Safety Assessment of Ubiquinone Ingredients as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (June 28, 2020) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

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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]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated.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 Reviw (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 Unpublished data are provided by the cosmetics industry, as well as by other interested parties.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 definition, chemical structure, and reported cosmetic function 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.

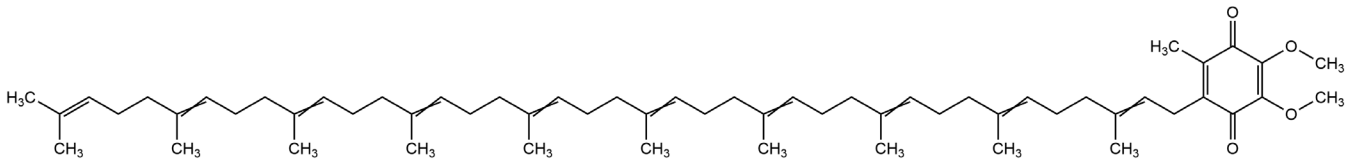


Figure 1. Ubiquinone

Many of 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]

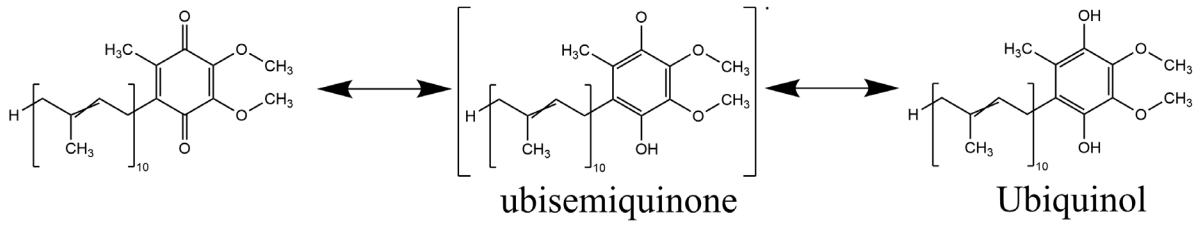


Figure 2. Redox and Ubiquinol

Physical and 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, CoQ_9 is the predominant form. In humans, the predominant form of Ubiquinone is CoQ_{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}; all

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

Natural Occurrence

In 1957, Ubiquinone was isolated from beef heart mitochondria by British researchers 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 9 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 early adulthood and decline in human tissue with age.[13]

Method of Manufacture

Ingredient-specific methods of manufacture were neither found in the publically available literature nor submitted as unpublished data. However, a number of general methodologies were found and 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 disphosphate, 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 CoQ8 and CoQ9, 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 *Eschericia coli*, *Saccharomyces cerevisiae* (yeast), and plants provide the advantage of genetic manipulation to optimize Ubiquinone yields.

High hydrostatic pressure treatment, ultraviolet (UV) radiation, 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]

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).[26] The results of the concentration of use survey conducted by the Council in 2019 indicate that the maximum leave-on use concentration in this ingredient group is 0.05% for Ubiquinone, in body and hand products.[27] No

uses were received from VCRP or the industry survey for Disodium Ubiquinone. The Council has yet to survey 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.

All of the Ubiquinone ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[28] The Norwegian Food Safety Authority states an estimated 0.25 mg/kg bw/d margin of safety for cosmetic Ubiquinone exposure, based upon the oral, systemic no-observed-adverse-effect-level (NOAEL) for hypotension.[2] This estimated value takes into account the 1% typical daily use concentration of Ubiquinone in cosmetic formulations, the assumed 2% skin penetration rate, and variable systemic exposure doses, resulting from frequency of use and body surface area application.

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.[11,29] Hydroxydecyl Ubiquinone has been approved for pharmaceutical use in Japan since 1984.[30]

Ubiquinone was also listed in the European Pharmacopeia (EP) in 2001 and the United State 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] In many clinical trials, Ubiquinone has been tested for the treatment of heart disease, hypertension, breast cancer, Alzheimer's disease, and Parkinson's disease.[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).[31]

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.[32] 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.[20,33]

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.[34]

Dermal Penetration

Ubiquinone

Dermally applied Ubiquinone (amount not specified), in ethanol, was able to penetrate the stratum corneum of live porcine skin, reaching concentrations of approximately 20% in the epidermis and 2% in the dermis.[13] (No further details provided). A solution of 1% Ubiquinone, in olive oil, when applied to live rat skin (amount not specified) was found to reach a concentration of 8 µg/g after 2 h, and 15 µg/g after 4 h.[2] (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.[35,36] The maximum serum concentration of orally ingested Ubiquinone being captured between 6 – 8 h (T_{max}), on average, in solubized formulations, suggests slow absorption of this large and hydrophobic molecule in the intestine.[32,37] Although structurally distinct, Ubiquinol is the predominant metabolite of Ubiquinone, and has higher biovailability than Ubiquinone.[38] Most endogenous Ubiquinone is reduced to, and exists as, bioreactive Ubiquinol in the mitochondria, endoplasmic reticulum, lysosomes, peroxisomes, and plasma membranes of eukaryotic cells.[32-34,38,39]

Animal

Oral

Hydroxydecl Ubiquinone

Hydroxydecyl Ubiquinone metabolism is characterized by reduction of the quinone ring and subsequent conjugation to form 1- or 4- phenyl sulfates or glucoronides of the hydroquinone derivatives.[30] 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.[30] 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.[35] 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.[40] 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 solubized Ubiquinone (10 mg/kg; solvent not provided), and 10 blood samples were taken 0.1 – 48 h after injection.[39] 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.[41] 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.[30,42] 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 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. Subjects repeatedly dosed with 450 and 2250 mg/d Hydroxydecyl Ubiquinone reported gastrointestinal disturbances, headaches, and urine discoloration.

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.[43] The Ubiquinol half-life in subjects who received a single dose of 150 or 300 mg was estimated to be 48 h, while plasma Ubiquinol levels in repeated dose subjects showed a 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 related 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.[35] 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.[35] 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.[36] The area-under-the-curve over 10 h ($AUC_{(0\text{-}10h)}$) 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.[44]

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 in mice and rats was determined to be ≥ 10,000 mg/kg.[45,46] The acute oral LD_{50} of Ubiquinone in mice was reported to be > 4000 mg/kg,[29,47] while the acute oral LD_{50} in rats was reported to be > 2000 mg/kg.[19,29]

Short-Term and Chronic Toxicity Studies

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

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 wks.[4] 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 wks 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] 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.[45] 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. 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.[45] 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 wks.[33] Statistically significant increases in hepatic blood chemistry enzymes were observed in rats dosed with > 300 mg/kg Ubiquinol; a few 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 wks, with 1200 mg/kg/d Ubiquinone as a reference control.[33] 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 Ubiqunol, in gelatin, via gavage, for 13 wks, with 600 mg/kg/d Ubiquinone as a reference control.[33] Soft feces were observed in the 300 and 600 mg/kg/d Ubiquinol groups, estrus hemorrhage in 1 female each in the control and 300 mg/kg Ubiquinol groups. Vomiting and statistically significant changes in eosinophil and platelet counts, expected to reflect effects upon the liver, were seen in males and females, respectively, which was 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.[29,47] 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 decrease in the 1500 mg/kg group, decrease of red blood cells and hemoglobin in the 500 and

1500 mg/kg groups, white blood cell increase in all dosage groups, and triglyceride decrease in the 1500 and 3000 mg/kg groups, while, for females, ovary weight was 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.[33] 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.[40] 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.[29] 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.[33] 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.[48] 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 fertitily 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. [45] 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-implanation 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.[29] Groups of 10 male mice were given up to 10,000 mg/kg bw Ubiquinone, via gavage, for 5 d to test for defects in sperm morphology.[47] 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 biochemic, histologic, or morphologic 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.[49] 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.[29]

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.[38] Similarly, Ubiquinone was neither genotoxic with or without metabolic activation in multiple Ames tests, at up to 5000 µg/plate, nor in chromosomal aberration tests using CHL/IU cells at up to 5000 µg/mL.[15,17,29,47,50] In vivo, no genotoxicity was observed with Hydroxydecyl Ubiquinone, at up to 5000 mg/kg/d (in mice),[3] Ubiquinol, at up to 2000 mg/kg/d (in rats),[38] or Ubiquinone, at up to 10,000 mg/kg/d (in mice).[29,47]

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 wks.[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 wks.[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.[51] Fifteen previously unaffected patients presented with vitiligo after daily use of over-the-counter Ubiquinone-containing cosmetics (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 ultraviolet light (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).[52] 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. Concommitantly, 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, solubized in 1 N sodium hydroxide, and analyzed for cell melanin content.[52] 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.[52] 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.[53] 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.[52] Murine melanoma B16F10 cells (1 x 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 with the same.[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 .[54,55] 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-clottting factors, such as the international normalized ratio and prothrombin time, were observed in 24 patients taking warfarin and 100 mg Ubiquinone.[56] However, in a 16-wk longitudinal study, there was a stastistically significant association between bleeding events and the concomitant intake of Ubiquinone and warfarin (OR 3.91, 95% CI: 2.09-7.3).[57] 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.[2,55,58]

Furthermore, the Norwegian Food Safety Authority states that the margin of safety for dermal Ubiquinone exposure, is 0.25 mg/kg bw/d, which accounts for bleeding risk in statin users.[2] This margin of safety value is extrapolated from a calculated oral systemic NOAEL, in which Ubiquinone consumption does not have a hypotensive effect in users, and, is equivalent to a daily dose of 1% Ubiquinone (assuming no more than 15% absorption) in body lotion.

DERMAL IRRITATION AND SENSITIZATION STUDIES

No dermal irritation or sensitization 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,[59] inflammation and aging,[60,61] diabetes,[62-64] cancer,[65] and muscular and neurogenerative diseases.[3,4,30,66,67] 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.[5,66] 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.[68,69]

Supplement Use Studies

Ubiquinol

In a single-dose study, 15 healthy volunteers were dosed with up to 300 mg Ubiquinol, in diglycerol monoleate, rapeseed oil, soy lecithin, and beeswax, after consuming breakfast.[43] Subjects either received 300 mg Ubiquinol or 150 mg Ubiquinol with 5 placebo capsules (same as excipients), taken with 180 mL of water. Blood samples were collected up to 48 h after dosing. One female in the 300 mg group withdrew due to enterocolitis on day 1. Soft stool and tachycardia were observed in 2 females who were dosed with 150 mg of Ubiquinol. Statistically significant changes in hematological markers or mineral content were not considered clinically relevant. In the same study, 8 groups of 10 men and 10 women were given up to 300 mg Ubiquinol capsules to take after breakfast and dinner, with 180 mL of water, for 28 d.[43] Subjects received 10 capsules, including placebo, to equal a daily dose of 0, 90, 150 or 300 mg/d Ubiquinol. Blood samples were collected before administration, day 1, day 14, day 28, and up to 6 mos after treatment. Slight increase in eosinophil percentage at wk 4 of treatment (12%) and 2 wk after completion of treatment (18%) compared to the the initial value (6%) was observed in one male in the 90 mg group. One male in the 150 mg group exhibited a slight increase in low density lipoprotein levels at wk 4 of treatment (162 mg/dL vs. 130 mg/dL). Adverse events included common cold symptoms, dizziness, headache, musculoskeletal problems, menstrual discomfort/irregularities, and most commonly gastrointestinal troubles across all dosage levels. There were no clinically significant differences between placebo and active treatment with regards to biomarkers or incidence of adverse events.

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 wks at doses of 0, 300, 600, and 900 mg/d in a double-blind, placebo-controlled trial.[70] 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.

Case Reports

Dermal

A 47-year-old woman had a 0.5 % Hydroxydecyl Ubiquinone, 'anti-aging' cream applied as part of a facial treatment in the salon.[71] 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 for the anti-aging 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 0.5% Hydroxydecyl Ubiquinone anti-aging cream, a 43-year-old woman developed an itchy eruption.[2] Topical applications of corticosteroid were used for 5 d to dissolve 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.[72] The patient had a history of guttate psoriasis, but no background of atopic eczema or contact allergy. Periorbital eruption and infraorbital oedema was clinically diagnosed as allergic contact dermatitis, and was 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 Hydroxydecyl Ubiquinone 1% 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 2019 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.

Dermally applied Ubiquinone, in ethanol, was able to penetrate the stratum corneum of porcine skin, at approximate concentrations of 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, solubized, 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 8h and exhibited a half-life of 4.5, 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 admistered up to 1200 mg/kg/d was 10.7 to 15.2 h. After a one-time intravenous injection of 10 mg/kg solubized Ubiquinone, 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. Subjects repeatedly dosed with 450 and 2250 mg/d Hydroxydecyl Ubiquinone reported gastrointestinal disturbances, headaches, and urine discoloration. The half-life of Ubiquinol was estimated to be 48 h in 8 healthy subjects who received a single dose of 150 or 300 mg, for up to 28 d. One subject in the 300 mg group withdrew on day 1 due to diarrhea and leukocytosis related to the test substance; other adverse events were mild and moderate in severity and were not of clinical significance. 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 area-under-the-curve over 10 h ($AUC_{(0\text{-}10h)}$) 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 in rats was determined to be ≥ 10,000 mg/kg. 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.

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 wks. Wistar rats administered up to 500 mg/kg/d Hydroxydecyl Ubiquinone for 4 wks, 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 wks, 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 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. In a 26-wk study of Wistar rats administered up to 1000 mg/kg/d, mucosal thickening, hyperkeratosis, red spots, hyperplasia, necrosis, edema, and ulceration observed in the forestomach were reversible and of limited toxicological relevance. 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 wks. Beagle dogs admistered 500, 750, or 1000 mg/kg d Hydroxydecyl Ubiquinone for 39 wks 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 stastistically 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 wks. 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 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 statisticaly 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 fertitily 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, via gavage (composition not specified), and corn-oil-treated controls. Except for an increase in seminiferous epithelium heights, no biochemic, histologic, or morphologic 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, 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 Hydroxydecyl Ubiquinol, at up to 5000 mg/kg/d, Ubiquinol, at up to 2000 mg/kg/d, or Ubiquinone, at up to 10,000 mg/kg/d, in several in vivo mammalian erythrocyte micronucleus tests in mice and Sprague-Dawley rats.

ICR mice fed a daily dose of up to 2000 mg/kg Hydroxydecyl Ubiquinone via diet for 103 wks, 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 wks. The incidence of these neoplasms was lower than expected for this strain, and only in males.

Ubiquinone exposure was shown to cause depigmentation in individuals susceptible to ROS-triggered-vitiligo and 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. 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 a MTT assay. Cytotoxic effects were not observed after 24 h exposure to 1 - 2 µM Ubiquinone.

Due to similar chemical structures, sensitization to vitamin K and atovaquone also have the potential to cross-react with or cause allergenicity to Hydroxydecyl Ubiquinone. In spite of conflicting clinical trial data, simultaneous Ubiquinone and statin use may be contraindicated. According to the Norwegian Food Safety Authority, the extrapolated margin of safety, or systemic NOAEL, for dermal Ubiquinone exposure, is 0.25 mg/kg bw/d, which accounts for bleeding risk in statin users. Hydroxydecyl Ubiquinone, Ubiquinol, and Ubiquinone have been tested for safety and efficacy in the treatment of various diseases at doses up to 1200 mg. Human subjects were given up to 300 mg Ubiquinol in a single dose, post-prandial study, with no clinically significant effects. In a 4-wk repeated dose study, eight groups of 10 men and 10 women were given up to 300 mg Ubiquinol capsules to take after breakfast and dinner, with 180 mL of water, for 28 d. Blood samples showed no clinically significant differencs between placebo and active treatment with regards to biomarkers or incidence of adverse events. 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 wks 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.

Four middle-aged women presented with facial eruptions and sensitization reactions in response to application of up to 1% Hydroxydecyl Ubiquinone in anti-aging face cream. Positive patch-test reactions occurred for 0.5% Hydroxydecyl Ubiquinone. These isolated incidents suggest elicitation responses to previous induction or sensitization.

INFORMATION SOUGHT

The CIR is seeking method of manufacture data specific to use in cosmetics for these ingredients; impurities data; data providing clarification for potential cross-reactivity and contraindication with concomitant drug use, and dermal irritation and sensitization data for Ubiquinone ingredients, at or above maximum concentrations of use.

TABLES

Table 1. Definition, cosmetic function, and chemical structure of ingredients in this report[1,CIR Staff]

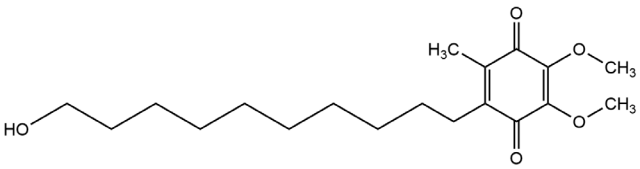
Ingredient (CAS No.)	Definition	Function(s)
Disodium Ubiquinone	Disodium Ubiquinone is the disodium salt of Ubiquinone.	Antioxidants; Hair Conditioning Agents; Skin Protectants; Skin-Conditioning Agents-Humectant
Hydroxydecyl Ubiquinone	Hydroxydecyl Ubiquinone is the organic compound that conforms to the structure: 	Antioxidants
Ubiquinol (992-78-9)	Ubiquinol is the organic compound that conforms to the structure in Figure 2.	Antioxidants, Skin Protectants; Skin-Conditioning Agents- Humectant
Ubiquinone (303-98-0; 60684-33-5)	Ubiquinone is the organic compound that comforms to the structure in Figure 1.	Antioxidants; Skin-Conditioning Agents-Miscellaneous

Table 2. Physical and Chemical Properties

Property	Value	Reference
Disodium Ubiquinone		
Formula Weight (g/mol)	865.38	[73]
Partition coefficient (log K_{ow})	20.23 (estimated)	[7]
Hydroxydecyl Ubiquinone		
Physical Form	solid	[30]
Molecular Weight (g/mol)	338.4	[74]
Topological Polar Surface Area (Å^2)	72.8 (estimated)	[74]
Melting Point (ºC)	52-54	[30]
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	Sparing	[8]
Ubiquinone		
Physical Form	Solid, crystalline powder	[9]
Color	Off-white to yellow-orange	[19,54]
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)	Sparing	[9]

Table 3. Frequency (2020)[26] and concentration of use (2019)[27] according to the duration and type of exposure for Ubiquinone ingredients

	# of Uses[26]	*Max Conc of Use (%)[27]*	*# of Uses[26]*	*Max Conc of Use (%)[27]*	*# of Uses[26]*	*Max Conc of Use (%)[27]*
	Hydroxydecyl Ubiquinone		**Ubiquinol**		**Ubiquinone**	
Totals*	**8**	**NR**	**19**	**NS**	**421**	**0.00006-0.05**
Duration of Use						
Leave-On	*7*	*NR*	*19*	*NS*	*387*	*0.00075-0.05*
Rinse-Off	*1*	*NR*	*NR*	*NS*	*34*	*0.000006-0.03*
Diluted for (Bath) Use	*0*	*NR*	*NR*	*NS*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NS	21	0.02
Incidental Ingestion	NR	NR	NR	NS	2	NR
Incidental Inhalation-Spray	2[a]; 3[b]	NR	7[a];10[b]	NS	202[a]; 126[b]	0.00075-0.01[a]
Incidental Inhalation-Powder	3[b]	NR	10[b]	NS	126[b]	0.05[c]
Dermal Contact	8	NR	19	NS	406	0.00075-0.05
Deodorant (underarm)	NR	NR	NR	NS	NR	NR
Hair - Non-Coloring	NR	NR	NR	NS	12	0.000006-0.01
Hair-Coloring	NR	NR	NR	NS	NR	NR
Nail	NR	NR	NR	NS	1	NR
Mucous Membrane	NR	NR	NR	NS	3	NR
Baby Products	NR	NR	NR	NS	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

NS – not yet surveyed

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.	[45,46]
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.	[45,46]
Ubiquinone	Mice	NR	NR	NR	>4000 mg/kg. No death or toxic symptoms were observed during the one-week observation period.	[29]
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.	[47]
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.	[29]
Ubiquinone	Rats	NR	Corn oil	1250, 2500, or 5000 mg/kg	>5,000 mg/kg	[29]

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	CD-1 mice (# not specified)	13 wk	NR	210, 640, 1280, 2000 mg/kg/d	Gastric irritation, mainly in the form of epithelial cell hyperplasia, histopathological abnormalities in the forestomach, and a general reduction of weight was observed. (Details not provided).	[4]
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	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	NR	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).	[45]
Hydroxydecyl Ubiquinone	Rats (strain and # not specified)	26 wk	NR	NR	Although no treatment-related changes were observed at necropsy, a dose of 500 mg/kg/d caused an increased incidence of diarrhea and vomiting. The non-toxic dose was determined to be 20 mg/kg/d (statistical significance not provided)	[45]
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 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)	5 wk	NR	Up to 500 mg/kg/d	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)	[45]
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 and γ-globulin in males in the 300 mg/kg group. Statistically significant prolongations in 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.	[33]
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. 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.	[33]
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/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.	[33]
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.	[47]
Ubiquinone	Rats (strain and # not specified)	5 wk	NR	0, 40, 200, 1000 mg/kg/d	No toxicity was observed in the hematology, blood chemistry, urinalysis, or post-mortem examinations at any dose level.	[29]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
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% hydromethylfibrin	0, 500, 1500, 3000 mg/kg/d; 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 of 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).	[33]
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	Sprague-Dawley rats (19/sex)	52 wk	Corn oil, via gavage	0, 100, 300, 600, or 1200 mg/kg/d, via gavage; 10/sex/group were selected at random in the 0, 600, and 1200 mg/kg/d dosage groups. These recovery group animals were treated for 52 wks, and maintained after the termination of dosing for 4 wks,	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.	[40]
Ubiquinone	White rabbits (# not specified)	23 d	NR	0, 6, 60, 600 mg/kg/d	No toxic effects, and no microscopic or gross lesions, were found at any dose level. (statistical significance not provided).	[29]
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).	[33]

Table 5. Repeated dose oral toxicity studies

Ingredient	Animals or Subjects/Group	Study Duration	Vehicle	Dose/Concentration/Protocol	Results	Reference
Ubiquinone	Beagle dogs (4/sex)	39 wk	Gelatin capsules	0, 1200, or 1800 mg/kg/d	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.	[48]

Abbrevations: A/G – albumin/globulin; ALT- alanine aminotransferase; AST – aspartate aminotransferase; NR- not reported; PT – prothrombin time

Table 6. Reproductive and Developmental 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 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).	[45]
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 Ubiqunone	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 maternotoxicity (statistical significance not provided). Based on body surface area comparisons , the NOAEL for embryofetal development was determined to be 1000 mg/kg/d.	[4]
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]

Table 6. Reproductive and Developmental Toxicity Studies

Test Article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
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. Maternotoxicity 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)	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).	[29]
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.	[47]
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 biochemic, histologic, or morphologic differences were observed between the Ubiquinone-treated, negative control, and vehicle control groups. (statistical significance not provided).	[49]
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).	[29]

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 (strain not specified)	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	[38]
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.	[38]
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	[47]
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 perfomed 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	[29]
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	[50]
			In Vivo		
Hydroxydecyl Ubiquinone*	1250-5000 mg/kg once or 5000 mg/kg/d	Mice (# not known)	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.	[38]

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	[47]
Ubiquinone	2000 mg/kg/d	Mice (# not known)	Micronucleus test	Not genotoxic	[29]

* Composition not specified
NR- not reported

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