Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 21, 2020
Panel Meeting Date:	September 14-15, 2020

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

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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, CIR

Date: August 21, 2020

Subject: Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics

Enclosed is the draft report of the Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics (identified as *ubiqui092020rep* in the pdf). This is the first time the Panel is seeing a safety assessment of these 4 cosmetic ingredients. A Scientific Literature Review (SLR) was announced on April 29, 2020.

In response to the SLR, the following data were received and have been added to the report:

- Anonymous. (2020) Method of manufacture, impurities, and dermal irritation/sensitization summaries for products containing 1% and 6.3% Ubiquinone (*ubiqui092020data2*)
- Clinical Research Laboratories, Inc. (2012) HRIPT for a cream containing 0.01% Hydroxydecyl Ubiquinone (*ubiqui092020data3*)

A risk assessment prepared by the Norwegian Food Safety Authority, to evaluate the safety of Hydroxydecyl Ubiquinone and Ubiquinone exposure, was found in the CIR search process (*ubiqui092020risk*). However, the relevance of this assessment to cosmetic ingredient safety was unclear to the CIR Staff, and thus was not incorporated in this draft report. Your guidance as to the relevance of this document is requested.

Comments on the SLR (*ubiqui092020pcpc*) that were received from the Council have been addressed. Also included in this package for your review are a flow chart (*ubiqui092020flow*), literature search strategy (*ubiqui092020strat*), ingredient data profile (*ubiqui092020prof*), ingredient history (*ubiqui092020hist*), 2020 FDA VCRP data (*ubiqui092020FDA*), and 2018 concentration of use data (*ubiqui092020data1)*.

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

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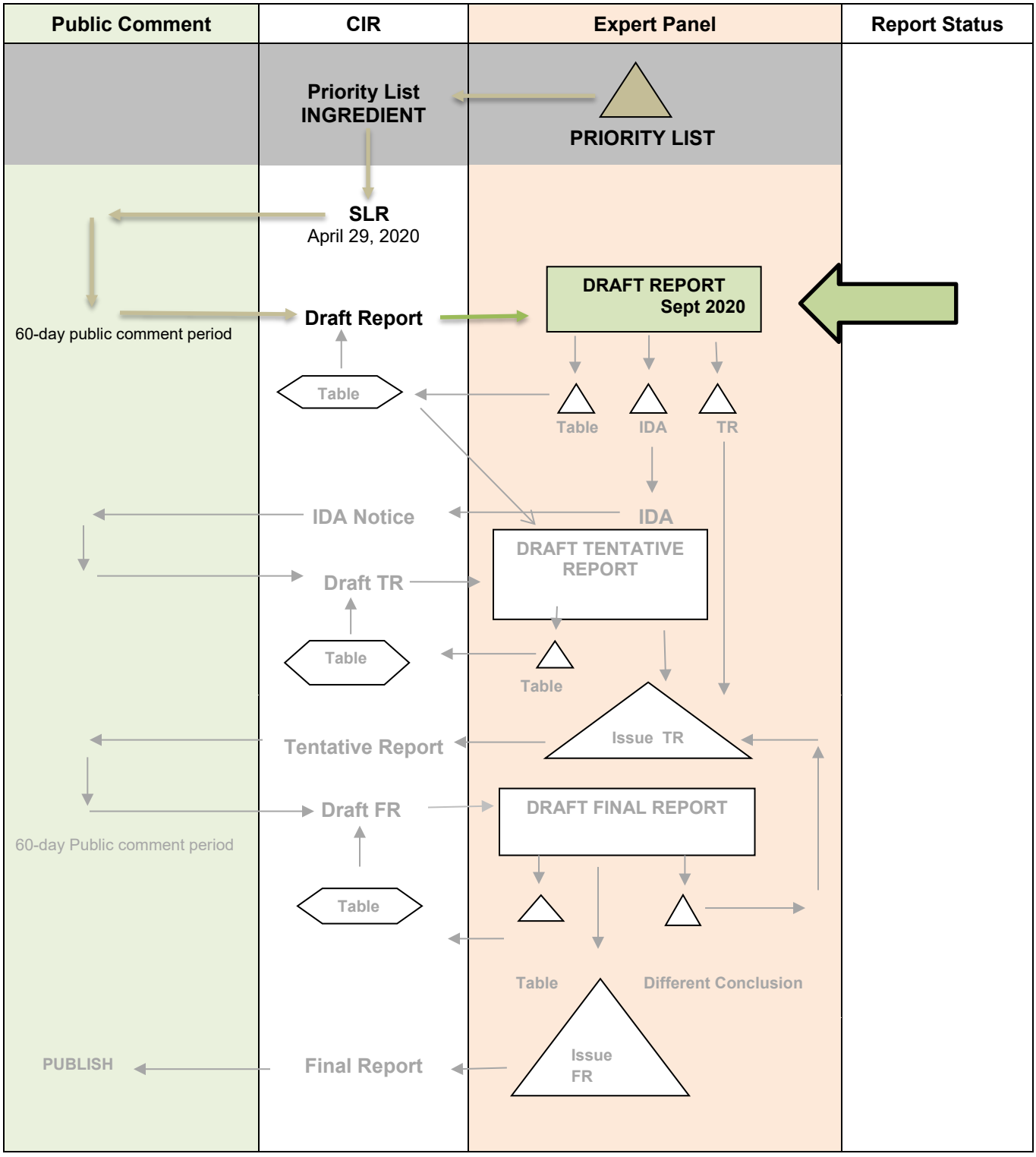
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Ubiquinone Ingredients

MEETING September 2020



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

-Ubiquinone ingredients SLR posted on the CIR website

Data received, by date:

June 25, 2020: Method of manufacture and impurities data for Ubiquinone

June 25, and July 20, 2020: Dermal irritation and sensitization data for Ubiquinone and Hydroxydecyl Ubiquinone

September 2020

-A Draft Report is being presented to the Panel.

Ubiquinone Ingredients Profile* – September 14-15th, 2020 – 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" indicates that data were available in a category for the ingredient

[Ubiquinone – 4 ingredients – September 14-15, 2020 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

Search Strategy

Typical Search Terms

- INCI names
- CAS numbers
- chemical/technical names
- additional terms were used as appropriate

[*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

- 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
- mucous membrane irritation – 0/1
- dermal sensitization – 0/0
- coenzyme q10 hypertension – 4/17

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)

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

Botanical Websites, if applicable

- Dr. Duke's - https://phytochem.nal.usda.gov/phytochem/search
- Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
- GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
- Sigma Aldrich plant profiler- http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html
- American Herbal Products Association Botanical Safety Handbook (database) - http://www.ahpa.org/Resources/BotanicalSafetyHandbook.aspx
- European Medicines Agency Herbal Medicines - http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/herbal_search.jsp
- National Agricultural Library NAL Catalog (AGRICOLA) https://agricola.nal.usda.gov/
- The Seasoning and Spice Association List of Culinary Herbs and Spices
- http://www.seasoningandspice.org.uk/ssa/background_culinary-herbs-spices.aspx

Fragrance Websites, if applicable

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

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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.

A safety assessment of Hydroxydecyl Ubiquinone and Ubiquinone, as used in cosmetics, was issued by the Norwegian Food Safety Authority in 2013,[2] and toxicological assessments of Hydroxydecyl Ubiquinone were issued by the European Medicines Agency and by the Australian Government Department of Health.[3,4] 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, chemical structures, and reported cosmetic functions 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,[5] 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.

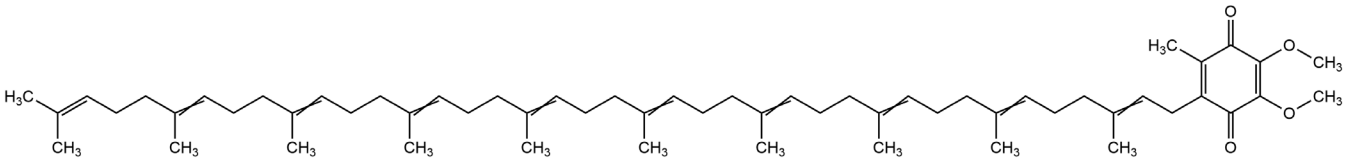

Figure 1. Ubiquinone

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.[6]

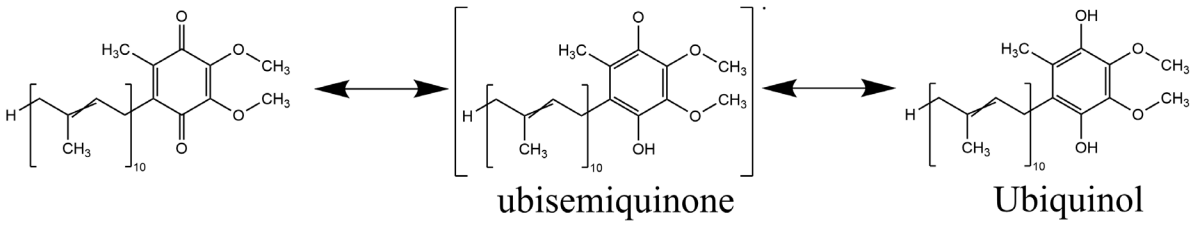

Figure 2. Redox and Ubiquinol

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.

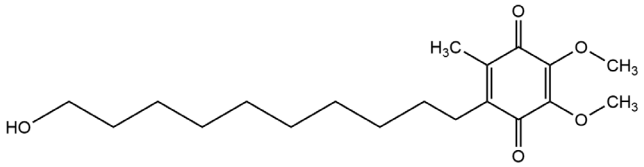

Figure 3. Hydroxydecyl Ubiquinone

Chemical Properties

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).[7] Both Ubiquinol and Ubiquinone are sparingly soluble in water.[8,9] The chemical properties of these ingredients are further outlined in Table 2**.**

Natural Occurrence

In 1957, Ubiquinone was isolated from beef heart mitochondria and was first chemically synthesized in 1958.[10,11] Ubiquinone is also found in a wide variety of dietary sources such as oily fish, organ meats, whole grains, and vegetables.[12]

Human skin is known to contain both enzymatic and non-enzymatic (antioxidant) mechanisms for protecting itself from oxidative stress.[13] 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.[14] Ubiquinone and Ubiquinol content is known to peak in human tissue in early adulthood, and decline with age.[13]

Method of Manufacture

Methods of manufacture specific to cosmetic ingredients were neither found in the published literature, nor submitted as unpublished data. However, several general methodologies are summarized below.

Ubiquinone

Ubiquinone is produced outside the body by one of three methods: extraction from biological tissues, chemical synthesis, or microbial fermentation.[2,15-17] 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.[15,18-20] 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.[21,22] The gram-negative bacterium, *Agrobacterium tumefaciens,* is often used for its relatively high synthesis rates.[2]

A few other natural producers of Ubiquinone include *Schizosaccharomyces pombe* (fission yeast), *Sporidiobolus johnsonii*, and *Rhodobacter sphaeroides* (a photosynthetic bacterium).[22] 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.[23] 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.[21] 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.[24] 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.[25]

According to data received from the industry, Ubiquinone produced by yeast fermentation, is purely in the *trans* form (does not contain *cis*-isomers).[26] 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.

USE

Cosmetic

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

According to 2020 VCRP survey data, Ubiquinone is reported to be used in 421 cosmetic products, of which 387 are leave-on products (Table 3).[27] The results of the concentration of use survey conducted by the Council in 2018 indicate that the maximum leave-on use concentration in this ingredient group is 0.05% for Ubiquinone, in body and hand products.[28] No uses were received from VCRP or the industry survey for Disodium Ubiquinone. The Council is currently surveying the industry for Ubiquinol concentrations of use; once those data are received, they will be included in this report.

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.[29]

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.[11,30] Hydroxydecyl Ubiquinone has been approved for pharmaceutical use in Japan since 1984.[31]

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.[16] Ubiquinone is commonly sold as a dietary supplement under the name of coenzyme Q10, referring to its biological function and structure.[32] Although consumed at much higher doses in those with pathological conditions, coenzyme Q10 is typically sold at doses of 100 - 200 mg.[32] 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.[5] 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).[33]

TOXICOKINETIC STUDIES

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.[20] 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.[34] 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.[20,35]

Endogenously, Ubiquinone is produced via the mevalonate pathway, in either the mitochondria or Golgi apparatus, of human cells.[22] 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. 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.[36]

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.[13] (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.[2] A dose-response relationship was observed between the amount of Ubiquinone applied and the concentration in skin. (No further details provided).

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.[37,38] 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.[34,39] Although structurally distinct, Ubiquinol is the predominant metabolite of Ubiquinone, and has higher bioavailability than Ubiquinone.[40] Most endogenous Ubiquinone is reduced to, and exists as, bioreactive Ubiquinol in the mitochondria, endoplasmic reticulum, lysosomes, peroxisomes, and plasma membranes of eukaryotic cells.[34-36,40,41]

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.[31] 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.[31] 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.[37] 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.[42] 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.[41] 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%, one day after injection, supporting the notion that Ubiquinol represents 90% of plasma Ubiquinone. However, two days 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.[43] 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.[31,44] 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.[45] 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 after 6 h of 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 adverse 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.[37] 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.[37] 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.[38] 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.[46]

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.[47,48] The acute oral LD_{50} of Ubiquinone in mice was reported to be > 4000 mg/kg,[30,49] while, in rats, it was reported to be > 2000 mg/kg.[19,30]

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.[3] 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 NOAEL was determined to be 200 mg/kg/d.[4] 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.[47] 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.[47] 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.[4] 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.[4] 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.[3,4] 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.[35] 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.[35] 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.[35] 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.[19] 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.[30,49] Sprague-Dawley rats received doses of 0, 500, 1500, or 3000 mg/kg/d Ubiquinone, in 0.5% hydromethylfibrin, over 90 d.[12] 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.[35] 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 was determined to be > 1200 mg/kg/d.[16] In a 52-wk study, groups of 19 Sprague-Dawley rats/sex were dosed with up to 1200 mg/kg/d of Ubiquinone.[42] 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 animals dosed for 23 d with up to 600 mg/kg Ubiquinone.[30] 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.[35] 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.[50] 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. [47] 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.[3,4] 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.[4] Rabbits, dosed at up to 150 mg/kg/d Hydroxydecyl Ubiquinone and observed for teratological abnormalities, displayed chromaturia in the highest dosage group.[3] 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.[4] 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.[3,4] The NOAEL for rat pup development was determined to be 500 mg/kg/d Hydroxydecyl Ubiquinone.[4]

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.[30] 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.[49] 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.[51] 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.[30]

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.[4] 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.[4] 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.[40] 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.[15,17,30,49,52] In vivo, no genotoxicity was observed in several micronucleus tests with Hydroxydecyl Ubiquinone, at up to 5000 mg/kg/d (in mice),[3] Ubiquinol, at up to 2000 mg/kg/d (in rats),[40] or Ubiquinone, at up to 10,000 mg/kg/d (in mice).[30,49]

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.[4] 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.[4] 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.[53] 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).[54] 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 solution (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.[54] 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.[54] 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.[55] 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.[54] 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.

Relative Contraindications

Hydroxydecyl Ubiquinone

Owing mostly to structural similarity, certain chemicals have the potential to cross-react and/or cause dermal sensitization to 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.[2] Additionally, Atovaquone, a 1,4-naphthoquinone derivative used to treat malaria and sometimes pneumonia, also closely resembles Hydroxydecyl Ubiquinone, and may cause a serious reaction in previously sensitized, immune-compromised individuals. As naphthoquinones, Hydroxydecyl Ubiquinone and Ubiquinone can also act as haptens, or sensitizers to each other; however, the longer side chain in Ubiquinone is expected to exhibit weak allergenic properties.

Ubiquinone

Mevalonic acid is the chemical precursor to both Ubiquinone and cholesterol, the latter of which requires HMGC reductase (HMGCR) to be formed.[22] 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 .[56,57] However, there have been conflicting results in clinical trials examining the interaction of statins and Ubiquinone. 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.[58] However, in a 16-wk longitudinal study, 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).[59] 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.[2,57,60]

Furthermore, the Norwegian Food Safety Authority states that the $NOAEL_{hypotension}$ for Ubiquinone exposure is 0.25 mg/kg bw/d.[2] This value is extrapolated from a calculated oral systemic NOAEL, in which up to 100 mg/d Ubiquinone consumption does not have a hypotensive effect in users, assuming 15% bioavailability and 60 kg body weight.

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.[61] 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 an unknown purity, was tested in groups of 10 Crj:Hartley guinea pigs in a maximization test, performed similarly to Organization for Economic Development test guideline (OECD TG) 406.[61] 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 controls; 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 DCNB. 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.[62] 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.[61] 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,[63] inflammation and aging,[64,65] diabetes,[66-68] cancer,[69] and muscular and neurogenerative diseases.[3,4,31,70,71] 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.[5,70] 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.[72,73]

Multiple studies have explored the hypotensive potential of Ubiquinone, with conflicting results.[74-80] 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.[81] Given the innate involvement of Ubiquinone in cellular metabolism, the Norwegian Food Safety Authority based its MoS estimates for 1% Ubiquinone use in cosmetic formulations upon a calculated systemic $NOAEL_{hypotension}$.[2]

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.[82] 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

Dermal

A 47-year-old woman had a cream containing 0.5 % Hydroxydecyl Ubiquinone applied as part of a facial treatment in a salon.[83] 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-year-old woman developed an itchy eruption.[2] 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-year-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.[2] Patch testing showed positive reaction to 0.5% Hydroxydecyl Ubiquinone.

A 38-year-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.[84] 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.

According to 2020 VCRP data, Ubiquinone has the highest reported use amongst these ingredients, in 421 cosmetic products, of which 387 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; please note, a survey has not yet been completed for Ubiquinol. According to VCRP data, Disodium Ubiquinone is not currently in use in cosmetic products.

The Norwegian Food Safety Authority calculated MoS values for the use of 1% Ubiquinone in a body lotion (10.2), face cream (52.1), hand cream (38.5), and for the overall exposure from cosmetics (8.5). Based upon the $NOAEL_{hypotension}$ and the estimated overall SED for Ubiquinone in cosmetics, the Norwegian Food Safety Authority stated that the overall MoS of 8.5 was sufficient to support the recommended use concentration of 1% Ubiquinone. Based on dermal irritation and sensitization data, Hydroxydecyl Ubiquinone was concluded to be safely used at 0.5% in cosmetic formulations.

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. 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.

In a 4-wk study, cRj Wistar rats dosed with 1000 mg/kg/d Ubiquinone did not produce noticeable changes in overall condition, body weight gain, or food consumption, in comparison to controls. 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 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 and atovaquone have the potential to cross-react, cause allergenicity, or sensitization, to Hydroxydecyl Ubiquinone. Despite conflicting clinical trial data, simultaneous Ubiquinone and statin use may be contraindicated. The MoS values from the Norwegian Food Safety Authority, for the cosmetic use of Ubiquinone, are based upon the systemic oral $NOAEL_{hypotension}$, for Ubiquinone exposure, 0.25 mg/kg bw/d, which accounts for bleeding risk in statin users concomitantly taking >100 mg/d Ubiquinone. 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 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 a 48-h exposure 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. A maximization test was performed similarly to OECD TG 406, using a test material containing 1.25% Ubiquinone, in groups of 10 Crj: Hartley guinea pigs. Slight erythema, occurring immediately after patch removal, regressed within 24 h; and, 6.3% Ubiquinone was not a skin irritant or sensitizer. An undiluted cream, containing 0.01% Hydroxydecyl Ubiquinone was tested 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 an undiluted test substance containing 1% Ubiquinone 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 middle-aged 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

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Definition, cosmetic function, and chemical structure 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	85
Partition coefficient (log K_{ow})	20.23 (estimated)	7
	Hydroxydecyl Ubiquinone	
Physical Form	solid	31
Molecular Weight (g/mol)	338.4	86
Topological Polar Surface Area (Å^2)	72.8 (estimated)	86
Melting Point (ºC)	52-54	31
Partition coefficient (log K_{ow})	3.88 (estimated)	7
	Ubiquinol	
Molecular Weight (g/mol)	865.4	8
Topological Surface Area (Å^2)	58.9 (estimated)	8
Partition coefficient (log K_{ow})	23.74 (estimated)	7
Water Solubility	Sparingly	8
	Ubiquinone	
Physical Form	Solid, crystalline powder	9
Color	Off-white to yellow-orange	19,56
Molecular Weight (g/mol)	863.3	9
Topological Surface Area (Å^2)	52.6 (estimated)	9
Melting Point (ºC)	50-52	9
Partition coefficient (log K_{ow})	16.51 (estimated)	7
Water Solubility (@ 20.5 ºC)	Sparingly	9

Table 3. Frequency (2020)[27] and concentration of use (2018)[28] according to the duration and type of exposure for Ubiquinone ingredients

	# of Uses[27]	*Max Conc of Use (%)[28]*	*# of Uses[27]*	*Max Conc of Use (%)[28]*	*# of Uses[27]*	*Max Conc of Use (%)[28]*
	Hydroxydecyl Ubiquinone		**Ubiquinol**		**Ubiquinone**	
Totals*	**8**	**NR**	**19**	**SIP**	**421**	**0.00006-0.05**
Duration of Use						
Leave-On	*7*	*NR*	*19*	*SIP*	*387*	*0.00075-0.05*
Rinse-Off	*1*	*NR*	*NR*	*SIP*	*34*	*0.000006-0.03*
Diluted for (Bath) Use	*0*	*NR*	*NR*	*SIP*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	SIP	21	0.02
Incidental Ingestion	NR	NR	NR	SIP	2	NR
Incidental Inhalation-Spray	2[a]; 3[b]	NR	7[a];10[b]	SIP	202[a]; 126[b]	0.00075-0.01[a]
Incidental Inhalation-Powder	3[b]	NR	10[b]	SIP	126[b]	0.05[c]
Dermal Contact	8	NR	19	SIP	406	0.00075-0.05
Deodorant (underarm)	NR	NR	NR	SIP	NR	NR
Hair - Non-Coloring	NR	NR	NR	SIP	12	0.000006-0.01
Hair-Coloring	NR	NR	NR	SIP	NR	NR
Nail	NR	NR	NR	SIP	1	NR
Mucous Membrane	NR	NR	NR	SIP	3	NR
Baby Products	NR	NR	NR	SIP	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

SIP – survey in progress

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.	47,48
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.	47,48
Ubiquinone	Mice	NR	NR	NR	>4000 mg/kg. No death or toxic symptoms were observed during the one-week observation period.	30
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.	49
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.	19
Ubiquinone	Rats	NR	NR	NR	>4000 mg/kg. No death or toxic symptoms were observed during the one-week observation period.	30
Ubiquinone	Rats	NR	Corn oil	1250, 2500, or 5000 mg/kg	>5,000 mg/kg	30

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).	3
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.	4
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	5 wk	NR	doses not stated; administered orally	Toxic effects observed at a dose of 2500 mg/kg/d proved reversible within a 5-wk recovery period. The non-toxic oral dose was determined to be 500 mg/kg/d (statistical significance not provided).	47
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)	47
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).	4
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)	47
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.	4
Hydroxydecyl Ubiquinone	Beagle dogs (# not specified)	39 wk, with 8-wk recovery	NR	0, 500, 750, 1000 mg/kg/d, via gavage	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).	3,4

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.	[35]
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.	[35]
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. An NOAEL of 600 mg/kg/d was determined.	[35]
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).	[30]

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	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).	[19]
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	No difference in the body weight, food intake, organ weights, or blood biochemistry of the treated animals compared to controls was observed.	[49]
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.	[30]
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.	[12]
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).	[35]
Ubiquinone	Sprague-Dawley rats (10/sex)	13 wk	Corn oil	0, 300, 600, 1200 mg/kg/d, via gavage	No deaths 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.	[16]
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).	[35]
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.	[50]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
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.	[42]

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).	[47]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	NR	Up to 500 mg/kg d	NR	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.	[3]
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).	[3]
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.	[4]
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.	[4]

Table 6. Developmental and Reproductive Toxicity Studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
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).	3
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).	4
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.	3,4
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).	4
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).	30
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.	49
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).	51
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).	30

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.	[4]
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.	[4]
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	[40]
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.	[40]
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	[17]
Ubiquinone, >98%	Up to 5000 µg/plate, with or without metabolic activation	*S. typhimurium* strains TA97, TA98, TA100, TA102	Ames test	Not genotoxic	[49]
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]
Ubiquinone*	Up to 5000 µg/plate	*S. typhimurium* strains TA98, TA100, TA1535, TA1537, and *E. coli* WP2 *uvr*A	Ames test	Not genotoxic	[30]
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.	[17]
Ubiquinone*	Up to 5000 µg/ml	Chinese hamster lung fibroblast cell line (CHL/IU)	Chromosomal aberration test	Not genotoxic	[52]
		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	[3]
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.	[40]

Table 7. Genotoxicity studies

Ingredient (Vehicle)	Dose/Concentration	Cell/Strain/Species	Method	Results	Reference
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	[49]
Ubiquinone	2000 mg/kg/d	Mice (# not stated)	Micronucleus test	Not genotoxic	[30]

* Composition not specified
NR- not reported

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2020 FDA VCRP Frequency of Use Data – Ubiquinone Ingredients
Total Use: 448

Hydroxydecyl Ubiquinone
Total: 8

CAS_NUMBER	INGREDIENT_NAME	CATEGORY_CODE	CATEGORY_DESCRIPTION	CPIS_COUNT
999001841	HYDROXYDECYL UBIQUINONE	12C	Face and Neck (exc shave)	3
999001841	HYDROXYDECYL UBIQUINONE	12F	Moisturizing	2
999001841	HYDROXYDECYL UBIQUINONE	12H	Paste Masks (mud packs)	1
999001841	HYDROXYDECYL UBIQUINONE	12J	Other Skin Care Preps	2

Ubiquinol
Total: 19

56275399	UBIQUINOL	03G	Other Eye Makeup Preparations	1
56275399	UBIQUINOL	12C	Face and Neck (exc shave)	9
56275399	UBIQUINOL	12D	Body and Hand (exc shave)	1
56275399	UBIQUINOL	12F	Moisturizing	4
56275399	UBIQUINOL	12G	Night	1
56275399	UBIQUINOL	12I	Skin Fresheners	2
56275399	UBIQUINOL	12J	Other Skin Care Preps	1

Ubiquinone
Total: 421

1339635	UBIQUINONE	03D	Eye Lotion	14
1339635	UBIQUINONE	03G	Other Eye Makeup Preparations	7
1339635	UBIQUINONE	05A	Hair Conditioner	1
1339635	UBIQUINONE	05F	Shampoos (non-coloring)	3
1339635	UBIQUINONE	05G	Tonics, Dressings, and Other Hair Grooming Aids	3
1339635	UBIQUINONE	05I	Other Hair Preparations	5
1339635	UBIQUINONE	07C	Foundations	4
1339635	UBIQUINONE	07I	Other Makeup Preparations	5
1339635	UBIQUINONE	08C	Nail Creams and Lotions	1
1339635	UBIQUINONE	09A	Dentifrices	1
1339635	UBIQUINONE	09C	Other Oral Hygiene Products	1
1339635	UBIQUINONE	10A	Bath Soaps and Detergents	1
1339635	UBIQUINONE	11A	Aftershave Lotion	1
1339635	UBIQUINONE	11E	Shaving Cream	1
1339635	UBIQUINONE	12A	Cleansing	9
1339635	UBIQUINONE	12C	Face and Neck (exc shave)	107
1339635	UBIQUINONE	12D	Body and Hand (exc shave)	19
1339635	UBIQUINONE	12F	Moisturizing	164
1339635	UBIQUINONE	12G	Night	26
1339635	UBIQUINONE	12H	Paste Masks (mud packs)	17
1339635	UBIQUINONE	12I	Skin Fresheners	4
1339635	UBIQUINONE	12J	Other Skin Care Preps	22
1339635	UBIQUINONE	13A	Suntan Gels, Creams, and Liquids	3
1339635	UBIQUINONE	13B	Indoor Tanning Preparations	1
1339635	UBIQUINONE	13C	Other Suntan Preparations	1

Concentration of Use by FDA Product Category – Ubiquinone, Disodium Ubiquinone and Hydroxydecyl Ubiquinone*

Ingredient	Product Category	Maximum Concentration of Use
Ubiquinone	Eye shadows	0.02%
Ubiquinone	Hair conditioners	0.000006-0.001%
Ubiquinone	Shampoos (noncoloring)	0.001%
Ubiquinone	Tonics, dressings and other hair grooming aids Not spray	0.01% 0.001%
Ubiquinone	Body and hand products Not spray	 0.05%
Ubiquinone	Moisturizing products Not spray	 0.005%
Ubiquinone	Paste masks and mud packs	0.03%
Ubiquinone	Other skin care preparations	0.01%
Ubiquinone	Indoor tanning preparations	0.00075%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2018

Table prepared January 17, 2019

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: June 25, 2020

SUBJECT: Ubiquinone

Anonymous. 2020. Method of manufacture and impurities: Ubiquinone.

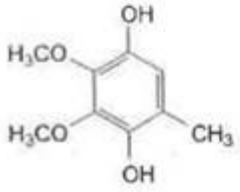
Anonymous. 2020. Study summaries: Skin irritation; Skin Sensitization (Ubiquinone).

June 2020

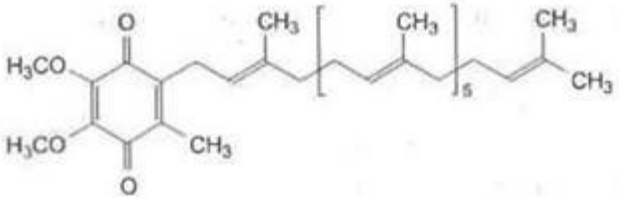
Method of Manufacture and Impurities - Ubiquinone

1. Microbial fermentation is used for manufacturing Ubiquinone (CoQ10).
   CoQ10 is produced by fermentation with yeast, it does not contain cis-isomer (all-trans type CoQ10). The content of CoQ10 is over 98%, with CoQ9 and CoQ11 as major impurities.

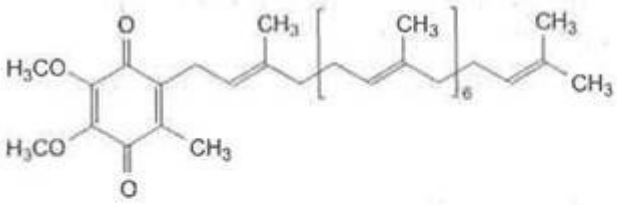
2. Impurity profile: According to European Pharmacopoeia 9.0 (EP) the following impurities are possible, where we only detect the impurity D with a concentration of less than 0.3%.



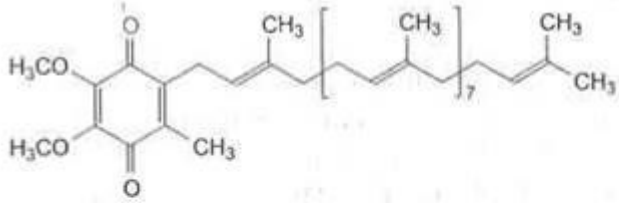
A. 2,3-dimethoxy-5-methylbenzene-1,4-diol,



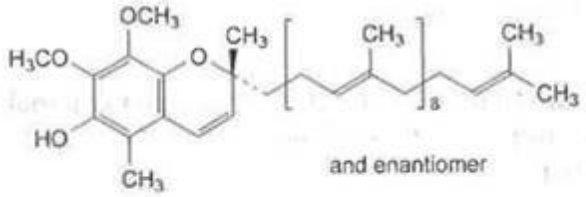
B. 2-[(*all-E*)-3,7,11,15,19,23,27-heptamethyloctadocosa-2,6,10,14,18,22,26-heptaenyl]-5,6-dimethoxy-3-methylbenzene-1,4-dione (ubiquinone-7),



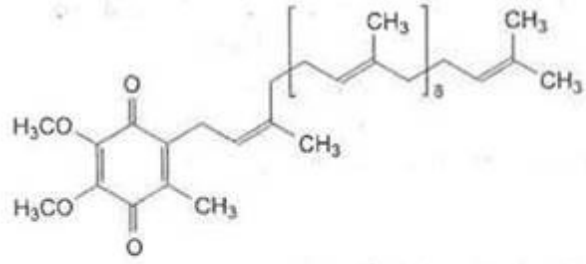
C. 5,6-dimethoxy-3-methyl-2-[(*all-E*)-3,7,11,15,19,23,27,31-octamethyldotriaconta-2,6,10,14,18,22,26,30-octaenyl]-benzene-1,4-dione (ubiquinone-8),



D. 5,6-dimethoxy-3-methyl-2-[(*all-E*)-3,7,11,15,19,23,27,31,35-nonamethylhexatriaconta-2,6,10,14,18,22,26,30,34-nonaenyl]benzene-1,4-dione (ubiquinone-9),



E. (2*RS*)-7,8-dimethoxy-2,5-dimethyl-2-[(*all-E*)-4,8,12,16,20,24,28,32,36-nonamethylheptatriaconta-3,7,11,15,19,23,27,31,35-nonaenyl]-2*H*-1-benzopyran-6-ol (ubicromenol),



F. 2-[(2*Z*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3,7,11,15,19,23,27,31,35,39-decamethyltetraconta-2,6,10,14,18,22,26,30,34,38-decaenyl]-5,6-dimethoxy-3-methylbenzene-1,4-dione (ubidecarenone (*Z*)-isomer),

June 2020

Content

Skin irritation

Reference	Examination of the Product "Substanz 312-01" Batch 405825 Concentration: undiluted by Human Patch Test
Study type	Human Patch Test
Guideline & deviations	COLIPA: Walker et al. (1996) Test Guidelines for assessment of skin compatibility of cosmetic finished products in man. Food Chem Toxicol. 34: 651-660.
GLP	No
Test substance/batch	[redacted] 1% Ubiquinone, 5% Tocopheryl Acetate, 94% Squalane
Test system	Human
Species/strain/sex	50 volunteers (of which 30 normal healthy human subjects, 6 eczema patients, 14 with sensitive skin, 0 allergy patients), sex not reported, age 18-65
Dosage/concentration	undiluted
Procedure	The test substance was applied undiluted in square test chambers (Haye's Test Chambers, HAL Allergie GmbH, Düsseldorf, Germany) to the back of panelists for 48 hours. Sodium Dodecyl Sulfate (1% SDS) 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 48h (30 min after patch removal) and 72 h after patch application.
Report date	July 23, 2003
Conclusion	A 1% formulation of ubiquinone is not irritating. An average score of 0.0 was observed for all three evaluation criteria at both time points.

Skin sensitization

Reference	Examination of the Product "Substanz 312-02" Charge 40930301 Concentration: undiluted by Repeated Human Patch Test (Cosmetic Trial)
Study type	Human Repeated Patch Test (HRIPT)
Guideline & deviations	COLIPA: Walker et al. (1996) Test Guidelines for assessment of skin compatibility of cosmetic finished products in man. Food Chem Toxicol. 34: 651-660.
GLP	No
Test substance/batch	[redacted] 1% Ubiquinone, 5% Tocopheryl Acetate, 94% Squalane
Test system	Human
Species/strain/sex	50 volunteers (of which 24 normal healthy subjects, 8 eczema patients, 18 with sensitive skin, 0 allergy patients), sex not reported, age 26-58
Dosage/concentration	undiluted
Procedure	The test substance was applied undiluted in square test chambers (Haye's Test Chambers, HAL Allergie GmbH, Düsseldorf, Germany) to the back of panelists for three weeks, three times weekly for a period of 24 h under occlusion. After 2 weeks without treatment, test-chambers filled with the test item were applied to both the previously treated and a previously untreated area to test for possible sensitization. Treatment sites were assessed for erythema, scaling and fissure formation using 5 point visual scores at 24h (30 min after patch removal), 48h, 72h and 96h after patch application.
Report date	March 28, 2007
Conclusion	A 1% formulation of ubiquinone did not cause irritation or sensitization after repeated administration. Average scores of 0.0 were observed for all three evaluation criteria, at all time points and for both application areas (pretreated / untreated).

Reference	A skin sensitization study of Coenzyme Q10 in guinea pigs (Maximization test)
Study type	Guinea Pig Maximization Test
Guideline & deviations	Similar to OECD Test Guideline 406
GLP	Not stated
Test substance/batch	Coenzyme Q10, batch not given, purity not given
Test system	Guinea Pig
Species/strain/sex	Crj:Hartley, SPF, 6 weeks old 10 animals per test group, 5 animals per control group
Dosage/concentration	Induction: intradermal: 1.25% dermal: 6.3% Challenge: 6.3% Negative control: physiological saline Positive control: 0.1% 2,4-dinitrochlorobenzene (DNCB), 10% SDS Vehicle: 0.5% methyl cellulose in water for intradermal application, petrolatum for dermal application.
Procedure	The highest non-irritating doses for induction and challenge were determined in a pre-experiment with doses of 0.005-5.0% (intradermal) and 0.24-25% (dermal).Further test procedure followed the OECD TG 406.
Report date	July 25, 1996
Conclusion	In the test item group and in the negative control group, no skin reactions were observed at the 24-72h readings. Occasional cases of very slight erythema were observed directly after patch removal bur regressed within 24h. In the positive control group, well defined erythema were observed in all animals after challenge with DCNB. Based on this test, coenzyme Q10 at a concentration of up to 6.3% is neither a skin irritant nor a sensitizer.

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 20, 2020

SUBJECT: Hydroxydecyl Ubiquinone

Clinical Research Laboratories, Inc. 2012. Repeated insult patch test (cream containing 0.01% Hydroxydecyl Ubiquinone).

Clinical Research Laboratories, Inc.

Final Report

Repeated Insult Patch Test

CLIENT: [redacted]

ATTENTION: Megan Nicoletti
Senior Clinical Test Scientist

TEST MATERIAL: Cream containing 0.01% Hydroxydecyl Ubiquinone
F#199361, B#199358,
REF#BPS12-06-PT53

CRL STUDY NUMBER: CRL70612 n=100 Sensitive Skin Panel

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

Anita Lee Cham, M.D.
Dermatologist

REPORT DATE: August 17, 2012

371 Hoes Lane, Suite 100 • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical Research Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL70612

Start Date: June 18, 2012

Completion Date: July 27, 2012

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Eileen Vogt
Signature of QA Auditor

8/17/12
Date

[redacted]

Clinical Research Laboratories, Inc.

FINAL REPORT

REPEATED INSULT PATCH TEST

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material on a panel of 100 subjects with at least 50% reporting self-perceived sensitive skin.

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane Suite 100
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by [redacted] and was received by Clinical Research Laboratories, Inc. on June 13th, 2012:

Test Material	Test Condition	Patch Type
Cream F#199361, B#199358, REF#BPS12-06-PT53	Applied to the patch as received	Semi-occlusive*

The test material was coded with the following CRL identification number:

CRL70612

STUDY DATES

This study was initiated on June 18, 2012 and was completed on July 27, 2012.

* Semi-occlusive Strip (Brady Medical, Mesquite,TX)

[redacted]

Clinical Research Laboratories, Inc.

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Subject Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;

b. At least 50% of the male and female subjects reporting self-perceived sensitive skin;

c. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;

d. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

e. Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

f. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

g. Subjects in generally good health who have a current Subject Profile/Medical History on file;

h. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;

b. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

c. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

[redacted]

Clinical Research Laboratories, Inc.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back (between the scapulae) and was allowed to remain in direct skin contact for a period of 24 hours.

Patches were applied to the same site on Monday, Wednesday, and Friday for a total of 9 applications during the Induction Period. This schedule may have been modified to allow for missed visits or holidays. If a subject was unable to report on an assigned test date, the test material was applied on 2 consecutive days during the Induction Phase and/or a makeup day was added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation 24 hours after removal of the patches by the subjects on Tuesday and Thursday and 48 hours after removal of the patches on Saturday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scoring Scale

0 No visible skin reaction
± Barely perceptible erythema
1+ Mild erythema
2+ Well defined erythema
3+ Erythema and edema
4+ Erythema and edema with vesiculation

If a "2+" reaction or greater occurred, the test material was applied to an adjacent virgin site. If a "2+" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than a "2+" may have been changed.

Following approximately a 2-week rest period, the challenge patches were applied to previously untreated test sites on the back. After 24 hours, the patches were removed by a CRL technician and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 48 and 72 hours. Subjects exhibiting reactions during the Challenge Phase of the study may have been asked to return for a 96-hour reading.

[redacted]

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RESULTS

This study was initiated with 112 subjects with a population of at least 50% self-perceived sensitive skin. Five subjects discontinued study participation for reasons unrelated to the test material. A total of 107 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 107 subjects and under the conditions of this study, the test material identified as Cream, F#199361, B#199358, REF#BPS12-06-PT53 did not demonstrate a clinically significant potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

[redacted]

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TABLE I

Summary of Dermal Scores

Test Material:	Cream F#199361, B#199358, REF#BPS12-06-PT53

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
1	0	0	0	0	0	0	0	0	0	0	0	0
2	0	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0
5	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	0	0	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0
8	0	0	0	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0
13	±	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0
17	0	±	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0
19	0	0	0	0	0	0	0	0	0	0	0	0
20	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0
23	0	Discontinued										
24	0	0	0	0	0	0	0	0	0	0	0	0
25	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

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TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Cream F#199361, B#199358, REF#BPS12-06-PT53

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
26	0	0	0	0	0	0	0	0	0	0	0	0
27	0	0	0	0	0	0	0	0	0	0	0	0
28	0	0	0	0	0	0	0	0	0	0	0	0
29	0	0	0	0	0	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0	0	0	0	0	0
31	0	0	0	0	0	0	0	0	0	0	0	0
32	0	0	0	0	0	0	0	0	0	0	0	0
33	0	0	0	0	0	0	0	0	0	0	0	0
34	0	0	0	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	0	0	0	0	0
36	0	0	0	0	0	0	0	0	0	0	0	0
37	0	Discontinued										
38	0	±	0	0	0	0	0	0	0	0	0	0
39	0	0	0	0	0	0	0	0	0	0	0	0
40	0	0	0	0	0	0	0	0	0	0	0	0
41	0	0	0	0	0	0	0	0	0	0	0	0
42	0	0	0	0	0	0	0	0	0	0	0	0
43	0	0	0	0	0	0	0	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0
45	0	0	0	±	0	0	0	0	0	0	0	0
46	0	0	0	0	0	0	0	0	0	0	0	0
47	0	0	0	0	0	0	0	0	0	0	0	0
48	0	0	0	0	0	0	0	0	0	0	0	0
49	0	0	0	0	0	0	0	0	0	0	0	0
50	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

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TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Cream F#199361, B#199358, REF#BPS12-06-PT53

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
51	0	0	0	0	0	0	0	0	0	0	0	0
52	0	0	0	0	0	0	0	0	0	0	0	0
53	0	0	0	0	0	0	0	0	0	0	0	0
54	0	0	0	0	0	0	0	0	0	0	0	0
55	0	Discontinued										
56	0	0	0	0	0	0	0	0	0	0	0	0
57	0	0	0	0	0	0	0	0	0	0	0	0
58	0	0	0	0	0	0	0	0	0	0	0	0
59	0	0	0	0	0	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0	0	0	0	0	0
61	0	0	0	0	0	0	0	0	0	0	0	0
62	±	±	0	0	0	0	0	0	0	0	0	0
63	0	0	0	0	0	0	0	0	0	0	0	0
64	0	0	0	0	0	0	0	0	0	0	0	0
65	0	0	0	0	0	0	0	0	0	0	0	0
66	0	0	0	0	0	0	0	0	0	0	0	0
67	0	0	0	0	0	0	0	0	0	0	0	0
68	0	0	0	0	0	0	0	0	0	0	0	0
69	0	0	0	0	0	0	0	0	0	0	0	0
70	0	0	0	0	0	0	0	0	0	0	0	0
71	0	0	0	0	0	0	0	0	0	0	0	0
72	0	0	±	0	0	0	0	0	0	0	0	0
73	0	0	0	0	0	0	0	0	0	0	0	0
74	0	0	0	0	0	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Cream F#199361, B#199358, REF#BPS12-06-PT53

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
76	0	0	±	0	0	0	0	0	0	0	0	0
77	0	0	0	0	0	0	0	0	0	0	0	0
78	0	0	0	0	0	0	0	0	0	0	0	0
79	±	0	0	0	0	0	0	0	0	0	0	0
80	0	0	0	0	0	0	0	0	0	0	0	0
81	0	0	0	0	0	0	0	0	0	0	0	0
82	0	0	0	0	0	0	0	0	0	0	0	0
83	0	0	0	0	0	0	0	0	0	0	0	0
84	0	0	0	0	0	0	0	0	0	0	0	0
85	0	0	0	0	0	0	0	0	0	0	0	0
86	0	0	0	0	0	0	0	0	0	0	0	0
87	0	0	0	0	0	0	0	0	0	0	0	0
88	0	0	0	0	0	0	0	0	0	0	0	0
89	0	0	0	0	0	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0	0	0	0	0	0
91	0	0	0	0	0	0	0	0	0	0	0	0
92	0	0	0	0	0	0	0	0	0	0	0	0
93	0	0	0	0	0	0	0	0	0	0	0	0
94	0	0	0	0	0	0	0	0	0	0	0	0
95	0	0	Discontinued									
96	0	0	0	0	0	0	0	0	0	0	0	0
98	0	0	0	0	0	0	0	0	0	0	0	0
97	0	0	0	0	0	0	0	0	0	0	0	0
99	0	0	0	0	0	0	0	0	0	0	0	0
100	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

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TABLE I
(Continued)

Summary of Dermal Scores

Test Material:	Cream F#199361, B#199358, REF#BPS12-06-PT53

Subject Number	Induction Scores									Challenge Scores		
	1	2	3	4	5	6	7	8	9	24 Hour	48 Hour	72 Hour
101	0	0	0	0	0	0	0	0	0	0	0	0
102	0	0	0	0	0	0	0	0	0	0	0	0
103	0	0	0	0	0	0	0	0	0	0	0	0
104	0	0	Discontinued									
105	0	0	0	0	0	0	0	0	0	0	0	0
106	0	0	0	0	0	0	0	0	0	0	0	0
107	0	0	0	0	0	0	0	0	0	0	0	0
108	0	0	0	0	0	0	0	0	0	0	0	0
109	0	0	0	0	0	0	0	0	0	0	0	0
110	0	0	0	0	0	0	0	0	0	0	0	0
111	0	0	0	0	0	0	0	0	0	0	0	0
112	0	0	0	0	0	0	0	0	0	0	0	0

[redacted]

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Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex	SS
1	JD	23249	65	M	Y
2	LB	10403	38	F	N
3	SP	27672	23	F	Y
4	AS	28452	25	F	Y
5	SC	28066	38	F	N
6	IT	24222	23	M	N
7	JC	28801	21	F	Y
8	JR	16675	50	M	Y
9	MP	12044	67	F	N
10	MA	28408	46	F	Y
11	TV	28165	69	M	Y
12	RB	17462	67	F	Y
13	MM	26453	43	F	Y
14	DB	20814	49	F	N
15	AB	23859	47	F	Y
16	DD	24488	47	M	Y
17	ER	28579	27	F	N
18	JR	27810	22	F	N
19	VW	28530	53	F	Y
20	AC	27383	27	M	Y
21	KS	26856	38	F	N
22	JM	27983	54	M	N
23	MG	12004	42	F	Y
24	ES	25974	38	F	Y
25	TY	19871	19	F	N
26	JB	5654	61	F	Y
27	YH	20126	20	F	Y
28	NB	26982	20	M	N

Subject Number	Subject Initials	CRL ID #	Age	Sex	SS
29	BK	28488	57	F	Y
30	AL	21695	49	F	N
31	PK	28231	51	M	N
32	ME	1693	56	F	Y
33	AZ	29282	52	F	Y
34	MT	28566	59	F	Y
35	NC	13743	53	F	N
36	NM	26036	20	F	N
37	GL	29232	57	F	N
38	CG	6152	55	F	Y
39	AM	28043	35	F	N
40	AM	29034	64	F	Y
41	HP	19293	50	F	Y
42	LD	8089	48	F	Y
43	SD	28052	51	F	N
44	JT	14794	29	M	N
45	MS	29410	40	F	Y
46	JH	29431	46	F	Y
47	OS	29248	31	F	N
48	ED	4270	59	F	N
49	RH	4483	66	F	Y
50	RM	28560	50	F	Y
51	EN	14911	58	F	Y
52	LM	21835	59	F	N
53	CL	23572	59	F	N
54	RJ	26054	55	M	Y
55	MQ	22705	48	F	N
56	EH	21115	64	F	Y

SS = Sensitive Skin

[redacted]

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Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex	SS
57	KM	23648	37	F	Y
58	KL	24236	21	M	N
59	MB	28768	47	F	N
60	DL	24237	53	F	Y
61	LE	5354	53	F	Y
62	SV	25776	41	F	N
63	JM	14638	53	M	Y
64	TF	15223	43	F	N
65	MC	6682	65	F	Y
66	JA	15371	42	F	N
67	DH	29206	38	F	Y
68	DH	25303	21	M	N
69	MM	15079	61	F	N
70	KK	23803	34	M	N
71	DS	27585	49	M	N
72	BT	25554	20	F	Y
73	ZQ	26318	66	F	Y
74	RS	5543	46	M	N
75	AG	21336	39	F	Y
76	SW	19412	50	F	N
77	TS	28702	38	F	Y
78	DP	22298	19	F	N
79	MS	25726	38	F	N
80	DB	12161	53	F	N
81	TC	20058	56	M	N
82	DH	27673	24	M	N
83	DG	11059	27	F	Y
84	AJ	23193	49	F	N

Subject Number	Subject Initials	CRL ID #	Age	Sex	SS
85	DR	29332	56	F	N
86	KH	15618	63	F	Y
87	RV	8103	34	F	N
88	PW	24387	60	F	Y
89	SL	23916	20	F	Y
90	AF	21927	51	F	N
91	JB	14759	60	F	Y
92	SP	17861	54	F	Y
93	MC	29195	27	F	Y
94	JA	21286	51	F	Y
95	TW	23785	33	F	N
96	EG	22803	23	F	N
97	IC	6700	56	F	N
98	LL	8362	58	F	N
99	KF	14304	56	F	N
100	NP	1958	42	F	N
101	SA	27861	47	F	Y
102	AB	28644	37	F	Y
103	LT	28423	42	F	Y
104	BS	28829	22	F	Y
105	MP	28968	50	F	Y
106	MB	9885	53	F	N
107	SB	27651	19	F	Y
108	DD	6570	54	F	Y
109	AS	25836	34	F	Y
110	CB	3339	58	F	Y
111	LA	28103	50	F	N
112	GM	20904	42	F	Y

SS = Sensitive Skin

	2008). However, see above for certain side effects occurring at ca. 100 mg/day when CoQ10 is used medicinally or consumed in the form of food supplements.

5. Exposure estimate and critical NOAEL / NOEL

NOAEL/NOEL critical	A NOAEL **based on ordinary toxicity effects** has not been derived in **humans** because of absence of well-defined critical adverse effect of CoQ10. The observations of certain transient adverse side effects occurring in ca. 2 % of the individuals related to exposure level of approximately 100 mg /day CoQ10 (oral intake) cannot be utilized in this connection. Here, we consider the hypotensive effect of CoQ10 as an **adverse** side effect in the context of cosmetic products. For background information and more details, see Annex 7. A sufficient safeguarding of the mentioned consumers (Annex 7) would be to restrict the use of CoQ10 in cosmetics so as to prevent occurrence of any significant hypotensive effects. The Norwegian MPA is of the opinion that CoQ10 causes blood pressure lowering at oral intakes in excess of 100 mg/day. The dosages being used in clinical tests for blood lowering effects are higher and in the range 120 – 200 mg/day. On this background we consider an oral intake of 100 mg/day a no adverse effect level in humans in relation to the hypotensive effect. We call it the NOAEL $_{hypotension}$ in order to distinguish it from the NOAEL established on the basis of ordinary animal toxicity data (*inter alia*). It has been established that the bioavailability of some commonly occurring supplements in humans varied from 10% to 22 % with a mean of 15 %. To estimate the **systemic** NOAEL $_{hypotension}$ corresponding to the oral NOAEL $_{hypotension}$ we assume a bioavailability of 15 %. Further, we apply the SCCS default value of 60 kg for the body weight (adult female). Thus, the calculated **systemic** NOAEL $_{hypotension}$ (i.e. hypotensive effect) is 100 x 0.15/60 = **0.25 mg /kg bw/day in humans**. A NOAEL of 1200 mg /kg bw /day **in rats** was derived from a 52-week chronic toxicity study (Williams *et al*., 1999; Hidaka *et al*., 2008), and from a 13-weeks sub chronic toxicity study in rats (Honda et al., 2007). Assuming a bioavailability in rats of 2% (*inter alia*) this NOAEL corresponds to a **systemic** NOAEL in rats of 24 mg/kg bw/day. The NOAEL $_{hypotension}$ is derived from **human data** and is 3 orders of magnitude less than the NOAEL derived from the **rat** study. For the purpose of estimating the margin of safety (MoS), we choose to use the NOAEL of 0.25 mg /kg bw /day as this value represent the most sensitive adverse effect (i.e. hypotension).
Exposure cosmetic products	The exposure calculations are based on default values[15] according to Cosmetic Europe (SCCS [online]). Anti-aging cream containing 1% CoQ10 was used to represent typical use levels.

[15] Default values for skin-care product are used for the calculations; cf. table 3, SCCS Notes of Guidance, 7th revision).

	SED = **A** (mg/kg bw/day) x **C** (%)/100 x **DA_p** (%)/100 • **Body lotion** Calculated relative daily exposure of product: 123.20 mg/kg bw/day Concentration of ingredient in the product: 1% = 0.01 Dermal absorption (assumed): 2% = 0.02 SED = 123.20 x 0.01 x 0.02 = **0.0246 mg /kg bw /day** • **Face cream** Calculated relative daily exposure of product: 24.14 mg/kg bw/day Concentration of ingredient in the product: 1% = 0.01 Dermal absorption (assumed): 2% = 0.02 SED = 24.14 x 0.01 x 0.02 = **0.0048 mg /kg bw /day** • **Hand cream** Calculated relative daily exposure of product: 32.70 mg/kg bw/day Concentration of ingredient in the product: 1% = 0.01 Dermal absorption (assumed): 2% = 0.02 SED = 32.70 x 0.01 x 0.02 = **0.0065 mg /kg bw /day** Overall SED (=body lotion + face cream) = 0.0246 + 0.0048 = 0.0294 mg/kg bw/day
Margin of Safety (MoS)	MoS calculations based on the $NOAEL_{hypotension}$ MoS = $NOAEL_{hypotension}$ /SED **MoS for body lotion**: SED = 0.0246 mg/kg bw/day MoS = 0.25 / 0.0246 = **10.2** **MoS for face cream**: SED = 0.0048 mg/kg bw/day MoS = 0.25 / 0.0048 = **52.1** **MoS for hand cream**: SED = 0.0065 mg/kg bw/day MoS = 0.25 / 0.0065 = **38.5** MoS (overall exposure from cosmetics): SED = 0.0294 mg/kg bw/day MoS = 0.25 / 0.0294 = **8.5** By comparison, if NOAEL instead is derived from the rat-data the MoS increases to (24/0.0246 =) 975 for the body lotion usage – and even higher for the usage of the two other product types.

7. Assessment

Coenzyme Q10 (CoQ10) is a naturally occurring component present in living cells, acting as an essential cofactor for ATP production (i.e cellular energy). It is also a potent lipophilic antioxidant, implicated in the protection of cellular components from free radical damage. Moreover, CoQ10 is capable of recycling and regenerating other antioxidants such as vitamin E and vitamin C.

CoQ10 came in use as a cosmetic ingredient in the late 90s and is today widely employed in this product segment. It functions as an active ingredient – and then for the most part in cosmetic products claiming an anti-wrinkling effect. *Idebenone* is a synthetic analog that found its way into anti-age cosmetics much later (2005) and that has not come much in use up till now. Molecule' sensitizing properties may possibly explain the lesser popularity.

General toxicity

On the basis of a one-year long toxicity study with rats a NOAEL amounting to large 1200 mg /kg bw /day has been determined (highest dose used). No carcinogenic effects of CoQ10 have been reported. Available data show no mutagenic potential. No reproductive generation toxicity studies with CoQ10 are available.

However, transient adverse effect like headache, dizziness, increased light sensitivity of the eyes, rashes, flu-like symptoms and fatigue occur in a few per cent of people taking in approximately 2 mg /Kg bw per day when treated with CoQ10 based products. Traditionally, these side effects have attracted but little attention. They have largely been ignored the interest in CoQ10 revolving around the different claimed beneficial health effects. Unfortunately, available clinical data are insufficient for estimation of no- adverse-effect levels.

The hypotension effect

There is evidence that CoQ10 possesses the ability to lower blood pressure significantly. The proposed physiological mechanism behind the effect makes us believe that CoQ10 has the ability to lower the blood pressure also in persons with lower blood pressure than normal. The Norwegian medicinal product agency considers CoQ10 a blood pressure lowering remedy at oral exposures exceeding 100 mg/day. The effect has been observed in clinical testing involving people with slightly increased blood pressure. The intake values then were in the range 120 – 200 mg/day. In the western societies millions of people have lower than normal blood pressure for some reason – meaning that a considerable proportion of the general population is affected. Health institutions have warned that unintended further blood pressure lowering in this population because of products containing high amounts of CoQ10, could involve even serious health complications.

Also an unintended further blood pressure lowering effect in people on regular prescribed hypertension medication would be a health problem because it could complicate the medicinal treatment. 12 % of the adult population (35 – 65 years) in the EU are on such medication (Wolf-Maier K 2003). This means that around 20 million people in the EU are affected.

Taking into account the low bio- availability of CoQ10 in humans - assuming 15 % as an average value - we estimate a systemic NOAEL $_{hypotension}$ of 0.25 mg/Kg bw/day. This level is 3 orders of magnitude lesser than the systemic NOAEL based on the rat toxicity data; 24 mg/Kg bw day.

It was only quite recently that it was fully realized CoQ10 actually possesses an inherent significant hypotension effect. Understandably, therefore, no-one has so far tried to find out whether the effect entails also topical exposure for CoQ10. So, as could be expected, there is a void in literature of data on hypotension effects because of use of cosmetics relying on CoQ10 for claimed effects.

Contrary to what would be the situation for a pharmaceutical product with the indication hypertension a hypotension effect would, naturally, be considered an adverse effect in relation to cosmetic products – and not a beneficial one.

Dermal sensitisation (topic treated in section 4 and Annex 4)

Both CoQ10 and Idebenone are naphtoquinones nearly all of which are allergens/haptens. A typical such hapten molecule is composed of a para-quinone moiety on to which is connected a lipophilic side chain. The allergenic potency depends on the length of the side chain. At a length of 11-12 C-units the potency reaches a maximum. The side chain of CoQ10 is 40 C-units long and so this naphtoquinone is expected to show only feebly weak allergenic properties. In compliance with this expectancy there is a complete absence in the literature of case reports on allergenic contact dermatitis reactions – this even though CoQ10 is widely used in cosmetic products.

The situation with Idebenone is radically different. The side chain is optimally long in relation to possessing a sensitizing property (11 C units). Moreover, the low patch test concentration of 0.5 % indicates Idebenone is a strong allergen according to the standards of the SCCS. Also there exist four case reports in the literature on allergic contact dermatitis. A dermatologist report states that they have seen many patients who developed contact dermatitis from skin care products containing Idebenone[17]- which is remarkable in view of the little use being made of the ingredient. This also is confirmed by at least some users experiencing allergic rashes etc. more often with Idebenone, also with seemingly renowned products[18]. It is presently unknown whether this is related to the compound per se or formulation of the products.

These findings raise concerns that allergic contact dermatitis may increase in coming years, with increased awareness and increased use of anti-aging products.

Risk for blood-clotting in persons taking CoQ10 in combination with anti-coagulants

On the background of information presented in Annex 3 we think the weigh of evidence is that taking CoQ10 together with anti-coagulant remedies may weaken the effect of the remedy so that risk for blood-clotting with serious health consequences increases. It remains unknown how common or rare this interaction is. The “NOAEL” for this interaction cannot be determined with any accuracy on the basis of available evidence. About 6 million people are on anti-coagulant remedies in the EU.

Probable cross-allergenicity with last resort 1,4-napthoquinone type drugs may cause life-threatening medicinal situations (topic treated in Annex 4)

Primarily this concerns Idebenone because of its apparent strong allergenicity. Two examples of (generic) drugs in this connection are vitamin K1 (indication: *hypoprothrombinemia*) and atovaquone. (indication: *pneumocystis jiroveci* pneumonia and malaria). Both drugs are allergens. They may be indispensable under particular therapeutic circumstances. Atovaquone may on rare occasions cause even a very serious allergic reaction. Idebenone resembles both vitamin K1 and atovaquone that much structurally, it seems highly probable it cross-react with both molecules meaning that individuals who are allergic to Idebenone also are allergic to vitamin K1 and atovaquone.

Persons havening acquired a Vitamin K1 allergy cannot undergo medicinal treatment with the substance and so may end up in life threatening situations. Vitamin K1 was banned in cosmetic in 2010 because of this health threat. Likewise persons allergic to Idebenone can receive neither vitamin K1 nor atovaquone therapy and might experience the same critical situation.

Margin of safety (MoS) for usage of different cosmetic products

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We estimate the MoS on the basis of the systemic NOAEL for the hypotension effect in humans. It is an adverse effect in relation to use of cosmetic products (*inter alia*). It is 3 orders of magnitude smaller than a NOAEL based on toxicity data obtained in studies with rats.

[17] http://www.skintherapyletter.com/2008/13.7/2.html

[18] http://www.savvyskin.com/prevage-md-vs-generic-idebenone

We calculate a MoS of 0.25 mg/Kg bw/day , taking into account systemic exposure doses (SED) varying according to e.g. surface area (total body, face, hands) of application and frequency of use per day. 1% CoQ10 represented typical use levels[19]. The skin penetration rate is assumed to be 2% taking into consideration that CoQ10 in at least some of the anti-age products is together with efficient vehicles in the formulation.

MoS (body lotion): = 0.25 / 0.0246 = **10.2**
MoS (face cream): 0.25 / 0.0048 = **52.1**
MoS (hand cream): 0.25 / 0.0065 = **38.5**

MoS (overall exposure cosmetics): 0.25 / 0.0294 = **8.5**

Because the NOAEL is based on human data, a MoS ≥ 10 represents a sufficient safety margin.

The MoS for the overall exposure is marginally lower than 10. In view of the uncertainties present and the limited chance a consumer uses both CoQ10-body lotions, CoQ10-face creams and CoQ10-hand creams concomitantly, we nevertheless think these data indicate that CoQ10 in topical cosmetic products at the recommended use levels (1%) is without safety concerns. It seems, though, that the concentration level ought not be much higher than 1 % for safety reasons. .

Food supplements:
According to current practice, a daily dose of 100 mg CoQ10 is accepted in dietary supplements in many European countries (including Norway). This is equivalent to (100/60) = 1.67 mg / kg bw /day[20]. More health instances have, however, warned against consumption of CoQ10 supplements by people having a low blood pressure for some reasons. Also the many million hypertensive persons on regular prescribed medication should abstain from CoQ10 supplements because it might otherwise complicate the treatment. The Norwegian Food Safety Authority is in the process of evaluation how these products can be better secured applying suitable measures.

Efficacy of the cosmetic products:
Controlled clinical trials in humans examining the role of antioxidants (including CoQ10) in preventing or decelerating skin aging, have failed to provide convincing evidence for their efficacy.

Pharmacological effects
In a letter 10 December 2007 from the Norwegian MPA to the Norwegian Food Safety Authority the MPA is of the view that usage of CoQ10 and Idebenone at a concentration of 1 % will not mean the product has medicinal properties. This concentration was laid to ground for the evaluation of the MPA because it came out as a “safe” concentration in a preliminary safety assessment applying the “Observed safe level” risk evaluation method[21].

[19] CoQ10 is used in concentrations in the range of 1-3% in anti-wrinkle creams, and less than 1% in general use as an antioxidant.

[20] The acceptable daily intake (ADI) is 12mg/kg/day, calculated from the no-observed-adverse-effect level (NOAEL) of 1200 mg/kg/day derived from a 52-week chronic toxicity study in rats, i.e., 720 mg/day for a person weighing 60 kg. Risk assessment for CoQ10 based on various clinical trial data indicates that the observed safety level (OSL) for CoQ10 is 1200 mg/day/person (Hidaka *et al*., 2007).

[21] Premises used at that time was a NOAEL in humans of 1200 mg/day – and in lack of data also a skin penetration rate of 100 % and a bio-availability of 100%.was applied. The hypotension effect had not been fully recognized in 2007.

8. Conclusion

- **CoQ10:**

Available safety studies indicate that use of CoQ10 in cosmetic products at a maximum concentration of 1 % is without safety concerns. For safety reasons this should be the maximum concentration in cosmetic products.

Warnings

If not in the form of warnings in the label consumers should be advised by use of other information measures to abstain from using products relying on CoQ10 for claimed effect in case they are on medications preventing blood- clotting (warfarin or other such medicine).

- **Idebenone:**

Based on the structural similarity to CoQ10 we are of the view Idebenone can be safely used in cosmetic (all products) up till a concentration of 0.5 %. For safety reasons this should be the maximum concentration in cosmetic products.

Remarks:

- The rational for the lower maximum concentration for Idebenone than for CoQ10 is due to its skin irritating or allergic effects.

- Recent case reports and clinical observations indicate that the use of skin care products containing *Idebenone* (typically 0.5-1%) is associated with increased risk for development of contact dermatitis. Internet search identified several users experiencing serious irritation or allergic reactions to products containing Idebenone, consistent with the view that it is a strong allergen.
  Thus, beware of skin care products with Idebenone. Patch test for at least 10 days on someplace other than your face is recommended.

Warnings

As an alternative to warnings on the label, consumers should be advised not to use cosmetic products with Idebenone if they are on medications preventing blood-clotting (warfarin or similar medication).

Annex 3

The CoQ10- warfarin interaction

Seemingly, in the literature there are 4 case reports that CoQ10 make anti-blood-clotting medications like warfarin or clopidigrel less effective (Sigset O 1994, Combs AB 1976, Landbo C 1998). The case of Landbo is typical. It concern a 70-yr-old woman who had been on warfarin for several years and who experienced a sudden drop in her INR 2 week after starting ubidecarenone 30 mg daily. Ubidecarenone was stopped, and her INR quickly returned to normal. On the interactions between the anti-coagulation remedies and CoQ10 see also Heck AM *et al* (2000).

Later Engelsen *et al* carried out a prospective placebo-controlled trial of 24 stable patients taking warfarin and 100 mg of coenzyme Q10 over four weeks. These authors found no significant change in prothrombin time and INR levels. They concluded that their study indicates Co Q10 do not influence the clinical effect of warfarin (Engelsen JN *et al* 2003). After starting CoQ10 when on anti-coagulation the authors, irrespective of their finds, advice that the INR is controlled within a week

The conflicting results may be due to use of different kinds of CoQ10 products and also differences as to the dosing used. Besides there are great individual differences as concerns the bio-availability. Rat studies suggest that CoQ10 accelerate the metabolism of warfarin. This probably accounts for the reduced anticoagulant effect of warfarin in rats upon concomitant exposure for the two remedies (Qingyu Z *et al* 2005).

On this background we think the weigh of evidence is that taking CoQ10 together with anti-coagulant remedies may weaken the effect of the remedy so that risk for blood-clotting with serious health consequences increases. It remains unknown how common or rare this interaction is.

Between June 1, 2001 and December 31, 2003, 15 persons on warfarin that also consumed CoQ10 took part in a prospective, longitudinal study the outcome of which actually indicate an unfortunate influence opposite of that of risk for blood clotting. The patients in question completed a 16-week diary by recording bleeding events and exposure to factors previously reported to increase the risk of bleeding and supratherapeutic INRs, including CoQ10 consumption. In an adjusted statistical model, statistically significant associations between the use of CoQ10 and bleeding events were identified: OR 3.91, 95% CI 2.09-7.3. (Shalansky S et al 2007). The authors concluded that

> "The use of CoQ10 by patients receiving warfarin is common, and consumption of coenzyme Q_{10} appears to increase the risk of bleeding in this population."

Discussing their find the authors wrote:

> "Previous research evaluating interactions between warfarin and coenzyme Q_{10} has produced conflicting results. Coenzyme Q_{10} is structurally related to menaquinone (vitamin K_2), and there have been several case reports of a decreased response to warfarin after starting coenzyme Q_{10}.(Heck AM *et al* 2000). However, in the only published, double-blind, randomized trial, 4 weeks of coenzyme Q_{10} 100 mg/day did not affect weekly INR results in 24 patients (Engelsen *et al* 2003). As far as we are aware, our study is the first to report an increased *risk of bleeding* in patients taking warfarin and coenzyme Q_{10}. This may represent a previously undetected interaction, or may be the play of chance owing to the small number of patients (15 patients) reporting consumption of coenzyme Q_{10}.

The medicinal therapist Ray Sahelian, M.D expressed that

> The results from studies have been inconsistent, and my impression is that low dosages of 30 mg a few times a week should not interfere with warfarin medication. [22]

[22] http://www.raysahelian.com/warfarin.html

If this estimate holds true – and we have no reason to distrust it – it means that a systemic dose of (30 x 0.15 / (60 x 3) = 0.025 mg/Kg bw/day involves a certain risk for bleeding incidence in a person on warfarin. This dose equals the systemic dose received daily using a body lotion to which CoQ10 is added up till 1%.

Hence it seems unsafe for people on warfarin to use this cosmetic product.

Warfarin remains the standard drug for patients with atrial fibrillation and a moderate or high risk of thrombosis (Wikipedia). It remains the most commonly prescribed “blood thinners” with more than 24 million prescriptions dispensed in the United States in 2006. There are 4.2 million patients in the US on chronic warfarin [23] - 1.2 million people in the UK. [24] More than 6 million patients in Europe are living on long-term oral anticoagulation. [25]

We hold it probable that in Europe many thousands on warfarin use cosmetics containing CoQ10 each day.

[23] http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtlt_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&cntvwrPtlt%7BactionForm.contentReference%7D=cap_today%2F0111%2F0111e_study.html&_pageLabel=cntvwr

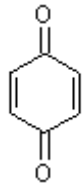
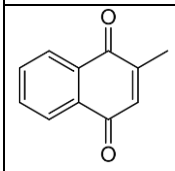
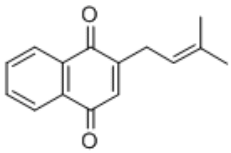
[24] http://www.roche.co.uk/portal/uk/2013_press_releases?siteUuid=re7208002&paf_gear_id=41800051&pageId=re7734007&synergyaction=show&paf_dm=full&nodeId=1414-9626b43b7b3811e2a065efe0692339e3&currentPage=0

[25] http://www.ismaap.org/

Annex 4

The probability that ubiquinone and idebenone cross-react with vitamin K1 and other important drugs as concerns allergy

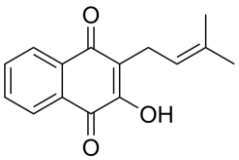
Data obtained over the years from case studies and studies with experimental animals makes it clear that spare a few exceptions[26] the known benzoquinones and naphthoquinones possess allergenic properties. It concerns chemicals that are strong electrophiles which react easily with nucleophilic groups of proteins (-NH2, -SH), acting thereby as pronounced haptens.[27][28] The following example molecules have been studied as to their sensitizing/allergenic potency (allergenic contact dermatitis).

Identity	Comments	References
 1,4-benzoquinone CAS No 106-51-4	The extreme sensitization potency of benzoquinone can be attributed to its high reactivity as a Michael acceptor The LLNA EC3 value is: 0.01 %	Roberts DW et al 2009
 Vitamin K3 (Menadione) INCI: Menadione INN: menadione CAS No 58-27-5	At least 4 case reports Guinea pig maximilisation test show strong eliciting effect Mentioned in CosIng (masking ingredient) Drug indication: Hypoprothrombinemia	Mukhyaprana M *et al* 2005 and the references 8,9 and 10 therein Schultz KH *et al* 1977
 Desoxylapachol	Significant contact allergen because of: proven strong contact allergenic effect in humans after short and/or almost negligible exposure taking into	Schlede E *et al* 2003

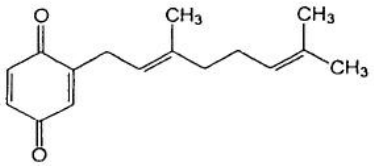
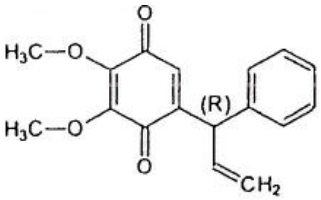
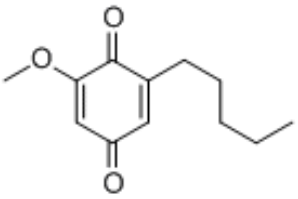
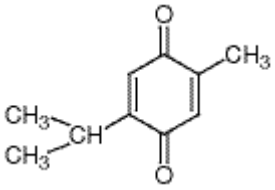
[26] For example the molecule 2,5-dimethoxy-1,4-benzoquinone (Cramer D *et al* 1987)

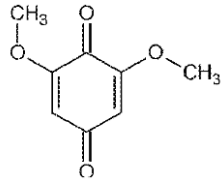
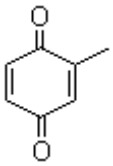
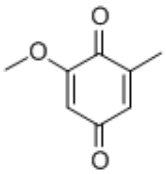
[27] The quinoid moiety lends itself to nucleophilic attack by protein side-chain-groups like the imidazole group of histidine, the epsilon amino group of lysine or the sulfhydryl group of cysteine.

[28] They also are generally known to be alkylating agents possessing high acute toxicity. With the exceptions of vitamin K1 (now forbidden in cosmetics), vitamin K3, CoQ10 and Idebenone no other benzoquinone or naphtoquinone seems to find use in cosmetic products. They also are very sparingly used for therapeutic medicinal purposes.

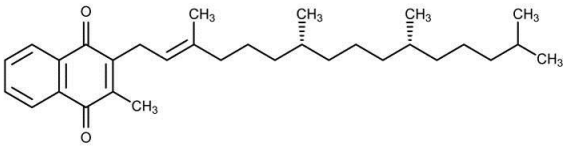
CAS No 3568-90-9	account existing animal data (One of the Category A allergens of Schlede E *et al*)' Not in CosIng	
 Lapachol Natural yellow 16 CI 75490 CAS No 84-79-7	Has similar reactivity as desoxylapachol. Medium reactivity (Guinea pig maximilisation) Not a sensitizer Anticoagulant activity in both rats and humans Therapeutic potential against enterovirus Not in CosIng	Dictionary of Contact Allergens[29] Contact Dermatitis, 5th edition (2011)- Reference is made to Estlander T *et al* 2001 and Lamminpaa A *et al* 1996 Hausen BM *et al* 1981 Cramer D *et al* 1987 Preusch PC *et al* 1984

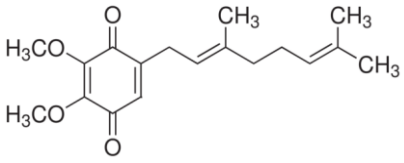
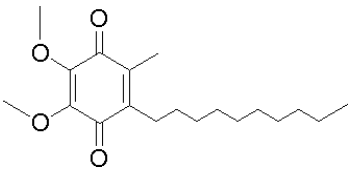
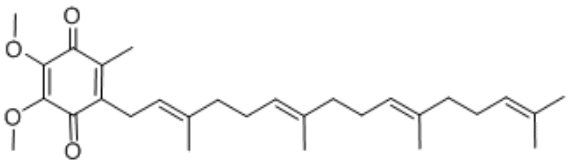
[29] http://desktopdrugreference.com/index.php?a=index&d=4-dictionary-of-contact-allergens

 Geranylbenzoquinone CAS No 61977-06-8  Dimethoxydalbergoin CAS No: 3755-64-4  Primin 2-methoxy-6-*n*-pentyl-*p*-benzoquinone CAS No: 15121-94-5	*All three haptens*: Significant contact allergen because of: proven strong contact allergenic effect in humans after short and/or almost negligible exposure taking into account existing animal data (members of the Category A allergens of Schlede E *et al*)' Primin: A parch test concentration of 0.01 % witness of an extremely sensitizing hapten (*inter alia*) Not in CosIng	Schlede E *et al* 2003 Cosmetics & Toiletry magazine 71, Vol 112, April 1997
 2-methyl-5-isopropy—1,4-benzoquinone CAS No 490-91-5	A relatively potent sensitizer	Cramer D *et al* 1987

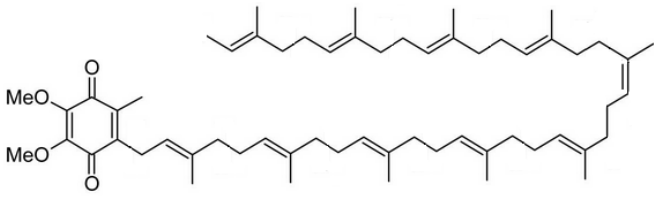
 2,6-dimethoxy benzoquinone CAS No: 530-55-2	Relatively weak effects in guinea pig maxilimisation test Epicutaneous tests with 1% solutions in Vaseline and acetone yielded negative results in man Not in CosIng	Hausen BM *et al 1990* Hausen BM *et al* 1981 Hausen *et al* 1990 Dictionary of Contact Allergens
  2-methyl-1,4-benzoquinone CAS No 553-97-9 2-methyl-6-methoxy-1,4-benzoquinone CAS No 611-68-7	Relatively week effect Not in CosIng	Cramer D *et al* 1987

Molecules whose molecular structure closely resembles that of ubiquinone and idebenone

 Vitamin K1 (phylloquinone) INCI: PHYTONADIONE INN: phytomenadione CAS No 84-80-0	Well documented case reports illustrate that its use in cosmetic products has caused allergic contact dermatitis. Also a recent LLNA indicated that Vitamin K1 is a skin sensitizer ('moderate' using SCCP scheme or 'weak' according to Kimber *et al*). The LLNA EC3 value is 76.7 %. Forbidden in cosmetic products (II/1371) Chain length C 16	SCCS opinion (SCCS/1313/10m- 24 March 2010)

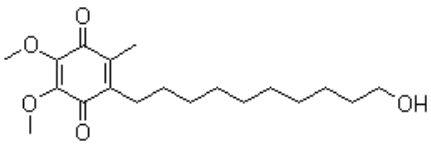
 2,3-dimethoxy-geranyl-1,4-benzoquinone A CAS No has not been provided	A remarkably strong sensitizer Not in CosIng Chain length C 8	Hausen BM 1995
 Decylubiquinone CAS No 55486-00-5	May cause moderate to severe erythema and moderate oedema Not in CosIng Chain length C 10	MP Biomedicals[30]
 Coenzyme Q4 CAS No 4370-62-1	Medium reactivity Not in CosIng Chain length : C 16	Hausen BM *et al* 1981

For comparison:



Ubiquinone.

Chain length: C 40

Idebenone 

[30] http://images.mpbio.com/docs/msds/ansi/en/195041-EN-ANSI.pdf

Chain length: C 11

Apparently, the length of the lipophilic side chain influences substantially on the sensitizing potency of this type of happens. Hausen BM *et al* (1995) set out to find out more about that. They synthetized 15 homologues derivatives of *primin* having linear side chains from C1 to C15 and 4 C6-ones with branched side chains. The different homologues were tested as to their potency applying the *in vivo* guinea pig maximilisation assay.

The results showed an increase of the sensitizing capacity with increasing length of the alkyl side chain from C1 to C10, reaching a maximum at C11 and C12. On further elongation up till C16, the sensitizing potency decreased beyond C13, reaching values as low as those of the C1 and C3 derivatives.

The authors saw that the results mirrored findings which formerly have been obtained with other non-quinonoid haptens. They became of the view that an *"ideal allergen"* consists of a quinonoid ring with a 10 or 11 carbon-membered side chain. Further, the more unsaturated the bonds in the tail the stronger the sensitizing power.

These finds of Hausen BM *et al* comply with the observed potency of the above mentioned long-chained molecules:

Compound	Length of side chain (C)	Potency
2,3-dimethoxy-geranyl-1,4-benzoquinone	8	strong
Vitamin K1	16	Moderate - week
Coenzyme Q4	16	Medium

The side chain of idebenone is 11 C long and we would, therefore, expect it to be strongly sensitizing As concern CoQ10 having a 40 C membered chain we, on the other hand, would think this molecule a feebly weak allergen.. This picture also complies with the data available to us as to the observed allergenic properties of these two compounds (*inter alia*).

The author Janco Pickert [31] noted that the inherent sensitizing potency of an allergen determine the magnitude of the patch test concentrations (PTC) to be used when testing for allerginicity**.** PTC is 0.5 % as concerns idebenone (*inter alia*). In the below table idebenone is compared to some other well known allergens as to the PTC. For the other ones also their LLNA EC3 values are displayed. As can be appreciated the applied PTC correlate well with the LLNA EC3 values in that the lower the PTC the lower the LLNA EC3 value. Hence, the less the PTC the more potent the allergen.[32].

Compound	Patch test concentration (%)	LLNA, EC_3 (%)
Idebenone	0,5	-
Cinnamal	1	2,0 – 3,1
Amyl cinnamal	2	10,6
Geraniol	2	11,4*
7-hydroxycitronellal	2 - 5	20 - 33
Vanillin	10	>50

On the basis of these data we would think that the LLNA EC3 value for idebenone is less than 2 %. The SCCP in a memorandum 19 December 2006 expresses the view that allergens for which the value is below 2 % is a strong allergen.

Cross-allergenicity poses considerable problems in the field of medicinal therapy - for example as concerns the use of antibiotics and corticosteroids. Therefore, over the years, this phenomenon has

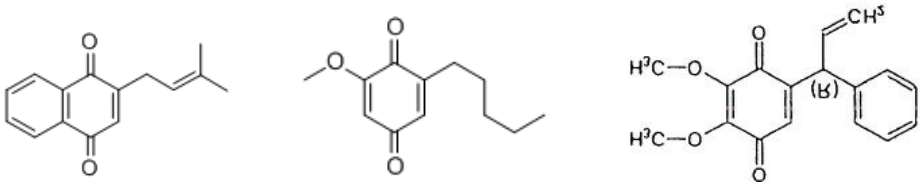
[31] Pickert J, Untersuchungen zur Bindung kontaktallergener Substanzen an nukleophile Aminosäureseitenketten , Dissertation, der Fakultät Mathematik und Naturwissenschaften der Technischen Universität Dresden Disputation am: 16. Dezember 2004

[32] All the values are collected from the dissertation of Pickert.

been devoted considerable attention clinically and scientifically. It has been realized that several factors plays in for the question of whether sensibility towards one allergen means sensibility towards also another allergen. However, also it has become clear that the molecular structural characteristic of the molecules in question is *the* major determinant for cross-reactivity. For example, as concerns protein-allergens cross-reactivity seems to require more than 70 % sequence identity. Proteins having < 50 % sequence identity are very seldom cross-reactive (Aaberese RC 2000).

So there are classes of allergens within which the individual members can cross-react with one another because of structural resemblance in sharing a particular molecular structural moiety. The corticosteroids is one class, the sulphonamides (-$SO_2(NH_2)$-) another and the aromatic amines (Ar-NH_2) a third one. The benzoquinoids and the naphtoquinoids also is a class *per se*. The general pattern is that nearly all the members of a class cross-react with one another.

Schultz KH *et al* (1977) in a study saw that allergic cross reactions could be obtained with 9 out of 14 different napthoquinones. Cramer D *et al* (1987) observed that for example the following three compounds cross-react with one another:

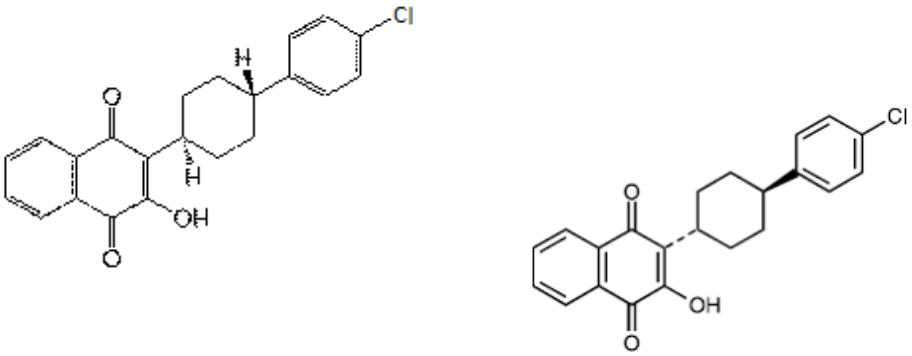


Primin

Also it has been observed that primin cross-react with 2,6-dimetoxy benzoquinone (Lepoittevin J-P *et al* 1991).

On this background we think it highly probable that idebenone cross-react with vitamin K1. Whether CoQ10 does is more uncertain since, apparently, CoQ10 is a rather weak allergen.

There are also other 1,4-naphtoquinone type drugs that may cross-react with idebenone and so cause serious therapeutic complications. One example is the anti-fungal/ protozoa remedy atovaquone:



Atovaquone

Trans-2-[4-(4-chlorophenyl)cyclohexyl]-3-hydroxy-1,4-naphthalenedione

CAS No 94015-53-9

Atovaquone is an authorized prescription drug in several countries. It is commercially available from GlaxoSmithKline since 2000 and is used to treat *Pneumocystis jiroveci* pneumonia (PCP[33]) and also

[33] PCP most likely affects people with human immunodeficiency virus [HIV]).

malaria. *Pneumocystis jiroveci* is a yeast-like fungus[34] the growth of which can be halted by exposure to atovaquone (MelinePlus[35].) A combination of the anti-microbial agents trimethoprim and sulfamethoxazole is by far the most commonly used medication against PCP. Some patients are, however, unable to tolerate that treatment due to allergies – meaning atovaquone may be a last resort medicine in certain instances (Wikipedia). Atovaquone also is used to prevent PCP in people who cannot take another medication.

A very serious allergic reaction to atovaquone may occur as a side effect – but rarely (WebMD[36]). It may also cause easy bruising or bleeding. (Rx List / the Internet drug index[37]).

According to the source Drugbank atovaquone closely resembles the structure of ubiquinone. And further that its antimicrobial inhibitory effect in pneumonia and malaria is comparable to ubiquinone.[38],[39]

We would believe the chances are grate that idebenone cross-react with atovaquone. Hence, people getting sensitised towards idebenone most probably also get allergic to atovaquone. The affected individuals might then probably risk experiencing a very serious allergic reaction upon medical treatment with atovaquone. Moreover, individuals allergic to most PCP remedies cannot be treated with atovaquone either in case they in advance have got allergic to idebenone.

[34] Pneumocystis jiroveci, earlier *Pneumocystis carinii*, is a micro-organism usually considered a mono-cellular organism -i.e. a protozoa. In view of its genetic properties is should, however, better be perceived as a fungus. *P. jiroveci* very seldom cause pneumonia in healthy people but in individuals suffering from a compromised immune system.
[35] http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693003.html
[36] http://www.webmd.com/drugs/drug-19791-atovaquone-proguanil+Oral.aspx?drugid=19791&drugname=atovaquone-proguanil+Oral
[37] http://www.rxlist.com/mepron-drug.htm
[38] http://www.drugbank.ca/drugs/DB01117
[39] Atovaquone can act by selectively affecting mitochondrial electron transport and parallel processes such as ATP and pyrimidine biosynthesis

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: June 19, 2020

SUBJECT: Scientific Literature Review: Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics (release date: April 29, 2020)

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

Key Issues

It would be helpful if the Introduction clearly stated that Ubiquinone is commonly used as a dietary supplement under the name coenzyme Q10. Somewhere in the report, it would also be helpful to state the typical dose of coenzyme Q10 in dietary supplements.

Cosmetic Use; Relative Contraindications; Summary - The Norwegian risk assessment for the use of Ubiquinone in cosmetics is not summarized correctly in either the Cosmetic Use or Relative Contraindications sections. The dose, 0.25 mg/kg bw/day, is the NOAEL used in the risk assessment not the margin of safety as stated in the SLR. How the NOAEL dose was determined should be stated in the CIR report (a dose of 100 mg/day in humans was considered to be a dose not affecting blood pressure; assuming oral absorption of 15% and a body weight of 60 kg a NOAEL dose of 0.25 mg/kg bw/day was calculated). Exposure was calculated for 3 products (body, face and hand lotions/creams) containing 1% Ubiquinone, assuming 2% dermal absorption, and exposure was compared to the NOAEL to get margins of safety (MoS) of 10.2 for body lotion, 52.1 for face cream and 38.5 for hand cream. An MoS greater than ten was considered sufficient because the NOAEL was based on human data. They concluded that Ubiquinone could be safely used in cosmetic products at a concentration of 1%.

The following statement in the Relative Contraindications section is incorrect: “is equivalent to a daily dose of 1% Ubiquinone (assuming no more than 15% absorption) in body lotion.” This statement mixes the dermal exposure information (1% in body lotion) with the oral absorption rate (15%). As stated above, the mg/kg/day NOAEL was

calculated from a dose of 100 mg/day assuming 15% oral absorption and a 60 kg body weight. When calculating exposure from lotions containing Ubiquinone, the Norwegians used 2% dermal absorption.

The Norwegian conclusion for idebenone (Hydroxydecyl Ubiquinone) should also be included in the CIR report. They concluded that idebenone is safe in cosmetics at concentrations up to 0.5% based on the data for Ubiquinone and the greater irritation/sensitization potential of idebenone.

As the potential of Ubiquinone to lower blood pressure serves as the basis for the Norwegian risk assessment, information about this endpoint should be presented in the CIR report.

Dermal Irritation and Sensitization - The following (copied from reference 2 where it is cited to Hoppe et al. 1999 (reference 13 in the CIR report) "0.3% CoQ10 did not cause irritancy in a double blind randomized trial, using in vivo occlusive patch test conducted in volunteers" should be added to the CIR report (perhaps Hoppe et al. 1999 will provide a lead to the primary reference for this study).

Additional Considerations

Natural Occurrence - Rather than 9 times more, 3.53 vs 0.35 nmol/g is 10 times more.

Dermal Penetration; Summary - Rather than "concentrations" in the epidermis and dermis, 20% and 2% represent the percentage of the administered dose that was found in the epidermis and dermis, respectively.

Dermal Penetration - The dermal penetration study in rats cited to the Norwegian risk assessment (reference 2) stated that two concentrations were tested. When citing a published paper to a secondary reference, it is misleading to state: "No further details provided". If further details are needed, the primary reference should be obtained. In this case it is listed as: Giovannini L, Bertelli AA, Scalori V, Dell'Osso L, Alessandrì MG, Mian M. Skin penetration of CoQ10 in the rat. *Int J Tissue React*. 1988;10(2):103-5. PubMed PMID: 3182185.

ADME, Other Routes, Ubiquinone; Summary - Please correct: "solubized"

ADME, Other Routes, Ubiquinone; References - If the information from reference 39 was taken just from the abstract, the CIR report should make this clear. The reference section should also note that this is a Russian language study.

ADME, Human, Oral - The following sentence does not belong in the ADME section: "Subjects repeatedly dosed with 450 and 2250 mg/d Hydroxydecyl Ubiquinone reported gastrointestinal disturbances, headaches, and urine discoloration."

Acute; Summary - Stating that an LD_{50} is greater than or equal to a specific dose does not make sense. Table 4 indicates that the LD_{50} was >10,000 mg/kg in mice and male rats and ~10,000 mg/kg in female rats. The LD_{50} values should also be stated specifically in the text.

Short-Term and Chronic, Hydroxydecyl Ubiquinone - Did the 4-week study in rats identify a NOAEL?

Short-Term and Chronic, Ubiquinol - Which enzymes "were within in-house historical control data"?

DART - As reference 29 is a review, can the primary reference for the mouse study of Ubiquinone be obtained to identify the strain and numbers of mice used. The CIR report should make it clear that this is being cited to a secondary reference that included limited details.

Table 6 indicates that the test of Ubiquinone in male mice included a period of 35 days after the 5 day dosing period before sperm morphology was assessed. The 35 day period also needs to be mentioned in the text as the study does not make sense without it. Five days is not long enough to see an effect on sperm morphology.

DART; Summary; Table 6 - It is not clear what is meant by "biochemic". The abstract of reference 47 uses the word "biochemical". Biochemic medicine uses minerals prepared using homeopathic methods.

Depigmentation; Summary - What happened to the controls in the zebrafish embryo study (reference 52)?

Dermal Irritation and Sensitization - This section should note that clinical data, including case reports, indicate that Hydroxydecyl Ubiquinone can be a sensitizer.

Summary - In the Summary, please state the tissue/compartment in which the concentrations of Ubiquinone reached 8 μg/g after 2 hours, and 15 μg/g after 4 hours.

Please add "h" after 4.5 (the half-life of Hydroxydecyl Ubiquinone in rat plasma)..

Please correct "admistered" (this misspelling occurs twice in the Summary)

In what compartment(s) were Ubiquinol levels increased in Wistar rats by 89%?

What compound was tested in the 26-week study in Wister rats?

The duration of dosing (5 days) and period after dosing before assessment (35 days) for the male mouse study needs to be stated in the Summary.

The statement: "Ubiquinone exposure was shown to cause depigmentation in individuals susceptible to ROS-triggered-vitiligo" is not consistent with the Depigmentation section. The Depigmentation section states that 15 patients that used Ubiquinone-containing cosmetics developed vitiligo and that this effect may have been a result of hydrogen peroxide from oxidized Ubiquinone. It does not state that Ubiquinone itself caused depigmentation.

Table 5 - Based on the information in this table, the endpoints examined in these studies are not always clear. The Results column states the changes observed; the endpoints examined that showed no effects is not always clear. For example, were histopathologic examinations of tissue completed in the 13-week study of Ubiquinol in Sprague-Dawley rats? How was reproductive and developmental toxicity assessed in the 4-week study of Hydroxydecyl Ubiquinone in juvenile Wistar rats?

The Protocol section of the 52-week rat study of Ubiquinone suggests that there was one 4-week recovery group; the Results section gives results of Ubiquinone levels in the liver 10 days after treatment ended. How many recovery groups were included in this study?

The definition of LDH should be added at the end of this table.

Table 7 - Please delete "(strain not specified)" from the study on human peripheral lymphocytes.

For studies for which some indication of purity is stated in the first column "*" (composition not specified) is not needed.

Please revise "(# not known)" to "(number not stated)"