Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics

Status:	Draft Final Report for Panel Review
Release Date:	February 11, 2022
Panel Meeting Date:	March 7-8, 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.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel members involved in this assessment: James G. Marks, Jr., M.D; Lisa, A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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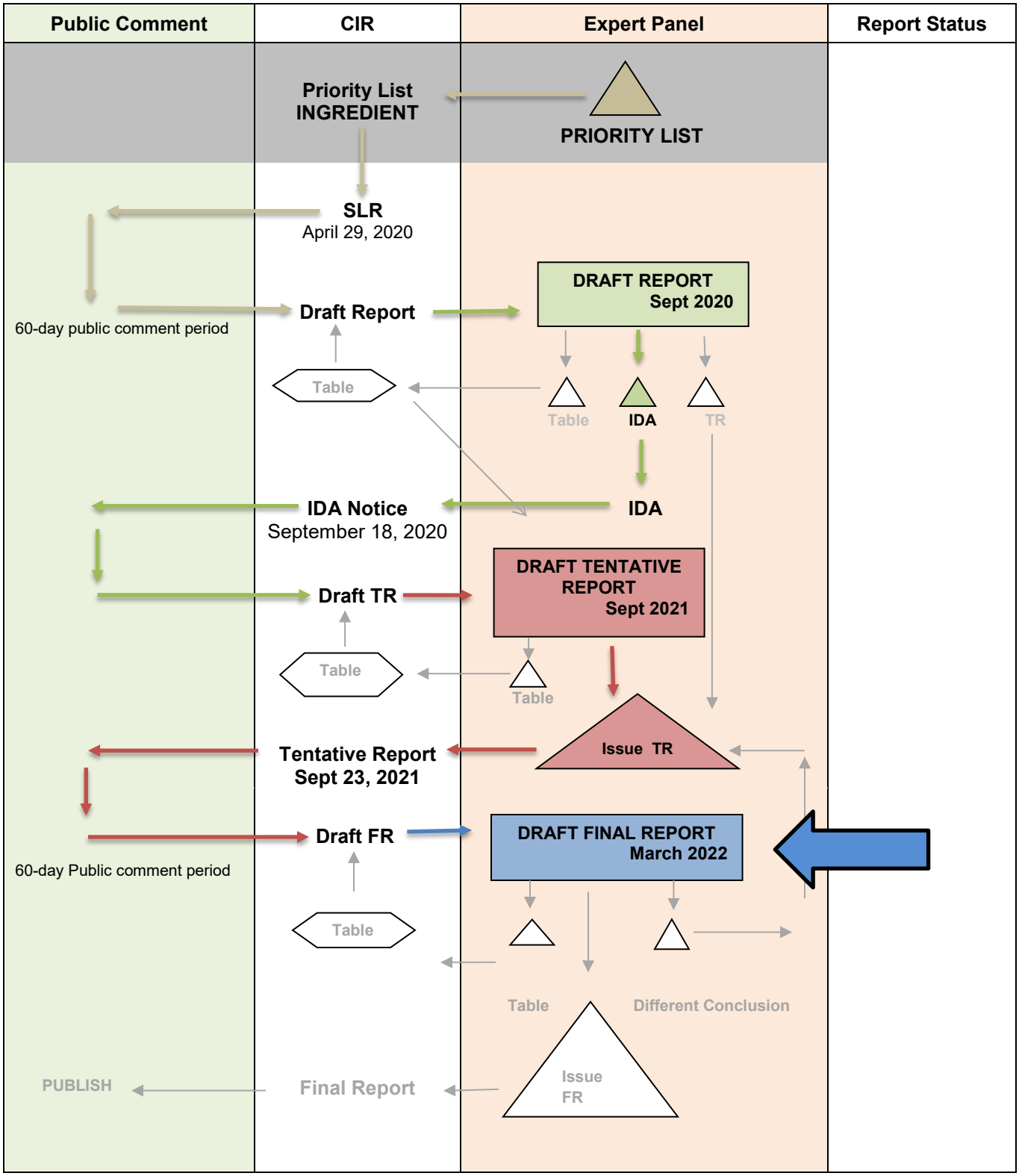
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Ubiquinone Ingredients

MEETING March 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: February 11, 2022

Subject: Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics

Enclosed is the Draft Final Report of the Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics (identified as *report_Ubiquinone_032022* in the pdf). This is the third time the Panel is seeing a safety assessment of these 4 cosmetic ingredients. At the September 2021 meeting, the Panel considered the available data and issued a Tentative Report for public comment with the conclusion that the following 4 Ubiquinone ingredients are safe in cosmetics in the present practices of use and concentrations described in the safety assessment.

Published data on ex vivo Ubiquinone dermal penetration, as well as the photostability, and radical formation potential of Ubiquinone and Ubiquinol were found and have been added to the report. The latter study has been placed in the chemistry section; we request the Panel's opinion of whether it is useful. Data from 2022 FDA VCRP were also received and have been incorporated (*VCRP_Ubiquinone_032022*). Use categories have remained the same, with negligible changes in the reported uses from the previous year. Total reported uses of Ubiquinone decreased from 231 to 221 formulations, while Hydroxydecyl Ubiquinone and Ubiquinol use remained mostly the same. Changes reflecting updated VCRP data and newly added data are highlighted in yellow.

Comments on the Tentative Report that were received from the Council (*PCPCcomments_Ubiquinone_032022*) have been addressed, and follow this memo. A comments response checklist is also included (*responsePCPC*comments*_Ubiquinone_032022*).

Also included in this package for your review are a flow chart (*flow_Ubiquinone_032022*), literature search strategy (*search_Ubiquinone_032022*), ingredient data profile (*dataprofile_Ubiquinone_032022*), ingredient history (*history_Ubiquinone_032022*), and transcripts from the previous meetings (*transcripts_Ubiquinone_032022*).

The Panel should carefully consider the newly added data, the Abstract, Discussion, and Conclusion, and be prepared to 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: October 7, 2021

SUBJECT: Tentative Report: Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics (report released September 23, 2021)

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

Figure 2 – It would be helpful if the structure of Ubiquinone was also labelled.

Natural Occurrence – Please move the statement that Ubiquinone was first chemically synthesized to the Method of Manufacture section.

Function in Mitochondrial Electron Transport Chain – The sentence concerning the plasma concentration of Ubiquinone in humans should be moved to the Natural Occurrence section.

Short-Term, Subchronic and Chronic – Please state the compound that was studied in the 13-week study in Sprague-Dawley rats in which the NOAEL was >1200 mg/kg/day.

Summary – Please revise the following sentence: "In a 4-wk study, cRj Wistar rats dosed with 1000 mg/kg Ubiquinone did not produce noticeable changes in overall condition, body weight gain, or food consumption, in comparison to controls." The current sentence structure indicates that that rats, rather than Ubiquinone did not produce the changes.

Summary – Please correct: "were found in in the incidence of sperm abnormalities" (delete duplicate "in")

Discussion, Conclusion – As one of the ingredients is Ubiquinone, please change "Ubiquinone-derived ingredients to "Ubiquinone ingredients". This language would be consistent with the language used in the Abstract and Introduction.

Table 5 – It would be helpful to include more information about the protocol in the protocol column. The endpoints examined should be stated, not just the negative observations. What were the developmental and reproductive endpoints examined in the study of Hydroxydecyl Ubiquinone conducted in juvenile Wistar rats? The recovery period of the 5-week study of Hydroxydecyl Ubiquinone in rats is only mentioned in the Results column.

Ubiquinone Ingredients - March 7-8th, 2022 Panel Meeting – Preethi Raj			
Comment Submitter: Personal Care Products Council **Date of Submission: October 7, 2021 (comments received on Tentative Report after September 2021 meeting)**			
#	**Report section/Comment**	**Response/Action**	**Needs Panel Input**
1	Figure 2 – request to label Ubiquinone structure	Labelled	
2	Natural Occurrence – move first sentence about chemical synthesizing to Method of manufacture section	Moved	
3	Function in Mitochondrial… - move sentence re: plasma Ubiquinone conc in humans to Natural Occurence	Moved	
4	Short-Term, Subchronic, and Chronic – state the compound that was studied in the 13-wk study of SD rats, with a NOAEL > 1200 mg/kg/d	Stated (Ubiquinone)	
5	Summary – revise sentence to reflect that the changes were caused by the test article (Ubiquinone)	Revised	
6	Summary – remove additional 'in' in sentence	Editorial - removed	
7	Discussion, Conclusion – change 'Ubiquinone-derived Ingredients' to 'Ubiquinone ingredients'	Changed	
8	Table 5 – provide more endpoint details in the Protocol column -including the DART endpoints in the Wistar Hydroxydecyl Ubiquinone (HU) study -Mention recovery period of 5-wk study of HU in rats (only mentioned in Results column)	Have added endpoint details, where available – for the Wistar rat study (ref#3: Australian assessment), not much is said about DART endpoints besides "subsequent development of the animals or on reproductive function" Have included 5-wk recovery period in Protocol column	

CIR History of:

Disodium Ubiquinone, Hydroxydecyl Ubiquinone, Ubiquinol, and Ubiquinone

January 2019

-Concentration of use data submitted by Council

January 2020

-FDA frequency of use data obtained

April 2020

- SLR posted on the CIR website

June 2020

-June 25: Method of manufacture and impurities data

-June 25, and July 20: Dermal irritation and sensitization data

September 2020

A Draft Report was presented to the Panel. The Panel issued an IDA - the additional data needs to determine safety for these cosmetic ingredients were:

- Method of manufacture for Hydroxydecyl Ubiquinone and Ubiquinol
- Concentration of use data for Hydroxydecyl Ubiquinone and Ubiquinol

Council surveyed and reported no concentrations of use for Ubiquinol in 2020. No additional data were received.

January 2021

-Updated frequency of use data were received from the US FDA VCRP program

September 2021

A Draft Tentative Report was presented to the Panel. The Panel issued a Tentative Report for public comment with the conclusion that these 4 Ubiquinone-derived ingredients are safe in cosmetics in the present practices of use and concentrations described in the safety assessment. In the absence of method of manufacture, impurities, and concentration of use data for Hydroxydecyl Ubiquinone and Ubiquinol, the Panel's safety concerns were mitigated due to the natural occurrence of Ubiquinone in living tissues, use as a food additive and nutritional supplement, as well as the abundance of negative results for developmental and genetic toxicity, and sensitization.

October 2021 – Council comments on the Tentative Report were received

January 2022

-Updated frequency of use data were received from the US FDA VCRP program

March 2022 - A Draft Final Report is being presented for Panel review.

Ubiquinone Ingredients Profile* – March 7-8, 2022 – Writer, 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
Disodium Ubiquinone				X																									
Hydroxydecyl Ubiquinone	X			X		X		X			X			X	X	X		X						X					X
Ubiquinol	X			X		X					X				X	X													
Ubiquinone	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

[Ubiquinone – 4 ingredients – March 7-8, 2022 Panel Meeting]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Ubiquinone	303-98-0 60684-33-5	✓	✓	✓	✓	✓*	✓*	NR	NR	NR	NR	NR	✓*	✓*	✓*	NR	✓*	NR	✓
Disodium Ubiquinone	303-98-0	✓	NR	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Hydroxydecyl Ubiquinone	58186-27-9	✓	✓	NR	NR	✓*	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	✓
Ubiquinol	992-78-9	✓	✓	NR	✓*	✓*	NR	✓*	NR	NR	NR	NR	✓*	NR	NR	NR	✓*	NR	✓

✓- in database
✓*- in database, but no safety data

[*total # useful hits / # total hits*]
On the Web:
Physical/chemical properties of:
-Ubiquinone/Ubiquinol: 4/263,000
-Disodium Ubiquinone: 0/10
-Hydroxydecyl Ubiquinone: 4/2,010
Comprehensive review ubiquinone supplementation – 15/115,000
Ubiquinone manufacturing – 3/ 325,000
Ubiquinone reproductive toxicity – 4/161,000

In PubMed:
((((coenzyme q10) OR ubiquinone) OR ubidecarone) OR 303-98-0) OR 60684-33-5) OR ubiquinol) OR 992-78-9) OR hydroxydecyl ubiquinone) OR idebenone) OR 58186-27-9) OR disodium ubiquinone) **AND**:

- statin interaction – 3/16
- cosmetics – 7/55
- melanin – 2/13
- toxicity – 16/630
- manufacturing – 0/16
- impurities – 3/7
- reproductive toxicity – 1/20
- dermal penetration - 0/5
- dermal irritation – 0/5
- mucous membrane irritation – 0/1
- dermal sensitization – 0/0
- coenzyme q10 hypertension – 4/17
- ocular irritation – 0/1
- contact allergy – 4/6
- clinical safety – 5/132
- developmental toxicity – 0/9
- carcinogenicity – 0/3
- mutagenicity – 5/10
- anti-cancer – 1/88
- genotoxicity – 2/6

Updated search (01/19/2022):
(((((disodium ubiquinone) OR (hydroxydecyl ubiquinone)) OR (idebenone)) OR (ubiquinone)) OR (ubidecarone)) AND (toxicity) – 768/2

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)
- Connected Papers - https://www.connectedpapers.com/

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://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/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

SEPTEMBER 2020 PANEL MEETING – INITIAL REVIEW/DRAFT REPORT

Belsito Team – September 14, 2020

DR. BELSITO: So, this is also a first timer for us: four ingredients; function as antioxidant, skin protectant, and skin-conditioning agents; 421 uses, most of them leave-ons. And as soon as my Levulinic Acid gets saved. Okay. Ubiquinone.

So, again, I'm presuming the comments from PCPC that we got in that second wave will be included. And the first question I had, Dan, is are you okay with the title and with the grouping and rationale?

DR. LIEBLER: Title's okay. Grouping and rationale's okay.

DR. BELSITO: Okay.

DR. LIEBLER: Because it's really driven by that ring system.

DR. BELSITO: Okay.

DR. LIEBLER: Not the chains.

DR. BELSITO: Okay. And then it says something about -- okay, it says, "Ubiquinone is produced outside the body by one of three methods: extraction from biological tissues..." So, do we have the issue with prions, et cetera? This is PDF page 11 under method of manufacture.

MS. RAJ: I didn't come across that, but obviously if you all might be aware.

DR. BELSITO: I mean, it says, biological tissues. It doesn't further define them, right?

MS. RAJ: Right. Right.

DR. BELSITO: So, what do you think? Paul, Curt?

DR. SNYDER: Yeah, I agree. I didn't catch that. I think that's a good catch. I think we --

DR. LIEBLER: I think the dominant methods are probably chemical synthesis and microbial fermentation simply because, purifying it from tissues, it's a low abundance molecule. It would be expensive and very tedious. So, I think, it maybe that you're saying, Preethi, that it's there in tissues, but I'm not sure that could possibly be a viable way to produce this as a product.

MS. RAJ: Yes, actually -- I mean, going back to that same page 11, you'll see it's under natural occurrence because, I guess, it's found primarily in tissue that is involved in cellular energy processes or that has a lot of mitochondria in it.

DR. LIEBLER: Yeah, bioenergetics, right.

MS. RAJ: Yeah. Yes, you're correct in what you said, Dr. Liebler, about it primarily being microbial fermentation.

DR. BELSITO: Okay. So, but we have this still biological tissues that can be extracted from, so that would be in the discussion that we assume it's not being produced by biological tissues, that it's being either synthesized or produced by microbial fermentation? Is that correct?

MS. RAJ: I can definitely do that.

DR. LIEBLER: Yeah, I think we need to just verify that.

DR. SNYDER: Yeah. I don't think we want to assume; we want to verify.

DR. LIEBLER: I think the thing, Preethi, is it's -- you know, natural occurrence is one thing, but method of manufacture -- if you say it's produced by one of three methods and you imply it comes from tissues, unless you really know that, you probably want to just delete that.

MS. RAJ: Okay. I can definitely do that.

DR. LIEBLER: Well, that's the way to verify it.

DR. SNYDER: That one sentence down further says from plant derived, so is it --

MS. RAJ: Wait a minute. Where are you looking, Dr. Snyder?

DR. SNYDER: The fourth sentence of that same paragraph, "Each of which is catalyzed by various enzymes using sources like plant-derived solanesol."

DR. LIEBLER: So, you're using the solanesol as a catalyst in the synthesis.

DR. SNYDER: Oh, okay. Okay. Sorry. I misread that.

DR. LIEBLER: Yeah, it's okay.

MS. RAJ: Thank you.

DR. BELSITO: And, as long as we're looking at that, do you have all the concerns with the impurities particularly the benzoquinone?

DR. LIEBLER: No, I think that that was fine. With the exception of the ambiguity on the source, I was fine with the method of manufacture, composition, impurities.

DR. BELSITO: Okay.

DR. SNYDER: They had lots of human absorption data, lots of tox data. And then the only other issue was this depigmentation issue again, Don.

DR. BELSITO: Right.

DR. SNYDER: And then the sensitization cross reactions, did you read that? What do we think about that?

DR. BELSITO: Okay. So, the pigmentation we need to discuss. I haven't gotten down there yet. I didn't like this Relative Contraindication paragraph. What did you guys think of it? This is PDF page 17. I didn't like the title in particular.

DR. SNYDER: Yeah, that's that cross reaction I was talking about. Yeah, I didn't --

DR. BELSITO: With this vitamin K1, I thought maybe if you wanted to include this, it should go under Miscellaneous Biological Effects, not Relative Contraindications.

MS. RAJ: Okay. Sure. I think, it was also supported or taken from the Norwegian assessment. But, yeah, I can definitely rephrase it or move it.

DR. BELSITO: Okay. And then the last sentence in the Relative Contraindication, it says, "As naphthoquinones, Hydroxydecyl... and Ubiquinone can act as haptens... However, the longer side chain is exhibited in weak allergenic response." If that's included at all, it really should be included in the Sensitization section, not here.

DR. LIEBLER: Yeah. So, I just disagree that these can act as haptens. These quinone -- these are fully substituted quinones that aren't able to undergo addition to biological nucleophiles, proteins, and so forth. They're fully substituted on all four possible reactive positions on the quinone ring, and so they're not reactive towards proteins.

DR. BELSITO: So then that sentence can just disappear completely.

DR. LIEBLER: Yeah, I think it's just incorrect to say that.

MS. RAJ: Dr. Liebler, thank you. Do you think maybe even if we delete that sentence, should any of what you just said go in the discussion?

DR. LIEBLER: I don't think it needs to.

MS. RAJ: Okay.

DR. LIEBLER: Yeah. I don't think there's a data issue we're responding to.

MS. RAJ: Okay.

DR. LIEBLER: I mean, unsubstituted naphthoquinones, Preethi, definitely can be protein reactive and act as haptens. But these are fully substituted, so there's not any open position for an addition to, like, a cystine group on a protein, so that just can't happen. So, we just cut that whole last sentence of that paragraph out, and we're good to go.

MS. RAJ: Okay. Thank you.

DR. BELSITO: You're talking about striking a whole paragraph or just the last two sentences of that?

DR. LIEBLER: The last two.

DR. BELSITO: Yeah. Well, actually the last two.

DR. LIEBLER: Okay. Yeah. See, it says Hydroxydecyl Ubiquinone -- okay. Oh, I see. "Additionally, Atovaquone, a 1,4-naphthoquinone derivative used to treat malaria and sometimes... also resembles..." So, I don't think the structure that Atovaquone, but, if it does have an open spot on the ring, then that can react with proteins. And then the analogy to the Hydroxydecyl Ubiquinone is inappropriate.

DR. BELSITO: Yeah, so I just struck the last two sentences.

DR. LIEBLER: Yeah.

DR. SNYDER: And move that to the Sensitization section, right?

DR. BELSITO: No, don't move it anywhere.

DR. SNYDER: No? Oh, okay.

DR. BELSITO: What Dan is saying is that there's no reactive areas. They're all taken up.

MS. RAJ: Dr. Liebler, on PDF page 73, you'll see we've put an excerpt of the Norwegian risk assessment, so, if you wanted to look at that chemical structure of Atovaquone, it's there.

DR. LIEBLER: Yeah, I just pulled it up on Wikipedia. I see the structure here. It doesn't have an open spot either, honestly.

MS. RAJ: Okay.

DR. LIEBLER: I mean, the only thing it can do would be act as an oxidant. Some of these quinones can act as oxidants towards proteins.

MS. RAJ: Mm-hmm.

DR. SNYDER: So, it's a different --

DR. BELSITO: Okay. And then, in the subsequent paragraph under Relative Contraindications, the one, two, the third sentences, so the fourth line down in that paragraph, it says, "There have been conflicting results in clinical trials examining the interaction of statins and Ubiquinone." And statins aren't even mentioned. The clinical -- it was all with anticoagulants and particularly with warfarin. So, I don't know where the statins came in.

MS. RAJ: That was, I think, also an annex in the Norwegian assessment. If you look under the risk assessment -- let me see. I think it was Annex 3. This is PDF page 65.

DR. BELSITO: And that's CoQ10 and warfarin, which is not a statin.

MS. RAJ: Okay. So, I guess warfarin is an anticoagulant?

DR. BELSITO: Yes. But it's only -- it's one of many anticoagulants, so it's particularly warfarin. I mean, there's heparin. There are other -- there's rivaroxaban. There are number of different anticoagulants out there. This interaction was specifically with warfarin.

DR. LIEBLER: Yeah, if you scroll down on that page, towards where it says, " Discussing their find, the authors wrote:" and there's a paragraph there, but they point out that CoQ10 is structurally related to menaquinone, a source of vitamin K. So, it's presumably interfering with either the absorption or action of vitamin K which is involved in clotting factor synthesis. And warfarins inhibit vitamin K to kind of clotting factor synthesis, so it's a more complicated mechanism of action, but that's probably what's going on.

DR. BELSITO: Yeah. I mean, anyway, the statement about the statins of that paragraph of that sentence needs to be deleted.

MS. RAJ: Okay. So that's, I think, is that the first sentence? Where is that?

DR. BELSITO: No, it's the -- under Ubiquinone, it's the fourth line down, "There have been conflicting results in clinical trials examining the interaction of statins and Ubiquinone." Just strike that.

MS. RAJ: Okay. But I can leave everything else?

DR. BELSITO: Yeah.

MS. RAJ: Okay.

DR. BELSITO: And it should go under -- I just don't like the title Contraindications. I would just say Miscellaneous Biological Effects.

MS. RAJ: Would that maybe be under Clinical Studies?

DR. BELSITO: These aren't really clinical studies though, are they?

MS. RAJ: Well, they are for oral consumption, which, I guess, maybe there should be a distinction made that any kinds of these effects are for oral consumption as opposed to topical, you know.

MS. FIUME: I guess this is where the Panel could decide if they want Clinical Studies to refer specifically to dermal effects. And, if it's not dermal, that it would go under Other Relevant Studies, or would you like studies that have oral exposure under Clinical Studies?

DR. SNYDER: We have so much data on this ingredient. We can fast track this to safe as used because the highest concentration of use leave ons is 0.05 percent. So that data doesn't really anything because we have so much other tox data and everything else. And so, as long as the sensitization is cleared, I don't see there's anything to hold this up.

MS. RAJ: Okay. Since you all brought it up, I wanted to ask, I guess, how did the Panel feel in general about including any data such as what we just discussed from the Norwegian risk assessment. Like, even if you saw in the excerpt that we put there, they did do like a risk assessment of cosmetic products. What were your thoughts on the relevancy of that and should it stay out of the report? Should this kind of stuff that's under the current title Relative Contraindications about the NOAEL for hypertension, should all that be cut out?

DR. BELSITO: I mean, they assumed a hundred percent absorption of the material, and they were looking at hypertension as an endpoint. I really don't think -- and they were coming up with margins of safety for a sensitization endpoint. And, you know, I mean, we're not really seeing a lot in terms of sensitization. I mean, we have an HRIPT in 50 subjects at one percent hydroquinone. It's not a hundred, but the maximum leave-on use is 0.05.

DR. SNYDER: I mean, 107 at 0.01 percent.

DR. BELSITO: Right. So, you know, I mean, I thought, we don't need the Norwegian study to clear sensitization safety, and it's the most bizarre study I've ever seen to use a NOAEL for hypertension? And then assume the dermal absorption of a hundred and come up with safe levels and say what's used in cosmetics are safe with sensitization?

MS. RAJ: Was the dermal absorption really a hundred percent though, Dr. Belsito? I thought they said two percent, but, in any case, you're right.

DR. BELSITO: Oh, yeah. You're right. They said two percent, which was the highest.

MS. RAJ: But we do agree the calculations were strange, which is why we're now asking you.

DR. BELSITO: Yeah, I don't think we need to include any of the Norwegian data.

MS. RAJ: Okay.

DR. SNYDER: Yeah, I thought this is one of the most complete data sets we've had in a long time.

DR. BELSITO: Yeah.

MS. RAJ: Popular ingredient.

DR. BELSITO: Yeah.

MS. RAJ: And also, about the grouping, I think you kind of touched on this that three of the ingredients, I think, maybe chemically and maybe more structurally related than the Hydroxydecyl Ubiquinone. Would you want to, I guess, elaborate on that in the discussion?

DR. LIEBLER: I don't think it's necessary.

MS. RAJ: Okay.

DR. LIEBLER: I don't think there's a situation where the Hydroxydecyl -- this sort of obviously does not belong.

MS. RAJ: Mm-hmm.

DR. LIEBLER: It's a shorter chain synthetic analog. You could simply add a sentence, the Panel felt the shorter chain synthetic analog could reasonably be grouped with the others because of the shared bioactive ring structure.

MS. RAJ: Okay. Thank you.

DR. BELSITO: I mean, the only issue with the Hydroxydecyl is we don't know the current concentration of use. But again, in the absence of that, we wouldn't be assuming that it's used at no more than 0.05 in a leave on.

DR. SNYDER: But all of our tox data is really high levels.

DR. BELSITO: Yeah.

DR. SNYDER: We're way -- we've got to be magnitudes away from any issues in my mind. I mean, we've got repro tox, we've got repro data, we've got carci data, we've got short-term chronic. We've got everything. We have lots of human absorption data also.

DR. BELSITO: Okay. So, we're getting rid of all the references to the Norwegian study, which, I guess, then eliminates the comment I had that we don't have a definition of SED, which is from the Norwegian study, so that gets rid of that.

MS. RAJ: And you all were going to talk about depigmentation.

DR. BELSITO: It's not a cosmetic effect.

MS. FIUME: Preethi, I believe that was just letting you know that would be a discussion point because that's listed as a function to identify that that's not a cosmetic function in the United States and, therefore, doesn't fall under the purview of the Panel --

MS. RAJ: Okay. Thank you.

MS. FIUME: -- and that they're not considering that effect.

DR. BELSITO: So, do we want -- I mean, if we're going safe as used and we're not asking Council to go out and get concentrations of use for the other two, then we don't have it. Is that correct? We're just assuming that there not going to be used at 0.05 or higher?

DR. SNYDER: Well, that's what --

DR. EISENMANN: The survey --

DR. SNYDER: Sorry, Carol.

DR. EISENMANN: The survey of Ubiquinone is ongoing, so it will have a little bit of data on that. So far, I've gotten I think one response, and it's the point that's lower than the maximum concentration of use is lower.

DR. BELSITO: Okay. So, basically, in the discussion, we have the respiratory boilerplate that we're assuming that it's not manufactured using biological tissues. If we can't confirm that that is not a way that it's presumed and that the induction of the vitiligo would not be a cosmetic effect and we would expect the manufacturers would formulate to avoid any evidence of depigmentation, and then safe as used, correct?

DR. SNYDER: Agreed.

DR. LIEBLER: Yes.

MS. RAJ: And this is for the whole group of ingredients, correct?

DR. BELSITO: Yes. Any other comments?

MS. RAJ: Anything else to go in the discussion, please let me know.

DR. BELSITO: I didn't have any, just the boilerplate and the assumption that it shouldn't be formulated to cause depigmentation; it's not a cosmetic effect. And we were assuming it's not manufactured using biological tissues.

DR. SNYDER: Job well done.

DR. BELSITO: Anything else?

MS. RAJ: Thank you. Thank you all.

DR. LIEBLER: Thanks, Preethi.

DR. BELSITO: 3:30. Woah.

DR. SNYDER: Before five?

DR. BELSITO: Yeah.

DR. LIEBLER: Yeah, that's right.

DR. BELSITO: Yeah.

DR. SNYDER: We all wish.

DR. BELSITO: Okay. Well, we'll see you tomorrow at 8:30 in the morning, and we'll spar with the Marks' team at that point for the last time with Jim.

DR. SNYDER: That's right.

DR. LIEBLER: That's right. It is.

DR. BELSITO: Okay. Great. See you all then.

DR. SNYDER: Thanks, Don.

DR. LIEBLER: Have a good evening.

DR. SNYDER: Thanks, Bart. Bye.

MS. FIUME: Have a nice evening.

MS. KOWCZ: Have a great night, everybody.

DR. KLAASSEN: Good night. Bye.

MS. FIUME: Bye.

DR. BELSITO: Good-bye.

Marks Team – September 14, 2020

DR. MARKS: Okay. This was my favorite ingredient.

DR. PETERSON: Was it?

DR. MARKS: Anything that has a name ubiquinone I thought was -- I just liked the sound of the name.

DR. ANSELL: It should be something that Superman is allergic to.

DR. MARKS: Or at least will sap his strength. So, this is -- Preethi, you're still up, and this is the first time we've seen these four cosmetic ingredients. And there was some reference in the third paragraph, I guess, that's to the Norwegian Food Safety Authority, and Preethi asked our guidance with reference to this document. And actually, Alex, in her September 4th memo asked, "Does the Norwegian Food Safety report belong in this assessment? Should the wording be changed?" So, let me see.

So, there're four ingredients. They're found in living organisms. Ubiquinone is the same as coenzyme 10, which we see advertised a lot. I don't know if anybody on the Panel has taken coenzyme 10, but one of the issues on page 16 is depigmentation. So, we'll have to address that.

I think, Wilma, you mentioned that right in the introduction this morning. And actually, it's kind of interesting how it's come in a cluster. This is now the forth ingredient in the last couple meetings where depigmentation has come up. And one of them, which is a final, was pomegranate. Could we use similar discussion in that? In this set of ingredients we have scutellaria, and then we also have ascorbyl glucoside -- all have issues with depigmentation or inhibition of tyrosinase, et cetera. Let me see. So, Lisa, Ron, Tom, are all four of these ingredients okay?

DR. PETERSON: So, I had it was missing a manufacture and impurities for the Hydroxydecyl.

DR. MARKS: Okay. Are the ingredients okay, Lisa? You didn't have any problems with the four ingredients?

DR. PETERSON: No, I'm sorry. I did not have problems with the four ingredients.

DR. MARKS: Okay. Great. And Ron and Tom, you're okay with the four ingredients?

DR. SHANK: I am, yes.

DR. MARKS: Okay. And so, Lisa, you had the -- so that would be an insufficient data announcement.

DR. SLAGA: For the hydroxy.

DR. MARKS: Huh. Where do I have that? The hydroxy. So, you don't think -- now, this is an interesting one because, at least when I look at the ingredient profile, I don't see method of manufacture on three out of the four ingredients. Would you need it for the other two that we don't have it, or can we read across from the ubiquinol?

DR. PETERSON: Oh, yes. We do need it for the ubiquinol, you know, just how are they doing the conversion.

DR. MARKS: Okay. So how they get to disodium, how they get Hydroxydecyl and ubiquinol and method of manufacture for all those.

DR. PETERSON: Yeah. Yes.

DR. HELDRETH: Because we did supply it for the ubiquinone.

DR. PETERSON: Right, right. And some of it is buried in the impurities for ubiquinone, and I think it just needs to be pulled up into -- the second paragraph of the impurity section has the industry's method of manufacture for the ubiquinone, which is one of the options given in the method of manufacturing section. So that's reference 26. It just needs to be added. But how they do the conversion from ubiquinone to ubiquinol and then the others all need method of manufacturing, then impurities.

DR. MARKS: Okay. Method of manufacture and impurities for the disodium, Hydroxydecyl, and the ubiquinol.

DR. PETERSON: Right.

DR. MARKS: Okay. That would be an insufficient data announcement -- one of the needs. Ron, any other -- Lisa, needs you have?

DR. SHANK: We need to the use concentration for the Hydroxydecyl compound. We have an HRIPT at 0.01 percent, but there's no use concentration given in the report.

DR. MARKS: Yeah. And so, David, that'll be one of the things you'll be focused on is, when you look at the ingredients, that's what I meant when I said combining the profile page with the uses and concentration of use. And so you may have some safety data on sensitivity for an ingredient, but if you don't have the use concentration, you can't say it's safe because you don't know what concentration's being used. Okay. Any other -- Ron and Tom, any other needs?

DR. SHANK: That was it.

DR. MARKS: That was it. So how do you -- Tom, you were fine, then, otherwise?

DR. SLAGA: Yeah.

DR. MARKS: How do you deal with the depigmentation?

DR. SLAGA: In the discussion.

DR. MARKS: Okay. Preethi, let me see here. If we go in pomegranate, I kind of like the -- this is in the discussion of pomegranate. "Nevertheless, cosmetic formulators should only use punica granatum" -- that's pomegranate -- "extracts and products in a manner that does not cause depigmentation." So, decide whether or not -- and it gives -- before that, it acknowledges the skin lightening effect. And then under the scutellaria, "Nevertheless, the Panel noted that cosmetic formulators should only use scutellaria B root extract and products in a manner that does not cause depigmentation."

So, we're getting sort of a rhythm in terms of, in the discussion, including that sentence to try and address -- not try, to address the depigmentation issue. And I put in my notes margin of safety for depigmentation, but we aren't going to get that. We've had that discussion before.

DR. COHEN: Jim, that recommendation just kind of seems very ethereal. What does that mean: don't use in a manner that causes depigmentation?

DR. MARKS: I'll let you address that with the Panel members in the future, David. It passed Lisa and Dan's sniff test for pomegranate, so we'll see. But I agree. There's a bit of a -- oftentimes, in the discussion we alert formulators to issues that we consider that could be a significant toxicologic effect, but we don't think it rises to the level that we need to put in the conclusion, like we just talked about formulate to be nonirritating.

If we were strongly felt about the depigmentation or skin lightening, we would have it in the conclusion: formulate to be no depigmentation. I think I have that sense right. Is that correct, Lisa, Tom, and Ron? And I gather, Ron, you and Wilma --

DR. BERGFELD: That's correct.

DR. ANSELL: Yeah. Let me -- this is Jay. Just let me throw out depigmentation would be a drug effect.

DR. MARKS: Yes.

DR. ANSELL: A product which was going to cause depigmentation would be a drug, not a cosmetic. And, so, within the context of a cosmetic, it would be considered by the Panel an adverse effect. So, the warning that is trying to balance the -- walk the tightrope between a cosmetic and a drug.

DR. MARKS: Thank you, Jay, because that's also mentioned in that paragraph in both pomegranate and the scutellaria. It specifically says, "However, the Panel note that skin lightening is considered to be a drug effect and should not occur during the use of these cosmetic products." The other one -- yeah. That reference is in there, too.

I'll let you look at those paragraphs later on, David. But you'll see. You'll have another shot at this since this is the first time seeing it. So, I'm going to be moving for our team tomorrow that an insufficient data announcement be issued, and the needs are method of manufacture and impurities for disodium, Hydroxydecyl, and the ubiquinol and that we have the use concentration for the Hydroxydecyl and then that we would handle the depigmentation or skin lightening in the discussion.

DR. SLAGA: Sounds good.

DR. MARKS: Sound good, Lisa, Ron? I don't know how much you can hear, Ron.

DR. SHANK: Some of it. What I heard was good.

DR. MARKS: Okay.

MS. RAJ: Thank you, everyone.

DR. MARKS: Thank you, Preethi.

Full Panel – September 15, 2020

DR. MARKS: So, this is the first time the Panel is considering the safety of four Ubiquinone ingredients. And, these ingredients are found in living organism. Ubiquinone -- I love that name -- is equal to coenzyme q10. There are some depigmentation issues, and perhaps we can address those -- this is probably more for discussion -- but in the discussion.

So, our team felt that we should issue an insufficient data announcement that we wanted the method of manufacture and impurities for the Disodium, Hydroxydecyl, and Ubiquinol, along with use concentration for the Hydroxydecyl. And handle the depigmentation issue in the discussion as we've done with the other ingredients that this was an issue.

DR. BERGFELD: Dr. Belsito?

DR. BELSITO: Well, we thought they were safe as used, so I'll let Dan address method of manufacturing.

DR. LIEBLER: So, I think we did have a discussion on method and manufacture yesterday, but it was that in the description of method of manufacture it suggested that extraction from tissues is a means by which this ingredient is produced for cosmetic products. And, that appears not to be true but it implies that in the report. And, if that so, then we probably would need a lot more information about the method of manufacture. And, we'd also need the animal, you know, product boilerplate.

It seems like it would be very unlikely that that's true, because it would be relatively cumbersome and expensive. The other methods, synthesis and microbial fermentation, appeared to be the major routes of production. So, I thought method of manufacture, with the exception of that caveat about the extraction from tissues, is okay.

Impurities, I thought was acceptable, but if there are specific concerns about impurities I'd like to hear them.

DR. BERGFELD: Lisa, do you have a comment, or Jim?

DR. MARKS: I'll defer to Lisa.

DR. PETERSON: Well, I believe that it's just one of these i-dotting t-crossing kinds of things. But, there is really no information about the Hydroxydecyl.

DR. LIEBLER: Yeah, you're right. The descriptions are really limited to Ubiquinone.

DR. PETERSON: Yeah, and not the Ubiquinol, and so how do they do the transformation? And, I wasn't the only one in my group that came up with that, so.

DR. LIEBLER: Okay. Well, I think that's a good point. We should add that to the insufficiencies. So, method and manufacture and impurities for Hydroxydecyl.

DR. BELSITO: And Ubiquinol.

DR. LIEBLER: I don't think it's necessary for Ubiquinol. I mean, it's basically just a reduction product, the Ubiquinol.

DR. PETERSON: Don't you care about how they reduced it and purified it? What they used? I'm just throwing it out there, I mean, there's no information. So, it depends on what they used, right, whether you would maybe have some concerns or not?

DR. LIEBLER: Yep.

DR. PETERSON: You know, the absence of data, you can make up all kinds of stories but there's no data to even hang your hat on anything.

DR. LIEBLER: All right, let's add that as well. I agree; thank you.

DR. MARKS: Aye, I, for my final meeting I really like Lisa that you are having a discussion with Dan. Somebody standing up to Dan before has been a little bit absent other than with Ron and Tom. So, the chemist in here thanks you Lisa.

DR. PETERSON: We both got our teeth cut with Fred Gingrich (phonetic), so.

DR. LIEBLER: Mine are still bleeding.

DR. BERGFELD: Dr. Marks, do you want to restate where we stand, and then make sure that Dr. Belsito approves?

DR. MARKS: Well, I think Don needs to withdraw his motion and then perhaps either he can suggest the IDA motion or I can.

DR. BELSITO: It was your motion. I just pointed out we went safe as used, so it was your motion, Jim.

DR. MARKS: Yeah, I'm sorry, Don, you're absolutely right. So, again, what we moved was issuing an insufficient data announcement and that we wanted method of manufacture and impurities. And I know we discussed back and forth, but what I had from yesterday's meeting was the Disodium, Hydroxydecyl, Ubiquinol, and then the use concentration for Hydroxydecyl. I'd probably ask for all that to begin with and then let's see what we get.

DR. BERGFELD: So, you're going to ask for all three?

DR. MARKS: Yeah, I would, but again, I'll leave it to Lisa and Dan, if they want to modify that, fine.

DR. BERGFELD: Comments by Dan and Lisa?

DR. BELSITO: I thought it was just Ubiquinol and Hydroxydecyl.

DR. PETERSON: Yes, those are the two that I think, because we have the information for the Ubiquinone.

DR. BERGFELD: Dan, comment?

DR. MARKS: So, you don't need the Disodium?

DR. BELSITO: No.

DR. LIEBLER: Right.

DR. MARKS: Okay.

DR. BERGFELD: Is that a second then, Don?

DR. BELSITO: Yes.

DR. BERGFELD: Okay. Any other discussion?

MS. RAJ: Dr. Bergfeld, may I interject?

DR. BERGFELD: Sure.

MS. RAJ: I'd like to ask the Panel, yesterday in the Belsito team it was brought up it is in the report that we referenced a Norwegian safety assessment for a lot of the data. And they also had done their own risk assessment, which was referenced throughout the report.

And, I think the Belsito team made it very clear that they were not in agreement with this data. Whether it was in the relative contraindication section, which I believe is on PDF Page 17, I want to say. And, it's also briefly mentioned in the clinical studies section summary and intro-sections. And, it sounded to me like they wanted all reference to that assessment to be cut out. So, I just wanted to get the Panel's consensus on this.

DR. BELSITO: You're correct with that statement. We did not think the Norwegian study was needed. We didn't like looking at sensitization and irritation based upon a NOAEL related to hypotension.

DR. MARKS: Unless Tom, Ron or Lisa has any comments; our team concurs with you, Don.

DR. BERGFELD: Okay.

DR. SHANK: I agree too.

DR. BERGFELD: Lisa?

DR. PETERSON: Sure. Yeah.

DR. BERGFELD: Okay. Fine, that's going to be considered editorial. All right, any other comments before we call the question?

MS. RAJ: Thank you all, and just want to let Dr. Marks know it's been a pleasure. And, he said my name right. Please do keep in touch, all the best to you.

DR. MARKS: Thank you.

DR. BERGFELD: That's nice. Thank you. I'm going to call the question. All those against sending out an IDA for this particular ingredient, please indicate by stating your name. Hearing no one, I'm going to assume it's unanimous we're going forward with Ubiquinone with an insufficient data announcement. Now we're moving on to another ingredient, Dr. Belsito, Amino Acid Diacetates.

SEPTEMBER 2021 PANEL MEETING – SECOND REVIEW/DRAFT TENTATIVE REPORT

Belsito Team – September 13, 2021

DR. BELSITO: Okay, so, ubiquinone. The ubiquitous ubiquinone. Okay, so, at the September 2020 meeting, we issued an insufficient data for the four ingredients. We wanted method of manufacturing for hydroxydecyl ubiquinone and ubiquinol, which we didn't receive. Concentration of use data for hydroxydecyl ubiquinone and ubiquinol, which we didn't receive. We did get updated frequency of use and ubiquinone decreased from 421 to 231 when the hydroxydecyl ubiquinol, which we asked for data that we didn't get, was about the same volume of use.

So, where are we with this discussion, or this material, rather?

DR. LIEBLER: So, I actually like Preethi's draft discussion, the second paragraph, the one that says the Panel stated that although hydroxydecyl, I actually like the logic expressed there. I agree with the reasoning. We're unlikely to get method of manufacturing, impurities for the unused ingredients.

DR. BELSITO: What page are you on, Dan?

DR. LIEBLER: PDF 29. So, we asked for method of manufacture and impurities for everything.

DR. BELSITO: Right.

DR. LIEBLER: We still only have it for ubiquinone.

DR. BELSITO: That's correct.

DR. LIEBLER: But the logic expressed in the draft discussion captures my opinion on the widespread use and safety of ubiquinone mitigates concern about the others, particularly ubiquinol, which is just the reduction product of ubiquinone. So, it's in rapid biological equilibrium where you administer and absorb ubiquinone and take that into cells, it rapidly is reduced into ubiquinol anyway. So, I'm not concerned about that.

I know Lisa raised the hypothetical about, well, what is the reduction agent? Could there be contaminant from the reduction process? I suppose hypothetically that can be an issue we need to consider, but I think, based on the widespread use and safety data for ubiquinone, I don't have strong enough concern about that to throw out ubiquinol or to go insufficient on it. So that's how I feel about this one, and I think the reasoning for supporting mitigation of concern is nicely captured in Preethi's second paragraph in the draft discussion. So, I don't have anything else to add to it.

DR. BELSITO: So, you would get a safe as used for all four ingredients?

DR. LIEBLER: I would.

DR. BELSITO: Okay, Paul?

DR. SNYDER: I had no issues.

DR. BELSITO: Okay. So, I appreciate the discussion. So, we're going to have a conclusion safe as used.

DR. LIEBLER: Correct.

DR. BELSITO: Anything else in this report that needs to be looked at? I did not have anything.

DR. SNYDER: Me either.

DR. LIEBLER: Nope.

Cohen Team – September 13, 2021

DR. COHEN: Okay, we'll move on to ubiquinone ingredients. This is a draft tentative report. In September, we issued an IDA looking for methods of manufacturing for hydroxydecyl ubiquinone and ubiquinol, and concentration of use for hydroxydecyl ubiquinone and ubiquinol.

I don't believe we have much new information. We have data that it's not irritating. I'll come back to some of the irritation sensitization, but I'll ask for comments from the group first. Tom?

DR. SLAGA: Well, we asked for some data. I think that was mainly from Ron. But I have that, although we don't have maybe methods of manufacturing for the two -- the hydroxydecyl ubiquinone and the ubiquinol, there are some data on it, and we do have it for ubiquinone, and I have that it should be safe.

DR. SHANK: The quinone and quinol, we have the necessary tox data to support safety. It's the hydroxydecyl ubiquinone --

DR. SLAGA: Okay.

DR. SHANK: -that was tested at HRIPT at 0.01 percent, but that's below the use concentration. So, we asked for more skin sensitization data on that one, and we did not get it.

DR. SLAGA: Okay.

DR. SHANK: So, we either say that's insufficient or perhaps we could put a concentration limit on it based on the HRIPT data that we have.

DR. BERGFELD: Ron, does it make any difference that it's Q10?

DR. COHEN: CoQ10.

DR. BERGFELD: Right. Yeah, it's taken by pill, a supplement, by a large population and it's also naturally occurring in humans.

DR. SHANK: Yeah, but that's ubiquinone, right?

DR. BERGFELD: Yeah.

DR. SLAGA: Right.

DR. SHANK: I'm talking about the hydroxydecyl --

DR. BERGFELD: Hydroxydecyl.

DR. SHANK: -- ubiquinone.

DR. SLAGA: Yeah. Yeah, there's really no detail.

DR. SHANK: The ubiquinone and the ubiquinol are safe as used.

DR. SLAGA: Right.

DR. SHANK: But we don't have the skin sensitization data for the hydroxydecyl ubiquinone, unless I missed it.

DR. COHEN: No, no. I think we have 107 subjects for hydroxydecyl ubiquinone at 0.01 percent.

DR. SHANK: Yes.

DR. COHEN: Right? And we -- I'm not sure we have max use reported on that.

DR. SHANK: Let me check.

DR. COHEN: One other thing, which seems to come up now and again, and I think I know what Bart's gonna say, but, you know, there's a Canadian case report of 0.5 percent hydroxydecyl in a product, a corroborating case report with the same concentration, and another case report with one percent. So, we're looking at max use in the tables that are different than the case reports that come in, and sometimes even our HRIPT data has higher concentrations than the max use. That kind of implies to me that maybe the max use is just what's getting reported to us, but in reality, we're seeing data where it's higher use. It's come up at other meetings, but my eye keeps going to this now.

DR. PETERSON: Yeah, I noticed that for another report too, and I had the same question.

DR. COHEN: Now, Bart, are you going to say this is what's reported to us, and this is what we're supposed to be reviewing?

DR. BERGFELD: Yeah.

DR. HELDRETH: To some extent, yes. You know, now, I understand your concern, and it gives me the same heartburn thinking of (audio gap). I think the thing we have to remember is the conclusion that we provide, if we say that these are safe as used, per se, we're only saying up to the max use that we have reported in this document.

So even if there's a five percent concentration use in a product out there that we don't have data on, we're not saying that that's safe. We're saying here the max concentration of use is 0.05. We're saying that products that contain these ingredients up to no more than that in these use categories are safe.

If someone's using it at a higher concentration, then it's up to that company to either provide the expert Panel with that information so that we can determine safety. Or the onus that was originally on the manufacturer falls back to them to do their own safety assessment and make sure that those ingredients are safe at those higher concentrations.

DR. BERGFELD: We can also declare that in the discussion.

DR. HELDRETH: Right, right.

DR. COHEN: I think we should because, in our manuscript, we're judging HRIPT data on higher concentrations, and then making a statement about safe as used based on that higher concentration, even though we're sort of saying, yeah, but the table says one concentration and our adjudication is on a concentration that may be two or three X higher. Couldn't one conclude, well, the Panel's conclusion are really based on sensitization data three X of max use, so this report is okay at that higher HRIPT data? I may be splitting hairs, and it's because I'm new, so I just want to get comfortable. I understand conceptually how this is going.

DR. HELDRETH: Right, no, and I agree with you. You know, it does make sense that we're saying, well, it could be safe at that higher concentration because the data we have are suggesting so, but a couple issues that make me you know, not want to include such in a conclusion is, typically those studies, like an HRIPT, it's a test material.

We don't know if it -- how related it is to the cosmetic, and typically, we don't know what exposure type was intended. So, we may have an HRIPT at five percent, but we may not know that the product that that's actually used in may be intended for mucus membrane application or near the eye, and maybe those results aren't as relevant to those types of uses. So, I hear what you're saying, and I totally agree, but I think we can only conclude on what we have concrete data on.

DR. COHEN: Yeah, yeah, I certainly understand that. I mean, we're dealing with large amounts of data and trying to draw a general conclusion to the best we can. Did I miss -- we don't have ocular tox on this, but I saw nine products of eye lotions and products near the eyes.

DR. HELDRETH: Yes.

DR. COHEN: Do we need ocular tox on this?

DR. SHANK: I'm looking.

DR. COHEN: Yep.

DR. HELDRETH: Yeah, it's reported up to 0.02 percent in the eye.

DR. COHEN: Right. In eye shadows.

DR. SHANK: Yeah, it says we have no ocular irritation data on any of them.

DR. SLAGA: Who would -- but generally, we don't hold up an ingredient because of ocular. If we have irritation data in general, we usually accept that. That it's not going to be irritating even to the eye.

DR. BERGFELD: Correct.

DR. COHEN: Okay. So, irritancy data is a surrogate in some or many circumstances.

DR. SLAGA: Right.

DR. BERGFELD: Depending on concentration.

DR. SLAGA: Right. The eye, as we all know, is very sensitive, and that's why there's a lot of dispute over how to even do those studies.

DR. COHEN: Okay, so, Lisa, what do you see us needing further information or how do we come out on this?

DR. PETERSON: Well, I think it was already stated. I mean, I had the question about why the method of manufacturing was still missing, but I think that overall, I didn't have any concerns. I think there were some clinical reports on the hydroxydecyl, so that I thought there needed to be some qualifier perhaps, but I sort of leave that -- defer to the experts on the Panel in regards to that. But I'm okay with the overall seems safe, you know?

DR. COHEN: So, are we going safe as used right now without any further requirements?

DR. SHANK: For ubiquinone and ubiquinol, safe as used, under the present conditions of use in concentration. The hydroxydecyl, insufficient for skin sensitization.

DR. PETERSON: Well, there was an HRIPT [sic] on that up to 0.01 percent.

DR. SLAGA: Yeah.

DR. COHEN: We just don't know the max use concentration on it.

DR. SLAGA: Right.

DR. COHEN: So, if we knew that and this --

DR. SHANK: So, if you say they're all three safe as used under the -- well, you still have the problem of no information on the concentration in cosmetic products for the hydroxydecyl.

DR. BERGFELD: But I thought we considered putting some of that in the discussion and discussing the concentrations that we have.

DR. COHEN: Yeah, we could put safe as used and discuss the 0.01 percent for the hydroxydecyl and the HRIPT, and finish this off. And, if we get further information that it's used in lower concentration, it stays, and, if we have higher concentration, we would qualify it.

DR. SLAGA: But do we have to set a limit in the conclusion?

DR. BERGFELD: Not if you put in the discussion.

DR. SLAGA: Well, if it's in the discussion, hmm.

DR. BERGFELD: Well, it's a matter of just calling it out because of the discrepancy of what was tested and what is used. Or not.

DR. SLAGA: Well, I personally don't think it's a concern, so I would still go with overall safety, safe, and the discussion is fine.

DR. PETERSON: Yeah. I think there's some evidence that there's probably a problem with higher concentrations with the hydroxydecyl, so I think, I guess if having it in the discussion covers the bases, then I think it's fine. I guess I was thinking there might need to be an upper limit, that it was safe up to the 0.01 percent, but we don't really know about that.

DR. HELDRETH: Commonly, when we have these types of conclusions, where there's ingredients that we don't know a max use concentration for, we'll have a caveat in the conclusion, a little asterisk at the bottom of it stating that for those ingredients which we don't have a max concentration of use data, the expectation is that they'll be used in the same exposure types and at concentrations no higher.

DR. SHANK: That would be good.

DR. SLAGA: Yeah.

DR. HELDRETH: So, then the safety conclusion for the hydroxydecyl ubiquinone would be only covered at no higher than 0.05 percent, as is that's the max concentration for the ubiquinone.

DR. COHEN: I think that's very satisfying.

DR. SLAGA: Right.

DR. COHEN: And it allows us to move along. Okay.

MS. RAJ: Does the Panel have any other comments on the discussion to modify or --

DR. SHANK: Not from me.

DR. COHEN: Do we put anything about eye contact in here, or --

DR. SLAGA: No.

DR. COHEN: Okay. Preethi, are we okay on this one?

MS. RAJ: Yes, I think I heard so we don't need to add a statement about the ocular data, is that right?

DR. SHANK: That's right.

MS. RAJ: Okay, thank you.

Full Panel – September 14, 2021

DR. BELSITO: At the September 2020 meeting we issued an insufficient data announcement for the four ingredients with the following needs, method of manufacture for Hydroxydecyl Ubiquinone and Ubiquinone, concentration of use data for Hydroxydecyl Ubiquinone and Ubiquinol. And, we did receive updated frequency of use data, and the uses of Ubiquinone have decreased a bit, almost in half. And, the uses of Hydroxydecyl Ubiquinone and Ubiquinol remain the same.

In looking at this document again, Dan felt that the method of manufacture and impurities, for Hydroxydecyl Ubiquinone and Ubiquinol, were really covered by Ubiquinone itself, particularly given the presence in skin and the metabolism of these ingredients in skin. And, so, based on that, we went with a safe as used to that conclusion.

DR. BERGFELD: Dr. Cohen?

DR. COHEN: We would second that. And, we came to similar conclusions. One comment, we have no concentration of use, I believe, for Hydroxydecyl Ubiquinone but we have HRIPT data for 0.01 percent, and that concentration should be in our discussion. So are safe as used conclusion is collared by the concentration data limit that we have.

DR. BERGFELD: Don?

DR. BELSITO: Well, typically, David, when we say "safe as used," it's the range that's present in the group. So --

DR. COHEN: You mean the max --

DR. BERGFELD: Does it hurt to put it in the discussion? Does it reflect in any way against the document? It clarifies.

DR. BELSITO: No, but I mean, we're going to set a safety limit on sensitization because we have a HRIPT that is clean, so, then, if we're going to set that limit that would have to be in our conclusion. We did that in the past, oftentimes for, you know, we really weren't thinking it out particularly with things that could be irritating we'd set limits and then we realized, well, it's

really how you formulate it. You know, I mean, if you take lactic acid and you formulate it and become the lactate, it's very different in terms of its tolerance.

So, that's when we started changing to formulate to be non-irritating. But typically when we say safe as used, we're talking -- and we don't have a concentration for a particular material, we're assuming it could be used as high as Ubiquinone in this case.

DR. COHEN: So, I appreciate that, Don, because, you know, this is my third meeting and I don't have that institutional memory. If we had concentration of use for Hydroxydecyl at two percent, let's say it was listed in the table at two percent, and you were presented HRIPT data for 0.01 percent, what would you say; would that change how you would conclude?

DR. BELSITO: Not necessarily, David. I mean, because first of all what's going to happen when the product is applied on the skin, with Hydroxydecyl Ubiquinone. There really are no clinical reports on this being a problem. I mean, that doesn't mean that that's not the case, but we haven't always with sensitization required a HRIPT at the highest level of use; we've sort of used expert judgment.

DR. COHEN: Okay, I, you know --

DR. BERGFELD: But frequently we have used it too.

DR. SLAGA: Yeah.

DR. BERGFELD: So, it's really in the discussion of the experience.

DR. BELSITO: Well, yeah, it's in the context; it's expert opinion whether we go with a restriction. I mean, as we did with, you know, cocamidopropyl betaine (phonetic) where we're asking for when formulated to be non-sensitizing based upon a QRA, or other accepted methodologies. So, there's really no boilerplate that we've crafted for sensitization. It depends upon the materials.

DR. COHEN: But we're not suggesting a change to the conclusion, just merely a mention in the discussion.

DR. SNYDER: I wouldn't --

DR. BELSITO: But if you mention it in the discussion, you're restricting it to that level. Then that is part of your conclusion; there's a restriction there.

DR. SNYDER: Yeah, I wouldn't be against that because we have good data on Ubiquinol. We have a 90-day study up to 1,200mg/kg/day that's negative. So, even if we had a concentration of use, it's not likely the exposure of cosmetics is going to anywhere near reach 1,200 mg/kg/day.

DR. BELSITO: Paul, David's talking about sensitization.

DR. COHEN: Sensitization.

DR. SNYDER: Oh, I'm sorry.

DR. COHEN: Yeah, I hadn't come across too many circumstances where we had the HRIPT and I didn't have any concentration range on the product at all.

DR. BELSITO: Bart?

DR. BERGFELD: Bart?

DR. HELDRETH: Yeah, so, commonly with ingredients that have no reported use we'll add a little asterisk to that ingredient in the conclusion, with a statement such as "not reported to be in use, were ingredients in this group, not in current use, to be used in the future the expectation is that they would be used in product categories and at concentrations comparable to others in this group."

Would it be suitable to have a very similar asterisk in this situation, put it on the Hydroxydecyl and say "maximum concentration of use not reported, were this ingredient to be used in the future the expectation is that it would be used in product categories and at concentrations comparable to others in the group?

DR. BERGFELD: Is that acceptable, David?

DR. COHEN: Yeah.

DR. BERGFELD: I think that's a good compromise.

DR. COHEN: Yeah, I think so too.

DR. BERGFELD: All right, any other questions regarding this ingredient? It's been motioned; it's been seconded, so I'm going to move on to the vote. All those opposed? Abstaining? Unanimously approved. Thank you. Then moving on to the next ingredient, Dr. Cohen, Rosa damascena.

Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics

Status: Draft Final Report for Panel Review
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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.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. Previous Panel members involved in this assessment: James G. Marks, Jr., M.D; Lisa, A. Peterson, Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Preethi S. Raj, M.Sc., Senior Scientific Analyst/Writer, CIR.

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of 4 Ubiquinone ingredients as used in cosmetic formulations. These ingredients are mostly reported to function in cosmetics as antioxidants, while some are also reported to function as skin protectants, skin conditioning agents, and hair conditioning agents. The Panel reviewed relevant data relating to the safety of these ingredients in cosmetic formulations, and concluded these Ubiquinone ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

INTRODUCTION

This assessment reviews the available safety information of the following 4 Ubiquinone ingredients as used in cosmetic formulations:

Disodium Ubiquinone	Ubiquinol
Hydroxydecyl Ubiquinone	Ubiquinone

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these Ubiquinone ingredients are reported to function in cosmetics as antioxidants; some are also reported to function as skin protectants, skin conditioning agents, and/or hair conditioning agents (Table 1).[1] Ubiquinone is commonly known as coenzyme Q10.

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.

Toxicological assessments of Hydroxydecyl Ubiquinone were issued by the European Medicines Agency and by the Australian Government Department of Health.[2,3] Data summaries are available on the respective websites, and when deemed appropriate, information from the summaries has been included in this report.

CHEMISTRY

Definition and Structure

The definitions and chemical structures of the Ubiquinone ingredients included in this report, as given in the *Dictionary*, are provided in Table 1. These ingredients, which are a class of homologous benzoquinones, aptly named for their ubiquitous existence in the vast majority of living organisms,[4] have been grouped together because they share a 2,5-cyclohexadiene-1,4-dione core, with various alkyl chain substituents at the 2 position of the cyclohexadiene, to comprise the salts or metabolites, thereof.

Ubiquinone (CAS No. 303-98-0) is the organic compound which is depicted in Figure 1.[1] While some of the technical names for Ubiquinone provided in the *Dictionary* may seem to suggest a number of isoprenoid units other than 10 (e.g., Ubiquinone 50; although, the "50" therein refers to the number of carbon atoms, and is thus 10 isoprenoid units), the structure and formula provided in the monograph indicate 10 such repeat units.

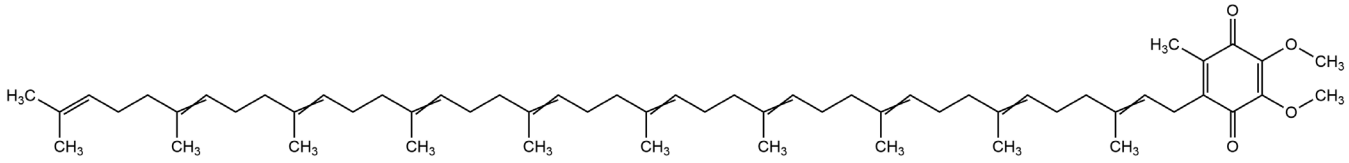


Figure 1. Ubiquinone

Many biological functions involving Ubiquinone result, in part, because of the redox reactions to/from Ubiquinol (CAS No. 992-78-9), through the radical intermediate, ubisemiquinone, as seen in Figure 2.[5]

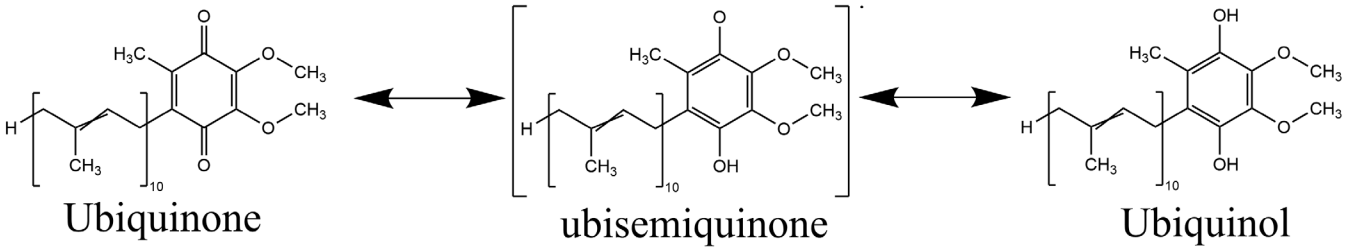


Figure 2. Redox between Ubiquinone and Ubiquinol

Hydroxydecyl Ubiquinone, however, is structurally dissimilar to the other 3 ingredients herein (Figure 3). This ingredient shares a benzoquinone core structure, as well as 1 methyl and 2 methoxy functional groups, in common with the other 3 ingredients. However, wherein the other 3 ingredients have a polyisoprenoid sidechain, the Hydroxydecyl Ubiquinone sidechain comprises a simple, 10-carbon alkyl chain with a terminal alcohol group.

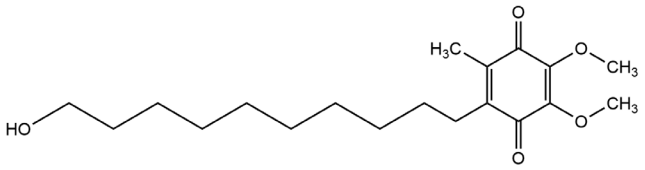


Figure 3. Hydroxydecyl Ubiquinone

These benzoquinone homologs consist of a redox active quinoid moiety, and a hydrophobic side chain comprising 6 to 10 isoprenoid units, depending on the species. In rats and mice, coenzyme Q_9 is the predominant form. In humans, the predominant form of Ubiquinone is coenzyme Q_{10}, referring to a side chain of 10 isoprenoid units. Disodium Ubiquinone, Hydroxydecyl Ubiquinone, Ubiquinol, and Ubiquinone have partition coefficients of 20.23, 3.88, 23.74, and 16.51, respectively (log K_{ow}; estimated).[6] Both Ubiquinol and Ubiquinone are sparingly soluble in water.[7,8] The chemical properties of these ingredients are further outlined in Table 2**.**

Natural Occurrence

Human skin is known to contain both enzymatic and non-enzymatic (antioxidant) mechanisms for protecting itself from oxidative stress.[9] There is 10 times more Ubiquinol (3.53 vs. 0.35 nmol/gm), and almost twice as much Ubiquinone (4.12 vs. 2.86 nmol/gm), in the human epidermis, compared to the dermis.[10] Ubiquinone and Ubiquinol content is known to peak in human tissue in early adulthood, and decline with age.[9] The plasma concentration of Ubiquinone in healthy humans ranges from 0.20 to 1.91 µmol/l, and the total body pool is estimated to be approximately 0.5 - 1.5 g.[11]

Method of Manufacture

Most of the methods of manufacture summarized below are general methodologies, and it is unknown if they apply to cosmetic ingredient manufacturing.

Ubiquinone

In 1957, Ubiquinone was isolated from beef heart mitochondria and was first chemically synthesized in 1958.[12,13] Ubiquinone is also found in a wide variety of dietary sources such as oily fish, organ meats, whole grains, and vegetables.[14]

Ubiquinone is produced outside the body by one of two methods, either chemical synthesis or microbial fermentation.[15-19] Chemical synthesis occurs sequentially via creation of a quinonoid ring, synthesis of decaprenyl diphosphate, and quinonoid ring modification, each of which is catalyzed by various enzymes, using sources like plant-derived solanesol.[15,20-22] Microbial fermentation is considered the most efficient and environmentally benign means of producing Ubiquinone as the process is easier to control, can be executed on a large scale with less time and resources, and requires less use of solvent.[23,24] The gram-negative bacterium, *Agrobacterium tumefaciens,* is often used for its relatively high synthesis rates.[16] According to one supplier, Ubiquinone produced via yeast fermentation can result purely in the all-*trans* form (does not contain any *cis*-alkenes).[19]

A few other natural producers of Ubiquinone include *Schizosaccharomyces pombe* (fission yeast), *Sporidiobolus johnsonii*, and *Rhodobacter sphaeroides* (a photosynthetic bacterium).[24] During the course of Ubiquinone production, it is possible for Ubiquinone species of varied isoprenoid chain lengths, such as coenzyme Q8 and coenzyme Q9, to be produced.[25] Natural or "native" producers of Ubiquinone do not produce other Ubiquinone species of varied chain length; however, in spite of initially higher Ubiquinone yields, production has not been optimized in these organisms. Heterologous "non-native" producers of Ubiquinone, such as *Escherichia coli*, *Saccharomyces cerevisiae* (yeast), and plants provide the advantage of genetic manipulation to optimize Ubiquinone yields.

High hydrostatic pressure treatment, ultraviolet light (UV), and diethyl sulfate treatment were utilized to induce mutagenesis during the submerged microbial fermentation process of Ubiquinone production from *A. tumefacians*, to test if mutant strains would effect higher yields of Ubiquinone than wild-type strains.[23] A mutant strain PK38 was shown to increase Ubiquinone production by 52.83% compared to the original strain. Exponential feeding, fed-batch culture strategy, using 30 µl sucrose, produced a final cell biomass, Ubiquinone production, and specific Ubiquinone production increase of 126.11, 173.12, and 22.76 %, respectively, compared to those of batch cultures.

Impurities

Ubiquinone

In a study assessing the ability of non-aqueous, reversed phase, high performance liquid chromatographic (NARP-HPLC) to distinguish Ubiquinone from its process-related impurities during pharmaceutical manufacturing, researchers detected 2,3-dimethoxy-5-methyl-*p*-benzoquinone, solanesol, solanesyl acetone, and isodecaprenol at trace amounts, with up to 100% recovery of Ubiquinone.[26] While analyzing the degradation products of Ubiquinone, through exposure to triethylamine (a base), under heat and ethanol, researchers discovered two unknown impurities, with isomeric qualities.[27]

According to data received from the industry, Ubiquinone produced by yeast fermentation, is purely in the all-*trans* form (does not contain all- or partially-*cis*-isomers).[19] The content is > 98% coenzyme Q10, with coenzyme Q9 and coenzyme Q11 as the two major impurities. The same source identifies additional impurities, which may occur in Ubiquinone: 2,3-dimethoxy-5-methylbenzene-1,4-diol; ubiquinone-7; ubiquinone-8, ubiquinone-9 (detected at < 0.3%), ubicromenol, and ubidecarenone (*Z*)-isomer.

Function in Mitochondrial Electron Transport Chain

Ubiquinone acts as a cofactor in the bioenergetic process of electron transfer in the mitochondrial electron transport chain, which is essential for adenosine triphosphate (ATP) production.[22] As an antioxidant, in its reduced form of Ubiquinol, it protects against free radical damage, functions in cell signaling and gene expression, and is capable of regenerating other antioxidants, such as tocopherol and ascorbate.[28] Due to the involvement of Ubiquinone and Ubiquinol in cellular energy production and respiration, Ubiquinol is present at higher concentrations than Ubiquinone in mitochondria-rich tissue, such as the liver, heart, kidney, and spleen, where it provides protection against oxidation in DNA and cell membrane lipids and proteins.[22,29]

Endogenously, Ubiquinone is produced via the mevalonate pathway, in either the mitochondria or Golgi apparatus, of human cells.[24] Acetyl coenzyme A (acetyl-CoA) is converted during an isopentyl-5-diphosphate (IPP)-limited cascade of 3-hydroxy-3-methylglutaryl-CoA (HMGC) catalysis to decaprenyl diphosphate synthase (DPS), which interacts with tyrosine to produce Ubiquinone. The chemical precursors for the quinone head and isoprene tail vary across species.

Photostability and Radical Formation

Ubiquinone; Ubiquinol

The relative photostability and radical formation of Ubiquinone and Ubiquinol, compared to esterified derivatives of Ubiquinol, were evaluated using artificial sunlight irradiation and singlet oxygen and superoxide assays.[30] For the photostability assay, 1 µmol/l, of ethanolic solutions of Ubiquinone, Ubiquinol, and Ubiquinol derivatives were irradiated once with artificial sunlight at 15,000 (1x) or with monochromatic light at 279, 310, 341, and 373 nm, using a multi-wavelength irradiation spectrometer in quartz cells, and residual concentrations were measured hourly for 5 h. Results from the photostability assay reveal that Ubiquinone and Ubiquinol both degraded at a faster rate than the ester derivatives (0.386 k/h and 0.327 k/h, respectively). At the wavelengths of 279 and 310 nm, degradation rates of Ubiquinone were 1.4- and 3.1-fold faster, respectively, compared to Ubiquinol rates, despite degradation rates being similar in both after irradiation. Thus, the authors surmised that Ubiquinone was affected by longer wavelengths of sunlight, while Ubiquinol was degraded around a wavelength of 310 nm. At the maximum degradation wavelength for all test solutions (279 nm), the Ubiquinol derivatives were 5.1-15-fold more photostable than Ubiquinone. For the radical formation assay, Ubiquinone and Ubiquinol ester derivatives, quinine (positive control), and sulisobenzone (negative control) were dissolved in a sodium phosphate buffer (pH = 7.4) containing 0.2% polyoxyethylene hydroxygenated castor oil, 2% dimethyl sulfoxide, and 0.1% glycerol. The solutions were treated and irradiated with artificial sunlight and ultraviolet A and/or ultraviolet B (UVA/UVB) light from a CL-1000 L 365 nm/CL-1000 M 302 nm UV Cross-linker for 3 h, and generated singlet oxygen and superoxide (ROS) levels were measured. Ubiquinone exhibited a dose-dependent generation of singlet oxygen levels when exposed to UVB irradiation, at a lower rate than quinine; Ubiquinone also generated dose-dependent superoxide when exposed to UVA irradiation, at a higher rate than quinine. Comparatively, the Ubiquinol ester derivatives generated these ROS in minimal amounts under both UV spectra.

USE

Cosmetic

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

According to 2022 VCRP survey data, Ubiquinone is reported to be used in 221 cosmetic products, of which 208 are leave-on products (Table 3).[31] The results of the concentration of use survey conducted by the Council in 2018 (and submitted to CIR in 2019) indicate that the maximum leave-on use concentration in this ingredient group is 0.05% for Ubiquinone, in body and hand products.[32] No concentrations of use were reported for Hydroxydecyl Ubiquinone or Ubiquinol in industry surveys conducted in 2018[32] and 2020[33], and no uses were reported in the VCRP or the industry survey for Disodium Ubiquinone.

Additionally, Ubiquinone has reported uses in products that may come in contact with the eyes; for example, Ubiquinone is used at up to 0.02% in eye shadows. Ubiquinone has reported use in oral hygiene products, which may lead to incidental ingestion, and bath soaps and detergents, which may lead to exposure to mucous membranes; concentration of use data were not reported in the industry survey for either of these reported uses.

None of the Ubiquinone ingredients named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[34]

Non-Cosmetic

Ubiquinone has been approved in Japan for use as a congestive heart failure drug since 1974, and as a food ingredient since 2001.[13,35] Hydroxydecyl Ubiquinone has been approved for pharmaceutical use in Japan since 1984.[36]

Ubiquinone was also listed in the *European Pharmacopeia* in 2001 and the *United States Pharmacopeia* in 2002.[15] The FDA has not approved the use of Ubiquinone as a drug; however, since the enactment of the Dietary Supplement Health and Education Act of 1994, use as a dietary supplement has expanded.[17] Ubiquinone is commonly sold as a dietary supplement under the name of coenzyme Q10, referring to its biological function and structure.[37] Although consumed at much higher doses in those with pathological conditions, coenzyme Q10 is typically sold at doses of 100 - 200 mg.[37] In many clinical trials, Ubiquinone has been tested for the treatment of heart disease, hypertension, breast cancer, Alzheimer's disease, and Parkinson's disease, and has been shown to be well tolerated at doses as high as 1200 mg/d.[4] Ubiquinol and Ubiquinone have been designated orphan drug status, in accordance with [21CFR316], and are pending FDA orphan indication approval, for the treatment of pediatric congestive heart failure (since 2004), as well as individually, for the treatment of Huntington's disease (in 2004) and mitochondrial cytopathies (since 1999).[38]

TOXICOKINETIC STUDIES

Dermal Penetration

Ubiquinone

Dermally applied Ubiquinone (amount not specified), in ethanol, was able to penetrate the stratum corneum of live porcine skin, and approximately 20% and 2% of the administered dose was found in the epidermis and dermis, respectively.[9] (No further details were provided). A solution of 1% Ubiquinone, in olive oil, was topically applied to rats (amount not specified); levels in the skin were 8 µg/g after 2 h, and 15 µg/g after 4 h.[16] A dose-response relationship was observed between the amount of Ubiquinone applied and the concentration in skin. (No further details provided).

Penetration Enhancement

Ubiquinone

Penetration of Ubiquinone, mixed in either a microemulsion formulation or a hydrophilic cream, was examined in female mammary tissue, and evaluated using a high performance liquid chromatography (HPLC) method.[39] A 20 mg dose of each formulation was applied evenly to the stratum corneum/donor compartment side of a circular piece of excised female mammary tissue (2 cm in diameter, 3.14 cm^2) mounted in Franz in vitro diffusion cells. The dermal side of the skin and the acceptor compartment were separated by filter gauze; the acceptor compartment was filled with 20 ml distilled water, and cell hydrodynamics were maintained with circulating water. The skin samples were incubated for 0.5, 2, and 6 h, after which the test formulation remaining on the skin was carefully removed by a cotton swab and three 6-mm diameter discs (0.2827 cm^2). These discs were sectioned into different slices using a cryo-microtome; the upper 10 µm slice represented the stratum corneum, 4 subsequent 20 µm slices were considered viable epidermal layer, and each of the dermis sublayers were represented by five 40 µm slices. Ubiquinone was extracted from each skin layer with 0.1 ml acetonitrile by shaking for 1 h,

and analyzed by HPLC. After 6 h, more than 90% of the applied Ubiquinone in the hydrophilic cream penetrated into viable epidermis, compared to only 60% penetration of Ubiquinone in the microemulsion formulation. The authors surmised that this effect was attributed to the lipophilic components of the microemulsion formulation (including 40% pentylene glycol), which the highly lipophilic Ubiquinone bound to. Additionally, the 2-ethyylhexyl laurate (10 %) appeared to work as a penetration enhancer for Ubiquinone in the hydrophilic cream.

Absorption, Distribution, Metabolism, and Excretion (ADME)

Ubiquinol and Ubiquinone are known to be poorly soluble in water, and therefore have limited bioavailability in the body, unless dissolved in another lipophilic substance, or consumed with a meal containing fat.[40,41] The maximum serum concentration of orally ingested Ubiquinone being captured between 6 - 8 h (T_{max}), on average, in solubilized formulations, suggests slow absorption of this large and hydrophobic molecule in the intestine.[28,42] Although structurally distinct, Ubiquinol is the predominant metabolite of Ubiquinone, and has higher bioavailability than Ubiquinone.[43] Most endogenous Ubiquinone is reduced to, and exists as, bioreactive Ubiquinol in the mitochondria, endoplasmic reticulum, lysosomes, peroxisomes, and plasma membranes of eukaryotic cells.[11,28,29,43,44]

Animal

Oral

Hydroxydecyl Ubiquinone

Hydroxydecyl Ubiquinone metabolism is characterized by oxidation of the isoprenoid side chain, β- oxidation, reduction of the quinone ring, and subsequent conjugation to form 1- or 4-phenyl sulfates or glucuronides of the hydroquinone derivatives.[36] These metabolites are generally regarded as pharmacologically inactive. In a pharmacokinetic study performed in rats and dogs, peak plasma Hydroxydecyl Ubiquinone levels in rats plateaued at 8 h and later reduced, with a half-life of 4.5 h.[36] In dogs, no Hydroxydecyl Ubiquinone level plateau occurred, and plasma levels showed a biphasic decline with half-lives of 2.2 and 15.4 h. In both species, elimination was almost complete in 48 h.

Ubiquinone

In a pharmacokinetic study, male Sprague-Dawley rats had 3.33 mg/kg bw of lipid-soluble Ubiquinone, mixed with water, delivered directly to the stomach using an oral tube.[40] Ubiquinone uptake rates peaked at 10 h after intake at 0.183 ± 0.017 µg/ml. In a 1 – yr chronic toxicity study of Ubiquinone, Wistar rats were administered 100, 300, 600, or 1200 mg/kg/d.[45] At the end of dose administration, Ubiquinone was found to exhibit a half-life range of 10.7 to 15.2 h in rats.

Other Routes

Ubiquinone

In a study examining the ratio of oxidized and reduced forms of Ubiquinone in living systems, Wistar rats were dosed with a one-time intravenous injection of solubilized Ubiquinone (10 mg/kg; solvent not provided), and 10 blood samples were taken 0.1 - 48 h after injection.[44] The blood samples were immediately centrifuged, frozen, and stored at -20 °C, for up to 2 wk. Results showed an increase in Ubiquinol, up to 89%, 1 d after injection, supporting the notion that Ubiquinol represents 90% of plasma Ubiquinone. However, 2 d after administration, serum Ubiquinone levels were still higher than at baseline.

Human

Oral

Hydroxydecyl Ubiquinone

Experimental data have shown that Hydroxydecyl Ubiquinone passes the blood-brain barrier and has a high first pass metabolism.[46] Most of the ingested dose is excreted through the kidneys as conjugates and metabolites of Hydroxydecyl Ubiquinone.

Healthy male subjects were assigned to receive a single oral dose of 150 mg (Group A: 13 men) or 750 mg (Group B: 12 men) Hydroxydecyl Ubiquinone after eating breakfast.[36,47] After a washout period of 7 d, Group A received the same dose 3 times a day, for a total of 450 mg/d, while Group B received a 750 mg dose three times a day, for a total of 2250 mg/d, for a period of 14 d. After a single oral administration of 150 or 750 mg, Hydroxydecyl Ubiquinone values peaked in plasma within 2 h on average. During repeated dosing in both groups, the pre-dose plasma concentrations were only slightly above the lower limits of quantification, indicating that there was no relevant accumulation of the test substance. The primary metabolites resulting from Hydroxydecyl Ubiquinone oxidation, which are found in free and conjugated (C) forms, are 6-(9-carboxynonyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (QS10), 6-(7-carboxyheptyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (QS8), 6-(5-carboxypentyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (QS6), and 6-(3-carboxypropyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone (QS4). After single and repeated oral administration of Hydroxydecyl Ubiquinone, most of the test substance (~ 50%) was excreted in urine as free and conjugated QS4 (40%), QS6 (6%), QS10 (< 1%), and Hydroxydecyl Ubiquinone (< 1%). At the 750 mg dose, a slightly higher proportion of free and conjugated metabolites were excreted (~ 60%), with 50% QS4, 9% QS6, 1.5% QS10, and < 1% of Hydroxydecyl Ubiquinone.

Ubiquinol

Eighty healthy men and women received either a placebo, or a 90, 150, or 300 mg oral dose of Ubiquinol, emulsified in diglycerol monooleate, rapeseed oil, soy lecithin, and beeswax, with 180 ml water, for up to 28 d.[48] The Ubiquinol half-life in subjects who received a single dose of 150 or 300 mg was estimated to be 48 h. The maximum concentration (C_{max}) of mean plasma Ubiquinol 6 h after administration was 1.88 µg/ml for the 150 mg group, and 3.19 µg/ml for the 300 mg group; the area-under-the-curve over 48 h ($AUC_{(0-48h)}$) was 74.61 µgh/ml and 91.76 µgh/ml, respectively. Plasma Ubiquinol levels showed a non-linear dose-dependent increase, reaching steady-state (2.1 - 2.8-fold increase) around 2 wk after treatment. Slight increases in eosinophil percentage, and low-density lipoprotein levels of 2 males in the 150 mg dosage group were not considered clinically significant. One subject in the 300 mg group withdrew on day 1 due to diarrhea and leukocytosis, both unrelated to the test substance; other events were mild and moderate in severity and were not of clinical significance.

Ubiquinone

Twenty healthy males were administered, either fasting or post-prandially, 60 mg lipid-soluble Ubiquinone capsules along with 200 ml of water.[40] Blood samples were collected before Ubiquinone intake and up to 24 h after intake to measure serum levels. In the fasting group, the uptake rate was 0.018 ± 0.006 µg/ml/h, while in the post-prandial group the uptake rate was 0.026 ± 0.008 µg/ml/h. According to another study, the absorption rate of Ubiquinone is about 3%, when consumed with food.[40] In a double-blind, single-dose, bioavailability study, 5 healthy subjects from both sexes consumed 120 mg lipid-soluble Ubiquinone, in capsule form, on an empty stomach before breakfast.[41] The area-under-the-curve over 10 h ($AUC_{(0-10h)}$) was determined to be 4.9 µg/ml/h. In a pharmacokinetic study, a single, oral dose of 100 mg deuterium-labelled Ubiquinone was administered to 16 healthy male subjects and exhibited an elimination half-life of 33.19 ± 5.32 h.[49]

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

The acute oral toxicity studies summarized below are described in Table 4.

The acute oral LD_{50} of Hydroxydecyl Ubiquinone was determined to be > 10,000 mg/kg in mice and male rats, and ~ 10,000 in female rats.[50,51] The acute oral LD_{50} of Ubiquinone in mice was reported to be > 4000 mg/kg,[35,52] while, in rats, it was reported to be > 2000 mg/kg.[21,35]

Short-Term, Subchronic, and Chronic Toxicity Studies

Details of the short-term, subchronic, and chronic oral toxicity studies summarized below are provided in Table 5.

In a 4-wk study, Wistar rats were administered up to 500 mg/kg/d Hydroxydecyl Ubiquinone, via gavage.[2] Dose-dependent increases in the incidence of/severity of forestomach submucosal inflammation, erosions, ulcerations, and hyperkeratosis were observed. In another study, juvenile rats dosed at up to 1000 mg/kg/d Hydroxydecyl Ubiquinone for 4 wk exhibited slight reduction of body weight in the mid- and high- dose groups, as well as an increased incidence and severity of hyaline droplet accumulation in the renal tubules, and reversible lowered bone density; the no-observed-adverse-effect level (NOAEL) was determined to be 200 mg/kg/d.[3] The non-toxic, oral dose of Hydroxydecyl Ubiquinone was determined to be 100 mg/kg/d in in a 5-wk study of Beagle dogs dosed at up to 500 mg/kg/d.[50] In two studies, 5-wk and 26-wk, using rats, the non-toxic dose for Hydroxydecyl Ubiquinone was determined to be 500 mg/kg/d and 20 mg/kg/d, respectively.[50] Gastric irritation, mainly in the form of epithelial cell hyperplasia, histopathological abnormalities in the forestomach, and a general reduction of weight, was observed in CD-1 mice which were administered up to 2000 mg/kg/d Hydroxydecyl Ubiquinone for 13 wk.[3] Wistar rats dosed with up to 1000 mg/kg/d Hydroxydecyl Ubiquinone for 26 wk exhibited mucosal thickening, hyperkeratosis, red spots, hyperplasia, necrosis, edema, and ulceration in the forestomach.[3] These effects were considered reversible and rodent-specific, and therefore of limited toxicological relevance. In a 39-wk study, Beagle dogs (number not specified) were administered 500, 750, or 1000 mg/kg/d Hydroxydecyl Ubiquinone over 39 wk, via gavage.[2,3] Aside from a dose-dependent increase in gastrointestinal disturbances, as well as reduced heart rate in all groups, mild liver hypertrophy and pulmonary hyperplasia in a few animals in the 1000 mg group, no patterns were evident and these results were not considered toxicologically significant.

Groups of 10 Sprague-Dawley rats were administered 0, 300, 600, or 1200 mg/kg/d Ubiquinol, in corn oil, via gavage, for 13 wk.[29] Statistically significant increases in aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase activity were observed in rats dosed with > 300 mg/kg Ubiquinol; prothrombin time and activation partial thromboplastin time were within in-house historical control data. Histopathological examinations revealed test-article related effects in the spleen, mesenteric lymph, and livers of females, as well as fine vacuolation of Kupffer cells in multiple females dosed with > 300 mg/kg Ubiquinol. No deaths or adverse clinical effects were observed during treatment, and the NOAEL was conservatively estimated to be 600 mg/kg/d in males and 200 mg/kg/d in females.

In a follow-up study, groups of 10 female Sprague Dawley rats were administered 0, 75, 150, 200, 300, or 1200 mg/kg/d Ubiquinol, in corn oil, via gavage, for 13 wk, with 1200 mg/kg/d Ubiquinone as a reference control.[29] No deaths or toxicologically significant changes related to the test material were observed. Groups of 3 Beagle dogs received doses of 0, 150, 300, or 600 mg/kg/d Ubiquinol, in gelatin, via gavage, for 13 wk, with 600 mg/kg/d Ubiquinone as a reference control.[29]

Soft feces were observed in the 300 and 600 mg/kg/d Ubiquinol groups, and estrus hemorrhage in 1 female each in the control and 300 mg/kg Ubiquinol groups. Vomiting was observed in all dosage groups, while statistically significant decreases of eosinophils in males in the 150 and 600 mg/kg group, and platelet counts in females in the 300 mg/kg group were observed; however, these values were not considered test article related and were within testing facility ranges. The NOAEL for Ubiquinol was determined to be 600 mg/kg/d in Beagle dogs.

In a 4-wk study, dosing cRj Wistar rats with 1000 mg/kg Ubiquinone in corn oil, via gavage, did not produce noticeable changes in overall condition, body weight gain, or food consumption, in comparison to controls.[21] Upon necropsy in the Ubiquinone-treated group, one male had enlarged adrenals, and one male had tan-colored lungs. One female from the control group, and several males and females from the Ubiquinone-treated group, also exhibited hemorrhagic and localized pulmonary lesions. In oral studies with Ubiquinone in which rats were dosed for 30 d (up to 2250 mg/kg/d, via gavage) or 5-wk (up to 1000 mg/kg/d), no mortality, noticeable changes, or toxic effects were reported.[35,52] Sprague-Dawley rats received doses of 0, 500, 1500, or 3000 mg/kg/d Ubiquinone, in 0.5% hydromethylfibrin, over 90 d.[14] Statistically significant changes in males included body weight decreases in the 1500 mg/kg group, decreases of red blood cells and hemoglobin in the 500 and 1500 mg/kg groups, white blood cell increases in all dosage groups, and triglyceride decreases in the 1500 and 3000 mg/kg groups, while, for females, ovary weights were slightly decreased in the 1500 mg/kg group, and hematocrit levels were decreased in the 1500 and 3000 mg/kg groups. Groups of 10 Sprague-Dawley rats were dosed with 1200 mg/kg/d Ubiquinone for 13 wk, and served as a reference control.[29] Two males and 3 females exhibited a yellow focus in the lung, mild granuloma of the liver was present in females, and an accumulation of foam cells in lung alveoli was observed in 2 males and 3 females. In another 13-wk study of Sprague-Dawley rats, the NOAEL for Ubiquinone was determined to be > 1200 mg/kg/d.[17] In a 52-wk study, groups of 19 Sprague-Dawley rats/sex were dosed with up to 1200 mg/kg/d of Ubiquinone.[45] One female and 3 males from the 600 mg/kg/d group died during weeks 33, 38, 48, and 52. One male from the 1200 mg/kg/d group died of malignant lymphoma during week 33. Ubiquinone accumulated in the liver during dosing; however, levels returned to pretreatment levels in the recovery animals within 10 d of stopping treatment. In white rabbits, no toxic effects and no microscopic or gross lesions were found in animals dosed for 23 d with up to 600 mg/kg Ubiquinone.[35] Groups of 3 Beagle dogs dosed with 600 mg/kg/d Ubiquinone in corn oil for 13 wk (as a reference control) exhibited soft feces with traces of the test article, vomiting, and a statistically significant increase in neutrophils.[29] A dark red focus of the heart was observed in 1 male, while 1 male and 1 female exhibited an enlarged liver. Opacity of the posterior lens capsule was observed in 1 female, which also occurred in 1 male and 1 female from the control group. Groups of 4 Beagle dogs, which were dosed with 1200 or 1800 mg/kg/d Ubiquinone in gelatin capsules, for 39 wk, had unabsorbed Ubiquinone in stool, and vomiting occurred in all dogs exposed to the highest dose.[53] No deaths occurred during treatment. A white focus was observed in the lungs of one control female dog, and, one male dog from the 1200 mg/kg/d group. These gross pathological findings were not considered toxicologically significant.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Details of the developmental and reproductive toxicity studies summarized below are provided in Table 6.

No adverse effects on fertility or reproductive performance were observed in a study in which male and female Wistar rats were dosed orally with up to 500 mg/kg bw Hydroxydecyl Ubiquinone prior to mating, during gestation, and until day 22 post-partum. [50] In several other studies, no statistically significant adverse effects upon reproductive performance or fetal development were seen in rats dosed at up to 1000 mg/kg/d Hydroxydecyl Ubiquinone, although a higher incidence of post-implantation loss was reported in some studies (details not provided).[2,3] The NOAELs, based on body surface area comparisons, were determined to be up to 1000 mg/kg/d for embryofetal development, and 500 mg/kg/d and 1000 mg/kg/d, for male and female fertility, respectively.[3] Rabbits, dosed at up to 150 mg/kg/d Hydroxydecyl Ubiquinone and observed for teratological abnormalities, displayed chromaturia in the highest dosage group.[2] In Japanese rabbits dosed at up to 500 mg/kg/d Hydroxydecyl Ubiquinone, one abortion was observed in the highest dosage group, but was not considered significant due to the spontaneous abortion rate in the animal strain; no statistically significant embryofetal differences were reported between controls and treated groups.[3] No treatment-related changes were observed in the F_1 generation, or in the dams, of rats dosed at up to 500 mg/kg/d Hydroxydecyl Ubiquinone.[2,3] The NOAEL for rat pup development was determined to be 500 mg/kg/d Hydroxydecyl Ubiquinone.[3]

Treatment with Ubiquinone had no effect on fetal death, weight, or postnatal toxicity in primigravid mice (strain and number not specified) dosed at up to 600 mg/kg/d, from day 7 to day 13 of gestation.[35] Groups of 10 male mice were given up to 10,000 mg/kg bw Ubiquinone, via gavage, for 5 d, followed by a 35-d latency period, to test for defects in sperm morphology.[52] No significant differences were found in the incidence of sperm abnormalities between Ubiquinone-treated mice and the negative controls (treated with corn oil). Except for an increase in seminiferous epithelium heights, no biochemical, histological, or morphological differences were observed between 8 male Wistar rats dosed at 10 mg/kg bw/d Ubiquinone for 14 d and negative control and vehicle control groups.[54] Treatment with Ubiquinone had no effect on fetal death, weight, or postnatal activity in primigravid rats dosed at up to 600 mg/kg/d, from day 9 to day 15 of gestation.[35]

GENOTOXICITY

Details of the genotoxicity studies summarized below are described in Table 7.

Positive mutagenic responses in L5178Y TK +/- mouse lymphoma cells tested with Hydroxydecyl Ubiquinone were not reproducible, dose-related, or statistically significant.[3] In a chromosomal aberration test with Hydroxydecyl Ubiquinone in human peripheral lymphocytes, positive results were attributed to the redox properties of test substance, and the test substance was not considered clastogenic.[3] Ubiquinol was not genotoxic, with or without metabolic activation, in an Ames test at up to 5000 µg/plate, or in a chromosomal aberration test using Chinese hamster lung (CHL/IU) cells at up to 5000 µg/ml.[43] Similarly, Ubiquinone was not genotoxic with or without metabolic activation in multiple Ames tests, at up to 5000 µg/plate, or in chromosomal aberration tests using CHL/IU cells at up to 5000 µg/ml.[15,18,35,52,55] In vivo, no genotoxicity was observed in several micronucleus tests with Hydroxydecyl Ubiquinone, at up to 5000 mg/kg/d (in mice),[2] Ubiquinol, at up to 2000 mg/kg/d (in rats),[43] or Ubiquinone, at up to 10,000 mg/kg/d (in mice).[35,52]

CARCINOGENICITY STUDIES

Hydroxydecyl Ubiquinone

ICR mice (number not specified) were administered a daily dose of 650, 1280, or 2000 mg/kg Hydroxydecyl Ubiquinone via diet for 103 wk.[3] Dosing had no effect on mortality/survival rates. Treatment with Hydroxydecyl Ubiquinone did not influence the incidence, time of onset, location, size, or multiplicity of palpable masses. No increase in the incidence of forestomach tumors was observed. Mice in the mid- and high-dose groups exhibited a low incidence of benign tumors, including hemangioma and leiomyoma, and malignant sarcomas, including fibrosarcoma, leiomyosarcoma, and endometrial sarcoma. These incidences were within the historical ranges of the testing facility for this mouse strain.

Similarly, Sprague-Dawley rats (number not specified) were administered a daily dose of 500 or 1000 mg/kg Hydroxydecyl Ubiquinone via diet for 104 wk.[3] Dosing had no effect on mortality/survival rates. Gross observations of yellow, thickened mucosa correlated with an increased incidence of squamous cell hyperkeratosis; gastritis, forestomach erosions, and basal cell hyperplasia were also observed. Due to the forestomach being a rodent-specific organ, the researchers stated that these findings were not considered clinically relevant. Incidences of lung alveolar carcinoma, adrenal carcinomas, liver and pancreas sarcomas, squamous cell papillomas, thyroid follicular cell carcinomas, and thyroid C-cell adenomas were also observed. (Details on occurrence by dosage group not provided). The researchers stated that the neoplasms were only reported in males, and that the incidences of these neoplasms were below the spontaneous incidence rate for this strain and were without a dose-dependent relationship.

OTHER RELEVANT STUDIES

Depigmentation

Ubiquinone

Vitiligo, a skin disorder characterized by depigmentation, is known to result from oxidative/nitrative stress in the epidermis and body.[56] Fifteen previously unaffected patients presented with vitiligo after daily use of over-the-counter Ubiquinone-containing skin preparations (concentrations not reported). Clinicians suspected that a small percentage of the Ubiquinone had oxidized to yield hydrogen peroxide, a skin-bleaching agent, causing depigmentation in susceptible individuals. Chemical reduction of the epidermal hydrogen peroxide was achieved by treating patients with topical application of narrowband, mid-wavelength UV (UVB)-activated propseudocatalase cream (PC-KUS), resulting in eventual repigmentation. The authors concluded that the concentration of Ubiquinone use in cosmetics or supplements should be carefully considered, especially in individuals who are susceptible to reactive-oxygen-species (ROS)-triggered-vitiligo.

The effect of Ubiquinone was investigated upon long-wavelength UV (UVA)-irradiated cultured human keratinocyte (HaCaT) cells and murine melanoma (B16F10) cells exposed to alpha-melanocyte stimulating hormone (α-MSH).[57] In preparation for UVA irradiation, HaCaT cells were pretreated with either 1 - 4 µM Ubiquinone in 0.1% propanol, or only 0.1% propanol, for 24 h. Cells were washed with phosphate-buffered saline (PBS), resuspended in Dulbecco's modified Eagle medium containing 10% fetal bovine serum, and then exposed to UVA radiation at doses of 5-15 J/cm^2, λ_{max} 365 nm, for 30 to 90 min. In contrast to an increase of ROS normally seen in UVA-exposed keratinocytes, Ubiquinone pretreatment was shown to suppress ROS-mediated α-MSH production, thus inhibiting melanogenesis, even in un-irradiated HaCaT cells. Concomitantly, B16F10 cells were pretreated with 1 - 2 µM of Ubiquinone, with or without exogenous α-MSH, for 2 h. The cells were then incubated for up to 72 h, washed twice with PBS, solubilized in 1 N sodium hydroxide, and analyzed for cell melanin content.[57] In spite of α-MSH -stimulation, Ubiquinone was shown to inhibit melanogenesis associated transcription factor expression.

Zebrafish embryos (9 h post-fertilization) were treated with 2 µM of Ubiquinone for 72 h and observed for depigmentation; a comparison was made with controls that were treated with 0.2 mmol/l 1-phenyl-2-thiourea or propanol.[57] Zebrafish body pigmentation remarkably decreased by 56% at 48 h and 66% at 72 h, when exposed to Ubiquinone.

Mouse melanoma (B16) cells were measured for melanin content and tyrosinase (a key enzyme for melanin synthesis) activity after treatment with 0.5, 1, or 2 µM Ubiquinone, or sodium ascorbate, for 72 h.[58] Ubiquinone treatment resulted in

decreased melanin content in a dose-dependent manner, which corresponded to inhibited tyrosinase activity in treated cells. The authors noted that exposure to 2 µM Ubiquinone showed similar inhibitory effects as that of 0.5 mM ascorbic acid.

Cytotoxicity

Ubiquinone

In a melanin synthesis study, the cell lines were first tested for viability using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) colorimetric assay.[57] Murine melanoma B16F10 cells (1×10^5 cells/well in 24-well plates) were exposed to 1-2 µM Ubiquinone for 24 h. One ml of 0.5 mg/ml MTT in PBS were then added to each well and incubated at room temperature for 1 h. After incubation, equal volumes of 0.8 ml dimethyl sulfoxide were added to dissolve the MTT formazan crystals. Measurements were taken 24, 48, and 72 h after exposure, at a wavelength of 570 nm using an enzyme-linked immunosorbent assay microplate reader. Ubiquinone did not exhibit cytotoxic effects on B16F10 cells under these study conditions.

Miscellaneous Biological Effects

Hydroxydecyl Ubiquinone

Vitamin K1 is a structurally similar molecule that has the potential to sensitize individuals to Hydroxydecyl Ubiquinone, to cross-react, or cause allergenicity to Hydroxydecyl Ubiquinone.[16]

Ubiquinone

Mevalonic acid is the chemical precursor to both Ubiquinone and cholesterol, the latter of which requires HMGC reductase (HMGCR) to be formed.[24] Oral consumption of Ubiquinone is a contraindication to statin, cholesterol-lowering, or anticoagulant drugs, because it targets HMGCR inhibitors, and may have vitamin K-like procoagulant effects .[59,60] In a 4-wk, prospective placebo-controlled trial, no significant changes in blood-clotting factors, such as the international normalized ratio and prothrombin time, were observed in 24 patients taking warfarin and 100 mg Ubiquinone.[61] However, in a 16-wk longitudinal study, in which subjects took an unspecified amount of Ubiquinone and an average weekly dose of 33.5 mg warfarin, there was a statistically significant association between bleeding events and the concomitant intake of Ubiquinone and warfarin (OR 3.91, 95% CI: 2.09 - 7.3).[62] These discrepancies may be attributed to differences in test substances, higher dosing, risk in the elderly, and those at risk for cardiovascular disease and stroke.[16,60,63]

DERMAL IRRITATION AND SENSITIZATION STUDIES

Irritation

Human

Ubiquinone

A patch test was performed in 50 subjects, using an undiluted test substance containing 1% Ubiquinone, 5% tocopherol acetate, and 94% squalane.[64] Thirty of the subjects were healthy volunteers, 6 had eczema, and 14 had sensitive skin; subjects were aged 18-65, and none reported to have allergies. The test substance was applied in square test chambers (Haye's) to the back for 48 h (occlusion not specified). Sodium dodecyl sulfate (SDS; 1%) and water were used as positive and negative controls, respectively. Treatment sites were assessed for erythema, scaling and fissure formation using 5 point visual scores at 30 min and 24 h after patch removal. Average scores for all 3 evaluation criteria were 0.0 at both time points, and the 1% Ubiquinone formulation was deemed non-irritating.

Sensitization

Animal

Ubiquinone

Ubiquinone, of unknown purity, was tested in groups of 10 Crj:Hartley guinea pigs in a maximization test, in a manner similar to OECD TG 406.[64] During the induction phase, 1.25% Ubiquinone, in 0.5% aqueous methyl cellulose, was injected intradermally, while 6.3% Ubiquinone in petrolatum was dermally applied (number of applications and induction period not stated). During challenge, Ubiquinone was dermally applied at 6.3%, and readings were scored at 24 and 72 h. Physiological saline served as the negative control, while 0.1% 2,4-dintrochlorobenzene (DNCB) in 10% sodium dodecyl sulfate served as positive control; 5 animals were used per control group. No skin reactions were observed in the test and negative control groups at the 24 and 72 h readings. A few cases of very slight erythema were observed immediately after patch removal, but regressed within 24 h. Well-defined erythema was observed in all animals after challenge with DNCB. Hence, Ubiquinone at a concentration of 6.3% was not a skin irritant or sensitizer.

Human

Hydroxydecyl Ubiquinone

A cream containing 0.01% Hydroxydecyl Ubiquinone was tested in a human repeat insult patch test (HRIPT) in 107 subjects, 50 of which reported having sensitive skin.[65] The test material was applied, undiluted, using semi-occlusive patches to the upper back for 24 h, 3 times a week, for a total of 9 applications, made over a 3-wk induction period. The test sites were graded two times a week, 24 h after removal of test patches, and were scored on a 5-point scoring system, including: 0 for no visible skin reaction, ± for barely perceptible erythema, 1+ for mild erythema, 2+ for well-defined erythema, 3+ for erythema and edema, and 4+ for erythema and edema with vesiculation. After a 2-wk period, a 24-h challenge application was made to a previously untreated site in the same manner as in the induction applications, and reactions were scored at 24, 48, and 72 h. The only visible reactions included 5 subjects exhibiting barely perceptible erythema (±) once during induction. The researchers concluded that the test material did not demonstrate clinically significant dermal irritation or sensitization.

Ubiquinone

An HRIPT was performed in 50 subjects with a test substance containing 1% Ubiquinone, 5% tocopherol acetate, and 94% squalane.[64] Twenty-four of the subjects were healthy volunteers, 8 had eczema, and 18 had sensitive skin. The test substance was applied undiluted, under occlusion, in square test chambers (Haye's) to the back for a total of 9, 24-h applications, made over a 3-wk induction period. After a 2-wk period, chambers filled with the test article were applied to both the previously treated site and an untreated site to test for possible sensitization. Treatment sites were assessed for erythema, scaling and fissure formation using 5-point visual scores at 24 h (30 min after patch removal), 48 h, 72 h, and 96 h after patch application. Average scores for all 3 evaluation criteria were 0.0 at all time points for both previously treated and untreated sites, and the 1% Ubiquinone formulation was deemed non-irritating and non-sensitizing.

OCULAR IRRITATION STUDIES

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

CLINICAL STUDIES

Numerous studies have investigated the efficacy and safety of Hydroxydecyl Ubiquinone, Ubiquinol, and Ubiquinone use for the treatment of cardiovascular disease,[66] inflammation and aging,[67,68] diabetes,[69-71] cancer,[72] and muscular and neurogenerative diseases.[2,3,36,73,74] Among higher doses of Ubiquinone tested for the treatment of neurodegenerative diseases, 1200 mg Ubiquinone was established as safe and well tolerated in a 16-month trial of 80 patients with early Parkinson's disease.[4,73] Hydroxydecyl Ubiquinone and Ubiquinone are being studied for their use as novel therapeutic targets in carcinogenesis, owing to mevalonate pathway involvement in anti-proliferative effects and cell survival, respectively.[75,76]

Multiple studies have explored the hypotensive potential of Ubiquinone, with conflicting results.[77-83] Although study findings can vary, the hypotensive potential of Ubiquinone is generally attributed to its improvement of blood lipid profiles, and endothelial function, both of which affect cardiovascular health and hypertension.[84]

Ubiquinone

The safety and tolerability of 98% Ubiquinone was tested in groups of 11 healthy men and women (only 22 men in the highest dosage group) for 4 wk at doses of 0, 300, 600, and 900 mg/d in a double-blind, placebo-controlled trial.[85] The test substance was in capsule form, containing 150 mg Ubiquinone and several excipients. Placebo capsules contained only safflower oil. Each subject took 3 capsules twice a day, in the morning and evening after meals. A physical examination, hematological tests, serum chemistry examination, and urinalysis were performed before, after 4 wk of administration, and 2 wk after study completion. Symptoms of the common cold and gastrointestinal effects were observed in all dosage groups, with some vomiting (number unknown) in the 900 mg group. Differences in symptom frequency, hematology, blood biochemistry, and urinalysis were not dose-related or considered clinically significant, demonstrating the safety of Ubiquinone in healthy adults, at an intake of up to 900 mg/d.

Case Reports

A 47-yr-old woman had a cream containing 0.5 % Hydroxydecyl Ubiquinone applied as part of a facial treatment in a salon.[86] Within 24 h, she developed severe edematous and vesicular dermatitis of the face, ears, and neck. Lesions were treated with a 2-wk course of oral prednisone. Patch test readings with the North American Contact Dermatitis Group standard test series were taken on day 2 and day 3, and only showed a positive rating to the cream of (++) on day 2 and (+++) on day 4. Individual ingredients were then premixed with petrolatum at finished product concentration and patch-tested. Second- and fourth-day readings showed a (++) and (+++) reaction, respectively, to 0.5% Hydroxydecyl Ubiquinone. No reaction was observed in 20 control subjects tested with the same ingredient.

In response to a 2-d prior application of a cream containing 0.5% Hydroxydecyl Ubiquinone, a 43-yr-old woman developed an itchy eruption.[16] Topical applications of corticosteroid were used for 5 d to resolve the dermatitis. The patient

had positive patch-test reactions to 0.5% Hydroxydecyl Ubiquinone and the cream. In a similar case report, a 50-yr-old woman showed an acute onset of symptoms, with heat and tightness, 4 h after application of a 0.5% Hydroxydecyl Ubiquinone cream, followed by erythema and periorbital swelling the next day.[16] Patch testing showed positive reaction to 0.5% Hydroxydecyl Ubiquinone.

A 38-yr-old woman presented with a red, itchy, burning, swollen face after the second application of a facial cream (amount not specified) containing 1% Hydroxydecyl Ubiquinone.[87] The patient had a history of guttate psoriasis, but no background of atopic eczema or contact allergy. Periorbital eruption and infraorbital edema were clinically diagnosed as allergic contact dermatitis, and were treated with 1% hydrocortisone ointment and aqueous cream BP, a hydrocarbon-based emollient emulsion, applied twice daily. The eruption resolved, with desquamation, over 4 weeks. A 2-d patch test was conducted with allergens found in the British Contact Dermatitis Society baseline series, cosmetic and facial series, fragrances, and the patient's own products. Positive reactions readings were observed on day 2, 4, and 7 with nickel sulfate 0.5% (++), propolis 10% (++), and the facial cream (+++). Further patch testing was done using the individual constituents of the product provided by the manufacturer. These constituents were applied for 2 d using IQ Ultra chambers and readings were taken at day 2, 4, and 7. A positive reaction to 1% Hydroxydecyl Ubiquinone in a vehicle (unknown) was observed at day 4 and day 7.

SUMMARY

The safety of Disodium Ubiquinone, Hydroxydecyl Ubiquinone, Ubiquinol, and Ubiquinone, as used in cosmetics, is reviewed in this safety assessment. These ingredients have been grouped together because they share a 2,5-cyclohexadiene-1,4-dione core, with various alkyl chain substituents at the 2-position of the cyclohexadiene, to comprise the salts or metabolites, thereof. These ingredients are all reported to function in cosmetics as antioxidants, and some are also reported to function as skin protectants, skin conditioning agents, and/or hair conditioning agents.

Ubiquinone was shown to photodegrade in response to a 6 - h exposure to artificial sunlight at a faster rate, and to produce higher levels of singlet oxygen and superoxide in response to 3 - h, UVA/UVB irradiation, in comparison to ester derivatives of Ubiquinol.

According to 2022 VCRP data, Ubiquinone has the highest reported use amongst these ingredients, in 221 cosmetic products, of which 208 are leave-on formulations. The results of the 2018 concentration of use survey conducted by the Council indicate that the maximum leave-on use concentration in this ingredient group is 0.05% Ubiquinone in body and hand products. No use concentrations were reported in industry surveys of Hydroxydecyl Ubiquinone and Ubiquinol, and, according to VCRP and industry data, Disodium Ubiquinone is not currently in use in cosmetic products.

Dermally applied Ubiquinone, in ethanol, was able to penetrate the stratum corneum of porcine skin, at approximately 20% in the epidermis and 2% in the dermis. In an HPLC analysis of the penetration of 2 formulations containing Ubiquinone in excised female mammary tissue, 90% of the Ubiquinone dissolved in a hydrophilic cream was shown to penetrate to the viable epidermis, compared to 60% penetration of Ubiquinone in a microemulsion formulation. A solution of 1% Ubiquinone, in olive oil, was found to reach concentrations of 8 µg/g after 2 h, and 15 µg/g after 4 h, when applied to live rat skin. The average T_{max} of orally ingested, solubilized, Ubiquinone being captured between 6 - 8 h (T_{max}), suggests slow absorption and limited bioavailability in the intestine. In pharmacokinetic studies, rat plasma levels for Hydroxydecyl Ubiquinone plateaued at 8 h and exhibited a half-life of 4.5 h, while dog plasma levels had a biphasic decline with half-lives of 2.2 and 15.4 h. In both species, elimination was almost complete in 48 h. The range of Ubiquinone half-life in Wistar rats administered up to 1200 mg/kg/d was 10.7 to 15.2 h. After a one-time intravenous injection of 10 mg/kg solubilized Ubiquinone, plasma Ubiquinol levels had increased in Wistar rats by 89%, within one day of injection.

Twenty-five healthy male subjects were assigned to receive single doses of 450 or 750 mg/d Hydroxydecyl Ubiquinone, or repeated doses of up to 2250 mg/d Hydroxydecyl Ubiquinone, for 14 d, after eating breakfast. A slightly higher proportion of free and conjugated metabolites were excreted in the 750 mg group. The half-life of Ubiquinol was estimated to be 48 h in 80 healthy subjects who received a single dose of 150 or 300 mg; the Ubiquinol $AUC_{(0\text{-}48h)}$ was 74.61 µgh/ml and 91.76 µgh/ml, for the 150 and 300 mg groups. Twenty healthy males were administered, either fasting or post-prandially, 60 mg lipid-soluble Ubiquinone capsules along with 200 ml of water. In the fasting group, the uptake rate was 0.018 ± 0.006 µg/ml/h, while in the post-prandial group the uptake rate was 0.026 ± 0.008 µg/ml/h. The $AUC_{(0\text{-}10h)}$ was determined to be 4.9 µg/ml/h, in a single dose study, in which 120 mg lipid-soluble Ubiquinone was administered to 10 healthy subjects. In a pharmacokinetic study, a single, oral dose of 100 mg deuterium-labelled Ubiquinone was administered to 16 healthy male subjects and exhibited an elimination half-life of 33.19 ± 5.32 h.

The acute oral LD_{50} of Hydroxydecyl Ubiquinone was determined to be > 10,000 mg/kg in mice and male rats, and ~ 10,000 mg/kg in female rats. The acute oral LD_{50} of Ubiquinone was reported to be > 4000 mg/kg in mice, while the LD_{50} was > 2000 mg/kg in rats.

Wistar rats administered up to 500 mg/kg/d Hydroxydecyl Ubiquinone for 4 wk, exhibited a dose-dependent increase in the incidence and severity of forestomach mucosal inflammation, erosions, ulcerations, and hyperkeratosis. In another study, juvenile rats dosed at up to 1000 mg/kg/d Hydroxydecyl Ubiquinone for 4 wk, exhibited slight reduction of body

weight in the mid- and high-dose groups, as well as an increased incidence and severity of hyaline droplet accumulation in the renal tubules, and reversible lowered bone density; the NOAEL was determined to be 200 mg/kg/d. The non-toxic dose of Hydroxydecyl Ubiquinone was determined to be 100 mg/kg/d in Beagle dogs, administered with up to 500 mg/kg/d over 5 wk. The highest non-toxic, oral Hydroxydecyl Ubiquinone doses were determined to be 500 mg/kg/d and 20 mg/kg/d, in a 5-wk, and a 26-wk study of rats, respectively. Gastric irritation, forestomach histopathology, and a general reduction of weight was observed in CD-1 mice administered 2000 mg/kg/d Hydroxydecyl Ubiquinone for 13 wk. In a 26-wk study of Wistar rats administered up to 1000 mg/kg/d Hydroxydecyl Ubiquinone, mucosal thickening, hyperkeratosis, red spots, hyperplasia, necrosis, edema, and ulceration observed in the forestomach were reversible and of limited toxicological relevance. Beagle dogs administered 500, 750, or 1000 mg/kg/d Hydroxydecyl Ubiquinone for 39 wk exhibited gastrointestinal disturbances and reduced heart rate across all groups, as well as mild liver hypertrophy and pulmonary hyperplasia in a few animals in the 1000 mg group. These results were not considered statistically significant.

Groups of 10 Sprague-Dawley rats were dosed at up to 1200 mg/kg/d Ubiquinol. Fine vacuolation of the hepatic Kupffer cells and statistically significant increases in hepatic blood chemistry enzymes, were observed in rats dosed with ≥ 300 mg/kg Ubiquinol. No deaths, or adverse clinical effects were observed, and the NOAELs were conservatively estimated to be 600 mg/kg/d in males, and 200 mg/kg/d in females. In a follow-up study, groups of 10 female Sprague-Dawley rats were dosed at up to 1200 mg/kg/d, and no toxicologically significant changes related to the test material were observed. Groups of 3 Beagle dogs were dosed at up to 600 mg/kg/d Ubiquinol for 13 wk. Soft feces were observed in the 300 and 600 mg/kg/d Ubiquinol groups, and estrus hemorrhage in 1 female each in the control and 300 mg Ubiquinol groups. The NOAEL for Ubiquinol was determined to be 600 mg/kg/d in male rats, 200 mg/kg/d in female rats, and 600 mg/kg/d in Beagle dogs.

No noticeable changes in overall condition, body weight gain, or food consumption, were seen in cRj Wistar rats, in comparison to controls, during 4-wk treatment with 1000 mg/kg/d Ubiquinone. Upon necropsy, a few abnormalities were observed in the adrenals and lungs of several treated male and female rats in the Ubiquinone-treated group. No mortality or toxicity occurred in rats dosed at up to 2250 mg/kg/d Ubiquinone. Groups of 15 Sprague-Dawley rats which were dosed at up to 3000 mg/kg/d over 90 d exhibited statistically significant changes in hematological markers and ovary weights in the two highest dosage groups. Groups of 10 Sprague-Dawley rats dosed with 1200 mg/kg/d Ubiquinone for 13 wk, showed a statistically significant higher food consumption in females, mild granuloma of the liver in females, as well as yellow lung foci and accumulation of foam cells in lung alveoli in 2 males and 3 females. The NOAEL was determined to be ≥ 1200 mg/kg/d in a 13-wk study of Sprague-Dawley rats. In a 52-wk study, one female and three male Sprague-Dawley rats died from the 600 mg/kg/d group, and one male from the 1200 mg/kg/d group died of malignant lymphoma. No toxic effects and microscopic, or gross, pathologies were found in white rabbits dosed for 23 d with up to 600 mg/kg Ubiquinone. Groups of 3 Beagle dogs dosed with 600 mg/kg/d Ubiquinone for 13 wk, exhibited soft feces with traces of test article, vomiting, and a statistically significant increase in neutrophils. A dark red focus of the heart was observed in 1 male, while 1 male and 1 female exhibited enlarged livers; opacity of the posterior lens capsule in 1 Ubiquinone-treated female was observed, which also occurred in control group animals. No deaths occurred during the treatment of Beagle dogs dosed at up to 1800 mg/kg/d for 39 wk, and gross pathological findings were not considered toxicologically significant.

No adverse effects on fertility or reproductive performance were observed in a study in which male and female Wistar rats were dosed orally with up to 500 mg/kg bw Hydroxydecyl Ubiquinone prior to mating, during gestation, and until day 22 post-partum. The NOAELs for embryofetal development, and male and female fertility were determined to be 500 mg/kg/d and 1000 mg/kg/d. In rabbits dosed at up to 500 mg/kg/d Hydroxydecyl Ubiquinone, one abortion was observed in the highest dosage group, but was considered spontaneous, and not significant. In peri/post-natal studies of rats, no treatment-related changes were observed in dams, and the NOAEL for pup development was determined to be 500 mg/kg/d Hydroxydecyl Ubiquinone. No effect on fetal death, weight, or postnatal toxicity was observed in primigravid mice dosed with up to 600 mg/kg/d Ubiquinone, from day 7 to day 13 of gestation. No statistically significant differences were found in the incidence of sperm abnormalities in male mice dosed with up to 10,000 mg/kg bw Ubiquinone for 5 d, via gavage, and were assessed after a 35-d observation period, compared to corn-oil-treated controls. Except for an increase in seminiferous epithelium heights, no biochemical, histological, or morphological differences were observed between 8 male Wistar rats dosed at 10 mg/kg bw/d Ubiquinone for 14 d, and negative control and vehicle control groups. Treatment with Ubiquinone had no effect on fetal death, weight, or postnatal activity in primigravid rats dosed at up to 600 mg/kg/d, from day 9 to day 15 of gestation.

Hydroxydecyl Ubiquinone exhibited a positive mutagenic response in a mutation induction test with L5178Y TK +/- mouse lymphoma cells and a chromosomal aberration test with human peripheral lymphocytes; however, these results were attributed to the redox properties of the test substance and were not considered significant. Ubiquinol and Ubiquinone were not genotoxic, with or without metabolic activation, in multiple Ames test or chromosomal aberration tests at up to 5000 µg/plate. No genotoxicity was observed in several in vivo micronucleus tests, with Hydroxydecyl Ubiquinone, at up to 5000 mg/kg/d in mice, Ubiquinol, at up to 2000 mg/kg/d in Sprague-Dawley rats, or Ubiquinone, at up to 10,000 mg/kg/d, in mice.

ICR mice fed a daily dose of up to 2000 mg/kg Hydroxydecyl Ubiquinone via diet for 103 wk, exhibited a low incidence of benign tumors in the mid- and high-dose groups; the incidence was within the expected range for this mouse strain. Adverse forestomach effects and the incidence of various malignancies were observed in Sprague-Dawley rats fed a

daily dose of up to 1000 mg/kg Hydroxydecyl Ubiquinone via diet for 104 wk. The incidence of these neoplasms was lower than expected for this strain, and only in males.

Vitiligo-susceptible individuals experienced depigmentation when exposed to skin preparations containing oxidized Ubiquinone, ostensibly due to the bleaching effects of an oxidation byproduct, hydrogen peroxide. Ubiquinone was shown to inhibit melanogenesis in UVA-irradiated HaCaT and B16F10 cells stimulated with α-MSH. Zebrafish embryos treated with 2 μM of Ubiquinone post-fertilization for 72 h exhibited up to a 66% reduction in body pigmentation, compared to controls treated with 0.1% propanol. Decreased melanin content in B16 cells treated with up to 2 μM Ubiquinone for 72 h corresponded with inhibited tyrosinase activity. In a melanin synthesis study, B16F10 cells were tested for viability in an MTT assay. Cytotoxic effects were not observed after 24 h exposure to 1 - 2 μM Ubiquinone.

Due to structural similarities, vitamin K has the potential to cross-react, cause allergenicity, or sensitization, to Hydroxydecyl Ubiquinone. Clinically, Hydroxydecyl Ubiquinone, Ubiquinol, and Ubiquinone have been tested for safety and efficacy in the treatment of various diseases at doses up to 1200 mg. The safety and tolerability of 98% Ubiquinone was tested in groups of 11 healthy men and women (only 22 men in the highest dosage group) for 4 wk at doses of 0, 300, 600, and 900 mg/d in a double-blind, placebo-controlled trial. Symptoms of the common cold and gastrointestinal effects were observed in all dosage groups, with some vomiting (number unknown) in the 900 mg group. Differences in symptom frequency, hematology, blood biochemistry, and urinalysis were not dose-related or considered clinically significant; Ubiquinone intake was deemed safe at doses of up to 900 mg/d in healthy adults.

A 48 - h patch test was performed (occlusion not specified) in 50 subjects, using an undiluted test substance containing 1% Ubiquinone, 5% tocopherol acetate, and 94% squalene. After patch removal, test sites were evaluated for erythema, scaling, and fissure formation at 30 min and 24 h after patch removal. Average scores were 0.0 at all time points for all 3 evaluation criteria, and the 1% Ubiquinone formulation was deemed non-irritating. In a guinea pig maximization test, a test material containing 1.25% Ubiquinone in 0.5 % aqueous methyl cellulose was injected intradermally, and 6.3% Ubiquinone in petrolatum was applied dermally, during induction, to groups of 10 Crj:Hartley guinea pigs. During challenge, 6.3% Ubiquinone was dermally applied, and readings were scored at 24 and 72 h. Slight erythema, occurring immediately after patch removal, regressed within 24 h; 6.3% Ubiquinone was not a skin irritant or sensitizer. A cream containing 0.01% Hydroxydecyl Ubiquinone was tested neat in a semi-occlusive HRIPT completed in 107 subjects, 50 of which reported having sensitive skin. The researchers determined that the test material did not demonstrate clinically significant dermal irritation or sensitization. An occlusive HRIPT of a test substance containing 1% Ubiquinone, applied neat, was performed in 50 subjects, of which 18 reported having sensitive skin. Average scores were 0.0 for all 3 evaluation criteria and the 1% Ubiquinone formulation was deemed non-irritating and non-sensitizing.

Four women presented with facial eruptions and sensitization reactions in response to application of creams containing up to 1% Hydroxydecyl Ubiquinone. Positive patch-test reactions occurred for 0.5% and 1.0% Hydroxydecyl Ubiquinone.

DISCUSSION

This assessment reviews the safety of 4 Ubiquinone ingredients as used in cosmetic formulations. The Panel concluded that these 4 Ubiquinone ingredients are safe in the present practices of use and concentrations described in this safety assessment.

The Panel stated that although Hydroxydecyl Ubiquinone is a synthetic analog of Ubiquinone with a shorter chain structure, it could reasonably be grouped with the other ingredients because of its shared bioactive ring structure. The Panel also discussed that the inefficiency and expense of extracting these ingredients from biological tissues would most likely make either chemical synthesis, or, microbial fermentation, the primary means of production. In the absence of method of manufacture, impurities, and concentration of use data for Hydroxydecyl Ubiquinone and Ubiquinol, the Panel's safety concerns were mitigated due to the natural occurrence of Ubiquinone in living tissues, use as a food additive and nutritional supplement, as well as the abundance of negative results for developmental and genetic toxicity, and sensitization.

Data included in this report indicate that Ubiquinone may have a skin lightening effect. The Panel noted that skin lightening is considered to be a drug effect and should not occur during the use of cosmetic products. Because of that caveat, and based on the low concentrations of use of these ingredients in cosmetic products, the Panel's knowledge of the mechanism of action (i.e., inhibition of tyrosinase activity resulting in reduced melanin synthesis), the results of the in vitro studies of Ubiquinone, and clinical experience, concern for this effect in cosmetics was mitigated. Nevertheless, cosmetic formulators should only use these Ubiquinone ingredients in products in a manner that does not cause depigmentation.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that the following 4 Ubiquinone ingredients are safe in cosmetics in the present practices of use and concentrations described in the safety assessment:

Disodium Ubiquinone*	Ubiquinol
Hydroxydecyl Ubiquinone**	Ubiquinone

*Not reported to be in current use. Were this ingredient not in current use to be used in the future, the expectation is that it would be used in product categories and at concentrations comparable to others in this group.

**Maximum concentrations of use not reported. The expectation is that this ingredient would be used in product categories and at concentrations comparable to others in this group.

TABLES

Table 1. Definitions, reported cosmetic functions, and chemical structures of ingredients in this report[1,CIR Staff]

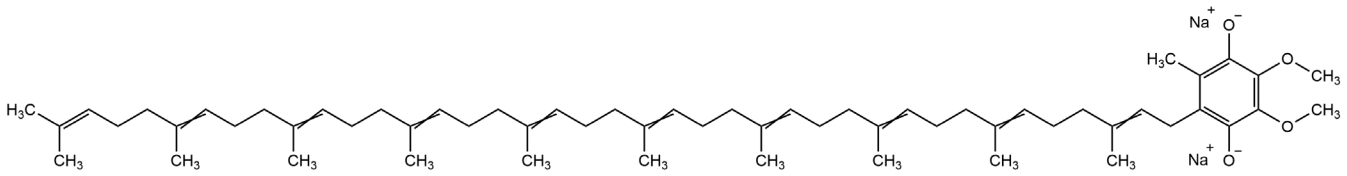
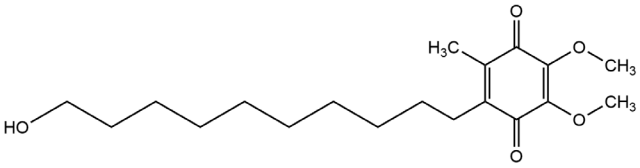
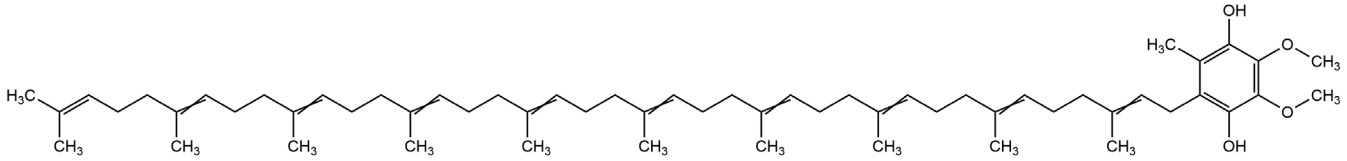
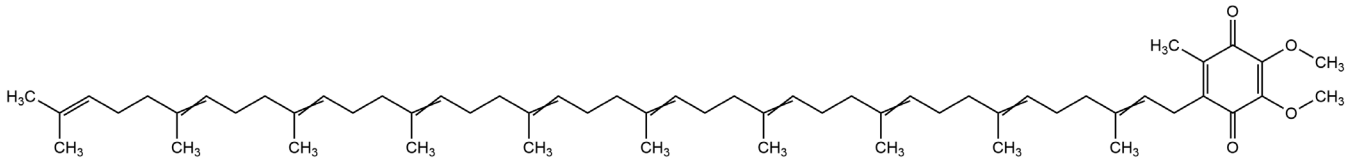
Ingredient (CAS No.)	Definition	Function(s)
Disodium Ubiquinone	Disodium Ubiquinone is the disodium salt of Ubiquinone.	Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents-Humectant
		
Hydroxydecyl Ubiquinone	Hydroxydecyl Ubiquinone is the organic compound that conforms to the structure:	Antioxidants
		
Ubiquinol (992-78-9)	Ubiquinol is the organic compound that conforms to the structure:	Antioxidants, Skin Protectants; Skin-Conditioning Agents- Humectant
		
Ubiquinone (303-98-0; 60684-33-5)	Ubiquinone is the organic compound that conforms to the structure:	Antioxidants; Skin-Conditioning Agents-Miscellaneous
		

Table 2. Chemical properties

Property	Value	Reference
	Disodium Ubiquinone	
Formula Weight (g/mol)	865.38	88
Partition coefficient (log K_{ow})	20.23 (estimated)	6
	Hydroxydecyl Ubiquinone	
Physical Form	Solid	36
Molecular Weight (g/mol)	338.4	89
Topological Polar Surface Area (Å^2)	72.8 (estimated)	89
Melting Point (ºC)	52-54	36
Partition coefficient (log K_{ow})	3.88 (estimated)	6
	Ubiquinol	
Molecular Weight (g/mol)	865.4	7
Topological Surface Area (Å^2)	58.9 (estimated)	7
Partition coefficient (log K_{ow})	23.74 (estimated)	6
Water Solubility	Sparingly	7
	Ubiquinone	
Physical Form	Solid, crystalline powder	8
Color	Off-white to yellow-orange	21,59
Molecular Weight (g/mol)	863.3	8
Topological Surface Area (Å^2)	52.6 (estimated)	8
Melting Point (ºC)	50-52	8
Partition coefficient (log K_{ow})	16.51 (estimated)	6
Water Solubility (@ 20.5 ºC)	Sparingly	8

Table 3. Frequency (2022) and concentration of use (2018) according to the duration and type of exposure for Ubiquinone ingredients

	# of Uses[31]	*Max Conc of Use (%)*[32]	*# of Uses*[31]	*Max Conc of Use (%)*[33]	*# of Uses*[31]	*Max Conc of Use (%)*[32]
	Hydroxydecyl Ubiquinone		**Ubiquinol**		**Ubiquinone**	
Totals*	**16**	**NR**	**6**	**NR**	**221**	**0.00006-0.05**
Duration of Use						
Leave-On	*15*	*NR*	*6*	*NR*	*208*	*0.00075-0.05*
Rinse-Off	*1*	*NR*	*NR*	*NR*	13	*0.000006-0.03*
Diluted for (Bath) Use	*0*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	11	0.02
Incidental Ingestion	NR	NR	NR	NR	1	NR
Incidental Inhalation-Spray	6[a]; 6[b]	NR	2[a]; 4[b]	NR	142[a]; 39[b]	0.00075 – 0.01[a]
Incidental Inhalation-Powder	6[b]	NR	4[b]	NR	39[b]	0.05[c]
Dermal Contact	16	NR	6	NR	218	0.00075-0.05
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	2	0.000006-0.01
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	2	NR
Baby Products	NR	NR	NR	NR	NR	NR

*Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[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 4. Acute oral toxicity studies

Ingredient	Species	No./Group	Vehicle	Dose/Protocol	LD_{50}/Results	Reference
Hydroxydecyl Ubiquinone	Mice	NR	NR	NR	>10,000 mg/kg for male and female mice. Besides decreased locomotor activity in mice with the highest exposure, no statistically significant changes were noted in treated animals.	50,51
Hydroxydecyl Ubiquinone	Rats	NR	NR	NR	>10,000 mg/kg for male rats ~10,000 mg/kg for female rats Besides decreased locomotor activity in high dosed rats, no statistically significant changes were noted in treated animals.	50,51
Ubiquinone	Mice	NR	NR	NR	>4000 mg/kg. No death or toxic symptoms were observed during the one-week observation period.	35
Ubiquinone, >98% purity	ICR mice	10/sex	Composition not specified	20,000 mg/kg bw via gavage	>20,000 mg/kg; No clinical signs, adverse effects, or mortality was observed.	52
Ubiquinone	cRj Wistar rats	3/sex/dose	Corn oil	2000 mg/kg via gavage	>2,000 mg/kg. No deaths and pathological changes in organs or tissues was observed.	21
Ubiquinone	Rats	NR	NR	NR	>4000 mg/kg. No death or toxic symptoms were observed during the one-week observation period.	35
Ubiquinone	Rats	NR	Corn oil	1250, 2500, or 5000 mg/kg	>5,000 mg/kg	35

NR-not reported

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Hydroxydecyl Ubiquinone	Wistar rats (# not specified)	4 wk	NR	20, 100, 500 mg/kg/d, via gavage	Local effects in the forestomach mucosa were observed (details on which dosage group not provided), such as yellow coloration, mucosal thickening, occasional dilation and appearance of red spots. Dose-dependent increases included incidence/severity of submucosal inflammatory infiltrates, forestomach erosions and ulcerations, hyperkeratosis, epithelial and basal cell hyperplasia, focal necrosis, and edema (statistical significance not provided).	[2]
Hydroxydecyl Ubiquinone	juvenile Wistar rats (# not specified)	4 wk	NR	Up to 1000 mg/kg/d (further details not provided)	A slight reduction of body weight was observed in the mid- and high-dose groups, as well as an increased incidence and severity of hyaline droplet accumulation in the proximal renal tubules of male rats in the 1000 mg dosage group. Lowered bone density in the femur and lumbar vertebrae of females in the high dose group were reduced with recovery. No effects on development or reproductive function were observed (statistical significance not provided). The NOAEL was determined to be 200 mg/kg/d.	[3]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	5 wk	NR	doses not stated; administered orally, with a 5-wk recovery period	Toxic effects observed at a dose of 2500 mg/kg/d proved reversible within the recovery period. The non-toxic oral dose was determined to be 500 mg/kg/d (statistical significance not provided).	[50]
Hydroxydecyl Ubiquinone	Beagle dogs (# not specified)	5 wk	NR	Up to 500 mg/kg/d; administered orally	Diarrhea and soft feces were observed in both sexes at a dose of 500 mg/kg/d, and in males dosed with 100 mg/kg/d. The non-toxic oral dose was determined to be 100 mg/kg/d (statistical significance not provided)	[50]
Hydroxydecyl Ubiquinone	CD-1 mice (# not specified)	13 wk	NR	210, 640, 1280, 2000 mg/kg/d, administered orally	Gastric irritation, mainly in the form of epithelial cell hyperplasia, histopathological abnormalities in the forestomach, and a general reduction of weight was observed. (Further details not provided).	[3]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	26 wk	NR	doses not stated; administered orally	Although no treatment-related changes were observed at necropsy, a dose of 500 mg/kg/d caused pathological changes in the gastric mucosa. The non-toxic dose was determined to be 20 mg/kg/d (statistical significance not provided)	[50]
Hydroxydecyl Ubiquinone	Wistar rats (# not specified)	26 wk	NR	30, 100, 300, 1000 mg/kg/d, via gavage	Mucosal thickening, hyperkeratosis, red spots, hyperplasia, necrosis, edema, and ulceration were observed in the forestomach of the animals (groups not specified) upon necropsy. Similar effects were seen in the glandular stomach, including red spots, hyperplasia, and ulceration. These effects were reversible, considered rodent-specific, and of limited toxicological relevance.	[3]
Hydroxydecyl Ubiquinone	Beagle dogs (# not specified)	39 wk	NR	0, 500, 750, 1000 mg/kg/d, via gavage; with an 8-wk recovery period	A dose-dependent incidence of vomiting of mucus, yellow/orange fluid and/or feed, loose feces, diarrhea, body weight loss, and lower food consumption was observed. (doses not specified). The incidence and severity of these clinical signs were greatest in animals dosed at 1000 mg/kg/day and all reported changes were reversible. A non-dose-dependent decrease in mean heart rate was recorded in all groups (occasionally prior to dosing) at wk 26 and wk 39 especially in male dogs, when compared to controls. These cardiac symptoms were associated with lower activity, food consumption, weight loss, and were not observed in 8 wk recovery group. Two animals in the 1000 mg dose group showed mild liver hypertrophy, without further indication of hepatic injury, and 2 additional animals in this dosing group exhibited lung fibrosis, edema, inflammation, and alveolo-bronchiolar hyperplasia. (statistical significance not provided).	[2,3]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Ubiquinol	Sprague-Dawley rats (10/sex)	13 wk	Corn oil	0, 300, 600, or 1200 mg/kg/d, via gavage 1200 mg/kg/d Ubiquinone was used as a reference control group (see Ubiquinone studies for results).	No deaths, or adverse clinical effects, were observed during treatment. A statistically significant higher food consumption was observed in the both males and females in the 600 mg/kg/d group, on day 91 and 31 of dosing, respectively. Elevated AST, ALT, and LDH activity was seen in females in the ≥300 mg/kg groups. Significantly lower A/G ratios were seen in 300 and 1200 mg/kg females; as well as a higher value in the proportion of β-globulin in the protein fractions of females in the 1200 mg/kg group, and γ-globulin in males in the 300 mg/kg group. Statistically significant prolongations in APTT and PT were observed in 1200 mg/kg males, but were within in-house historical control data. Histopathological examinations revealed test-article related effects in the spleen, mesenteric lymph, and within the liver of females only. A yellow focus in the lung was observed in 1 female each in the 300, 600, and 1200 mg/kg groups. Fine vacuolation of Kupffer cells in the liver was present in multiple females dosed with ≥300 mg/kg. The NOAEL was conservatively estimated to be 600 mg/kg/d for males and 200 mg/kg/d for female rats.	[29]
Ubiquinol	Sprague-Dawley rats (10, only females)	13 wk	Corn oil	0, 75, 150, 200, 300, 1200 mg/kg/d, via gavage; this study served as a follow-up trial to the study listed above. Reference control group received 1200 mg/kg/d Ubiquinone	No deaths or significant changes related to the test material were observed. There were no abnormal ophthalmic findings. Food consumption was not affected. Histopathological examinations revealed fine vacuolation in hepatocytes in 3 females in the 200 mg/kg Ubiquinol group, 4 females in the 300 mg/kg Ubiquinol groups, and 3 females in the Ubiquinone group. Mild accumulation of macrophages was also observed in the spleen of 1 female in the 300 mg/kg Ubiquinol group, and in 3 females each in the 300 mg/kg Ubiquinol and Ubiquinone groups. A mild accumulation of foam cells and slight infiltration in the alveoli was seen in 1 female each in the 300 mg/kg Ubiquinol and Ubiquinone groups. (statistical significance not provided). Yellow focus of the lung was observed in 1 female in the 150 mg/kg Ubiquinol group, and 2 females each in the 300 mg/kg Ubiquinol group and Ubiquinone groups. Statistically significant changes in AST activity were observed within animals in the 300 mg/kg group, suggesting effects on the liver. However, these changes were not dose-related, and were observed in controls.	[29]
Ubiquinol	Beagle dogs (3/sex)	13 wk	Gelatin capsules; corn oil for the negative control group	0, 150, 300, or 600 mg/kg/d, via gavage 600 mg/kg/d Ubiquinone was used as a reference control group (see Ubiquinone studies for results).	Minimal Ubiquinol-related effects were observed in body weight, food consumption, ophthalmology, electrocardiogram, urinalysis, hematology, blood chemistry, or histopathological examination. Soft or mucous feces, containing test article or control-like material, were observed during treatment in 1 male in the 150 mg/kg group, 2 males and 1 female in the 300 mg/kg group, and in all males and females in the 600 mg/kg group. Vomiting of foamy fluid was observed in all dosage groups, and vomit containing test article-like material was observed sporadically in the 300 and 600 mg/kg dosage groups; however, vomiting was also observed in controls and was considered unrelated to treatment. Yellow discoloration of the liver was observed in 1 male in the 600 mg/kg group, and a dark red focus was observed in the duodenum of 1 female in the 150 mg/kg group. Estrus hemorrhage was observed in 1 female in the control and 1 female in the 300 mg/kg Ubiquinol group. Statistically significant higher AST, ALT, and LDH values were observed in females in the 300 mg/kg group during wk 13 of dosing, and low A/G ratios were observed in males in the 600 mg/kg group in wk 7 and 13 of dosing, but these effects were judged to be incidental. A statistically significant low proportion of eosinophils was observed in males in the 150 and 600 mg/kg group, as was a low platelet count in females in the 300 mg/kg group; however, these values were not considered test article related and were within testing facility ranges. Yellow discoloration of the liver was observed in 1 male in the 600 mg/kg group. A NOAEL of 600 mg/kg/d was determined.	[29]
Ubiquinone	White rabbits (# not specified)	23 d	NR	0, 6, 60, 600 mg/kg/d; administered orally	No toxic effects, and no microscopic or gross lesions, were found at any dose level. (statistical significance not provided).	[35]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Ubiquinone	cRj Wistar rats (6/sex)	4 wk	Corn oil	1000 mg/kg/d, via gavage; general toxic signs, food consumption, body and organ weights, hematology and urinalysis, and gross and micropathological changes were observed	Ubiquinone did not produce notable changes in the overall condition, body weight gain, or food consumption, of the test animals when compared with controls. Upon necropsy in the Ubiquinone-treated group, one male had enlarged adrenals, and one male had tan-colored lungs, which was attributed to administration errors. One female from the control group, and several males and females from the Ubiquinone-treated group, exhibited hemorrhagic lesions, and localized pulmonary changes. (statistical significance not provided).	[21]
Ubiquinone, >98% purity	Sprague-Dawley rats (10/sex)	30 d	Composition not specified; corn oil for controls	0, 560, 1130, 2250 mg/kg/d, via gavage; body and relative organ weights, food intake, and blood biochemistry were observed	No difference in the body weight, food intake, organ weights, or blood biochemistry of the treated animals compared to controls was observed.	[52]
Ubiquinone	Rats (strain and # not specified)	5 wk	NR	0, 40, 200, 1000 mg/kg/d; administered orally	No toxicity was observed in the hematology, blood chemistry, urinalysis, or post-mortem examinations at any dose level.	[35]
Ubiquinone, 99.8% purity	Sprague-Dawley rats (15/sex); 1/3 of the rats were used as a 15-d recovery group before sacrifice	90 d	0.5% hydromethyl-fibrin	0, 500, 1500, 3000 mg/kg/d, via gavage; 5/sex/group were maintained after the termination of dosing, and served as recovery group animals	Male rat body weights decreased during treatment in the 1500 mg/kg group. In female rats, food consumption was reduced in the 3000 mg/kg group in week 1, week 3, and week 7. Red blood cells and hemoglobin decreased in the 500 mg/kg and 1500 mg/kg male dosage group, while white blood cells increased in all males for all dosages. Hematocrit levels in the 1500 mg/kg and 3000 mg/kg female groups were also decreased. Triglycerides decreased in the 1500 mg/kg and 3000 mg/kg male dosage groups. Ovary weight was slightly decreased in the 1500 mg/kg group, while uterus-to-body weight ratio was elevated in the 3000 mg/kg dosage group. All these changes were statistically significant. No significant differences or toxic effects were observed in the recovery group.	[14]
Ubiquinone	Sprague-Dawley rats (10/sex)	13 wk	Corn oil	1200 mg/kg/d, via gavage (Reference controls for the 13-wk Ubiquinol study)	A statistically significant higher food consumption was observed in females on day 4 and 31 of dosing. Statistically significant prolongations in PT were observed in 1200 mg/kg males, but were within in-house historical control data. Two males and 3 females exhibited a yellow focus in the lung. Mild granuloma was present in the livers of females, as well as an accumulation of foam cells in lung alveoli in 2 males and 3 females. (statistical significance not provided).	[29]
Ubiquinone	Sprague-Dawley rats (10/sex)	13 wk	Corn oil	0, 300, 600, 1200 mg/kg/d, via gavage; clinical observations, body and organ weights, food consumption, blood chemistry, and histopathology were observed	No deaths or changes in food consumption occurred during treatment. The test substance was excreted in the stool of rats in the 1200 mg/kg group. Other incidental observations among rats in the 1200 mg/kg group included mononuclear cell infiltration in the pancreas, mineralization in the kidney medulla and duct of the parotid gland, lymphocyte infiltration in the submucosa of the bladder, and cysts in the parathyroid of rats in the 1200 mg/kg group. These changes were considered to be unrelated to the test substance as they are known to occur spontaneously. (statistical significance not provided). The NOAEL was determined to be > 1200 mg/kg/d.	[17]
Ubiquinone	Beagle dogs (3/sex)	13 wk	Corn oil	600 mg/kg/d, via gavage (Reference controls for the 13-wk Ubiquinol study)	Soft feces, with apparent traces of Ubiquinone, were observed during treatment in 2 males and 2 females. Soft, mucous, or watery feces were also observed 10 times in 1 reference control male and 1 time in a female from the control group. Vomiting was also observed in 1 male and 2 females during dosing. Estrus hemorrhage was observed in 1 female from wk 9 to 11 of dosing. A statistically significant increase in proportion of band neutrophils was observed in Ubiquinone-treated males at wk 7, but was not detected at wk 13. A dark red focus of the heart was observed in 1 male; 1 male and 1 female exhibited an enlarged liver. Opacity of the posterior lens capsule was observed in 1 of the 3 females, but also occurred in 1 male and 2 females in the control group. (statistical significance not provided).	[29]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Ubiquinone	Beagle dogs (4/sex)	39 wk	Gelatin capsules	0, 1200, or 1800 mg/kg/d; administered orally, via gelatin capsules	Unabsorbed Ubiquinone was observed in the stool of all male and females who received 1200 or 1800 mg/kg/d. Vomiting occurred in one male and 3 females in the 1200 mg/kg/d group and in all dogs in the 1800 mg/kg/d group. No deaths were observed during treatment. Upon necropsy, a white focus was observed in the lungs of one control female and one male from the 1200 mg/kg/d group. One male in the control group was found to have hypoplasia of the epididymis. These gross pathological findings were not considered toxicologically significant.	53
Ubiquinone	Sprague-Dawley rats (19/sex)	52 wk	Corn oil, via gavage	0, 100, 300, 600, or 1200 mg/kg/d, via gavage; 10 animals of random sex were selected from the 0, 600, and 1200 mg/kg/d dosage groups. These 3 groups of recovery animals were treated for 52 wk, and maintained after the termination of dosing for 4 wk,	One female and three males from the 600 mg/kg/d group died during weeks 33, 38, 48, and 52. One male from the 1200 mg/kg/d group died of malignant lymphoma during week 33. No statistically significant differences were observed in body weight, ophthalmology, or clinical and anatomical pathology. Increased incidence of large, finely vacuolated (foamy) macrophages in the lymph nodes and hepatic periportal cells, attributed to phagocytic activity, were observed in the 600 and 1200 mg/kg/d groups. Although Ubiquinone accumulated in the liver, in recovery groups, levels returned to pretreatment levels within 10 d of stopping treatment. During treatment, red nasal discharge was observed in one female control, and in both sexes in the mid and high dose groups. Orange material was found in the feces during treatment and upon necropsy, was found in the lungs and in the nasal turbinates, which was attributed to external incidental exposure to crystallized Ubiquinone.	45

Abbreviations: A/G – albumin/globulin; APTT – activated partial thromboplastin time; ALT- alanine aminotransferase; AST – aspartate aminotransferase; LDH – lactate dehydrogenase; NR- not reported; PT – prothrombin time

Table 6. Developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
				ORAL		
Hydroxydecyl Ubiquinone	Wistar rats (# not specified)	NR	20, 100, or 500 mg/kg bw, via gavage	Male and female Wistar rats were dosed with Hydroxydecyl Ubiquinone, starting at 9 and 2 wk before mating, respectively, and dosing was maintained until day 22 after delivery. Females were evaluated on day 13 of pregnancy and day 22 postpartum.	The two higher dose groups displayed transient salivation after dosing, and red-brown urine (attributed to the presence of a metabolite). No adverse effects were observed on estrus cycle, copulation rate, gestation period, parturition, suckling, litter size, pup mortality, morphological and functional development, reflexes, emotionality, spontaneous activity, learning, or reproductive ability after pups reached maturation (statistical significance not provided).	50
Hydroxydecyl Ubiquinone	Rats (males and females; strain and # not specified)	NR	Up to 500 mg/kg d	Fertility and early embryonic development study (details not provided)	A higher rate of post-implantation losses and lower number of live embryos was observed in female rats (statistical significance not provided). No other adverse effects were seen at any dose on reproductive performance or on embryogenesis.	2
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	NR	NR	Teratology study (details not provided)	Chromaturia (dark colored urine) was the main effect reported. No effect on fetal development or the growth of F_1 animals was observed, and a NOAEL of 500 mg/kg/d was determined (statistical significance not provided).	2

Table 6. Developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	NR	Up to 1000 mg/kg/d	Fertility study (detail not provided)	A slightly higher rate in the of post-implantation losses and lower number of live embryos were seen at the highest dose. Differences between treated rats and controls were not statistically significant. Based on body surface area comparisons, the NOAELs for male and female fertility were determined to be 500 and 1000 mg/kg/d, respectively.	[3]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	NR	NR	Embryofetal study (details not provided)	No differences were seen in the number of visceral and skeletal malformations, and fetal abnormalities, even in the presence of maternal toxicity (statistical significance not provided). Based on body surface area comparisons, the NOAEL for embryofetal development was determined to be 1000 mg/kg/d.	[3]
Hydroxydecyl Ubiquinone	Rabbits (strain and # not specified)	NR	Up to 150 mg/kg/d	Teratology study (details not provided)	Chromaturia was observed at the highest dose, and no further effects were reported (statistical significance not provided).	[2]
Hydroxydecyl Ubiquinone	Japanese white rabbits (# not specified)	NR	Up to 500 mg/kg/d	Embryofetal study (details not provided)	One abortion was observed in the highest dose group, but was considered spontaneous due to the spontaneous abortion rate (3%) in this rabbit strain. No statistically significant embryofetal differences were reported between the control and treated groups. Maternal toxicity was evident in this study (both food consumption and body weight gain were suppressed in high dose dams).	[3]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	NR	Up to 500 mg/kg/d	Peri/post-natal studies (details not provided)	Chromaturia was observed in the F_0 generation of the 100 mg and 500 mg pups, and transient hypersalivation occurred immediately after dosing the highest dosage group. No treatment-related differences in body weight, length of gestation, parturition, nursing, and necropsy findings was observed. No treatment-related changes were observed in the F_1 generation or in the dams.	[2,3]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	NR	Up to 1000 mg/kg/d	Peri/post-natal studies (details not provided)	Decreased food consumption and body weight was observed in the high dosage group dams (statistical significance not provided). The NOAEL for pup development was determined to be 500 mg/kg/d (based on body surface area).	[3]
Ubiquinone	Mice (strain and # not specified; limited details were provided in this review paper)	NR	6, 60, or 600 mg/kg/d, via gavage	Primigravid mice were dosed with Ubiquinone from day 7 to day 13 of the mouse gestational period.	Treatment with Ubiquinone had no effect on fetal death, weight, or postnatal toxicity (statistical significance not provided).	[35]
Ubiquinone, >98% purity	10 male mice	Composition, not specified	2500, 5000, or 10,000 mg/kg bw, via gavage	Mice were administered the doses for 5 d to test for defects in sperm morphology. A sperm morphology test was performed on day 35 after dosing. Epididymides were minced in phosphate buffered solution and stained smears were prepared on slides. Corn oil and 40 mg/kg bw cyclophosphamine served as the negative and positive control, respectively.	No statistically significant differences were found in the incidence of sperm abnormalities between treated mice and negative controls.	[52]

Table 6. Developmental and reproductive toxicity studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
Ubiquinone	8 male Wistar rats	Nothing (negative controls) Corn oil (vehicle controls)	10 mg/kg bw/d, via gavage	Ubiquinone was administered via oral gavage for 14 d. Various spermatogenesis and testicular outcomes were compared between the treatment group and control groups. Approximately 5 ml of blood was collected from each rat to measure glutathione, superoxide dismutase, catalase, and malondialdehyde serum levels. Upon sacrifice, testis and epididymis were removed and cleaned, and semen samples were isolated from the cauda epididymal tissue; the left testicle was fixed in Bouin's solution for histological examination and slide preparation, and the right testicle was homogenized and centrifuged to measure various biomarkers.	Except for an increase in seminiferous epithelium heights, no biochemical, histological, or morphological differences were observed between the Ubiquinone-treated, negative control, and vehicle control groups. (statistical significance not provided).	[54]
Ubiquinone	Rats (strain and # not specified)	NR	6, 60, or 600 mg/kg/d, via gavage	Primigravid rats were dosed with Ubiquinone from day 9 to day 15 of the rat gestational period.	Treatment with Ubiquinone had no effect on fetal death, weight, or postnatal toxicity. (statistical significance not provided).	[35]

NR- not reported

Table 7. Genotoxicity studies

Ingredient (Vehicle)	Dose/Concentration	Cell/Strain/Species	Method	Results	Reference
		In Vitro			
Hydroxydecyl Ubiquinone*	NR	L5178Y TK +/- mouse lymphoma cells	Mouse lymphoma cells induced with the test substance were assayed to assess the ability of Hydroxydecyl Ubiquinone to induce mutation at the tk locus.	Positive mutagenic responses were not reproducible, dose-related, or statistically significant.	[3]
Hydroxydecyl Ubiquinone*	NR	Human peripheral lymphocytes	Chromosomal aberration test	Positive results were considered to be related to the redox properties of Hydroxydecyl Ubiquinone, and the test substance was not considered clastogenic.	[3]
Ubiquinol, 98.7% (acetone)	Up to 5000 µg/plate, with or without metabolic activation	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and *Escherichia coli* WP2 *uvr*A	Ames test	Not genotoxic	[43]
Ubiquinol, 98.7% (0.5% w/v sodium carboxymethyl cellulose solution)	6 h: 412-5000 µg/ml 24 h: 141-1201 µg/ml; with or without metabolic activation	Chinese hamster lung fibroblast cell line (CHL/IU)	Chromosomal aberration test. Growth inhibition tests (≥50%) were performed to determine concentration ranges for short term (6 h) or continuous (24 h) treatment.	Not genotoxic. Marked cell-growth inhibition was observed at higher doses in all treatments. Slight increase in percentage of polyploidy cells in all treatments was observed, but not considered significant.	[43]
Ubiquinone, 99.2% (acetone; water control)	≤313 µg/plate without metabolic activation; ≤1250 µg/plate with metabolic activation	*S. typhimurium* strains TA98, TA100, TA1535, TA 1537, and *E. coli* WP2 *uvr*A	Ames test	Not genotoxic	[18]
Ubiquinone, >98%	Up to 5000 µg/plate, with or without metabolic activation	*S. typhimurium* strains TA97, TA98, TA100, TA102	Ames test	Not genotoxic	[52]
Ubiquinone, 99.2% (acetone)	Up to 5000 µg/plate, with or without metabolic activation	*S. typhimurium* strains TA98, TA100, TA1535, and *E. coli* WP2 *uvr*A	Ames test	Not genotoxic. The assay was performed twice. Because precipitates were observed during the first assay, the second assay was performed at doses < 78 µg/plate without activation, and doses < 1250 µg/plate with activation. The number of revertant colonies were not different from those of negative controls and did not show any dose-dependency.	[15]

Table 7. Genotoxicity studies

Ingredient (Vehicle)	Dose/Concentration	Cell/Strain/Species	Method	Results	Reference
Ubiquinone*	Up to 5000 µg/plate	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* WP2 *uvr*A	Ames test	Not genotoxic	[35]
Ubiquinone, 99.2% (0.5% w/v carboxymethyl cellulose sodium solution)	625-5000 µg/plate; with or without metabolic activation	Chinese hamster lung fibroblast cell line (CHL/IU)	Chromosomal aberration test	Not genotoxic. The incidence of polyploid cells was less than 5% in all doses and treatments and judged to be negative.	[18]
Ubiquinone*	Up to 5000 µg/ml	Chinese hamster lung fibroblast cell line (CHL/IU)	Chromosomal aberration test	Not genotoxic	[55]
			In Vivo		
Hydroxydecyl Ubiquinone*	1250-5000 mg/kg once or 5000 mg/kg/d	Mice (# not stated)	Micronucleus test. Mice received a one-time dose of 1250, 2500, or 5000 mg, or a daily dose of 5000 mg for 4 d.	Not genotoxic	[2]
Ubiquinol, 98.7% (corn oil)	500-2000 mg/kg/d	Groups of 6 male Sprague-Dawley rats	Micronucleus test. Rats received two oral doses, at a 24 h interval. Animals were weighed and observed 24 h after the first dose, and sacrificed 24 h after the last dose.	Not genotoxic. No deaths occurred and no clinical signs were observed in any of the groups. Increases in micronucleated polyerythrocytes were not significant.	[43]
Ubiquinone, >98%	0, 250, 500, 10,000 mg/kg bw	Groups of 5 male and 5 female mice	Bone marrow micronucleus test. Mice were fed their assigned doses for 2 d. Negative and positive control groups were given corn oil and 50 mg/kg bw cyclophosphamine, respectively. Bone marrow smears were collected 6 h after end of treatment.	Not genotoxic	[52]
Ubiquinone	2000 mg/kg/d	Mice (# not stated)	Micronucleus test	Not genotoxic	[35]

* Composition not specified
NR- not reported

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2022 FDA VCRP Frequency of Use Data – Ubiquinone Ingredients
Total Use: 243

Hydroxydecyl Ubiquinone
Total: 16

CAS_NUMBER	INGREDIENT_NAME	CATEGORY_ CODE	CATEGORY_DESCRIPTION	CPIS_ COUNT
999001841	HYDROXYDECYL UBIQUINONE	12C	Face and Neck (exc shave)	6
999001841	HYDROXYDECYL UBIQUINONE	12F	Moisturizing	5
999001841	HYDROXYDECYL UBIQUINONE	12H	Paste Masks (mud packs)	1
99001841	HYDROXYDECYL UBIQUINONE	12I	Skin Fresheners	1
999001841	HYDROXYDECYL UBIQUINONE	12J	Other Skin Care Preps	3

Ubiquinol
Total: 6

56275399	UBIQUINOL	12C	Face and Neck (exc shave)	3
56275399	UBIQUINOL	12D	Body and Hand (exc shave)	1
56275399	UBIQUINOL	12F	Moisturizing	2

Ubiquinone
Total: 221

1339635	UBIQUINONE	03D	Eye Lotion	9
1339635	UBIQUINONE	03G	Other Eye Makeup Preparations	2
1339635	UBIQUINONE	05F	Shampoos (non-coloring)	1
1339635	UBIQUINONE	05G	Tonics, Dressings, and Other Hair Grooming Aids	1
1339635	UBIQUINONE	07C	Foundations	1
1339635	UBIQUINONE	09C	Other Oral Hygiene Products	1
1339635	UBIQUINONE	10A	Bath Soaps and Detergents	1
1339635	UBIQUINONE	12A	Cleansing	4
1339635	UBIQUINONE	12C	Face and Neck (exc shave)	35
1339635	UBIQUINONE	12D	Body and Hand (exc shave)	4
1339635	UBIQUINONE	12F	Moisturizing	127
1339635	UBIQUINONE	12G	Night	14
1339635	UBIQUINONE	12H	Paste Masks (mud packs)	6
1339635	UBIQUINONE	12J	Other Skin Care Preps	15