague-Dawley rats using a single gavage exposure of 0, 1000, 2000, or 5000 mg/kg Hydroxyacetophenone, in corn oil.[2] The animals were observed for 14 d prior to necropsy. No animals in the control and 1000 mg/kg group died, while 3 male and 3 female rats from the 2000 mg/kg group and 4 male and all 5 female rats from the 5000 mg/kg group died; all animals died within 24 h of exposure. During the 14-d observation period, 8 of the 5000 mg/kg group animals, all 10 of the 2000 mg/kg group animals, and 8 of the 1000 mg/kg group animals exhibited one of the following: oral discharge, nasal discharge, ocular discharge, alopecia, abnormal respiration, tremors, abnormal stools, lethargy, and/or moribundity. Two of the control animals exhibited abnormal stools on day 0 while 1 animal exhibited a stained coat on day 3-9 of the observation period. Upon post-mortem examination, fluid was found in either the stomach, duodenum, jejunum, and/or ileum. The acute oral LD_{50} was determined to be 2240 mg/kg bw.

Short-Term Toxicity Studies

Oral

In a 28-d oral toxicity study, Hydroxyacetophenone (99.8% pure) was administered in propylene glycol, once daily by gavage, to groups of 5 male and 5 female Crl:WI(Han) rats at doses of 0, 40, 150, or 600 mg/kg bw, in accordance with Organisation for Economic Cooperation and Development (OECD) test guideline (TG) 407.[2] No substance-related mortality or changes in body weight gain occurred during the study period. No toxicologically significant changes were noted in hematology, clinical pathology, or organ weights, or upon gross and microscopic examination. The no-observed-adverse-effect-level (NOAEL) of Hydroxyacetophenone in rats was determined to be 600 mg/kg bw/d.

Inhalation

In an inhalation toxicity study, 10 male Sprague-Dawley rats and concurrent controls (number not specified) were exposed, whole body, 6 h/d and 5 d /wk for 4 wk, to a dust concentration of 42 mg/m^3 Hydroxyacetophenone (99.7% pure).[2] No mortality occurred during observation. The average mass median aerodynamic diameter (MMAD) was measured as 11 µm, with a standard deviation of 2.0 µm. More than 48% of the detected particles were found to be ≤ 10 µm. In addition to weekly physical examination and monitoring of body weights, hematology measurements were performed on all animals at wk 4 and clinical chemistry metrics were measured at week 1 in 5 animals/group and at week 4 in all animals. After the 4-wk exposure, all animals were sacrificed and the brain, kidneys, liver, lungs, testes, and spleen were weighed and relative organ weights were calculated (compared to the brain). Complete gross and histological examination of the kidneys, liver, lungs, spleen, testes/epididymides were conducted in all animals. The only statistically significant change was a decrease in albumin, observed after the first week of exposure; however, these values returned to normal levels by the fourth week. The no-observed-adverse- effect-concentration (NOAEC) for inhalation toxicity in rats was determined to be 42 mg/m^3.

Subchronic Toxicity Studies

Oral

Groups of 20 male and 20 female Sprague-Dawley rats were dosed with 0, 5, 15, or 45 mg/kg Hydroxyacetophenone (100% pure), in corn oil, via gavage, in accordance with OECD TG 408, for 90 d.[2] One mid-dose female was sacrificed moribund on day 57, 1 control male was found dead on day 12, and mortality in 7 animals distributed across the groups was considered due to accidental deaths. Several (1-3) male animals from the control and most treated groups exhibited chromodacryorrhea or lacrimation, which were not considered treatment-related. No treatment-related effects were seen upon body weight, ophthalmoscopic examination, urinalysis data, and pathology. Mean food consumption was slightly elevated in males from the 45 mg/kg group during the last 4 wk, but these increases were generally not dose-related and therefore were not considered toxicologically significant. A month and a half into the study, a dose-related increase in reticulocytes was seen in males and females (groups not specified), which was not statistically significant. The NOAEL for Hydroxyacetophenone in rats was determined to be 45 mg/kg bw/d.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Oral

Groups of 5 male and 5 female Crl: WI (Han) rats were dosed with 0, 40, 150, or 600 mg/kg bw/d Hydroxyaceto-phenone, in propylene glycol, via gavage, in accordance with OECD TG 422.[2] Males were exposed for 30 d, including 2 wk prior to mating, up to the day before necropsy; females were exposed from 2 wk prior to mating up to at least 4 d of lactation, for a total of up to 46 d. Males were killed and examined shortly after mating, while females and pups were killed and examined after day 4 of lactation. One female in the 600 mg/kg group experienced total litter loss after delivery and was killed after 24 h; since other litters of the same group were comprised of live offspring, this finding was not considered toxicologically significant. No toxicologically significant changes or differences in fetal or pup body weights, viability, litter size, sex ratios, maturation, gross pathology, or developmental parameters were observed for any group. The NOAEL was determined to be 600 mg/kg bw/d for both males and females in the parental generation, as well as the F_1, generation.

GENOTOXICITY STUDIES

Details of the genotoxicity studies summarized below are described in Table 3.

Hydroxyacetophenone was not genotoxic in 3 separate bacterial reverse mutation assays, with concentrations ranging from 3 µmol/plate to 10,000 µg/plate.[2] In two gene mutation assays with L5178Y mouse lymphoma cells treated with concentrations of up to 1400 µg/ml Hydroxyacetophenone in the absence and up to 800 µg/ml in the presence of metabolic activation, diminished cell growth rate and increased mutant frequencies were observed only at very high toxicities, and, specifically, in the absence of metabolic activation for one study.[2] Hydroxyacetophenone was not genotoxic in Chinese hamster ovary cell lines at concentrations of up to 157 µg/ml without, or 1570 µg/ml with, metabolic activation in a sister chromatid exchange assay.[2] Groups of 5 male and 5 female ICR mice dosed via intraperitoneal (i.p.) injection with up to 450 mg/kg Hydroxyacetophenone in a micronucleus assay exhibited minimal clinical abnormalities, and 1 male from the 450 mg/kg group died on the third day following exposure; no significant increase in micronucleated polychromatic erythrocytes was noted in either sex at any dose.[2]

CARCINOGENICITY STUDIES

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

OTHER RELEVANT STUDIES

Tumor Promotion

The effect of Hydroxyacetophenone upon cells later treated with chemical carcinogens (not identified) was evaluated in an in vitro cell transformation assay.[2] BALB/C-3T3 cells were treated with concentrations of 62.5, 250, 400, 700, or 1125 mg/ml Hydroxyacetophenone and tested for abnormalities in vitro and for tumor growth when injected in immunosuppressed, syngeneic animals. Appropriate negative (solvent control and untreated cells) and positive controls (2.5 µg/ml of 3-methylcholanthrene) were used and gave expected results. The BALB/C-3T3 cells did not produce neoplastic tumors in the animals. No significant increase in the frequency of transformed foci was observed, corresponding to 19-114% cell survival for cultures treated with the lowest and highest concentration of Hydroxyacetophenone. Thus, the test article was considered inactive at effecting tumor promotion in the transformation assay.

DERMAL IRRITATION AND SENSITIZATION STUDIES

The dermal irritation and sensitization studies summarized below are described in Table 4.

Slight dermal irritation, including minimal erythema, without edema, was reported for 3 of 4 New Zealand white rabbits tested with a single, occlusive, 6 cm^2, application of 0.5 g Hydroxyacetophenone.[12] In a similar irritation study, a 4-h, 1 in^2 occlusive application of 0.5 g of Hydroxyacetophenone was not irritating to the skin of 6 New Zealand white rabbits.[2] Groups of 6 New Zealand white rabbits were exposed for 4 h to 0.5 ml of Hydroxyacetophenone at 3%, 5%, 15%, and 30% in 4 different vehicles: tetrahydrofuran (THF), dimethyl sulfoxide (DMSO), methanol (MeOH), or *N,N*-dimethylformamide (DMF); these vehicles were also tested for irritation potential in the absence of the test article.[2] Hydroxyacetophenone in THF produced the maximum mean Draize score of 7.5 at the 3% concentration, and 5.5 at the 30% concentration (with average primary dermal irritation index (PDII) values of 6.8 and 5.1, respectively); the test article did not significantly increase the dermal irritancy of any vehicle. No edema or erythema occurred when 1%, 10%, or 50% aqueous Hydroxyacetophenone was applied to the abraded and intact skin of New Zealand white rabbits (3/group), under occlusion.[13] In a Buehler test, performed in 19 Dunkin Hartley guinea pigs, 20% aqueous Hydroxyacetophenone was shown to be a non-sensitizer.[14] In a maximization test, male Hartley guinea pigs were induced twice with 5% Hydroxyacetophenone in propylene glycol, first by an intradermal injection (with and without Freund's adjuvant) and second by topical application 8 d later.[2] Animals were challenged with a topical application of 0.5 g of 75% in petrolatum for 24 h; the test article was not sensitizing.

In a single insult occlusive test (SIOPT), application of an SPF cream containing 0.05% Hydroxyacetophenone, tested as supplied (amount not specified), was not irritating to 22 subjects.[15] In another SIOPT, an occlusive application of 0.2 ml Hydroxyacetophenone was not irritating to 53 subjects.[16] In a 21-d cumulative irritation test of 32 subjects, using an SPF 70 cream containing 0.05% Hydroxyacetophenone, repetitive application of 0.05 ml of the test article exhibited negligible potential for irritation, with a total irritation score of 86, a mean cumulative irritation score of 2.69, a mean daily irritation score of 0.18, and a cumulative irritation index (CII) of 0.06 (compared to 773, 24.16, 1.61, and 0.54, respectively, for positive controls).[17] An SPF cream containing 0.5% Hydroxyacetophenone was tested in an HRIPT in 103 subjects; the test article was deemed non-sensitizing.[18] According to summary details from an HRIPT of 104 subjects, a test article containing 5% (in glycerin) Hydroxyacetophenone (99% pure) was deemed not sensitizing; 1 subject presented with two grade 0.5 skin reactions during induction.[19]

OCULAR IRRITATION STUDIES

The ocular irritation studies summarized below are described in Table 5.

The eyes of 4 healthy New Zealand white rabbits were treated with 0.1 g of undiluted Hydroxyacetophenone for 24 h, after which they were either rinsed with saline or remained unrinsed, and were observed for up to 21 d.[2] A Draize score of 63, out of a maximum score of 110, was recorded for the animal with the unrinsed eye, 48 h after treatment; this score is categorized as a severe irritant. The mean Draize score calculated for the 3 animals with rinsed eyes was 22, categorizing the test article as a moderate irritant. In another study, corneal opacity, severe ulceration, and mild iritis were observed in the eyes of 4 healthy New Zealand white rabbits treated with 0.1 ml of finely ground Hydroxyacetophenone.[12] Three of the 4 treated eyes were free of corneal effects 7 d after treatment; moderate redness and chemosis persisted through day 7 for all 4 test animals. Hydroxyacetophenone was considered a severe eye irritant to rabbit eyes under these study conditions.

CLINICAL STUDIES

Case Reports

A 79-yr-old man experienced dermatitis for 7 mo on the right upper and lower eye lid with the use of prescription eyedrops (not containing Hydroxyacetophenone) and a facial cream containing Hydroxyacetophenone (concentration in cream not provided).[20] In spite of the eyedrop prescription being changed several times, these lesions did not subside. A 2-d patch test was conducted on the back, with allergens found in the Spanish baseline series, Chemotechnique fragrance series, all previously used eye drops, and the facial cream. All patch test results were negative on day 2 and 4, except for a ?+ reaction to the face cream. Results from a repeated open application test conducted on the upper arm with the facial cream showed erythema, infiltration, and papules. Further patch tests conducted on manufacturer-supplied, individual ingredients in the face cream, revealed positive reactions only to 0.6% aqueous Hydroxyacetophenone (+ on day 2 and ++ on day 4). Furthermore, eczematous lesions resolved within 5- d use of tacrolimus, and lesions did not develop after discontinued use of the face cream. Patch test results for Hydroxyacetophenone in 10 controls were all negative.

SUMMARY

The safety of Hydroxyacetophenone, as used in cosmetics, is reviewed in this safety assessment. According to the *Dictionary*, Hydroxyacetophenone is reported to function as an antioxidant and skin-conditioning agent.

According to 2022 VCRP data, Hydroxyacetophenone is reported to be used in 791 formulations Concentration of use data from a 2020 survey indicate that the highest reported maximum concentration of use for Hydroxyacetophenone is at up to 5% in non-spray night products, in paste masks, and mud packs.

The acute dermal LD_{50} of Hydroxyacetophenone was > 2000 mg/kg bw in New Zealand white rabbits. Groups of 5 Sprague-Dawley rats were administered a single oral dose of up to 5000 mg/kg Hydroxyacetophenone, in corn oil, via gavage. Three male and 3 female rats from the 2000 mg/kg group, and 4 male and 5 female rats from the 5000 mg/kg group died within 24 h. During the 14-d observation period, 8 animals from the 5000 mg/kg group, all 10 in the 2000 mg/kg group, and 8 from the 1000 mg/kg group exhibited either oral discharge, nasal discharge, ocular discharge, alopecia, abnormal respiration, tremors, abnormal stools, lethargy, and/or moribundity; 2 control animals exhibited abnormal stools on day 0. The acute oral LD_{50} of Hydroxyacetophenone was determined to be 2240 mg/kg bw.

In a 28-d oral toxicity study, no toxicologically-significant findings were noted in rats administered up to 600 mg/kg bw Hydroxyacetophenone; the NOAEL was determined to be 600 mg/kg bw/d. In an inhalation study, no mortality occurred in rats exposed, whole body, 6 h/d and 5 d/wk, for 4 wk, with 42 mg/m^3 Hydroxyacetophenone; the only observed effect was a statistically-significant decrease in albumin after the first week of exposure; this value returned to normal levels by the fourth week. The NOAEC for inhalation toxicity in rats was determined to be 42 mg/m^3.

Groups of 20 male and 20 female Sprague-Dawley rats were dosed with up to 45 mg/kg Hydroxyacetophenone, in corn oil, via gavage, for 90 d. One control male was found dead on day 12, and mortality in 7 animals across the dose groups (number not specified) was considered accidental. Dose-related increases in the mean food consumption of males in the 45 mg/kg group and the reticulocytes in male and females (groups not specified) were not statistically significant. The NOAEL for Hydroxyacetophenone in rats was determined to be 45 mg/kg bw/d.

In an oral developmental and reproductive toxicity study, performed in accordance with OECD TG 422, groups of 5 male and 5 female Crl: WI (Han) rats were dosed with 0, 40, 150, or 600 mg/kg bw/d Hydroxyacetophenone, in propylene glycol, via gavage, for up to 46 d. One dam in the 600 mg/kg group experienced total litter loss; however, because other litters of the same group were comprised of live offspring, this finding was not considered toxicologically significant. No toxicologically significant changes or differences in fetal developmental parameters were seen and the NOAEL was determined to be 600 mg/kg bw/d Hydroxyacetophenone for both males and females in the parental, as well as the filial, generation.

Hydroxyacetophenone was not genotoxic in three separate bacterial reverse mutation assays, at concentrations of up to 10,000 µg/plate, in the presence or absence of metabolic activation. In two gene mutation assays, L5178Y mouse lymphoma cells treated at concentrations of up to 1400 µg/ml Hydroxyacetophenone, in the absence and up to 800 µg/ml in the presence of metabolic activation, exhibited a diminished cell growth rate and increase in mutant frequencies only at very high toxicities, and specifically, in the absence of metabolic activation for one study. Hydroxyacetophenone was not genotoxic in

Chinese hamster ovary cell lines at concentrations of up to 157 µg/ml without or 1570 µg/ml with metabolic activation in a sister chromatid exchange assay. A significant increase of micronucleated polychromatic erythrocytes was not observed in ICR mice administered up to 450 mg/kg Hydroxyacetophenone, via i.p. injection.

BALB/C-3T3 cells were tested with Hydroxyacetophenone, at concentrations of up to 1125 mg/ml, and subsequently treated with unidentified chemical carcinogens in an in vitro cell transformation assay. Hydroxyacetophenone was considered inactive at effecting tumor promotion.

Slight dermal irritation was reported for 3 of 4 New Zealand white rabbits treated with an occlusive, 6 cm^2 patch of 0.5 g Hydroxyacetophenone, moistened with saline, for 4 h. In a similar study, 0.5 g of Hydroxyacetophenone applied to rabbit skin in a 1 in^2, occlusive patch for 4 h, did not cause dermal irritation to control or treated sites. In a study comparing the dermal irritation potential of THF, DMSO, MeOH, or DMF, individually, and when 0.5 ml Hydroxyacetophenone was added to each, the test article did not increase the irritancy of any vehicle. Guinea pigs were not sensitized to 20% aqueous Hydroxyacetophenone in a Buehler test. In a maximization test, no sensitization occurred when male Hartley guinea pigs were induced twice with 5% Hydroxyacetophenone, in propylene glycol, and challenged with a topical application 0.5 g of 75% Hydroxyacetophenone in petrolatum for 24 h.

Hydroxyacetophenone was not irritating in 2 separate SIOPTs, either at 0.05% in an SPF product tested in 22 subjects, or at a dose of 0.2 ml, tested in 53 subjects. In a 21-d cumulative irritation test, a SPF cream, containing 0.05% Hydroxyacetophenone, was determined to have a negligible potential for irritation in 32 subjects, due to a total irritation score of 86, a mean cumulative irritation score of 2.69, and mean daily irritation score of 0.18, and a CII of 0.06. A SPF cream containing 0.5% Hydroxyacetophenone was found to be non-sensitizing in an HRIPT of 103 subjects. In spite of 1 subject presenting with 2, grade 0.5 reactions during induction, 5% Hydroxyacetophenone, in glycerin, was deemed a non-sensitizer in 104 subjects.

New Zealand white rabbit eyes treated with 0.1 g of undiluted Hydroxyacetophenone, unrinsed, produced a Draize score of 63, categorized as a severe irritant, while eyes rinsed with 0.9% saline for 30 sec produced a Draize score of 22, categorized as a moderate irritant. In another study, New Zealand white rabbit eyes treated with 0.1 ml, finely ground Hydroxyacetophenone showed signs of moderate to severe discharge, moderate chemosis, and moderate to severe redness when scored 24 h following treatment. Corneal effects dissipated in 3 of the 4 treated eyes within 7 d after treatment; moderate redness and chemosis persisted through day 7 for all treated eyes.

A 79- yr-old man presented with dermatitis for 7 mo on the right upper and lower eye lid with the use of prescription eyedrops and a facial cream containing Hydroxyacetophenone (concentration in cream not provided). Positive patch-test reactions occurred for 0.6% aqueous Hydroxyacetophenone, which resolved with use of tacrolimus and discontinuation of cream use.

DISCUSSION

This assessment reviews the safety of Hydroxyacetophenone as used in cosmetic formulations. The Panel reviewed the available data and concluded that this ingredient is safe in cosmetics in the present practices of use and concentration described in the safety assessment.

The Panel noted that this ingredient has GRAS status as a flavoring agent, and was not a dermal irritant or sensitizer when tested at 5% (which is the maximum reported concentration of use) in a guinea pig maximization test or in a human repeated insult patch test. Additionally, the Panel considered that Hydroxyacetophenone has a favorable toxicological profile. Negative results from multiple genotoxicity studies and the lack of structural alerts mitigated the need for carcinogenicity data.

The Panel acknowledged the ocular irritation observed in 2 studies in rabbits, in light of use in products applied near the eye (i.e., up to 0.23% in eye lotions and eye makeup removers). In both studies, irritation resulted from neat application, and in one study, from granular exposure. The Panel stated that manufacturers should be aware of the potential for ocular irritation when formulating products that contain this ingredient, for use near the eye, and that measures should be taken to ensure that these products are not irritating.

The Panel considered that Hydroxyacetophenone is reported to be used in baby products, without reported concentrations of use. Furthermore, the Panel discussed the maximum reported concentration of use for Hydroxyacetophenone, at up to 5% in non-spray night products, in paste masks, and in mud packs; the Panel reiterated their expectation that any unreported concentrations of use in baby products would not exceed the maximum reported use.

The Panel discussed the issue of incidental inhalation exposure resulting from use in sprays (e.g. in hair sprays at up to 0.5%) and in face powders (concentration of use not reported). Data available from a short-term inhalation study indicates little potential for respiratory effects at relevant doses, and, the Panel noted that in aerosol products, the majority of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or tracheobronchial 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 low

concentrations at which these ingredients are used in potentially inhaled products, 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.

The Panel's respiratory exposure resource document (see link above) notes that airbrush technology presents a potential safety concern, and that no data are available for consumer habits and practices thereof. As a result of deficiencies in these critical data needs, the safety of cosmetic ingredients applied by airbrush delivery systems cannot be assessed by the Panel. Therefore, the Panel has found the data insufficient to support the safe use of cosmetic ingredients applied via an airbrush delivery system.

CONCLUSION

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

TABLES

Table 1. Chemical properties of Hydroxyacetophenone

Property	Value	Reference
Physical Form (@ 20 °C and 1013 hPa)	Solid	[2]
Color	White to beige	[6]
Molecular Weight (g/mol)	136.15	[3]
Specific Gravity (@ 20 ºC)	1.27	[2]
Vapor pressure (mmHg @ 20 ºC)	0.000015	[2]
Melting Point (°C @ 1013 hPa)	110	[2]
Water Solubility (g/l @ 22 ºC)	10	[2]
log K_{ow} (@ 25 °C)	1.35 (estimated)	[2]
Disassociation constants (pK_a @ 25 ºC)	8.05	[2]

Table 2. Frequency (2022) and concentration (2020) of use of Hydroxyacetophenone

	# of Uses[7]	Max Conc of Use (%)[8]
Totals*	**791**	**0.00009 - 5**
Duration of Use		
Leave-On	*671*	*0.02 - 5*
Rinse-Off	*119*	*0.000099 -5*
Diluted for (Bath) Use	*1*	*0.25*
Exposure Type		
Eye Area	47	0.23
Incidental Ingestion	2	NR
Incidental Inhalation-Spray	4; 265[a]; 232[b]	0.3 – 0.5; 0.5[a]
Incidental Inhalation-Powder	3; 232[b]; 3[c]	0.075 – 0.3[c]
Dermal Contact	754	0.000099 - 5
Deodorant (underarm)	5[a]	NR
Hair - Non-Coloring	33	0.02 – 0.5
Hair-Coloring	NR	NR
Nail	2	NR
Mucous Membrane	23	0.000099 – 0.6
Baby Products	7	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] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – not reported

Table 3. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
			IN VITRO			
Hydroxyacetophenone	3 µmol/plate, with and without metabolic activation	ethanol	*Salmonella typhimurium* strains TA 98, 100	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive control gave expected results.	[21]
Hydroxyacetophenone, 99.97% pure	Up to 5000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* TA 98, 100, 1535, 1537, 1538	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive control gave expected results.	[2]
Hydroxyacetophenone	1.0 -10,000 µg/plate, with and without metabolic activation	DMSO	*S. typhimurium* strains TA 98, 100, 1535, 1537, 1538	Bacterial reverse mutation assay	Not genotoxic. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone, 99.97% pure	100- 1400 µg/ml without metabolic activation; 10-800 µg/ml with metabolic activation	DMSO	Mouse lymphoma L5178Y cells	Mammalian gene mutation assay	Clastogenic; the test article was positive for genotoxicity in the absence of exogenous metabolic activation, and the observed mutant frequencies roughly increased at the highest tested concentrations; genotoxicity was ambiguous in the presence of metabolic activation. Non-metabolically activated cultures treated with doses of 100-1400 µg/ml of the test article exhibited a growth rate of 103% to 34%, respectively, while activated cultures treated with concentrations of 10-800 µg/ml test article exhibited a growth rate of 76% to 13%, respectively. The non-activated portion of the study was repeated in order to obtain cultures with less than 34% growth rate; cloned cultures treated with 1570 to 1020 µg/ml of the test article exhibited growth rates from 8% to 72%. Four of these non-activated clone cultures, with growth rates > 10%, exhibited mutant frequencies at least twice the mean mutant frequency of solvent controls. A dose-dependent response was not noted in the treated cultures. An increase in the frequency of small colonies in treated cultures, compared to control cultures, was consistent with damage to multiple loci on chromosome 11 in addition to loss of the TK locus. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	188-1250 µg/ml without metabolic activation; 31.5- 500 µg/ml with activation	DMSO	Mouse lymphoma L5178Y cells	Mammalian gene mutation assay	Ambiguous genotoxicity; without metabolic activation, mutant cell frequencies were significantly increased only at very high toxicities (4.7 % relative growth). In the presence of metabolic activation, the test material was converted to more active form or forms. Treatments with 31.5 - 500 µg/ml test article when assayed produced mutant frequencies of 3.4- 5.6 fold, over a wide range of toxicities. Appropriate negative and positive controls gave expected results.	[2]
Hydroxyacetophenone	4.7-157 µg/ml without metabolic activation or 47-1570 µg/ml with metabolic activation	DMSO	Chinese hamster ovary cell line	Sister chromatid exchange assay	Not genotoxic. Appropriate negative and positive controls gave expected results.	[2]
			IN VIVO			
Hydroxyacetophenone, > 99% pure	0,113, 225, or 450 mg/kg	Corn oil	Groups of 5 male and 5 female ICR mice	Micronucleus assay. Animals were given a single intraperitoneal dose; cyclophosphamide was used for the positive controls.	Not genotoxic; clinical abnormalities after dosing included lethargy, rough hair coat, and hunched posture. One male from the 450 mg/kg group died on the third day after treatment. No significant increase in micronucleated polychromatic erythrocytes was noted in either sex or for any dosage. Appropriate negative and positive controls gave expected results.	[2]

Abbreviations: DMSO – dimethyl sulfoxide

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
ANIMAL					
Irritation					
Hydroxyacetophenone	0.5 g, moistened with saline	4 New Zealand white rabbits	A single, 6 cm^2, occlusive application of the test article, moistened with saline, was made to clipped skin, for 4 h. Test sites were evaluated 72 h after patch removal, using the Draize scoring system.	Slight dermal irritation was reported for 3 of the 4 animals, including minimal erythema, without edema. (No further details provided).	12
Hydroxyacetophenone, 99.97% pure	0.5 g, moistened with sterile water	6 New Zealand white rabbits	A single, occlusive application of the test article, moistened with sterile water, was made neat to a shaved skin area of 1 in^2 for 4 h; an untreated skin site on the same animal was used as the control. The test sites were observed for up to 72 h.	All control and treated sites were free of dermal irritation throughout the study period.	2
Hydroxyacetophenone, 99.87% pure	0.5 ml, at 3%, 5%, 15%, 30% (in THF, DMSO, MeOH, or DMF)	New Zealand white rabbits (6/group)	The test articles (0.5 ml) were applied under occlusion to a shaved area of 6 cm^2 for 4 h. An adjacent site on each treated animal was exposed to the respective vehicle (neat), and served as a vehicle control; an untreated site served as a negative control. After exposure, skin was wiped free of excess test material with an adsorbent pad and test sites were observed for up to 14 d. Test sites were evaluated for irritation using the Draize method, and all sites were scored 1, 24, 48, and 72 h after patch removal; test sites at which DMF and THF were used as the vehicle were observed at 7 d and up to 14 d, respectively. The maximum possible Draize score was 8.0. The PDII was calculated using Draize scores recorded at 1, 24, 48, and 72 h after exposure.	After 72 h, THF was shown be the most irritating vehicle, with a maximum mean Draize score of 7.5 (and average PDII of 6.5); Hydroxyacetophenone in THF produced maximum mean Draize scores of 7.5 at the 3% concentration, and 5.5 at the 30% concentration (with average PDIIs of 6.8 and 5.1, respectively). Lower scores were observed with the use of the other vehicles, and scores were comparable across the concentrations with each vehicle; at the 30% concentration, Hydroxyacetophenone in DMSO had a maximum mean Draize score of 1.2 (and average PDII of 0.3), in MeOH had a maximum mean Draize score of 0.7 (and average PDII of 0.2), and in DMF had a maximum mean Draize score of 0.3 (and average PDII of 0.1). Recovery times were > 14 d for THF, 7 d for DMF, and 3 d for DMSO and MeOH. The test article did not significantly increase the dermal irritancy of any vehicle.	2
Hydroxyacetophenone	1%, 10%, and 50% (aqueous)	New Zealand white rabbits (3/group)	Fur was removed from the test site 24 h prior to intended application; an occlusive application was made to both abraded and intact skin. Reactions were scored 24 and 72 h after application, averaged separately for erythema and edema, and then summed to arrive at the PII.	Not irritating; PII = 0 for all test concentrations	13
Sensitization					
Hydroxyacetophenone	20% w/v (aqueous)	Dunkin-Hartley guinea pigs (19 animals in the test group; 10 animals in the control group)	Delayed contact hypersensitivity test (Buehler test). Animals were patched with 20% aqueous test article at pH 5.3 (amount not specified) for both topical induction and challenge applications. (Specific details not provided). Readings for potential erythematous or sensitization reactions were taken 24 and 48 h after patch removal. Bodyweights were also monitored over the study duration of 4 wk.	Not sensitizing; all irritancy and severity scores were 0. One animal died during the test, but this death was not treatment-related. No significant body weight changes occurred.	14

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Hydroxyacetophenone	5% during induction in propylene glycol; 75% during challenge in petrolatum	20 male Hartley guinea pigs	Guinea pig maximization test. An intradermal injection of 5% test article (in propylene glycol, with and without FCA) was made during induction. Eight days later, the animals were induced for a second time with a topical application of 5% Hydroxyacetophenone in propylene glycol. Two wk after the second induction, a topical challenge application was made with 0.5 g of 75% Hydroxyacetophenone in petrolatum for 24 h. Dinitrochlorobenzene was used as a positive control (number of controls not specified).	Not sensitizing	[2]
HUMAN					
Irritation					
SPF 50 cream containing 0.05% Hydroxyacetophenone	applied neat	22	SIOPT; the test article (amount not specified) was applied for 24 h. An SPF 70 gel cream product was used as the control.	Not irritating; PII of 0.0	[15]
Hydroxyacetophenone	0.2 ml	53	SIOPT; A single, occlusive application of the test material was applied to the back using a 0.75 in^2 patch for 48 h. Readings were performed 48 and 72 h after application.	Not irritating	[16]
SPF 70 cream containing 0.05% Hydroxyacetophenone	applied neat; 0.05 ml	32	21-d cumulative irritation test. The test article was used as supplied. Occlusive applications were made using a 15 mm Webril patch, and scored on a 5-pt ICDRG grading scale upon removal, 5 d/wk for 3 consecutive weeks; patches applied on Friday remained in place until Monday. One site was also treated with 0.05 ml of 0.25% SLS as a positive control, and a plain cotton patch was applied as a negative control.	Negligible potential for irritation; the test article produced a total irritation score of 86, a mean cumulative irritation score of 2.69, a mean daily irritation score of 0.18, and a CII of 0.06 (compared to 773, 24.16, 1.61, and 0.54, respectively, for the positive controls).	[17]
Sensitization					
SPF 70 cream containing 0.5% Hydroxyacetophenone	applied neat; 0.2 g (induction and challenge)	103	In an HRIPT, 24- h occlusive patches containing 0.2 g of the test material were applied 3x/wk, for 3 wk, for a total of 9 induction applications. After a 2-wk non-treatment period, a 24-h challenge application was made to a previously untreated site in the same manner as the induction applications, and reactions were scored at 24, 48, 72, and 96 h after application.	Not sensitizing	[18]
Hydroxyacetophenone, 99% pure	5% in glycerin	104	A HRIPT was conducted (no further details were provided).	Not sensitizing; 1 subject presented with two, grade 0.5 skin reactions during induction	[19]

Abbreviations: CII- cumulative irritation index; DMF- *N,N*-dimethylformamide; DMSO – dimethyl sulfoxide; FCA – Freund's complete adjuvant; HRIPT- human repeat insult patch test; ICDRG- International Contact Dermatitis Research Group; MeOH – methanol; PDII – primary dermal irritancy index; PII – primary irritation index; SIOPT – single insult occlusive patch test; SLS- sodium lauryl sulfate; THF- tetrahydrofuran

Table 5. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
Hydroxyacetophenone, 99.97% pure	0.1 g, undiluted	4 New Zealand white rabbits	The untreated eye of each animal served as the control, and both eyes were observed for up to 21 d after exposure. Potential for ocular irritancy was examined in the first animal leaving the treated eye unrinsed. In the remaining 3 animals, anesthetic was used prior to dosing, even for control eyes, and treated eyes were rinsed with approximately 120 ml of 0.9% saline, for 30 sec.	In the animal with the unrinsed eye, corneal opacity, conjunctival redness, iridial irritation, chemosis, and discharge were noted, all of which resolved by 21 d. A Draize score of 63, out of a maximum score of 110, was recorded for the unrinsed eye, 48 h after treatment; this score is categorized as a severe irritant. In the animals with rinsed treated eyes, milder conjunctival effects were seen, but resolved within 7 d; the mean Draize score calculated for the 3 animals with rinsed eyes was 22, categorizing the test article as a moderate irritant.	[2]
Hydroxyacetophenone	0.1 ml, finely ground	4 New Zealand white rabbits	The right eyes of the animals were treated with 0.1 ml Hydroxyacetophenone (duration not provided), and ocular lesions were scored using the Draize method approximately 24 h and 7 d following treatment.	The treated eyes showed signs of moderate to severe discharge, moderate chemosis (swelling) and moderate to severe redness at the 24 h observation. Corneal opacity, severe ulceration, and mild iritis was observed in all 4 treated eyes. Three of the 4 treated eyes were free of corneal effects 7 d after treatment; moderate redness and chemosis persisted through day 7 for all 4 test animals. Hydroxyacetophenone was considered a severe eye irritant to rabbit eyes under these study conditions.	[12]

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2022 VCRP Frequency of Use Data – Hydroxyacetophenone

Total Uses: 791

INGREDIENT_NAME	Category Description	CPIS_Count
4-Hydroxyacetophenone	01A- Baby shampoos	1
4-Hydroxyacetophenone	01B - Baby lotions, oils, powders, and creams	3
4-Hydroxyacetophenone	01C - Other baby products	3
4-Hydroxyacetophenone	02B – Bubble baths	1
4-Hydroxyacetophenone	03D - Eye lotion	18
4-Hydroxyacetophenone	03E - Eye makeup remover	2
4-Hydroxyacetophenone	03G - Other eye makeup preparations	27
4-Hydroxyacetophenone	04E - Other fragrance preparation	4
4-Hydroxyacetophenone	05A - Hair conditioner	6
4-Hydroxyacetophenone	05F - Shampoos (non-coloring)	13
4-Hydroxyacetophenone	05G - Tonics, dressings, and other hair grooming aids	6
4-Hydroxyacetophenone	05I - Other hair preparations	7
4-Hydroxyacetophenone	07A- Blushers	3
4-Hydroxyacetophenone	07B - Face powders	3
4-Hydroxyacetophenone	07C - Foundations	17
4-Hydroxyacetophenone	07E - Lipstick	2
4-Hydroxyacetophenone	07F - Makeup bases	5
4-Hydroxyacetophenone	07H - Makeup fixatives	1
4-Hydroxyacetophenone	07I - Other makeup preparations	8
4-Hydroxyacetophenone	08E - Nail polish and enamel	2
4-Hydroxyacetophenone	10A - Bath soaps and detergents	9
4-Hydroxyacetophenone	10B - Deodorants (underarm)	5
4-Hydroxyacetophenone	10D - Feminine deodorants	3
4-Hydroxyacetophenone	10E - Other personal cleanliness products	8
4-Hydroxyacetophenone	11G - Other shaving preparation products	2
4-Hydroxyacetophenone	12A - Cleansing	49
4-Hydroxyacetophenone	12C - Face and neck (exc shave)	202
4-Hydroxyacetophenone	12D - Body and hand (exc shave)	27
4-Hydroxyacetophenone	12F - Moisturizing	236
4-Hydroxyacetophenone	12G - Night	16
4-Hydroxyacetophenone	12H - Paste masks (mud packs)	29
4-Hydroxyacetophenone	12I - Skin fresheners	6
4-Hydroxyacetophenone	12J - Other skin care preps	66
4-Hydroxyacetophenone	13B - Indoor tanning preparations	1