

## RISK PROFILE

### **Coenzyme Q10**

CAS No. 303-98-0  
and

### **Idebenone<sup>1</sup>**

CAS No. 58186-27-9

Date of reporting 15.01.2013

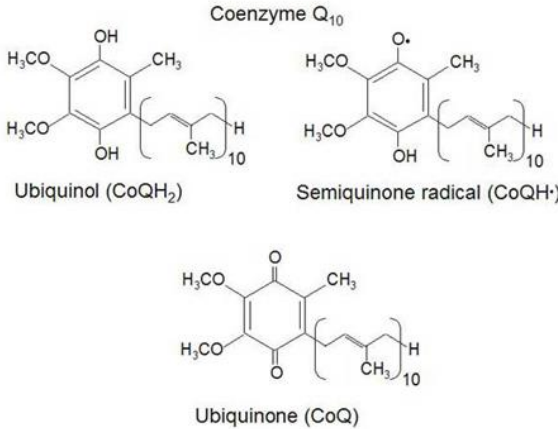
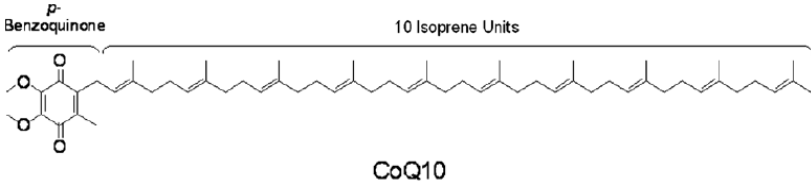
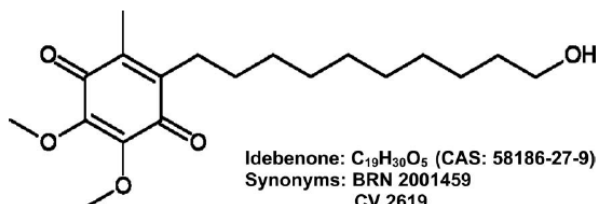
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## 1. Identification of substance

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| <b>Chemical name (IUPAC):</b> | 2,5-Cyclohexadiene-1,4-dione, 2-(3,7,11,15,19,23,27,31,35,39-decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontadecaenyl)-5,6-dimethoxy-3-methyl-, (all-E)- |
| <b>INCI</b>                   | Ubiquinone  |
| <b>Synonyms</b>               | Coenzyme Q10, CoQ10 (humans), CoQ (rodents),  |
| <b>CAS No.</b>                | 303-98-0 / 1339-63-5 / 60684-33-5   |
| <b>EINECS No.</b>             | 206-147-9 / 215-668-0   |
| <b>Molecular formula</b>      | C <sub>59</sub> H <sub>90</sub> O <sub>4</sub>  |
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<sup>1</sup> The risk assessment of the CoQ10 analogue Idebenone makes extensive reference to CoQ10 and no attempts have been made to review this analogue independent from CoQ10.

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| <p><b>Chemical structure</b></p>        | <ul style="list-style-type: none"> <li> <b>Coenzyme Q10 (CoQ)</b> <p><b>Chemical Structure of Coenzyme Q<sub>10</sub></b></p>  <p>Coenzyme Q<sub>10</sub></p> <p>Ubiquinol (CoQH<sub>2</sub>)      Semiquinone radical (CoQH<sup>•</sup>)</p> <p>Ubiquinone (CoQ)</p> <p>Coenzyme Q can exist in three oxidation states: the fully reduced ubiquinol form (CoQH<sub>2</sub>), the radical semiquinone intermediate (CoQH<sup>•</sup>), and the fully oxidized ubiquinone form (CoQ).</p> <p>Reference: Coenzyme Q10 [online], Linus Pauling Institute.</p>  <p><i>p</i>-Benzoquinone      10 Isoprene Units</p> <p>CoQ10</p> </li> <li> <b>Idebenone</b> (INCI: hydroxydecyl ubiquinone; CAS no: 58186-27-9)  <p>Idebenone: C<sub>19</sub>H<sub>30</sub>O<sub>5</sub> (CAS: 58186-27-9)<br/>Synonyms: BRN 2001459<br/>CV 2619</p> <p><i>Fig. 1.</i> Chemical structure of hydroxydecyl ubiquinone.</p> <p>Idebenone is a synthetic analog of coenzyme Q10 (of the quinone family), with a shorter side chain and increased solubility compared to CoQ10.</p> </li> </ul> |
| <p><b>Molecular weight</b></p>          | <p>863.36 g/mol (Ubiquinone C<sub>59</sub>H<sub>90</sub>O<sub>4</sub>), 376 g/mol (Idebenone)</p>   |
| <p><b>Contents (if relevant)</b></p>    |   |
| <p><b>Physiochemical properties</b></p> | <p>CoQ10 is insoluble in aqueous solutions, less than 1µg/L (1 ppb) in water, because of its long lipophilic chain (i.e. 10 isoprene units). The oil-water partition coefficient (logK<sub>o/w</sub>) of CoQ10 is 3.63 (Duan Pengjie <i>et al</i> 2008).</p> <p>Idebenone is also insoluble in water. The logK<sub>o/w</sub> of Idebenone is 3.57<sup>(2)</sup>.</p>  |

<sup>2</sup> <http://www.chemicalize.org/structure/#!mol=idebenone>

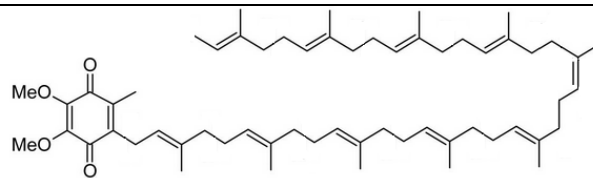
## 2. Uses and origin

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| <b>Uses</b> | <p>➤ <b>Cosmetic products:</b></p> <p><i>Functions according to</i></p> <ul style="list-style-type: none"><li>• CosIng database:<ul style="list-style-type: none"><li>○ “Antioxidant” – “Inhibits reactions promoted by oxygen, thus avoiding oxidation and rancidity”</li><li>○ “Skin conditioning” – “Maintains the skin in good condition”</li></ul></li><li>• Other:<ul style="list-style-type: none"><li>○ Anti-aging: photo-damaged skin; wrinkles (see Annex 1).</li></ul></li></ul> <p><i>Concentrations of CoQ10 being applied</i></p> <p>CoQ10 is generally used in the range of 0.5 – 1.0% in anti-wrinkle products (see e.g. Annex 2), and in some products up to 3%. In anti-oxidant products, CoQ10 is present at less than 1%.</p> <p><i>Frequency of use</i></p> <p><u>CoQ10:</u></p> <p>The EWG Skin Deep cosmetic database (EWG’s Skin Deep [online]):</p> <ul style="list-style-type: none"><li>• facial moisturizer/ treatment (128 products)</li><li>• anti-aging (110 products)</li><li>• sunscreen: moisturizer (34 products)</li><li>• around-eye cream (35 products)</li><li>• moisturizer (27 products)</li><li>• facial cleanser (22 products)</li></ul> <p>I.e. a total of 266 products containing CoQ10 (Ubiquinone, CAS no 303-98-0).</p> <p>The German codecheck.info [online] database lists 190 products for Coenzyme Q10 (302 products for Coenzyme Q).</p> <p><u>Idebenone:</u></p> <p>Only 6 products containing Idebenone is found in the EWG database, whereas the Codecheck database lists 13 products (mostly anti-ageing products).</p> <p>CoQ10 has been used in cosmetics since the late ‘90s<sup>3</sup>; Idebenone followed around 2005. Both are newcomers in cosmetics.</p> <p>➤ <b>Food including food supplements</b></p> <p>As an endogenous substance CoQ10 is present in almost all foodstuffs.</p> <p>In the developed world, the estimated daily intake is 3-6 mg (Pravstl <i>et al</i> 2010). Likewise, a daily intake of 3-5 mg was reported in a</p> |
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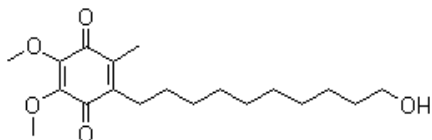
<sup>3</sup> [http://www.onlynature.co.uk/AHA\\_and\\_Q10.html](http://www.onlynature.co.uk/AHA_and_Q10.html)

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|  | <p>Danish intake study (Overvad K <i>et al</i> 1999).</p> <p>The intake of CoQ10 from food is modest compared to the exposure from dietary supplements, in which CoQ10 is increasingly used (Hathcock &amp; Shao, 2006). In US, the use of CoQ10 is only surpassed by omega-3 and multi-vitamins (NFT, 2011).</p> <p>For more details – see Annex 5</p> <p>➤ <b>Medicinal products</b></p> <p>○ <b>CoQ10</b></p> <p>There are several small studies suggesting that CoQ10 may be helpful in the treatment of various medical conditions, alone or in combination with other therapies, but there is insufficient evidence for clinical efficacy of CoQ10. For more details – see Annex 6: CoQ10 and various medical conditions.</p> <p>In clinical trials CoQ10 is typically used at doses ranging from 60 - 1200 mg/day, but doses as high as 2700 mg/day for 9 months has been reported (Kaufmann <i>et al</i> 2009).</p> <p>To our knowledge only two countries has granted access of CoQ10 to the market as approved proprietary pharmaceutical; Japan for one inland made product the indication being congestive heart failure (10 mg/day). Hungary for some products against heart failure (180 mg/day). The Danish medicinal product agency has not approved CoQ10 for the same indication due to insufficient evidence for a clinical effect (see footnotes in Section 4).</p> <p>See also Annex 6 summarizing “likely” or “possibly” effective use of CoQ10 in a clinical setting, including hypertension, heart disease and various other medical conditions.</p> <p>○ <b>Idebenone</b></p> <p>Idebenone was initially developed by Takeda Pharmaceutical Company for the treatment of Alzheimer disease and other cognitive defects. Wikipedia provides further information.</p> <p>➤ <b>Other products</b></p> <p>CoQuinone 30, Bio-Quinone Gold, Super Q10 and Bioaktiv Q10 are different formulations of CoQ10, usually with increased bioavailability as compared to the “pure” form. “Claims” that CoQ10 can prevent or treat statin-induced myopathies is not supported by clinical evidence (NFT, 2011).</p> <p>➤ Recommended daily doses of CoQ10 in these products range from 30 mg -180 mg.</p> |
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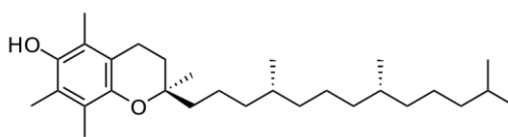
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| <p><b>Origin</b></p> <p>Natural (exo /endo)<br/>Synthetic</p> | <p><b>Coenzyme Q10 (CoQ10)</b> is the human form of coenzyme Q (<b>CoQ</b>), a naturally occurring, lipid-soluble substance synthesized by mammals and plants (i.e. a non-essential nutrient). CoQ10 consists of a benzoquinone ring structure with 10 isoprenoid units in the side chain, and hence is a highly lipophilic substance. The structure of CoQ is related to carotenoid, vitamin E – and especially to vitamin K (Bhagavan &amp; Chopra, 2006):</p> |
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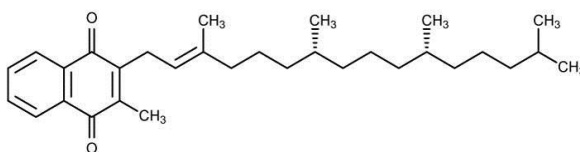
Co Enzyme Q10 (CoQ10)



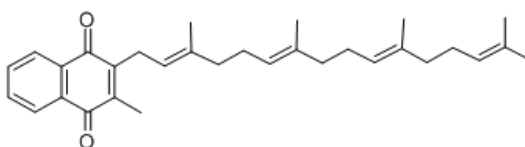
Idebenone



Alpha tocopherol (Vitamin E)



Vitamin K1 (phylloquinone)



Vitamin K2 (Menaquinone-4)

In mammals the same chemical pathways that make vitamin E, vitamin K and folic acid also make coenzyme Q. The human body produces sufficient amounts of coenzyme Q via metabolic pathways called the *skimate* and *chorismate pathways*.

CoQ10 plays important roles in at least two major physiological activities: (i) mitochondrial ATP synthesis (i.e. energy production) as part of the electron transport chain and (ii) anti-oxidant activity, in which the reduced form ubiquinol-10 is most potent (see section 1; Hathcock & Shao, 2006). As an antioxidant, CoQ10 is also capable of recycling and regenerating other antioxidants such as tocopherol (vitamin E) and ascorbate (vitamin C).

The total body pool of CoQ is estimated to be approx. 0.5 – 1.5 g in an average healthy adult (Bhagavan & Chopra, 2006), with highest

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|  | <p>levels in cells displaying high metabolic activity; e.g. heart and liver.</p> <p>In skin, the reduced form of CoQ10 (ubiquinol-10) also acts as an anti-oxidant, with 10-fold higher levels in the epidermis than the dermis (Shindo <i>et al</i> 1994).</p> <p>Under normal circumstances the body manage keeping the CoQ10 at adequate levels. The level naturally drop as people get older. Normal blood levels range from 0.7 to 1.0 µg/mL (Fuke C <i>et al</i> 2013).</p> <p><i>Industrial production</i></p> <p>To date, CoQ10 is produced by one of three methods: extraction from biological tissues, chemical synthesis, and microbial fermentation using beets and sugar cane as the raw materials. Microbial fermentation appears to be desirable due to less solvent usage and being cheaper to produce on a large scale and the bacteria <i>Agrobacterium tumefaciens</i> being commonly used due to good synthesis rates (Examine.com).<sup>4</sup></p> <p>There are no regulated manufacturing standards in place for this compound.<sup>5</sup></p> <p>Idebenone was first synthesized around 1970, and its potential use as an anti-aging agent in cosmetics is a spin-off from the sector of pharmaceuticals.</p> |
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### 3. Regulation

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| <b>Norway</b>            | CoQ10 and Idebenone are allowed at a maximum concentration of 1 % (w/w) in cosmetic products <sup>6</sup> (since 12 December 2007). This regulation is removed 11 July 2013 <sup>7</sup> |
| <b>EU</b>                | No regulation <sup>8</sup>   |
| <b>Rest of the world</b> | No regulation <sup>9</sup>   |

<sup>4</sup> <http://www.hindawi.com/journals/bmri/2012/607329/>

<sup>5</sup> <http://www.everydayhealth.com/drugs/coenzyme-q10-coq10>

<sup>6</sup> The Norwegian Cosmetics regulation implementing the EU Cosmetics Directive 76/768/EEC.

<sup>7</sup> The Norwegian Medicinal Products Agency consider that CoQ10 possesses pharmacological properties (blood pressure reduction in hypertensive humans) when taken in orally at levels exceeding 100 mg/day.

<sup>8</sup> The major market player in the Nordic countries the company Pharma Nord informs 25 June 2013 that the Hungarian medicinal products authorities approved of its products as medicinal products (180 mg/day); whereas the Danish medicinal products agencies on the other hand on the basis of exactly the same documentation refused to consider the products pharmaceuticals due to, in their eyes, too week evidencing of any effect (effect on the heart).

<sup>9</sup> In Japan CoQ10 has since 1974 been marketed as a drug for treatment of patients with congestive heart failure. This concerns an inland product. Other products have since the 80s been considered food supplements only.

## 4. Relevant toxicity studies

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| <p><b>Absorption</b><br/>Skin</p> | <p>In order to act as an anti-oxidant, CoQ10 needs to penetrate the skin. However, as said, the topical bioavailability of CoQ10 is limited by its lipophilic and thermo-labile properties, as well as a relatively high molecular weight (863 Da) (Lee &amp; Tsai, 2010). Only about 2-3% of orally administered CoQ10 was absorbed in one study with rats (Zhang <i>et al.</i>, 1995). Another study reported that CoQ10 (in ethanol as vehicle) was able to penetrate into stratum corneum of porcine skin, with 20% and 2% penetrating further into the viable layers of epidermis and dermis, respectively Hoppe <i>et al.</i> (1999).</p> <p>When a solution of 1% CoQ10 (in olive oil) was topically applied to rats, CoQ was found to reach levels in living rat skin of 8 µg /g after 2 hours and 15 µg /g after 4 hours. There also was a dose-response relationship between the amount of CoQ applied and the CoQ concentration in skin (Giovannini <i>et al.</i>, 1988).</p> <p>It is noted in this connection that porcine skin resembles closely human skin, whereas rat skin let through chemical substances much more easily than does human skin.</p> <p>Although the bioavailability of “pure” topical CoQ10 is poor, it is dependent on formulation (e.g. liposomes), treatment dosage and duration, as well as interaction with other factors (Miles, 2007; Lee &amp; Tsai, 2010). With the help of suitable enhancers the oral bio-availability may be increased many times – even up till 22 % (<i>inter alia</i>). How much the skin penetration rate can be enhanced using for example liposomes is unknown. On the basis of the finds of Hoppe <i>et al</i> 1999 we, as a first approximation, assume that it can reach up till at least 2 %.</p> |
| <p>GI tractus</p>                 | <p>The uptake and distribution of oral CoQ10, which appears to involve incorporation into chylomicrons for transport to the lymph and peripheral blood, has been reviewed by Miles (2007) and Bhavagan &amp; Chopra (2006). It is also noteworthy that oral CoQ10 intake elevates the epidermal CoQ10 levels (Ashida <i>et al.</i>, 2005).</p> <p>Apparently there is also a high degree of inter-individual variability in CoQ10 absorption (Kaikkonen <i>et al.</i>, 2002). A study involving 20 clinically healthy adult volunteers consumed (a single oral administration) 3 different commercially available dietary supplements (tablets) each containing 120 mg CoQ10. Serum concentration was monitored over 10 h and the AUC(0-10h) determined. The bioavailability varied from 10 % to 22 % with a mean of 15 % (Zheng-Xian L <i>et al</i> 2009).</p> <p>The bio-availability of CoQ10 is at best only moderate and there seems to be a constant search for means to enhance the availability (<i>inter alia</i>) One source alleges that only as little as 4% may reach the bloodstream (Livelonger) – another say 1 -3 % ( Belardinelli RM <i>et al</i> 2003). These figures, apparently, are for the bio-availability in humans. In one rodent (rat) study only about 2-3% of orally administered CoQ10 was absorbed (Zhang <i>et al.</i>, 1995).</p> <p>Seemingly, these days many of the commercial products are absorbed over the gut epithelium much better than that; 10 – 22 % (<i>inter alia</i>). Four products claiming a higher than average bio availability are CoQuinone</p>   |

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|   | <p>30<sup>10</sup>, Bio-Quinone Gold<sup>11</sup>, Super Q10<sup>12</sup> and Bioaktiv Q10<sup>13</sup>.</p> <p>The bioavailability of Idebenone is sparse; 1-10 % (Rathi AA <i>et al</i> 2011).</p>  |
| <b>Distribution</b>   | For distribution in various organs, either as CoQ10 or the reduced form, ubiquinol or hydroquinone, see Bhagavan & Chopra, 2006 - that also conveyed that when in circulation, 95% is in the reduced form (ubiquinol).  |
| <b>Metabolism</b>   | Limited data on the metabolism of CoQ in animals and humans are available (Bhagavan & Chopra, 2006). Pharmacokinetic studies suggest that exogenous CoQ10 does not influence the biosynthesis of endogenous CoQ10 (Hidaka <i>et al.</i> , 2005). The plasma peak (T <sub>max</sub> ) generally occurs 6–8 hours after oral administration, indicating a slow absorptive process from the gastrointestinal tract (Miles, 2007; Bhagavan & Chopra, 2006).   |
| <b>Excretion</b>  | Tomono <i>et al.</i> (1986) used deuterium-labelled crystalline CoQ10 to investigate pharmacokinetics in humans and determined an elimination half-time of 33 hours. Elimination half-time was ranging from 10.7 – 15.2 h in rats (Williams <i>et al.</i> , 1999).  |
| <b>Local toxic effects</b><br>Irritation<br><br><br><br><br><br><br><br><br><br>Sensitivity | <p>0.3% CoQ10 did not cause irritancy in a double blind randomized trial, using <i>in vivo</i> occlusive patch test conducted in volunteers (Hoppe <i>et al.</i>, 1999).</p> <p><i>Contact dermatitis</i></p> <p>Idebenone, the synthetic CoQ10 analogue, has been attributed a role as a contact allergen in four relatively recent case reports. The first case involved a 47-year-old woman who had an anti-aging cream applied at a salon (Sasseville <i>et al.</i>, 2007). Within 24 hours, she developed an oedematous vesicular dermatitis of the face, ears, and neck, requiring treatment with oral prednisone. Results of patch testing with the standard series of the North American Contact Dermatitis Group and with an extensive cosmetic series were entirely negative; the patient reacted only to the cream. A later patch-testing session with the individual ingredients of the cream showed a +++ reaction to Idebenone 0.5% in petrolatum (pet).</p> <p>The second patient was a 43-year-old woman who developed an itchy eruption at the sites where a new anti-aging cream had been applied two days previously (Natkunarajah &amp; Ostlere, 2008). Her dermatitis resolved within 5 days following applications of a topical corticosteroid, and she had positive patch-test reactions to her cream and to Idebenone 0.5% (pet).</p> <p>The third patient, a 50-year-old woman, had a more acute onset of symptoms, with heat and tightness after 4 hours, followed by erythema and periorbital swelling the next day (Fleming <i>et al.</i>, 2008). Patch testing showed positive reaction to 0.5% Idebenone - the same concentration</p> |

<sup>10</sup> [http://shop.usana.com/media/Shop/PIB/en\\_us\\_coquinone.pdf](http://shop.usana.com/media/Shop/PIB/en_us_coquinone.pdf)

<sup>11</sup> <http://www.pharmanord.com/products/details/bio-quinone-q10-gold-100-mg>

<sup>12</sup> <http://www.shopping4net.com/no/Helsekost/Kraft-energi/Q-10/Bio-Qinon-Q10-Super.htm>

<sup>13</sup> <http://www.sund-forskning.dk/artikler/aktivt-q10-hj%C3%A6lper-med-holde-t%C3%A6nder-og-tandk%C3%B8d-sundt>



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|                                      | <p>present in the marketed product.</p> <p>The last patient, a 38-year-old woman, presented with a red, itchy, burning, swollen face, which was caused by application of PreVage MD, an anti-aging facial cream containing 1% Idebenone (Mc Aleer &amp; Collins, 2008). Follow-up patch tests revealed that Idebenone was the responsible substance for the allergy.</p> <p>At least three of the patients had used the same brand of an antioxidant facial cream. The rapidity of onset of these reactions suggests that the patients had been <i>previously sensitized to Idebenone</i>. Because two patients claimed no prior contact with Idebenone, an alternative possibility is that they had been sensitized by earlier exposure to CoQ10, which has been present in over-the-counter products for more than 10 years.</p> <p>Positive patch testing in response to Idebenone (0.5 – 1 %) was demonstrated in all of the subjects, whereas 20 controls showed no reaction, indicating that the effect was not due to general irritation (see e.g. Fleming <i>et al.</i>, 2008).</p> <p>A case of CoQ10 hypersensitivity causing urticarial reactions has been reported (Schiavino E <i>et al</i> 1997).</p> <p>Both CoQ10 and Idebenone are benzoquinones nearly all of which are allergens. These compounds are haptens in that they are electrophiles that easily react with the nucleophilic groups of proteins. Read-across on the basis of data presented in Annex 4 indicate that Idebenone is a fairly potent allergen whereas CoQ10 is a feebly weak one.</p> |
| <p><b>Systemic toxic effects</b></p> | <p>No serious toxicity associated with long term use of CoQ10 has been reported – but some transient side effects.<sup>14</sup> The latter were observed also in an extensive Italian multicenter study of safety and efficiency of CoQ10 medication involving a dosing of 100 mg/day in patients suffering from congestive heart failure. The side effects appeared in 1.5 % of the patients (Baggio E <i>et al</i> 1994).</p> <p>To our knowledge the mentioned side effects has not been observed in relation with use of cosmetic products relying on CoQ10 for claimed effects.</p> <p>The absence of serious complicating toxicity is documented up to</p>  |

<sup>14</sup> According to the Mayo Clinic there are few serious reported side effects of CoQ10. Side effects are typically mild and brief, stopping without any treatment needed. Reactions may include nausea, vomiting, stomach upset, heartburn, diarrhea, loss of appetite, skin itching, rash, insomnia, headache, dizziness, itching, irritability, increased light sensitivity of the eyes, fatigue, or flu-like symptoms.(Mayo Clinic)

The American National Cancer Institute expresses the following view on its internet page (<http://www.cancer.gov/cancertopics/pdq/cam/coenzymeQ10/HealthProfessional/page6>): "No serious toxicity associated with the use of coenzyme Q<sub>10</sub> has been reported. Reviewed in Pepping J 1999, Overvad K *et al* 1999, Hodges S *et al* 1999 and Heller JH 1973 doses of 100 mg /day or higher have caused mild insomnia in some individuals. Reviewed in Pepping J 1999 liver enzyme elevation has been detected in patients taking doses of 300 mg/day for extended periods of time, but no liver toxicity has been reported. Reviewed in Pepping J 1999 researchers in one cardiovascular study reported that coenzyme Q<sub>10</sub> caused rashes, nausea and epigastric (upper abdominal) pain that required withdrawal of a small number of patients from the study. (Baggio E *et al* 1994) Other reported side effects have included dizziness, photophobia (abnormal visual sensitivity to light), irritability, (Baggio E *et al* 1994) headache, heartburn, and fatigue (Feigin A *et al* 1996).

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| <p>Acute<br/>Repeated dose</p>            | <p>ingested doses as high as 3000 mg /day in patients with Parkinson's disease and amyotrophic lateral sclerosis (Shults <i>et al.</i>, 2004; Ferrante <i>et al.</i>, 2005; reviewed in Bhagavan &amp; Chopra, 2007).</p> <p>CoQ10 dosage guidelines suggest well tolerated doses of 1200 mg/day for adults (Hathcock and Shao, 2006) and up to 10 mg /kg /day for children (see Miles, 2007).</p> <p>Acute (2000 mg/kg) or 4-wks repeated (1000 mg/kg) doses of CoQ10 did not produce toxic effects in in rats (Hatakeyama <i>et al.</i>, 2006). No clinical signs, adverse effects, abnormal behavior or mortality of tested animals were observed in response to acute, single dose toxicity tests of CoQ at doses of 20 g/ kg bw (i.e. LD<sub>50</sub> &gt; 20 g /kg) (Fu <i>et al.</i>, 2009).</p> <p>A 52-week chronic toxicity study in rats reported a NOAEL of 1200 mg /kg bw /day (Williams <i>et al.</i>, 1999; Hidaka <i>et al.</i>, 2008).</p> <p>In a sub-chronic 13-weeks oral toxicity study of CoQ10 in rats, CoQ10 was repeatedly administered orally to male and female Crl:CD(SD) rats at daily dose levels of 300, 600 and 1200 mg/kg. Neither death nor any toxicological signs were observed in any group during the administration period. No change related to the test substance administered was observed in any group with regard to body weight, food consumption, ophthalmoscopy, hematology, blood biochemistry, necropsy, organ weights or histopathology. Based on these results, the non-observed-adverse-effect level (NOAEL) of CoQ10 was considered to be 1200 mg/kg/day for male and female rats under these study conditions (Honda <i>et al.</i>, 2007).</p> <p>CoQ10 was well tolerated by male and female rats at dose levels up to 3000 mg/kg bw /day in a 90-day repeated dose toxicity study in rats (Zhipeng <i>et al.</i>, 2007).</p> |
| <p>Mutagenicity /genotoxicity</p>         | <p>The study by Fu <i>et al.</i> (2009) on the acute, sub-acute, and the genetic toxicity of Bio-Quinone Q10 in mice and rats support the safety of CoQ for oral consumption in relation to medicinal treatment and intake of food supplements.</p> <p>In a study on the <i>in vivo</i> and <i>in vitro</i> mutagenic potential based upon mouse bone marrow micronucleus, chromosomal aberration, and bacterial reverse mutation tests, CoQ10 did not exhibit any clastogenic activity when administered orally to mice at doses up to 2000 mg/kg/day. In addition, the CoQ10 did not induce chromosomal aberrations in CHL/IU cells exposed to high concentrations, nor did it induce reverse mutations in <i>S. typhimurium</i> and <i>E. coli</i> (Kitano M <i>et al</i> 2006).</p>  |
| <p>Carcinogenicity</p>                    | <p>Not reported</p>  |
| <p>Reprotoxicity /<br/>teratogenicity</p> | <p>No evidence found for reproductive toxicity of CoQ by Pubmed /Medline searches (last accessed Oct. 7, 2011).</p>  |
| <p>Other effects:</p>                     | <p>No cytotoxicity of CoQ10 was observed in cultured keratinocytes at a dose of 200 µg /ml, the limit of solubility (Hoppe <i>et al.</i>, 1999).</p> <p><u>Humans:</u><br/>No serious adverse effect causally related to CoQ10 has been identified. Clinical trial data show no serious toxic effect up till a level of 1200 mg /day /person (16 month trial period) (Hathcock &amp; Shao, 2006; Hidaka,</p>   |

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|  | <p>2008).</p> <p>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.</p> |
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## 5. Exposure estimate and critical NOAEL / NOEL

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| <p><b>NOAEL/NOEL critical</b></p>        | <p>A NOAEL <b>based on ordinary toxicity effects</b> has not been derived in <b>humans</b> 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.</p> <p>Here, we consider the hypotensive effect of CoQ10 as an <b>adverse</b> side effect in the context of cosmetic products. For background information and more details, see Annex 7.</p> <p>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.</p> <p>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.</p> <p>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<sub>hypotension</sub> in order to distinguish it from the NOAEL established on the basis of ordinary animal toxicity data (<i>inter alia</i>).</p> <p>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 <b>systemic</b> NOAEL<sub>hypotension</sub> corresponding to the <b>oral</b> NOAEL<sub>hypotension</sub> we assume a bioavailability of 15 %. Further, we apply the SCCS default value of 60 kg for the body weight (adult female).</p> <p>Thus, the calculated <b>systemic</b> NOAEL<sub>hypotension</sub> (i.e. hypotensive effect) is <math>100 \times 0.15/60 = \mathbf{0.25 \text{ mg /kg bw/day in humans}}</math>.</p> <p>A NOAEL of 1200 mg /kg bw /day <b>in rats</b> was derived from a 52-week chronic toxicity study (Williams <i>et al.</i>, 1999; Hidaka <i>et al.</i>, 2008), and from a 13-weeks sub chronic toxicity study in rats (Honda <i>et al.</i>, 2007). Assuming a bioavailability in rats of 2% (<i>inter alia</i>) this NOAEL corresponds to a <b>systemic</b> NOAEL in rats of 24 mg/kg bw/day.</p> <p>The NOAEL<sub>hypotension</sub> is derived from <b>human data</b> and is 3 orders of magnitude less than the NOAEL derived from the <b>rat</b> 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).</p> |
| <p><b>Exposure cosmetic products</b></p> | <p>The exposure calculations are based on default values<sup>15</sup> according to Cosmetic Europe (SCCS [online]).</p> <p>Anti-aging cream containing 1% CoQ10 was used to represent typical use levels.</p>   |

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

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|                                      | <p>SED = A (mg/kg bw/day) × C (%) / 100 × DA<sub>p</sub> (%) / 100</p> <ul style="list-style-type: none"> <li> <p><b>Body lotion</b></p> <p>Calculated relative daily exposure of product: 123.20 mg/kg bw/day<br/> Concentration of ingredient in the product: 1% = 0.01<br/> Dermal absorption (assumed): 2% = 0.02</p> <p>SED = 123.20 × 0.01 × 0.02 = <b>0.0246 mg /kg bw /day</b></p> </li> <li> <p><b>Face cream</b></p> <p>Calculated relative daily exposure of product: 24.14 mg/kg bw/day<br/> Concentration of ingredient in the product: 1% = 0.01<br/> Dermal absorption (assumed): 2% = 0.02</p> <p>SED = 24.14 × 0.01 × 0.02 = <b>0.0048 mg /kg bw /day</b></p> </li> <li> <p><b>Hand cream</b></p> <p>Calculated relative daily exposure of product: 32.70 mg/kg bw/day<br/> Concentration of ingredient in the product: 1% = 0.01<br/> Dermal absorption (assumed): 2% = 0.02</p> <p>SED = 32.70 × 0.01 × 0.02 = <b>0.0065 mg /kg bw /day</b></p> <p>Overall SED (=body lotion + face cream) = 0.0246 + 0.0048 = 0.0294 mg/kg bw/day</p> </li> </ul> |
| <p><b>Margin of Safety (MoS)</b></p> | <p>MoS calculations based on the NOEL<sub>hypotension</sub></p> <p>MoS = NOEL<sub>hypotension</sub> / SED</p> <p><b>MoS for body lotion:</b><br/> SED = 0.0246 mg/kg bw/day<br/> MoS = 0.25 / 0.0246 = <b>10.2</b></p> <p><b>MoS for face cream:</b><br/> SED = 0.0048 mg/kg bw/day<br/> MoS = 0.25 / 0.0048 = <b>52.1</b></p> <p><b>MoS for hand cream:</b><br/> SED = 0.0065 mg/kg bw/day<br/> MoS = 0.25 / 0.0065 = <b>38.5</b></p> <p>MoS (overall exposure from cosmetics):<br/> SED = 0.0294 mg/kg bw/day<br/> MoS = 0.25 / 0.0294 = <b>8.5</b></p> <p>By comparison, if NOEL 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.</p>   |

## 6. Other sources of exposure than cosmetic products

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| <p><b>Food stuffs including food supplement products.</b></p>       | <p>Fish and other seafood are good sources of CoQ10 (Weber <i>et al.</i>, 1994). No recommended intake level has been established for CoQ10. According to a statement by The Norwegian Food Safety Authority 25.03.2011, a daily dose of 100 mg CoQ10 in dietary supplements is accepted in several European countries, although the compound is differently regulated in EU. Confer also the above mentioned letter from the Norwegian medicinal products agency.</p> <p>In Denmark, The National Food Institute “Fødevarer instituttet” approved 3 dietary CoQ10 based supplements products in 2007. The institute was of the view there were no toxicological concerns with recommended daily doses of CoQ10 up to 180 mg. At the time it hadn't been fully realized that CoQ10 possesses a hypotensive effect.</p> <p>Using instead a NOAEL based on the outcome of the 52-week chronic toxicity study in rats, amounting to 1200 mg/kg bw/day (Hidaka <i>et al.</i>, 2008) and applying a safety factor of 100, gives acceptable daily (oral) intake (ADI) of 12 mg/kg/day.</p>   |
| <p><b>Pharmaceuticals</b></p>                                       | <p>The Norwegian Medicinal Agency (“Legemiddelverket”) does not classify CoQ10 as a medicinal agent at a daily dose up to 100 mg, if it is not intended to affect physiological functions (via pharmacological, metabolic or immunological mechanisms).</p>  |
| <p><b>Other sources</b></p>   |  |
| <p><b>Adverse side effects - from uses other than cosmetics</b></p> | <p>The published reports and clinical trial database indicate that CoQ10 does not induce serious toxic effects in humans when appreciated under a medicinal safety angle (Hidaka <i>et al.</i>, 2008); e.g. even 3600 mg/day was found to be well tolerated (Hyson <i>et al.</i>, 2010).</p> <p>Some adverse effects have been reported with a wide range of CoQ10 intake levels – see above about these (and Annex 6, 7). Some researchers have launched the theory that they might be related to the carrier (capsule or oil vehicle) because they were observed with similar frequency in the placebo-group subjects (Hathcock &amp; Shao, 2006).</p> <p>The carrier determines the magnitude of the bio-availability of CoQ10 and, therefore, also the degree to which CoQ10 impacts on the physiology. The safety evaluation of a cosmetic product entails both the ingredient carrier as well as the active ingredient (i.e. CoQ10).</p> <p>In a medicinal context, various side effects may be considered tolerable in the sense that they do not complicate medicinal treatment. However, loss of appetite, skin itching, rash, insomnia, headache, dizziness, irritability, increased light sensitivity of the eyes and fatigue is not compliant with the strict safety requirements laid down in the sector of cosmetics).</p> <p><b>Interactions</b></p> <ul style="list-style-type: none"> <li>• Use of CoQ10 reduces the effect of anti-coagulants and so may cause blood clotting with serious health consequences. Possibly interactions occur at CoQ10 systemic exposure levels comparable to systemic exposure because of use of body lotions containing CoQ10. Ca. 6 million people in Europe are on anti-coagulants. Annex 3 provides further details.</li> </ul> |

- Probable cross-allergenicity with vitamin K1 and also other drugs that are either p-naphtoquinone or p-benzoquinone derivatives may affect medical treatment and so cause life-threatening situations.

#### *Vitamin K1*

Vitamin K1 is since 2010 no longer allowed in cosmetic products (amending directive 2009/6/EC). The rationale for the ban appears from a SCCS opinion (SCCS/1313/10m- 24 March 2010) the scientific committee concluding as follows

*Although the risk for sensitisation from cosmetic products containing 1% Vitamin K1 cannot be quantified from the available data, case reports show that Vitamin K1 is a contact allergen in man. In cases of pre-existing sensitisation acquired by topical application of Vitamin K1 present in cosmetics, an individual might not be able to receive Vitamin K1 therapeutically or experience allergic reactions upon Vitamin K1 treatment. Therefore, the SCCS considers that vitamin K1 is not safe when used in cosmetic product in a concentration up to 1%.*

Need for Vitamin K1 may occur in different medicinal situations characterized by coagulation disturbances because of lack of the hormone or influencing on its activity (SCCS). Following injection of Vitamin K1 serious reactions resembling anaphylactic shock have been reported. This means that persons having acquired a Vitamin K1 allergy cannot undergo medicinal treatment with the substance and so may end up in life threatening situations.

Apparently, Idebenone is a sensitizing molecule as is the vitamin K1 molecule. Because the two molecules resemble each other closely as to the molecular structure it seems highly probable that people allergic to Idebenone also are allergic to vitamin K1. The two molecules probably cross-react in this respect. This would mean that people allergic to Idebenone cannot be treated medicinally with vitamin K1 and so would possibly be faced with a serious health threat in case they eventually come in need of vitamin K1 therapy. .

Seemingly, CoQ10 is a feebly weak sensitizer so that the risk for serious medicinal complication as mentioned also is much less probable.

Data supporting the hypothesis that idebenone cross-reacts with vitamin K1 are presented in Annex 4.

#### *Atovaquone*

Atovaquone is another 1,4-naphtoquinone derivative closely resembling CoQ10 / Idebenone as to the molecular structure. Also medicinal sources express that view. Medicinally, it is used to treat a particular type of pneumonia (PCP) and also malaria. PCP affects people with seriously compromised immune systems. By far the most commonly used medication against PCP is trimethoprim/sulfamethoxazole, but some patients are

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|  | <p>unable to tolerate this treatment due to allergies – meaning that atovaquone may be a last resort medicine under certain circumstances (Wikipedia).</p> <p>A very serious allergic reaction to atovaquone may occur as a side effect – but rarely (WebMD<sup>16</sup>).</p> <p>Chances are that atovaquone and Idebenone cross-react as concerns allergy. So people allergic to Idebenone, most probably, also are allergic to atovaquone. An immune compromised person having acquired sensibility towards Idebenone may face a very serious health threat if in need for atovaquone treatment.</p> <p>Annex 4 provides further information.</p> <ul style="list-style-type: none"><li>• Effects on medication for diabetes with possible kidney problems</li></ul> |
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<sup>16</sup> <http://www.webmd.com/drugs/drug-19791-atovaquone-proguanil+Oral.aspx?drugid=19791&drugname=atovaquone-proguanil+Oral>

## 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<sub>hypotension</sub> 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 naphthoquinones 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 naphthoquinone 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<sup>17</sup> - 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<sup>18</sup>. 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-naphthoquinone 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 having 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*

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.

<sup>17</sup> <http://www.skintherapyletter.com/2008/13.7/2.html>

<sup>18</sup> <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<sup>19</sup>. 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  $\geq$  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<sup>20</sup>. 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<sup>21</sup>.

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<sup>19</sup> 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.

<sup>20</sup> 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).

<sup>21</sup> 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 rationale 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).

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## 10. Annexes

### Annex 1: Proposed benefits (photo protection and anti-aging effects) of CoQ10 in cosmetic products

CoQ10 is a popular ingredient in 'anti-aging' cosmetic products. A 1999 study by German researchers reported that long-term topical use of CoQ10 reduced crow's feet (Blatt et al., 1999). These authors reported that reduced epidermal resistance against oxidative stress by UV irradiation is improved with topical application of Coenzyme Q10 and other antioxidants.

Idebenone is a synthetic CoQ10 analogue that has become popular in "anti-aging" topical products, claimed to neutralize free radicals and reduce wrinkles or other signs of aging (Pascoe et al., 2010; Muta-Takada et al., 2009). Idebenone was reported to improve the appearance of photodamaged skin in a non-placebo controlled study (McDaniel et al., 2005).

In women, aged 30–65, the ability of 0.5% or 1.0% idebenone to influence moderately photodamaged skin was examined. After six weeks' use of the 1.0% idebenone formula, a 26% reduction in skin roughness/dryness was observed, a 37% increase in skin hydration, a 29% reduction in fine lines/wrinkles, and a 33% improvement in overall global assessment of photo-damaged skin. For the 0.5% idebenone formulation, a 23% reduction in skin roughness/dryness was observed, a 37% increase in skin hydration, a 27% reduction in fine lines/wrinkles (McDaniel et al., 2005).

<http://truthinaging.com/face/what-is-it-co-enzyme-q10>

CoQ10 is capable of preventing some of the detrimental effects of photoaging (Hoppe et al., 1999). Because the body's CoQ10 levels naturally decrease with aging (as well as with stress and illness), it is frequently used in cosmetics and personal care products due to its potential anti-aging effects. CoQ10 can be either ingested or applied topically ([Wikipedia](#)). One study found that after 6 weeks of CoQ10 application to eye wrinkles (known as crow's feet), wrinkle depth was reduced by 27 percent; after 10 weeks of application, fine lines and wrinkles were decreased by 43 percent (Blatt et al., 1999).

However, Tournas et al. (2006) reported that CoQ10, idebenone, and kinetin provide ineffective photo-protection to skin when compared to a topical antioxidant combination of vitamins C and E with Ferulic Acid. These authors proposed that the slight photo-protective effect seen with commercial creams containing idebenone may be due to the sunscreen ingredients that they contain.

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## 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 clopidogrel less effective (Sigset O 1994, Combs AB 1976, Landbo C 1998). The case of Landbo is typical. It concerns a 70-yr-old woman who had been on warfarin for several years and who experienced a sudden drop in her INR 2 weeks after starting ubiquinol 30 mg daily. Ubiquinol 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 findings, advise 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 weight 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 indicates 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<sub>10</sub> appears to increase the risk of bleeding in this population.”

Discussing their findings the authors wrote:

“Previous research evaluating interactions between warfarin and coenzyme Q<sub>10</sub> has produced conflicting results. Coenzyme Q<sub>10</sub> is structurally related to menaquinone (vitamin K<sub>2</sub>), and there have been several case reports of a decreased response to warfarin after starting coenzyme Q<sub>10</sub>. (Heck AM *et al* 2000). However, in the only published, double-blind, randomized trial, 4 weeks of coenzyme Q<sub>10</sub> 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<sub>10</sub>. 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<sub>10</sub>.

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.<sup>22</sup>

<sup>22</sup> <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  $(30 \times 0.15 / (60 \times 3)) = 0.025$  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 <sup>23</sup> - 1.2 million people in the UK. <sup>24</sup> More than 6 million patients in Europe are living on long-term oral anticoagulation. <sup>25</sup>

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

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<sup>23</sup>

[http://www.cap.org/apps/cap.portal?\\_nfpb=true&cntvwrPtl\\_t\\_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&cntvwrPtl\\_t%7BactionForm.contentReference%7D=cap\\_today%2F0111%2F0111e\\_study.html&\\_pageLabel=cntvwr](http://www.cap.org/apps/cap.portal?_nfpb=true&cntvwrPtl_t_actionOverride=%2Fportlets%2FcontentViewer%2Fshow&cntvwrPtl_t%7BactionForm.contentReference%7D=cap_today%2F0111%2F0111e_study.html&_pageLabel=cntvwr)

<sup>24</sup>

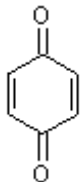
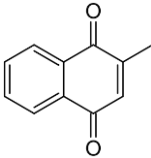
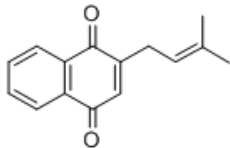
[http://www.roche.co.uk/portal/uk/2013\\_press\\_releases?siteUuid=re7208002&paf\\_gear\\_id=41800051&pageId=re7734007&synergyaction=show&paf\\_dm=full&nodeId=1414-9626b43b7b3811e2a065efe0692339e3&currentPage=0](http://www.roche.co.uk/portal/uk/2013_press_releases?siteUuid=re7208002&paf_gear_id=41800051&pageId=re7734007&synergyaction=show&paf_dm=full&nodeId=1414-9626b43b7b3811e2a065efe0692339e3&currentPage=0)

<sup>25</sup> <http://www.ismaap.org/>

## Annex 4

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

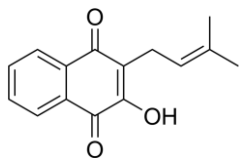
Data obtained over the years from case studies and studies with experimental animals makes it clear that spare a few exceptions<sup>26</sup> the known benzoquinones and naphthoquinones possess allergenic properties. It concerns chemicals that are strong electrophiles which react easily with nucleophilic groups of proteins (-NH<sub>2</sub>, -SH), acting thereby as pronounced haptens.<sup>27,28</sup> The following example molecules have been studied as to their sensitizing/allergenic potency (allergenic contact dermatitis).

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

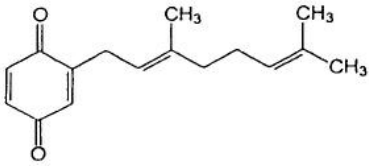
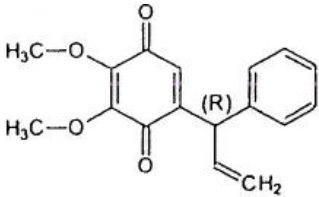
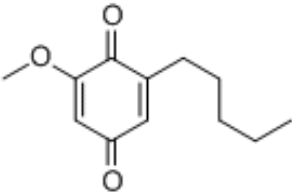
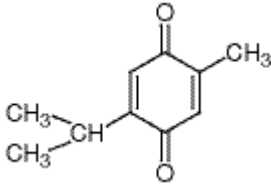
<sup>26</sup> For example the molecule 2,5-dimethoxy-1,4-benzoquinone (Cramer D *et al* 1987)

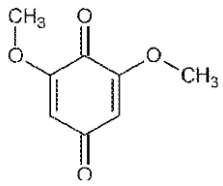
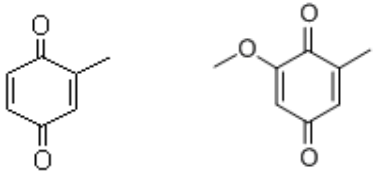
<sup>27</sup> The quinoid moiety lends itself to nucleophilic attack by protein side-chain-groups like the imidazole group of histidine, the epsilon amino group of lysine or the sulfhydryl group of cysteine.

<sup>28</sup> 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 naphthoquinone seems to find use in cosmetic products. They also are very sparingly used for therapeutic medicinal purposes.

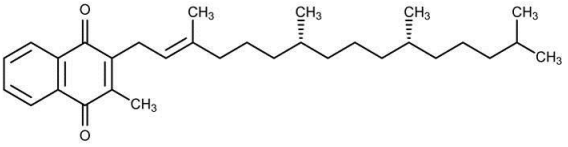
|  |  |   |
|--|--|---|
| <p>CAS No 3568-90-9</p>  | <p>account existing animal data (One of the Category A allergens of Schleder <i>et al</i>)'</p> <p>Not in CosIng</p>   |   |
| <div style="text-align: center;">  </div> <p>Lapachol</p> <p>Natural yellow 16<br/>CI 75490</p> <p>CAS No 84-79-7</p> | <p>Has similar reactivity as desoxylapachol.</p><br><br><br><br><br><br><p>Medium reactivity (Guinea pig maximilisation)</p><br><br><br><p>Not a sensitizer</p><br><br><br><p>Anticoagulant activity in both rats and humans</p><br><p>Therapeutic potential against enterovirus</p><br><p>Not in CosIng</p> | <p>Dictionary of Contact Allergens<sup>29</sup></p> <p>Contact Dermatitis, 5th edition (2011)- Reference is made to Estlander T <i>et al</i> 2001 and Lamminpaa A <i>et al</i> 1996</p><br><br><br><p>Hausen BM <i>et al</i> 1981</p><br><br><br><p>Cramer D <i>et al</i> 1987</p><br><br><br><p>Preusch PC <i>et al</i> 1984</p> |

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

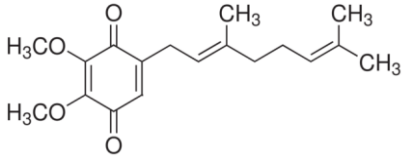
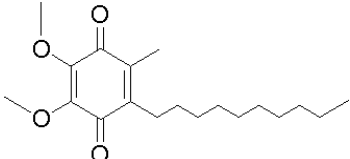
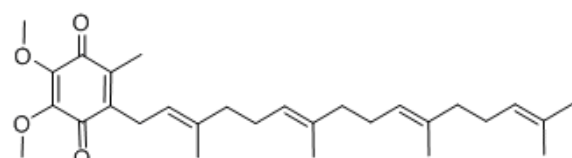
|  |   |   |
|--|---|---|
|  <p>Geranylbenzoquinone</p> <p>CAS No 61977-06-8</p>  <p>Dimethoxydalbergoin</p> <p>CAS No: 3755-64-4</p>  <p>Primin</p> <p>2-methoxy-6-n-pentyl-p-benzoquinone</p> <p>CAS No: 15121-94-5</p> | <p><i>All three haptens:</i></p> <p>Significant contact allergen because of: proven 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 <i>et al</i>)'</p> <p>Primin:</p> <p>A parch test concentration of 0.01 % witness of an extremely sensitizing hapten (<i>inter alia</i>)</p> <p>Not in CosIng</p> | <p>Schlede E <i>et al</i> 2003</p> <p>Cosmetics &amp; Toiletry magazine 71, Vol 112, April 1997</p> |
|  <p>2-methyl-5-isopropyl-1,4-benzoquinone</p> <p>CAS No 490-91-5</p>  | <p>A relatively potent sensitizer</p>   | <p>Cramer D <i>et al</i> 1987</p>   |

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

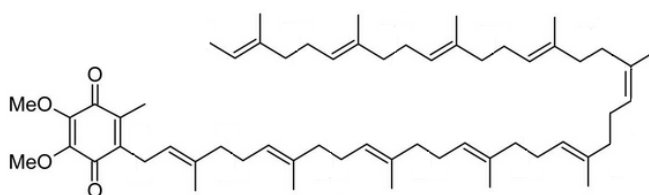
Molecules whose molecular structure closely resembles that of ubiquinone and idebenone

|   |   |  |
|---|---|--|
|  <p>Vitamin K1 (phylloquinone)<br/>INCI: PHYTONADIONE<br/>INN: phytomenadione<br/>CAS No 84-80-0</p> | <p>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 <i>et al</i>).</p> <p>The LLNA EC3 value is 76.7 %.</p> <p>Forbidden in cosmetic products (II/1371)</p> <p>Chain length C 16</p> | <p>SCCS opinion (SCCS/1313/10m- 24 March 2010)</p> |
|---|---|--|



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

For comparison:

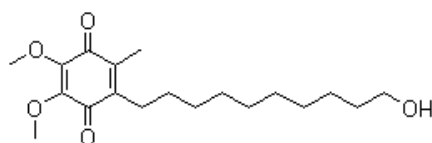


Ubiquinone.

Co Enzyme Q10 (CoQ10)

Chain length: C 40

Idebenone



<sup>30</sup> <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 synthesized 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 <sup>31</sup> noted that the inherent sensitizing potency of an allergen determine the magnitude of the patch test concentrations (PTC) to be used when testing for allergenicity. 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. <sup>32</sup>.

| Compound             | Patch test concentration (%) | LLNA, EC <sub>3</sub> (%) |
|----------------------|------------------------------|---------------------------|
| 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

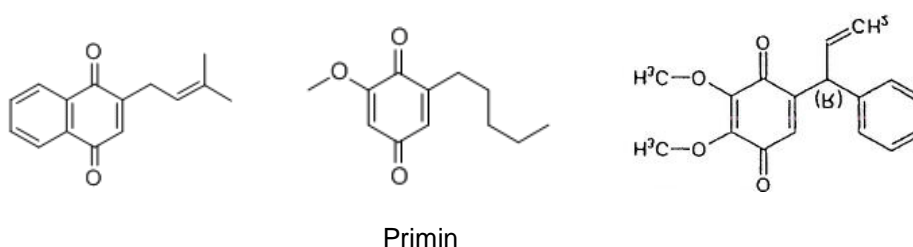
<sup>31</sup> Pickert J, Untersuchungen zur Bindung kontaktallergener Substanzen an nukleophile Aminosäureseitenketten , Dissertation, der Fakultät Mathematik und Naturwissenschaften der Technischen Universität Dresden  
Disputation am: 16. Dezember 2004

<sup>32</sup> All the values are collected from the dissertation of Pickert.

been devoted considerable attention clinically and scientifically. It has been realized that several factors play 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<sub>2</sub>(NH<sub>2</sub>)-) another and the aromatic amines (Ar-NH<sub>2</sub>) a third one. The benzoquinoids and the naphthoquinoids also is a class *per se*. The general pattern is that nearly all the members of a class cross-react with one another.

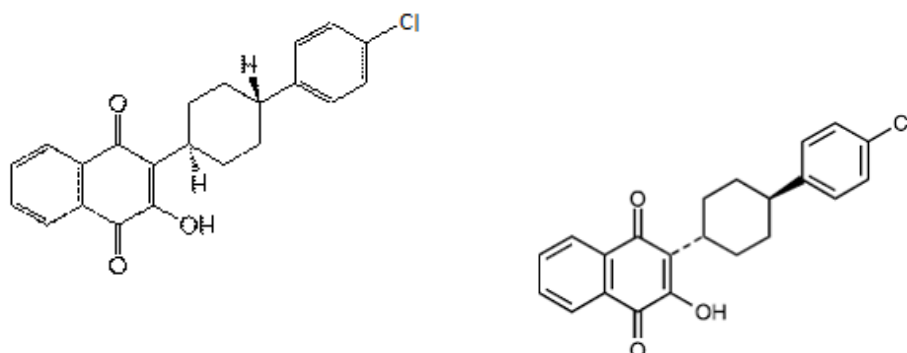
Schultz KH *et al* (1977) in a study saw that allergic cross reactions could be obtained with 9 out of 14 different naphthoquinones. Cramer D *et al* (1987) observed that for example the following three compounds cross-react with one another:



Also it has been observed that primin cross-react with 2,6-dimethoxy 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-naphthoquinone 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<sup>33</sup>) and also

<sup>33</sup> PCP most likely affects people with human immunodeficiency virus [HIV]).

malaria. *Pneumocystis jiroveci* is a yeast-like fungus<sup>34</sup> the growth of which can be halted by exposure to atovaquone (MelinePlus<sup>35</sup>.) 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<sup>36</sup>). It may also cause easy bruising or bleeding. (Rx List / the Internet drug index<sup>37</sup>).

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.<sup>38 39</sup>

We would believe the chances are great 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.

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<sup>34</sup> *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 it 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.

<sup>35</sup> <http://www.nlm.nih.gov/medlineplus/druginfo/meds/a693003.html>

<sup>36</sup> <http://www.webmd.com/drugs/drug-19791-atovaquone-proguanil+Oral.aspx?drugid=19791&drugname=atovaquone-proguanil+Oral>

<sup>37</sup> <http://www.rxlist.com/mepron-drug.htm>

<sup>38</sup> <http://www.drugbank.ca/drugs/DB01117>

<sup>39</sup> Atovaquone can act by selectively affecting mitochondrial electron transport and parallel processes such as ATP and pyrimidine biosynthesis

## Annex 5: CoQ10 in food, including food supplements

As an endogenous substance CoQ10 is present in almost all foodstuffs. In the developed world, the estimated daily intake has been determined at 3–6 mg, derived primarily from meat (Pravstl *et al* 2010). Danish intake studies showed a daily intake in the range 3-5 mg (Overvad *K et al* 1999).

This intake is small compared to intake because of use of one or the other of the numerous dietary supplement products currently on the market; 30 – 180 mg/day. Since 1974, there have appeared over 250 commercial preparations of CoQ10 supplied by more than 80 pharmaceutical companies. It is reported that in Japan alone these days nearly 12 million now use CoQ10 each year, primarily for mild congestive heart failure and other disorders. (Fuke *et al* 2013 ). Next to the Japanese it is the Americans that enjoy CoQ10 the most. In the US the use of CoQ10 is only surpassed by omega-3 and multi-vitamins (NFT, 2011).

According to the company Pharma Nord in the Nordic countries more than 1 million people consume CoQ10 on a daily basis (Pharma Nord 2013). So, probably, at least 4.7 % of the adult Nordic population (> 15 years of age) takes in CoQ10 each day.<sup>40</sup>

In 2006 the global consumption of coenzyme Q10 reached more than 300 tons, of which the consumption of functional foods accounted for about 60%, about 20% consumption of drugs whereas cosmetics accounted for about 8%. In the US around the year 2006 the annual growth rate was 15% to 20%.<sup>41</sup> Over the 5-year period 2005-2010 the North American market grew by 60%. The growth was primarily driven by surging importance of CoQ10 in food and beverage processing industries and emerging role of the Coenzyme in heart health, cognitive health and anti-ageing sectors (Global Industry Analysis Ltd USA.<sup>42</sup>).

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<sup>40</sup> Pharma Nord arrived at this figure by dividing their sales volume with recommended daily intake (30 mg for one of the product 100 mg for the other)

<sup>41</sup> <http://dr-m.achimo.com/losses-of-domestic-producers-of-coenzyme-q10-why-changing-faces-coenzyme-medicine-medicine-pha/>

<sup>42</sup> [http://www.prweb.com/releases/coenzyme\\_Q10/CoQ10/prweb4223894.htm](http://www.prweb.com/releases/coenzyme_Q10/CoQ10/prweb4223894.htm)

## Annex 6: CoQ10 and various medical conditions

Over the 40 years since the detection of this endogen molecule it has been reported that CoQ10 levels are comparatively low in patients with some chronic diseases such as heart conditions, muscular dystrophies, Parkinson's disease, cancer, diabetes, and HIV/AIDS. Further, it soon became clear that the levels of CoQ10 in the body could be increased taking in CoQ10 orally. This coincidence fostered believes in may courts that CoQ10 may possibly be used to remedy medicinally with many of the named ailments. Numerous deliverers of CoQ10 then sprang up – and, actually, in a few countries the medical product authorities also allowed marketing of the products as proprietary pharmaceuticals (Japan and Hungary). Mostly, however, applications made to the different MPA around the globe were rejected the products then being placed on the market as food supplements instead.

Products that claim effects against a disease fall under the scope of medicinal products legislation in the EU. Food supplements can claim health benefits but not medicinal effects.

Some years ago the European Commission adopted the so-called “claims regulation” inviting marketers in the food sector to apply for allowance to use different health related claims. Then the Commission also received a number of applications that concerned claims about the usefulness of CoQ10 in remedying with different health problems. EFSA (2010) looked into the submitted documentation and concluded none of the claims could be evidenced. Apparently, lack of mechanistic explanations counted in heavily for the different judgments.

As concerns the claim “*Maintenance of normal blood pressure*” the target population was assumed to be the general population. On this particular claim EFSA commented as follows:

“In weighing the evidence, the Panel took into account that most of the studies presented have been conducted in hypertensive patients on pharmacological treatment for hypertension, that the evidence provided does not establish that interactions between coenzyme Q10 and antihypertensive treatment can be excluded, and that only one intervention study, which had considerable weaknesses, reported a significant effect of coenzyme Q10 supplementation on blood pressure.”

The medicinal service MedlinePlus has looked into whether the different put *medicinal claims* are trustworthy. MedlinePlus is a service of the US National Library of medicine /The National Institute of Health.<sup>43</sup>

The outcome of numerous clinical test were laid to ground for their evaluation. Below is shown the opinion of MedlinPlus as concerns the different ailments for which an effect is likely or possibly effective. The dosages shown have been studied in scientific research.<sup>44</sup>

### *Likely effective category*

- **Coenzyme Q-10 deficiency** - which is a very rare condition. The symptoms include weakness, fatigue, and seizures. 150 mg daily.
- **Inherited or acquired disorders that limit energy production in the cells of the body (mitochondrial disorders)**. Improvement in symptoms is slow. Some people have to take coenzyme Q-10 for six months to get the most benefit. Dosing: 150-160 mg, or 2 mg/kg/day. In some cases, doses may be gradually increased to 3000 mg per day.

<sup>43</sup> <http://www.nlm.nih.gov/medlineplus/druginfo/natural/938.html>

<sup>44</sup> These data are collected from the source: [http://www.webmd.com/vitamins-supplements/ingredientmono-938-Coenzyme%20Q10%20\(COENZYME%20Q-10\).aspx?activeIngredientId=938&activeIngredientName=Coenzyme%20Q10%20\(COENZYME%20Q-10\)](http://www.webmd.com/vitamins-supplements/ingredientmono-938-Coenzyme%20Q10%20(COENZYME%20Q-10).aspx?activeIngredientId=938&activeIngredientName=Coenzyme%20Q10%20(COENZYME%20Q-10))

### Possibly effective category

- **Congestive heart failure (CHF).** There is some evidence (though controversial) that it might be helpful when taken in combination with other heart failure medications and treatments. Dosing: 100 mg per day.
- **Decreasing the risk of additional heart problems in people who have had a recent heart attack (myocardial infarction, MI).** When started within 72 hours of MI and taken for one year, coenzyme Q-10 appears to significantly lower the risk of heart-related events including non-fatal MI. 120 mg daily.
- **Preventing blood vessel complications caused by heart bypass surgery.** There is some evidence that taking coenzyme Q-10 by mouth for a week before surgery might help to reduce blood vessel damage. But not all research agrees with this finding.
- **High blood pressure (hypertension).** Taking coenzyme Q-10 by itself or along with other medications for treating high blood pressure seems to help lower blood pressure even more. 120-200 mg per day
- **Preventing migraine headache.** Taking coenzyme Q-10 by mouth seems to help prevent migraine headaches. 100 mg three times daily. A dose of 1-3 mg/kg has also been used in pediatric and adolescent patients.
- **Parkinson's disease.** Some research shows that taking coenzyme Q-10 supplements might slow decline in people with early Parkinson's disease. 300 mg, 600 mg, 1200 mg, and 2400 mg per day
- **Improving the immune system of people with HIV/AIDS.** 200 mg per day
- **Muscular dystrophy, an inherited disorder involving muscle wasting.** Taking coenzyme Q-10 by mouth seems to improve physical performance in some patients with muscular dystrophy. 100 mg per day

"Claims" that CoQ10 can prevent or treat statin-induced myopathies is not supported by clinical evidence (NFT, 2011).

Also the Norwegian medicinal products agency (mpa) has gone through the different studies for the claimed effects. In a letter to the Norwegian Food Safety authority 25 May 2012 the MPA is of the view that more studies document that (oral) intake of CoQ10 lower blood pressure in hypertensive patients significantly. The MPA bases its view on the studies of Yamagami T. *et al* 1999, Singh *et al* 1999, Singh *et al*, 1991, Tiano, L. *et al*. 2007, Ho, M. J. *et al.*, Burke BE *et al*, 2001, Langsionen P *et al*, 1994.

The MPA has, therefore, arrived at the view that CoQ10 may be considered a pharmacologically active substance – i.e. a generic medicine with the indication hypertension - at daily dosages exceeding 100 mg. Any concrete CoQ10 based product has, however, not been approved as a proprietary pharmaceutical in Norway.

Seemingly, it has not been fully cleared up which mechanism underlies the anti-hypertensive effect. One theory is that the effect is secondary to the anti-oxidative effect. It is thought that CoQ10 mimic the effect of superoxide dismutase (SOD) in scavenging superoxide radical, except that the nitric oxide (NO) radical is spared and so preserved. NO plays a critical role in endothelial relaxation and capillary dilation. The vasodilation in blood vessels causes the blood pressure to drop (Examine). Another theory is that CoQ10 executes a direct vascular effect (references 9 and 10 in Belardinelli RM *et al* 2003).

According to authors Kaufman *et al* no safety concerns were reported at doses of CoQ10 up to 2700 mg/day for 9 months (Kaufmann *et al.*, 2009). There are, however, reports about side effects entailing long term use as stated in the present risk profile.

## Annex 7: NOAEL based on a possible hypotensive effect of CoQ10 – background

Use in cosmetic products of pharmacologically active substances may – but need not necessarily - provide a significant pharmacological effect in the body. The magnitude of the dose is of crucial importance in this respect. It goes without saying that precautionary measures are imperatively required so that the dose does not become that pronounced it causes a pharmacological effect that strong it poses a threat to the health directly or indirectly. For example, significant anesthetic effects should not occur because that would make one of body' important "alarm systems" partially invalid and, therefore, pose an indirect health threat.

Lowering of the blood pressure is another example of a pharmacological effect that may have also serious unfortunate health consequences. It seems evidenced that CoQ10 possesses an inherent ability to lower blood pressure. The mechanism behind that effect may probably involve endothelial relaxation and capillary dilation (*inter alia*). Hence, the probability is that the substance may make blood pressure drop irrespective of the blood pressure status – i.e. not only in hypertensive persons. A blood pressure drop in healthy people and especially in persons with lower than normal blood pressure, would potentially put the health at risk – and could even be critical.

Normal average blood pressure (systolic / diastolic) is 120/90 mm Hg. The term "*low blood pressure*" is commonly used for pressures below 90 / 60 mm Hg. Some individuals routinely have blood pressure numbers of 90/50 with no symptoms. Hence, some people have naturally low blood pressure without suffering from any disease or disorder. Others again have low blood pressure because of a medicinal condition (heart failure) or they are taking a medication that causes hypotension - like diuretics, alpha blockers, beta blockers, drugs that treat Parkinson's disease and some types of antidepressants (textbook). Millions in the western societies are on such medication.

A blood pressure drop in healthy people/medicated people can cause fainting, dizziness, or nausea – which all are among the reported adverse side effects entailing use of CoQ10 food supplements<sup>45</sup>.

A sudden drop in blood pressure of more than 30% can be a medical emergency. When blood pressure drops too far, too quickly, blood stops circulating the way it should. This can lead to a life-threatening condition (textbook). We saw no reports in the litterateur about any life-threatening condition occurring because of intake of CoQ10.

The Mayo Clinic in the US warns about decreased blood pressure effect in hypotensive individuals (Mayoclinic):

"CoQ10 may decrease blood pressure, and caution is advised in patients with low blood pressure or taking blood pressure medications"

Apparently, also the American Family Physician Association has warned that a further blood pressure lowering in hypotensive people could lead to serious health complications.<sup>46</sup>

Also the medicinal service MedlinePlus thinks it prudent to be cautious taking CoQ10 in combination with low blood pressure. They say "*It also might lower blood pressure, so check your blood pressure carefully if you have very low blood pressure*"<sup>47</sup>.

An unintentional blood pressure reduction in hypertensive persons may complicate regular medicinal treatment. Therefore, exposure for CoQ10 – whatever the non-medicinal source - should be avoided in people having a serious hypertensive health problem requiring medication.<sup>48</sup>

<sup>45</sup> <http://www.squidoo.com/coq10-eide-effects>

<sup>46</sup> <http://www.howdietnutrition.com/archives/20130605/coenzyme-q10-and-hypotension.html>

<sup>47</sup> <http://www.nlm.nih.gov/medlineplus/druginfo/natural/938.html>

<sup>48</sup> On the basis of a review meta-study Ho *et al* recently concluded that it is still uncertain if coenzyme Q10 could be a useful hypertension treatment. (Ho MJ *et al* 2009). Therefore, it is important that medicated people continue using their prescribed medicine. They should not turn to a less efficient, unreliable and non-authorized products like CoQ10 food supplements.



We observe that hypertension is a worldwide epidemic. Hypertension is defined as systolic blood pressure equal to or greater than 140 mm Hg and diastolic blood pressure as equal or more than 90 mm Hg or defined as those taking medication for hypertension. In 2003 the age- and sex-adjusted prevalence of hypertension in the population 35 – 65 year of age was 28% in the North American countries and 44% in the European countries at the 140/90 mm Hg threshold (Wolf-Maier K *et al*, 2003).

This means that about 20 % of the inhabitants in the EU are hypertensive by common standards. So, larger parts of the general population are slightly hypertensive without being on any regular blood pressure medication.

We would think that it is primarily all the many million consumers who are hypotensive for some reason that need protection against unintended hypotensive effects entailing use of cosmetics relying on CoQ10 for its cosmetic effect.