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Risk assessment of "other substances" – Coenzyme Q10

Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2015:26
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Risk assessment of "other substances" – Coenzyme Q10

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Assessed and approved

The opinion has been assessed and approved by Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics. Members of the panel are: Inger-Lise Steffensen (Chair), Ellen Bruzell, Berit Granum, Ragna Bogen Hetland, Trine Husøy, Jens Rohloff, Trude Wicklund.

(Panel members in alphabetical order after chair of the panel)

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the risk of "other substances" in food supplements and energy drinks sold in Norway. VKM has assessed the risk of doses given by NFSA. These risk assessments will provide NFSA with the scientific basis while regulating the addition of "other substances" to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional and/or physiological effect*. It is added mainly to food supplements, but also to energy drinks and other foods. In this series of risk assessments of "other substances", VKM has not evaluated any potential beneficial effects from these substances, only possible adverse effects.

The present risk assessment of coenzyme Q10 (CoQ10) is based on previous risk assessments and articles retrieved from a literature search.

According to information from NFSA, CoQ10 is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of intake of 100 mg/day of CoQ10 in food supplements.

CoQ10 (CAS no. 303-98-0) is a naturally-occurring, lipid-soluble compound present in all tissues in humans. Ubiquinone is the totally oxidized form (CoQ10), whereas ubiquinol ($CoQ10H_2$) is the totally reduced form. Meat and fish are the food sources richest in CoQ10. CoQ10 intake from the diet ranges between 3 and 6 mg/day in developed countries. The total body pool of CoQ10 is estimated to be approximately 0.5–1.5 g in an adult.

Several studies of CoQ10 (both oxidized and reduced form) have been performed in healthy humans (adults) and animals, showing fairly similar results. The adverse effects reported in a small number of human subjects were generally limited to mild gastrointestinal symptoms such as nausea and stomach upset. In humans, orally ingested CoQ10 was well tolerated at doses up to 900 mg/day (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) over periods up to one month. With regard to animal studies, the lack of adverse effects of CoQ10 doses up to 1200 mg/kg per day in long-term toxicity studies supported and extended the results from the human studies. No studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that age affects tolerance for CoQ10. Therefore, in this risk characterisation the same tolerance as for adults was assumed for these age groups (adjusted for body weight).

From a daily dose of 100 mg CoQ10, the daily exposure is 2.3 mg/kg bw for children (10 to <14 years), 1.6 mg/kg bw for adolescents (14 to <18 years), and 1.4 mg/kg bw for adults (≥18 years). For the risk characterization, the values used for comparison with the estimated exposure are 900 mg/day (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) based

on human studies (4 weeks) and the no observed adverse effect level (NOAEL) of 1200 mg/kg bw per day based on a long-term toxicity study in rats (52 weeks).

The margin of exposure (MOE) approach is used for the rat study; that is the ratio of the NOAEL to the exposure. An acceptable MOE value for a NOAEL-based assessment of CoQ10 based on an animal study is ≥100, which includes a factor 10 for extrapolation from animals to humans, and a factor 10 for interindividual human variation. Comparing the NOAEL from a long-term toxicity study in rats with the estimated exposure for the different age groups, it is unlikely that a daily dose of 100 mg/day of CoQ10 causes adverse health effects in children above 10 years, adolescents and adults.

Comparing the dose reported to be well tolerated for healthy adults directly with the estimated exposure, it is unlikely that a daily dose of 100 mg/day of CoQ10 causes adverse health effects in children above 10 years, adolescents and adults.

VKM concludes that it is unlikely that a daily dose of 100 mg of CoQ10 from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Short summary

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of intake of 100 mg/day of coenzyme Q10 in food supplements. For the risk characterization, the values used for comparison with the estimated exposure are 900 mg/day (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) based on human studies (4 weeks) and the NOAEL of 1200 mg/kg bw per day based on a long-term toxicity study in rats (52 weeks). No specific studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that age affects tolerance for CoQ10. Therefore, a tolerance as for adults, based on body weight, was assumed for children and adolescents, in the comparison with human data.

VKM concludes that it is unlikely that a daily dose of 100 mg of CoQ10 from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

Key words: Adverse health effects, coenzyme Q10, food supplement, negative health effects, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, ubidecarenone, ubiquinol, ubiquinone, VKM

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetting av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Disse risikovurderingene vil gi Mattilsynet vitenskapelige grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC som *stoffer som har en ernæringsmessig og/eller fysiologisk effekt, og som ikke er vitaminer og mineraler*. Stoffene tilsettes i hovedsak til kosttilskudd, men også til energidrikker og andre næringsmidler. I disse risikovurderingene har VKM ikke sett på potensielle gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

I denne rapporten har VKM vurdert risiko ved inntak av koenzym Q10 (CoQ10), og risikovurderingen er basert på tidligere risikovurderinger av CoQ10 og artikler som er funnet ved et litteratursøk.

Ifølge informasjon fra Mattilsynet er CoQ10 en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å vurdere risiko ved inntak av 100 mg/dag av CoQ10 fra kosttilskudd.

CoQ10 (CAS no. 303-98-0) er en naturlig forekommende, fettløselig forbindelse som finnes i alle vev hos mennesker. Ubiquinone er den oksiderte formen (CoQ10), mens ubiquinol ($CoQ10H_2$) er den reduserte formen. Kjøtt og fisk er den maten som inneholder mest CoQ10. Inntak av CoQ10 fra kosten ligger på 3-6 mg per dag i industrialiserte land. Den totale mengden CoQ10 i kroppen er estimert til å være omtrent 0,5-1,5 g hos voksne.

Flere studier av CoQ10 (både oksidert og redusert form) er utført på voksne friske mennesker og på dyr, og de gir lignende resultater. De negative effektene som er rapportert hos et fåtall av personene var generelt begrenset til milde mage-tarm symptomer som kvalme og urolig mage. Det er godt dokumentert at voksne mennesker tåler godt et oralt inntak av opptil 900 mg CoQ10 per dag (korresponderer til 12.9 mg/kg for en person på 70 kg) over perioder opptil en måned. Dyrestudiene, som ikke viser skadelige effekter opp til 1200 mg/kg kroppsvekt per dag i kroniske toksisitetsstudier, støtter og utdyper resultatene fra de humane studiene. Det ble ikke funnet studier gjort spesifikt på barn (10 til <14 år) og ungdom (14 til <18 år). Ut i fra den inkluderte litteraturen var det ikke grunn til å anta at alder påvirker toleranse for CoQ10, og derfor ble samme toleransegrense som for voksne, men basert på kroppsvekt, brukt for barn og ungdom, i sammenligningen med human eksponering.

Ved inntak av en daglig dose på 100 mg CoQ10 blir eksponeringen 2.3 mg/kg kroppsvekt for barn (10 til <14 år), 1.6 mg/kg kroppsvekt for ungdom (14 til <18 år), og 1.4 mg/kg kroppsvekt for voksne (≥18 år). I risikokarakteriseringen sammenlignes henholdsvis 900 mg/dag (basert på humane studier, som tilsvarer 12.9 mg/kg kroppsvekt per dag) og 1200

mg/kg kroppsvekt per dag («null-effektsnivået» (NOAEL), basert på en kronisk toksisitetsstudie i rotter) med den estimerte eksponeringen.

Risikokarakteriseringen er basert på beregning av eksponeringsmargin ('margin of exposure' (MOE)), som er ratio mellom NOAEL-verdien og eksponeringen. En akseptabel MOE-verdi for CoQ10 i en risikovurdering basert på NOAEL fra et dyreforsøk er 100, som inkluderer en faktor 10 for ekstrapolering fra dyr til mennesker og en faktor 10 for interindividuell variasjon mellom mennesker. En sammenligning av NOAEL fra langtids toksisitetsstudier (rotte) med den estimerte eksponeringen viser at det er usannsynlig at en daglig dose på 100 mg av CoQ10 forårsaker negative helseeffekter hos barn over 10 år, ungdom og voksne.

En direkte sammenligning med en dose som er rapportert å være godt tolerert for friske voksne viser at det er usannsynlig at en daglig dose på 100 mg av CoQ10 forårsaker negative helseeffekter hos barn over 10 år, ungdom og voksne.

VKM konkluderer at det er usannsynlig at en dose på 100 mg av CoQ10 per dag forårsaker negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Kort sammendrag

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av 100 mg per dag av koenzym Q10 i kosttilskudd. I risikokarakteriseringen sammenlignes henholdsvis 900 mg/dag (basert på humane studier, som tilsvarer 12.9 mg/kg kroppsvekt per dag) og 1200 mg/kg kroppsvekt per dag («null-effektsnivået» (NOAEL), basert på en langtids toksisitetsstudie i rotter) med den estimerte eksponeringen. Det ble ikke funnet studier gjort spesifikt på barn og ungdom. Ut i fra den inkluderte litteraturen var det ikke grunn til å anta at alder påvirker toleranse for CoQ10. Derfor ble det brukt samme toleransegrense som for voksne, men basert på kroppsvekt, for barn (10 til <14 år) og ungdom (14 til <18 år), i sammenligningen med human eksponering.

VKM konkluderer at det er usannsynlig at en dose på 100 mg av CoQ10 per dag forårsaker negative helseeffekter hos barn (10 til <14 år), ungdom (14 til <18 år) og voksne (≥18 år).

Abbreviations and glossary

Abbreviations

ADME - Absorption, distribution, metabolism and excretion
AESAN - the Spanish Agency for Food Safety and Nutrition
CoQ - coenzyme Q
CoQ9 - coenzyme Q9
CoQ10 - totally oxidized coenzyme Q10
$CoQ10H_2$ - totally reduced coenzyme Q10
EC - European Commission
EFSA - European Food Safety Authority
GLP - good laboratory practice
GRAS - Generally Regarded as Safe
MOE - Margin of Exposure
NFSA - Norwegian Food Safety Authority [*Norw.*: Mattilsynet]
NOAEL - no observed adverse effect level
VKM - Norwegian Scientific Committee for Food Safety [*Norw.*: Vitenskapskomiteen for Mattrygghet]

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (The European Parliament and the Council of the European Union, 2006).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition established by EFSA for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to other foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

In Norway, a former practice of classification of medicines had constituted an effective barrier against the sale of potentially harmful "other substances". Ever since this practice was changed in 2009, it has become challenging to regulate and supervise foods with added "other substances". Meanwhile, in the recent years, the Norwegian market has witnessed a marked growth in the sales of products containing "other substances". In 2011, food supplements containing "other substances" constituted more than 50% of the market share.

While within the European Economic Area, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods (FVM, 2014).

The Norwegian Food Safety Authority (NFSA) is working on the establishment of a regulation on the addition of "other substances" to foods at a national level. The regulation will include a list of substances with permitted maximal doses, based on the substances and doses found in products on the Norwegian market. In preparation for a regulation, NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, in consultation with the industry, has compiled a list of "other substances" found in products marketed in Norway. Only substances with a purity of minimum 50% or concentrated 40 times or more have been included in the list. Substances regulated by other legislations like those for novel foods, food additives, flavourings, foods for special medical purposes, etc. have been excluded from the list.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) has requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of coenzyme Q10 in food supplements at the following dose: 100 mg/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance to the guidance document developed in Phase 2) at the doses specified (Phase 3). Safety assessments of "other substances" present in food supplements shall be carried out for the general population, ages 10 years and above.

Assessment

1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional and/or physiological effect*, and may be added to food supplements or e.g. energy drinks.

This risk assessment regards the substance coenzyme Q10 (CoQ10) per se, and no specific products.

VKM has in this series of risk assessments of "other substances" not evaluated documentation of any potential beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway. Thus, potential high intake consumer groups of the substance may not be identified and therefore not included in the assessment.

According to information from the Norwegian Food Safety Authority (NFSA), CoQ10 is an ingredient in food supplements purchased in Norway. NFSA has requested a risk assessment of the intake of 100 mg/day of CoQ10 from food supplements. The total exposure to CoQ10 from other sources than food supplements, such as foods and cosmetic products, is not included in the risk assessment.

CoQ10 intake from food has been reported to range between 3 and 6 mg/day in developed countries (AESAN, 2012). The total body pool of CoQ10 is estimated to be approximately 0.5–1.5 g in a healthy adult (Greenberg and Frishman, 1990), and the plasma concentrations in healthy individuals range between 0.20 and 1.91 µmol/l (Bhagavan and Chopra, 2006). In this risk assessment, the intake of 100 mg/day is assessed.

CoQ10 (CAS no. 303-98-0; EINECs no. 206-147-9) is a naturally-occurring, lipid-soluble compound present in all tissues in humans. Ubiquinone is the totally oxidized form (CoQ10, also called ubidecarenone), whereas ubiquinol (CoQ10H2) is the totally reduced form. CoQ10 is an essential carrier for the electron transfer in the mitochondrial respiratory chain for ATP production. Another important function of CoQ10 is as a lipophilic antioxidant. Tissues with high-energy requirements and metabolic rates such as the heart and the skeletal muscle contain relatively high concentrations of CoQ10. Data on the subcellular distribution of CoQ10 show that a large portion (40–50%) is localized in the mitochondrial inner membrane, with smaller amounts in the other organelles and also in the cytosol (Bhagavan and Chopra, 2006). A major portion of CoQ10 in tissues is in the reduced form as CoQ10H2, with the exception of brain and lungs. This appears to be a reflection of increased oxidative stress in these two tissues (Bhagavan and Chopra, 2006).

2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on a previous risk assessment of coenzyme Q10 by AESAN and articles retrieved from a literature search.

2.1.1 Previous risk assessments

The Scientific Committee for the Spanish Agency for Food Safety and Nutrition (AESAN) has addressed the conditions of use of certain other substances in food supplements, including CoQ10 and $CoQ10H_2$.

Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements – 1. Spain (AESAN, 2012)

In this report (AESAN, 2012), a proposal of the use of a maximum of 200 mg/day of **CoQ10** was addressed. This proposal (from AESAN) was based on the authorisation existing in Belgium and Italy for food supplements with a maximum of 200 mg/day of CoQ10.

The Spanish Scientific Committee concluded, based on the information available and taking into account the general considerations reflected in their report, that the AESAN proposal of a maximum amount of 200 mg/day of CoQ10 is acceptable from the safety point of view for use as a food supplement (AESAN, 2012).

Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements – 2. Spain (AESAN, 2013)

A large quantity of dietary supplements of $CoQ10H_2$ has been marketed. In this report (AESAN, 2013), a proposal of the use of a maximum of 200 mg/day of **$CoQ10H_2$** was addressed. The Scientific Committee concluded that, based on the information available and taking into account the general considerations reflected in the AESAN report with the reference number «AESAN-2012-008», the proposal of a maximum quantity of 200 mg/day of $CoQ10H_2$ is acceptable from the safety point of view for use as a food supplement (AESAN, 2013).

2.1.2 Literature search

2.1.2.1 Search strategy

Literature searches were performed in MEDLINE, EMBASE, Global Health and Web of Science in order to retrieve publications on adverse effects caused by coenzyme Q10. These databases were chosen to ensure comprehensive study retrieval. The literature searches were performed by a librarian in February 2015. The search strategy is included in Appendix 1.

2.1.2.2 Publication selection

The literature search identified 67 articles. In the primary screening, titles and abstracts of all publications retrieved were independently screened against the inclusion criteria checklist.

Inclusion criteria checklist:

- Adverse effects in relation to the substance alone are addressed
- Route of exposure for humans is oral
- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetic is equal to oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of the assessed substance
- Animal model studies address adverse effects relevant to human health

The inclusion criteria checklist was developed by members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Articles that did not appear to meet the inclusion criteria were excluded from further analysis. In situations where it was unclear whether the publication was of relevance to the study, it was retained for further screening. The primary screening was performed independently by two persons.

The full text of articles that passed the primary screening was retrieved for secondary screening. In this screening, the full text articles were reviewed and compared against the inclusion criteria checklist. The secondary screening was performed by one person.

The secondary screening resulted in 7 full text articles. Additionally, the references cited in the included studies were screened. Eight studies from the manual search were identified and included. A final total of 15 publications were identified and included in the results in this report (see Figure 2.1.2.2-1).

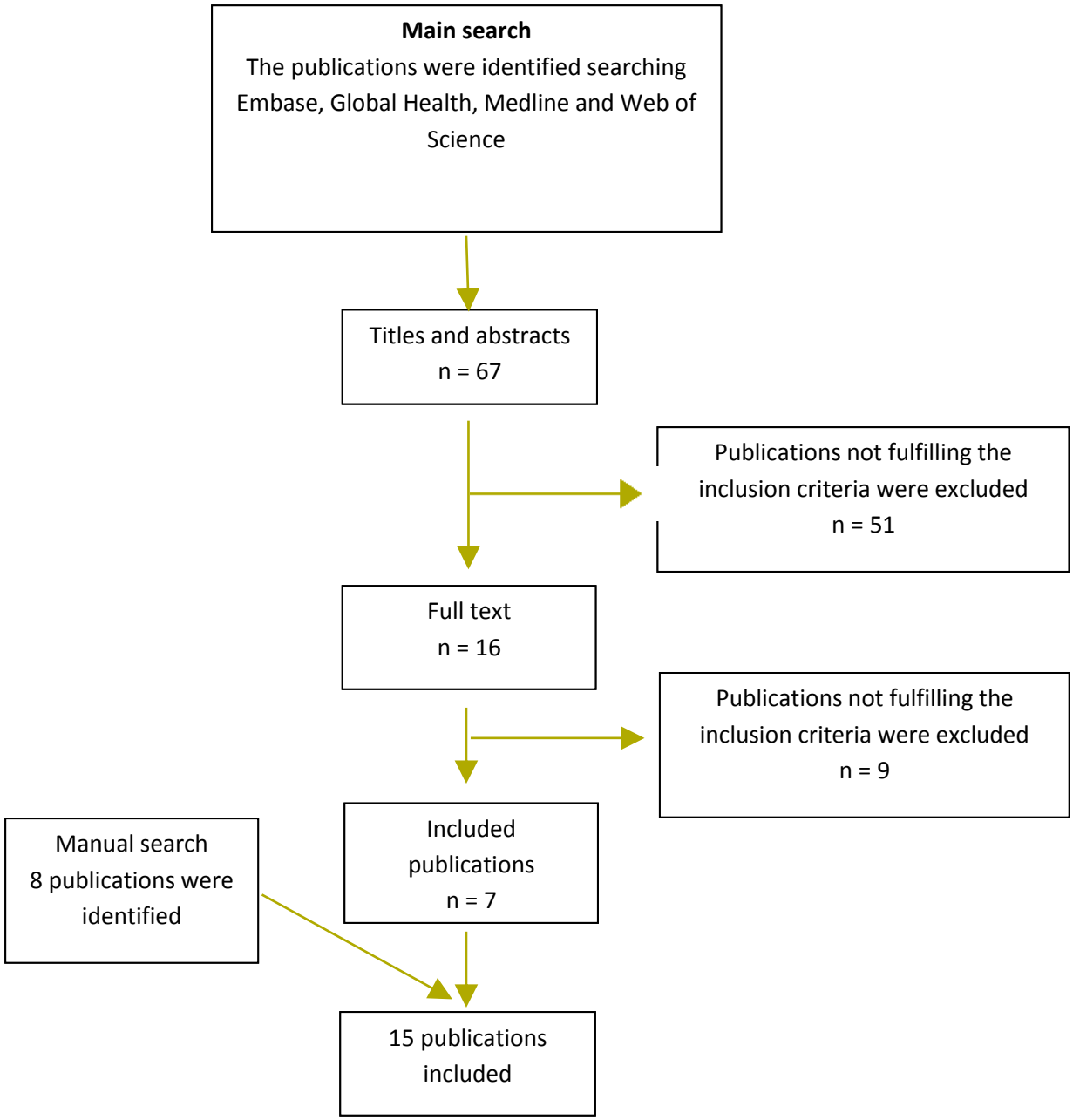

Figure 2.1.2.2-1 Flowchart for the literature search for coenzyme Q10 and the subsequent publication selection.

2.2 General information

2.2.1 Chemistry

Coenzyme Q 10 belongs to a homologous series of compounds (coenzyme Q) that share a common benzoquinone ring structure but differ in the length of the isoprenoid side chain. In humans, the side chain is comprised of 10 isoprene units, hence it is called coenzyme Q10 (Bhagavan and Chopra, 2006). In rodents, the predominant form of coenzyme Q is coenzyme Q9 (Bhagavan and Chopra, 2006).

Coenzyme Q10 (CoQ10, CAS no. 303-98-0; EINECS no. 206-147-9) may exist in three oxidation states, totally reduced as ubiquinol ($CoQ10H_2$), the intermediate form (CoQ10H), and totally oxidized ubiquinone (CoQ10, also called ubidecarenone) (Crane, 2001). The purified coenzyme is a crystalline powder insoluble in water (AESAN, 2012). CoQ10 is manufactured by organic synthesis, yeast fermentation, or bacterial fermentation. The structural formulas of ubiquinol ($CoQ10H_2$) and ubiquinone (CoQ10) are shown in Figure 2.2.1-1.

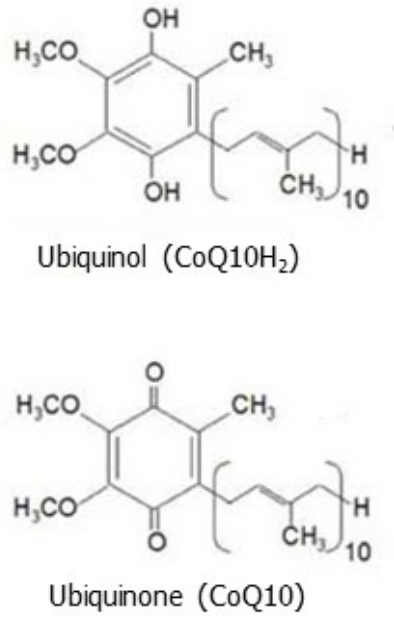

Figure 2.2.1-1 The structural formulas of ubiquinol ($CoQ10H_2$) and ubiquinone (CoQ10).

2.2.2 Occurrence

CoQ10 is a naturally occurring lipid-soluble compound. Tissues with high metabolic activity contain relatively high concentrations of CoQ10 (Ernster and Dallner, 1995). Meat and fish are the food sources richest in CoQ10. The amount of CoQ10 obtained from the diet ranges between 3 and 6 mg/day in developed countries. The dietary intake of CoQ10 does not significantly affect the plasma levels of the coenzyme (AESAN, 2012).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

The absorption of CoQ10 follows the same process as that of lipids in the gastrointestinal tract, and it is enhanced in the presence of lipids (Bhagavan and Chopra, 2006).

The efficiency of absorption of orally administered CoQ10 is poor because of its insolubility in water, limited solubility in lipids, and relatively large molecular weight (Bhagavan and Chopra, 2006). More soluble forms have been made to increase the absorption of CoQ10. Therefore, with respect to nutritional supplements, the quantity of CoQ10 absorbed will depend on the nature of the formula used, and water-soluble formulas are the most bioavailable (AESAN, 2012). Regardless of whether the supplement is in the form of ubiquinone (oxidized form) or ubiquinol (reduced form), the absorption efficiency increases for soluble forms (AESAN, 2012).

The plasma concentration of CoQ10 in healthy individuals ranges from 0.20 to 1.91 µmol/l (Bhagavan and Chopra, 2006). The total body pool of CoQ10 is estimated to be approximately 0.5–1.5 g in a normal adult (Greenberg and Frishman, 1990).

Tissues with high-energy requirements or high metabolic activity such as the heart, kidney, liver and muscle contain higher concentrations of CoQ10 than tissues with lower energy-requirements (Ernster and Dallner, 1995).

Data on the metabolism of CoQ10 in humans is very limited (Bhagavan and Chopra, 2006). In the majority of pharmacokinetic studies, it is reported that the maximum plasma concentration is reached 6.5 hours after its oral intake, with a second increase 24 hours later. Excretion is mainly through the bile and stool although a small fraction is excreted in urine (principally the phosphorylated metabolites). There is a certain enterohepatic circulation which may explain the second peak 24 hours after its oral intake, together with its redistribution that takes place from the liver to the circulation (AESAN, 2012).

2.3.2 Animal studies

In humans and most mammals, including dogs and rabbits, the predominant form of coenzyme Q is CoQ10, whereas the primary form in rodents is coenzyme Q9 (CoQ9) (Hatakeyama et al., 2006; Kitano et al., 2008). Since several studies of CoQ10 have been performed in rodents, the ADME of CoQ10 in rats and rabbit was determined (a study in Japanese described by Hatakeyama et al. (2006)), and it was demonstrated that the ADME of CoQ10 was similar in the two species.

2.4 Toxicological data/Adverse effects

2.4.1 Human studies

An overview of the included studies investigating CoQ10 (totally oxidized is CoQ10 and totally reduced is $CoQ10H_2$) and adverse health effects in humans is given in Table 2.4.1-1.

Table 2.4.1-1 An overview of human studies investigating coenzyme Q10 and adverse health effects (F; female; M; male).

Reference	Study design/ participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Duration of study	Adverse effect
			CoQ10	Control/ placebo				
Nukui et al. (2007)	Randomized, placebo-controlled, double-blind study. Adults	Japan	23 (12 M and 11 F).	23 (11 M and 12 F)	**CoQ10** (a water soluble type; PureSorb-QTM40). 900 mg/day; placebo tablets	Physical examination, hematology, blood biochemistry, urinalysis	4 week intake, 2 weeks after end of intake	Common cold, headache, stomach ache, gastric discomfort. Similar symptoms in placebo group.
Kikkawa et al. (2007)	Randomized, double-blind, placebo-controlled study. Adults	Japan	20	20	**CoQ10** 900 mg/day	Physical examination, hematological and blood biochemical analysis, urinalysis	4 weeks daily ingestion	Soft feces and/or diarrhea, constipation, common cold, dizziness, headache, stiff shoulder and stomachache. In the placebo group, the following adverse events were noted: diarrhea (one case), headache (one case), nausea (one case), and common cold (2 cases).

Reference	Study design/ participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Duration of study	Adverse effect
			CoQ10	Control/ placebo				
Hosoe et al. (2007)	Single-blind, placebo-controlled, single dose and 4 weeks multiple dose trials. Adults	Japan	Single dose study: 10 (5 M and 5 F) Multiple dose study: 20 (10 M and 10 F)	Control for the multiple dose trial: 20 (placebo, 10 M+ 10 F)	**$CoQ10H_2$.** Single dose: 150 mg/day (5 M + 5 F) and 300 mg/day (5 M). Multiple dose: 90 mg/day (10 M + 10 F), 150 mg/day (10 M + 10 F), 300 mg/day (10 M + 10 F)	Hematology, prothrombin time, activated partial thromboplastin, urinalysis, blood chemistry, physical examination, vital signs and electrocardiography	4 weeks	No significant adverse effects occurred during a 4-week supplementation period at doses of up to 300 mg/day, and no safety concerns were noted on standard laboratory tests for safety or on assessment of adverse events for doses of up to 300 mg for up to 2 weeks after treatment completion.
Ikematsu et al. (2006)	Double-blind, placebo-controlled study. Adults	Japan	300 mg (11 M and 11F), 600 mg (11 M and 11 F), 900 mg (22 M)	20 (placebo, 11 M + 11 F)	**CoQ10** (a water soluble type; Kaneka $Q10^{TM}$; the CoQ10 content was over 98%). 0, 300, 600, 900 mg/day orally for 4 weeks	Physical examination, hematological and blood biochemical analysis, urinalysis	4 weeks	CoQ10 was well tolerated at doses up to 900 mg/day. No significant difference in the frequency of adverse effects as compared to placebo.
Hathcock and Shao (2006)	A risk assessment, including several studies of CoQ10	Several countries			**CoQ10**, different doses			Nausea and other adverse gastrointestinal effects. Evidence of safety is strong at intakes up to 1200 mg/day identified as 'observed safe dose'.

In a randomized, placebo-controlled, double-blind trial by Nukui et al. (2007), healthy subjects were randomly assigned to receive **CoQ10** (PureSorb-Q^{TM}40, a water soluble type CoQ10, the ingredients are CoQ10, maltodextrin, glycerin and modified food starch). The daily dose of CoQ10 was 900 mg or placebo. As the placebo, gardenia dye and cellulose were used instead of PureSorb-Q^{TM}40. The total number of participants in the study was 46, 23 in the PureSorb-Q^{TM}40 group (12 males and 11 females) and 23 in the placebo group (12 males and 11 females). The subjects in the two groups took 450 mg twice daily for 4 consecutive weeks. Subjects visited the clinic a total of 4 times; the first day of intake, 2 weeks after start of intake, 4 weeks after start of intake and 2 weeks after end of intake. At each visit, physician examinations, physical tests, hematological and blood biochemical tests and urinalysis test were performed. During the study period, in the PureSorb-Q^{TM}40 group, 5 subjects experienced common cold, headache, stomach ache and gastric discomfort, while in the placebo group, 4 subjects had rough skin, abdominal pain, swollen hands and face, diarrhea, cough and joint pain. Since subjective symptoms that were seen for the treatment group were commonly observed in daily living and were sporadic and transient, and similar symptoms were also seen in the placebo group, and no abnormalities were observed during physical examinations, the observed subjective symptoms were considered not clinically significant.

In a randomized, double-blind, placebo-controlled trial by Kikkawa et al. (2007), healthy subjects were assigned to the **CoQ10** group (daily dose of 900 mg CoQ10) or the placebo group. Minute changes in several tests were observed in physical examination, hematological and blood biochemical analysis, and urinalysis in the dose of CoQ10 and placebo. However, these changes were within normal ranges and thus considered not to be clinically significant. During the ingestion period, the following adverse events were noted in the CoQ10 group: soft feces and/or diarrhea (2 cases), constipation (one case), common cold (2 cases), dizziness (one case), headache (one case), stiff shoulder (one case) and stomachache (one case). In the placebo group, the following adverse events were noted: diarrhea (one case), headache (one case), nausea (one case) and common cold (2 cases). However, these events were temporal, slight and limited to a few persons. Moreover, no abnormalities were detected by the medical examination.

Hosoe et al. (2007) performed two studies, one single dose and one multiple dose, of **CoQ10H$_2$** (ubiquinol, the reduced form of CoQ10). The trials were single-blind, placebo-controlled, and of healthy subjects. In the single dose study, a dose of 150 or 300 mg was administered. In the multiple-dose study, doses of 90, 150 or 300 mg were administered for 4 weeks. The studies were carried out in single-blind fashion within the respective dose groups and in controlled fashion to test the effects of increasing oral doses of CoQ10H$_2$. Soft gelatin capsules containing 30 mg of CoQ10H$_2$ emulsified with diglycerol monooleate, rapeseed oil, soy lecithin and beeswax were used as an active formulation (active capsule), while capsules containing all of the ingredients other than CoQ10H$_2$ were used as a placebo formulation in the single-dose study. The subjects received 10 active capsules or the combination of 5 active capsules and 5 placebo capsules. In the 4-week multiple-dose study, subjects received 5 capsules twice daily for 28 days. Standard laboratory tests for safety

including hematology, prothrombin time, activated partial thromboplastin, urinalysis and blood chemistry as well as physical examination, vital signs and electrocardiography were performed before administration on the day of treatment (day 0) as baseline and on day 2 in the single-dose study. The same laboratory tests were performed before treatment, 2 and 4 weeks after starting treatment, and 2 weeks after completion of treatment in the 4-week multiple-dose study. Adverse event data were collected by monitoring and questioning of subjects by study personnel at 1, 2, 4, 6, 8, 12, 24 and 48 h after treatment in the single-dose study. In the 4-week multiple-dose study, adverse events were voluntarily reported by subjects and recorded each day, and were monitored with questioning by study personnel at 2 and 4 weeks after starting treatment, and again 2 weeks after completion. Any untoward changes, whether or not they appeared to be treatment-related, were considered to be adverse events. No clinically relevant changes in results of standard laboratory tests, physical examination, vital signs or ECG induced by $CoQ10H_2$ were observed in any dosage groups. In these studies, no significant adverse effects occurred during a 4-week supplementation period at doses of up to 300 mg/day, and no safety concerns were noted on standard laboratory tests for safety or on assessment of adverse events for doses of up to 300 mg for up to 2 weeks after treatment completion.

The safety of **CoQ10** (Kaneka $Q10^{TM}$, a water soluble type of CoQ10) was assessed in a trial by Ikematsu et al. (2006) in healthy Japanese adult volunteers (total n = 88). For the analysis, data from 3 subjects were not included (different reasons). The data for 20 subjects in the placebo group, 21 in the 300 mg group, 22 in the 600 mg group, and 22 in the 900 mg group were used for analysis. The content of CoQ10 in Kaneka Q10 was over 98%. The study was double-blind, randomized, placebo-controlled and the doses were 0, 300, 600 or 900 mg/day for 4 weeks. The results showed that the most commonly reported events included common cold symptoms and gastrointestinal effects such as abdominal pain and soft feces, which were not dose-dependent. Changes observed in hematology, blood biochemistry and urinalysis were not dose-related, and were judged not to be clinically significant. Overall, CoQ10 (Kaneka Q10TM) was well tolerated for healthy adults at doses of up to 900 mg/day.

Hathcock and Shao (2006) performed a risk assessment of **CoQ10**. From a large number of clinical trials using a range of CoQ10 doses, it was concluded that reports of nausea and other adverse gastrointestinal effects of CoQ10 cannot be causally related to the active ingredient because there is no dose-response relationship: the adverse effects are no more common at daily intakes of 1200 mg than at a 60 mg intake. The systematic evaluation of the research designs and data did not provide a basis for risk assessment and the usual safe upper level of intake derived from it. Therefore, the methods described as the "observed safe level" or "highest observed intake" were used, and it was reported that the evidence of safety was strong at intakes up to 1200 mg/day (together with vitamin E, derived from a clinical trial with a substantial cohort of 80 persons with Parkinson disease and fairly long duration of 16 months and a shorter and smaller clinical trial of 10 subjects with Huntington's disease of 6 months duration).

2.4.1.1 Interactions

Due to its structural similarity with vitamin K, a possible procoagulation action of CoQ10 has been suggested. This may implicate that patients receiving anticoagulant therapy may need to control their internationalised normalised ratio (INR) of prothrombin time and adjust the anticoagulating dose accordingly (AESAN, 2012).

Bhagavan and Chopra (2006) refers to reported CoQ10-drug interactions, including interactions with anthracyclines (anti-cancer drugs) and statins (cholesterol-lowering drugs), and that beta-blockers and oral hypoglycemic agents have been shown to decrease endogenous CoQ10 content.

Other interactions were not described in the literature included in the present risk assessment. The absence of information in the selected literature does not document an absence of interactions

2.4.1.2 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

2.4.2 Animal studies

An overview of the included studies investigating CoQ10 (totally oxidized is CoQ10 and totally reduced is $CoQ10H_2$) and adverse health effects in animals is given in Table 2.4.2-1.

Table 2.4.2-1 An overview of animal studies investigating coenzyme Q10 and adverse health effects (F; female; M; male).

Reference	Study	Dose and number in treatment group		Conclusion with regard to adverse effects
		CoQ10	Control/ placebo	
Fu et al. (2009)	Genotoxicity	Sperm morphology test: mice (M), randomly divided into groups (n = 10 per group) given daily doses of 2.5, 5.0 or 10.0 g **CoQ10** (in the form of Bio-Quinone, the CoQ10 purity was over 98%)/kg bw via oral gavage for 5 consecutive days. Micronucleated polychromatic erythrocytes in bone marrow; mice (M and F), randomly divided into groups (n = 10 per group, 5 per sex) given daily doses of 2.5, 5.0 or 10.0 g/kg bw for 2 days.	Sperm morphology test, mice (M), negative and positive control groups given corn oil and 40 mg/kg bw cyclophosphamine, respectively. Micronucleated polychromatic erythrocytes in bone marrow; mice (M+F) randomly divided into groups (n = 10 per group, 5 per sex), negative and positive control groups were given corn oil and 50 mg/kg bw cyclophosphamine, respectively.	No significant changes in sperm abnormality or micronucleus formation were observed.
Kitano et al. (2007)	Genotoxicity	Micronucleus test; rats (6 M per group), two oral doses of the **$CoQ10H_2$** (Kaneka QH brand of $CoQ10H_2$) separated by a 24-h interval, the doses were 500, 1000 or 2000 mg/kg bw per day; positive and negative control groups were included; 6 M per group)	Micronucleus test; positive and negative control groups (6 M per group).	$CoQ10H_2$ was evaluated as negative (to not have an effect) in rat bone marrow micronucleus tests under the conditions of these assays.
Kitano et al. (2006)	Genotoxicity	Mouse bone marrow micronucleus test ; 2 oral doses of **CoQ10** at 500, 1000 or 2000 mg/kg/day separated by a 24-h interval	Mouse bone marrow micronucleus; positive and negative control.	CoQ10 was devoid of clastogenic activity when administered orally to mice at doses up to 2000 mg/kg bw per day.
Fu et al. (2009)	Acute and subacute toxicity	LD50; **CoQ10** (in the form of Bio-Quinone) mice (n=20, 10 per sex). Thirty-day subacute toxicity; daily doses of 0, 0.56, 1.13 or 2.25 g **CoQ10** (in the form of **Bio-Quinone**) /kg bw in SD rats.		LD50 greater than 20 g/kg bw in both female and male mice. No clinical signs or adverse effects were detected by administration of CoQ10 in the form of Bio-Quinone.

Reference	Study	Dose and number in treatment group		Conclusion with regard to adverse effects
		CoQ10	Control/ placebo	
Hatakeyama et al. (2006)	Acute and subacute toxicity	A single (2000 mg/kg bw) toxicity study of **CoQ10** and its (2Z)-isomer; rats (3 M, 3 F). A 4-week repeated (1000 mg/kg bw) toxicity study of CoQ10 and its (2Z)-isomer; rats (6 M, 6 F in each group).		Neither CoQ10 nor its (2Z)-isomer produced toxic effects in these studies.
Kitano et al. (2008)	Subchronic toxicity	The initial study; Sprague-Dawley rats [Crj:CD(SD)IGS] (M, F, (10 per sex per group) given **$CoQ10H_2$**, 0, 300, 600 or 1200 mg/kg bw per day by gavage for 13 weeks. The second study; Sprague-Dawley rats (F, 10 per group) given **$CoQ10H_2$** at doses of 0, 75, 150, 200 or 300 mg/kg bw per day by gavage. The dog study (HRA Beagle); **$CoQ10H_2$** was given beagle dogs (F, M, 3 animals per sex per group) at dose levels of 0, 150, 300 and 600 mg/kg bw by gavage.	In both rat studies, animals in the negative control group received vehicle alone, whereas those in the reference-control group received CoQ10 at 1200 mg/kg. In the dog study, animals in the negative control group received vehicle alone, those in the reference-control group received CoQ10 at 600 mg/kg bw.	Histopathological examinations found effects on liver, spleen and mesenteric lymph nodes in female rats, but not in male rats. The NOAEL for $CoQ10H_2$ in rats was conservatively estimated to be 600 mg/kg bw per day for males and 200 mg/kg bw per day for females. The NOAEL for $CoQ10H_2$ in male and female dogs was estimated to be more than 600 mg/kg bw day.
Zhipeng et al. (2007)	Subchronic toxicity	90 days study; Sprague-Dawley rats given 500, 1500 and 3000 mg **CoQ10**/kg bw per day (150 rats randomly divided into groups of 15 animals per sex).	Control groups given either distilled water or vehicle (0.5% hydromethylfibrin).	CoQ10 was well tolerated by rats up to 3000 mg/kg bw per day.
Honda et al. (2007)	Subchronic toxicity	13 weeks study; Sprague-Dawley [Crl:CD(SD)] rats (10 M, 10 F per group) given 300, 600, 1200 mg **CoQ10**/kg bw per day.		The NOAEL was considered to be 1200 mg/kg bw per day for male and female rats.

Reference	Study	Dose and number in treatment group		Conclusion with regard to adverse effects
		CoQ10	Control/ placebo	
Yerramilli-Rao et al. (2012)	Long-term toxicity	39 week study; beagle dogs (Hazelton Research Animal strain), (two dosage-groups, a total of 24 dogs) given 1200 or 1800 mg/kg bw **CoQ10** per day.	Placebo.	Behavior, blood chemistry and detailed histopathology were normal. No deaths occurred.
Williams et al. (1999)	Long-term toxicity	1 year study; Crl:CD(SD)BR VAF/Plus rats (F, M, 247 animals per sex) randomly divided in groups, group 1-5 (toxicity); doses were 0, 100, 300, 600 and 1200 mg/kg bw per day of **CoQ10** (group 6-8 (toxicokinetic); doses were 300, 600 and 1200 mg/kg bw per day of **CoQ10**.		Overall, CoQ10 was well tolerated by male and female rats at dose levels up to 1200 mg/kg bw per day.

2.4.2.1 Genotoxicity

In a study by Fu et al. (2009), genetic toxicity of **CoQ10** in the form of Bio-Quinone was assessed. Bio-Quinone contained Kaneka Q10 produced by fermentation with yeast, and the CoQ10 purity was over 98%. The genotoxicity studies in animals included sperm morphology test and determination of micronucleated polychromatic erythrocytes in bone marrow. For the sperm morphology test, male mice (n = 50, 30–35 g) were randomly divided into five groups (n = 10 per group). Three CoQ10-treated groups were given daily doses of 2.5, 5.0 or 10.0 g/kg bw via oral gavage for 5 consecutive days. The negative and positive control groups were given corn oil and 40 mg/kg bw cyclophosphamine, respectively. For the determination of micronucleated polychromatic erythrocytes in bone marrow, male and female mice (n = 50, 25–30 g) were randomly divided into five groups (n = 10 per group, 5 per sex). Three CoQ10-treated groups were given daily doses of 2.5, 5.0 or 10.0 g/kg bw for 2 days. The negative and positive control groups were given corn oil and 50 mg/kg bw cyclophosphamine, respectively. No significant changes in sperm abnormality or micronucleus formation were observed.

To provide information to enable a Generally Regarded as Safe (GRAS) evaluation for the use of **$CoQ10H_2$** in selected foods, an OECD and good laboratory practice (GLP) toxicological study was conducted to evaluate the mutagenic and genotoxic potential of Kaneka QH brand of $CoQ10H_2$ by Kitano et al. (2007). No mortalities, no abnormal clinical signs and no significant increase in chromosomal damage were observed in an *in vivo* micronucleus test when CoQ10 was administered orally to rats (Crj:CD(SD)IGS[SPF]; two oral doses separated by a 24-h interval; the doses were 500, 1000 or 2000 mg/kg bw per day; positive and negative control groups were included; 6 males per group). $CoQ10H_2$ was evaluated as negative in rat bone marrow micronucleus tests under the conditions of these assays.

A series of toxicological studies was performed by Kitano et al. (2006) to evaluate the *in vivo* mutagenic potential of **CoQ10**. The tests included mouse bone marrow micronucleus test (ICR [Crj:CD-1(ICR), SPF]) mice; 2 oral doses of CoQ10 at 500, 1000 or 2000 mg/kg bw per day separated by a 24-h interval; positive and negative control. The test article, CoQ10, was devoid of clastogenic activity when administered orally to mice at doses up to 2000 mg/kg bw per day.

2.4.2.2 Acute and subacute toxicity

In a study by Fu et al. (2009), acute and subacute toxicity of **CoQ10** in the form of Bio-Quinone was assessed. Bio-Quinone contained Kaneka Q10 produced by fermentation with yeast, and the CoQ10 purity was over 98%. LD50 of CoQ10 by oral treatment was greater than 20 g/kg bw in both female and male ICR mice (n = 20, 10 per sex). Thirty day subacute toxicity was conducted with daily oral doses of 0, 0.56, 1.13 or 2.25 g/kg bw in SD rats. No significant changes in body weight, food intake, behavior, mortality, hematology,

blood biochemistry or vital organ weight were observed and no clinical signs or adverse effects were detected by administration of CoQ10. These results support the safety of CoQ10 for oral consumption at the doses studied.

A single (2000 mg/kg bw) and a 4-week repeated (1000 mg/kg bw) toxicity study in rats (Crj:Wistar; 3 males and 3 females in each group for the single dose study; 6 males and 6 females in each group for the repeated toxicity study) were performed by Hatakeyama et al. (2006) to compare the toxicological profiles of **CoQ10** and its (2Z)-isomer. The test compounds were administered through a disposable gastric tube. In the single-dose toxicity study, neither CoQ10 nor the (2Z)-isomer resulted in toxic signs or mortality in rats at a 2000 mg/kg bw dose. In the repeated-dose toxicity study, neither of the test compounds produced notable changes in overall condition, body weight gain or food consumption. Sporadic findings from urinalysis, hematology and blood chemistry examinations demonstrated significant differences in the treated animals, however, the differences compared to the control were slight and considered to be within physiological limits. In addition, as there was no change in organ weight and the pathological evaluation revealed no compound-related toxic effects, it was concluded that neither CoQ10 nor its (2Z)-isomer produced toxic effects in these studies.

2.4.2.3 Subchronic toxicity

The subchronic toxicity of **$CoQ10H_2$** (the reduced form of CoQ10) was evaluated and compared by Kitano et al. (2008) in Sprague-Dawley rats (strain SPF [Crj:CD(SD)IGS]) and beagle dogs (HRA Beagle). In the initial rat study, males and females (10 per sex per group) were given $CoQ10H_2$ at doses of 0, 300, 600 or 1200 mg/kg bw per day or CoQ10 at 1200 mg/kg bw per day by gavage for 13 weeks. This was followed by a second study, where females (10 per group) were given $CoQ10H_2$ at doses of 0, 75, 150, 200 or 300 mg/kg bw per day or CoQ10 at 1200 mg/kg bw per day in order to determine a no observed adverse effect level (NOAEL). In both studies, animals in the negative control group received vehicle alone, whereas those in the reference-control group received CoQ10 at 1200 mg/kg. In the dog study, $CoQ10H_2$ was administered to males and females (3 animals per sex per group) at dose levels of 0, 150, 300 and 600 mg/kg bw, and CoQ10 was included at 600 mg/kg bw. Animals in the negative control group received vehicle alone, those in the reference-control group received CoQ10 at 600 mg/kg bw. Clinical observations, mortality, body weights, food and water consumption, ophthalmoscopy, urinalysis, hematology, blood biochemistry, gross findings, organ weights and histopathological findings were examined. There were no deaths or test article-related effects in body weight, food consumption, ophthalmology, urinalysis or hematology in rats. Histopathological examinations revealed test article-related effects in the liver, spleen and mesenteric lymph node in female rats but not in male rats. In the liver, fine vacuolation of hepatocytes was observed in the $CoQ10H_2$ groups at 200 mg/kg bw and above. These changes were judged to be of no toxicological significance because they were not considered to induce cytotoxic changes. Microgranuloma and focal necrosis with accumulation of macrophages were observed in the $CoQ10H_2$ groups at 300 mg/kg bw and above. These findings were accompanied by slight increases in blood chemistry enzymes

(aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase), which were suggestive of either potential hepatotoxicity or a normal physiological response to $CoQ10H_2$ loading. Microgranuloma and focal necrosis were judged to be the only adverse effects induced by the test article based on their incidence and pathological characteristics. The changes observed in liver were thought due to uptake of the administered $CoQ10H_2$ by the liver as an adaptive response to a xenobiotic. The microgranulomas and focal necrosis were considered the results of excessive uptake of $CoQ10H_2$, which exceeded the capacity for adaptive response. Based on these findings, the NOAEL in rats was conservatively estimated to be 600 mg/kg bw per day for males and 200 mg/kg bw per day for females. In dogs, there were no deaths or $CoQ10H_2$ -related toxicity findings during the administration period. No test article-related effects were observed in body weight, food consumption, ophthalmology, electrocardiogram, urinalysis, hematology or blood chemistry. Histopathological examination revealed no effects attributable to administration of $CoQ10H_2$ or CoQ10 in any organs examined. Based on these findings, a NOAEL for $CoQ10H_2$ in male and female dogs was estimated to be more than 600 mg/kg bw day under the conditions of this study.

Potential toxicity of **CoQ10** was studied by Zhipeng et al. (2007) in Sprague-Dawley rats by oral gavage for 90 days at 500, 1500 and 3000 mg/kg bw per day (150 rats randomly divided into 5 groups of 15 animals per sex; control groups given either distilled water or vehicle (0.5% hydromethylfibrin). Hematological and blood chemistry parameters were evaluated, gross-pathologic and histopathologic examination was performed. No adverse changes in mortality and clinical signs occurred, however, some effects on body weights, food consumption and hematological data were observed. The authors concluded that CoQ10 was well tolerated by rats up to 3000 mg/kg bw per day, but that nevertheless, appetite, body weight, blood lipid and liver functions should be observed during the clinical administration of CoQ10.

A subchronic toxicology study of **CoQ10** was conducted by Honda et al. (2007). CoQ10 was administered daily (doses: 300, 600, 1200 mg/kg bw) to rats (Sprague-Dawley [Crl:CD(SD)], 10 males and 10 females per group) for 13 weeks. Death or toxicological signs were not observed in any group during the treatment period, and no changes with regard to body weight, food consumption, ophthalmoscopy, hematology, blood biochemistry, necropsy, organ weights or histopathology were observed. The NOAEL was considered to be 1200 mg/kg bw per day for male and female rats.

2.4.2.4 Long-term toxicity

Three studies in beagle dogs (Hazelton Research Animal strain) were conducted by Yerramilli-Rao et al. (2012). Two preliminary dose-range-finding studies were conducted to select appropriate dosages for the chronic toxicity study. In all studies the oxidized form of **CoQ10** was administered by oral gavage. The purpose of the chronic toxicity study was to determine any toxic effects of CoQ10 at the maximum feasible dosage over a 39 week period (two dosage groups, given 1200 or 1800 mg/kg bw CoQ10 per day, and a placebo group; 4

dogs of each sex per dosage group). CoQ10 reached steady state in plasma by 13 weeks. Behaviours, blood chemistries and detailed histopathology were normal. No deaths occurred. These results support the use of a 2400 mg/day dosage of CoQ10 in human clinical trials.

Williams et al. (1999) performed a combined toxicity and toxicokinetic study in rats (male and female Crl:CD(SD)BR VAF/Plus rats, n=496, 247 animals per sex) administered **CoQ10** by oral gavage for 1 year at 0, 100, 300, 600 and 1200 mg/kg bw per day. The animals were assigned computer-generated random numbers and allocated to 8 groups according to the relative rank of the random numbers. Group 1-5 (toxicity); doses were 0, 100, 300, 600 and 1200 mg/kg bw per day of CoQ10. Group 6-8 (toxicokinetic); doses were 300, 600 and 1200 mg/kg bw per day of CoQ10. No adverse changes in mortality, clinical signs, body weight, food consumption or clinical pathology results occurred. CoQ10 had elimination half-lives ranging from 10.7 to 15.2 hours. At 1200 mg/kg bw per day, a high incidence of orange granular, lumenal exudate in nasal turbinates occurred; microscopically, findings similar to those in the turbinates were occasionally observed in small granulomas within lung alveoli. A dose-related increased incidence of vacuolated macrophages (mesenteric lymph nodes) and vacuolated hepatic periportal cells was noted. Neither was associated with tissue damage or organ dysfunction, so they were not considered to be adverse. The nasal turbinate and lung findings were probably secondary to incidental exposure to crystallized test material. Overall, CoQ10 was well tolerated by male and female rats at dose levels up to 1200 mg/kg bw per day. Thus, a NOAEL of 1200 mg/kg bw per day was determined.

2.4.2.5 Interactions

There was no information concerning interactions in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of interactions.

2.4.2.6 Allergic sensitisation (including adjuvant effects)

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

2.4.3 *In vitro* studies

2.4.3.1 Genotoxicity

In a study by Fu et al. (2009), mutagenicity of **CoQ10** in the form of Bio-Quinone was assessed by Ames test. Bio-Quinone contained Kaneka Q10 produced by fermentation with yeast and complied with the European Pharmacopoeia specifications, and the CoQ10 purity was over 98%. For the Ames test, different concentrations of CoQ10 were incubated with special genotypic variants of *Salmonella typhimurium* strains (TA97, TA98, TA100 and

TA102) with and without metabolic activation and the test was assessed based on the number of revertant colonies. No significant changes in mutagenicity were observed by administration of CoQ10.

To provide information to enable a Generally Regarded as Safe (GRAS) evaluation for the use of **$CoQ10H_2$** in selected foods, a series of OECD and good laboratory practice (GLP) toxicological studies was conducted to evaluate the mutagenic and genotoxic potential of Kaneka QH brand of $CoQ10H_2$ by Kitano et al. (2007). $CoQ10H_2$ did not induce reverse mutations in *Salmonella typhimurium* strains TA100, TA1535, TA98 and TA1537 and *Escherichia coli* WP2uvrA at concentrations up to 5000 µg/plate, in either the absence or presence of exogenous metabolic activation by rat liver S9. Likewise, $CoQ10H_2$ did not induce chromosome aberrations in Chinese hamster lung fibroblast (CHL/IU) cells in short-term (6-h) tests with or without rat liver S9 at concentrations up to 5000 µg/ml or in a continuous (24-h) treatment test at concentrations up to 1201 µg/ml. $CoQ10H_2$ was evaluated as negative in the bacterial reverse mutation and the chromosomal aberration tests under the conditions of these assays.

Mutagenicity of organically synthesized **CoQ10** was determined by Ames assay in the presence and absence of S9 mix by Ikeda et al. (2005). The tester strains were *Salmonella typhimurium* TA98, TA100, TA1535, and TA1537, and *Escherichia coli* WP2 *uvr A*. CoQ10 displayed no mutagenicity in any tester strain at any dose tested. Therefore, organically synthesized CoQ10 was considered to possess no mutagenicity.

Genotoxicity of **CoQ10** manufactured by bacterial fermentation was determined by Ames assay and *in vitro* chromosome aberration test in compliance with the OECD guidelines for testing chemicals by Yamaguchi et al. (2009). The results indicated neither increase of revertant colonies nor chromosome aberration, suggesting that CoQ10 manufactured by bacteria fermentation has no genotoxic activities under the condition of this study.

A series of toxicological studies were performed by Kitano et al. (2006) to evaluate the *in vitro* mutagenic potential of CoQ10. The tests included chromosomal aberration and bacterial reverse mutation tests. The test article, **CoQ10**, did not induce chromosomal aberration in Chinese hamster lung fibroblasts (CHL/IU cells) exposed to concentrations up to 5.0 mg/ml, nor did it induce reverse mutations in *Salmonella typhimurium* and *Escherichia coli* at concentrations up to 5000 µg/plate.

2.4.4 Vulnerable groups

There is not enough information regarding the safety of the use of CoQ10 during pregnancy and breastfeeding (AESAN, 2012).

2.5 Summary of hazard identification and characterisation

With regard to mutagenicity and genotoxicity, CoQ10 (in the form of Bio-Quinone) caused no significant changes in mutagenicity and micronucleus formation, $CoQ10H_2$ (the Kaneka QH brand) was evaluated as negative (to not have an effect) in the bacterial reverse mutation, chromosomal aberration and rat bone marrow micronucleus tests, organically synthesized CoQ10 was considered to possess no mutagenicity and CoQ10 had no genotoxic activities (Fu et al., 2009; Hidaka et al., 2008; Ikeda et al., 2005; Kitano et al., 2007; Yamaguchi et al., 2009).

The human studies on healthy subjects indicated that CoQ10 was well tolerated at doses up to 900 mg per day for 4 weeks. The forms of CoQ10 tested included CoQ10 (the oxidized form), PureSorb-Q^{TM}40 (a water soluble type CoQ10), $CoQ10H_2$ (the reduced form) and Kaneka Q10^{TM} (over 98% CoQ10). No significant difference in the frequency of adverse effects as compared to placebo was reported (Hosoe et al., 2007; Ikematsu et al., 2006; Nukui et al., 2007). Hathcock and Shao (2006) performed a risk assessment of CoQ10. Using the "observed safe level" or "highest observed intake", Hathcock and Shao (2006) reported that the evidence of safety was strong at intakes of CoQ10 to up 1200 mg/day (together with vitamin E, derived from a clinical trial with a substantial cohort of 80 persons with Parkinson disease and fairly long duration of 16 months and a shorter and smaller clinical trial of 10 subjects with Huntington's disease of 6 months duration) (Hathcock and Shao, 2006; WHO, 2005).

With regard to subchronic toxicity studies, Kitano et al. (2008) reported that conservative NOAEL estimates for $CoQ10H_2$ in Sprague-Dawley strain SPF [Crj:CD(SD)IGS] rats were 600 mg/kg bw per day for males and 200 mg/kg bw per day for females after 13 weeks, based on effects on the liver, and that the NOAEL for $CoQ10H_2$ in male and female beagle dogs (HRA Beagle) was estimated to be more than 600 mg/kg bw per day. Zhipeng et al. (2007) reported that CoQ10 doses up to 3000 mg/kg per day were well tolerated by Sprague-Dawley rats, and Honda et al. (2007) reported that the NOAEL of CoQ10 for male and female Sprague-Dawley [Crl:CD(SD)] rats was considered to be 1200 mg/kg bw per day.

With regard to long-term toxicity studies, the lack of adverse effects, including on the liver, of CoQ10 doses up to 1200 mg/kg per day in Crl:CD(SD)BR VAF/Plus rats for 52 weeks (Williams et al., 1999) and doses up to 1800 mg/kg per day in beagle dogs (Hazelton Research Animal strain) for 39 weeks (Yerramilli-Rao et al., 2012) indicates the safety of CoQ10. In the chronic toxicity study in rats by Williams et al. (1999), a NOAEL of 1200 mg/kg bw per day was determined.

The values used for comparison with the estimated exposure in the risk characterization are 900 mg/day (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) based on human studies (4 weeks) and the NOAEL of 1200 mg/kg bw per day based on a chronic toxicity study in rats (52 weeks).

3 Exposure / Intake

3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 100 mg/day of CoQ10 in food supplements for children above 10 years old), adolescents and adults. The default body weights (bw) for these groups determined by EFSA were used to calculate the intake for these groups: 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults; 70.0 kg. From a daily dose of 100 mg CoQ10, the daily exposure is 2.3 mg/kg bw for children (10 to <14 years), 1.6 mg/kg bw for adolescents (14 to <18 years), and 1.4 mg/kg bw for adults (Table 3.1-1).

Table 3.1-1 Estimated exposure of children, adolescents and adults from CoQ10 in food supplements.

Group	Daily dose (mg)	Body weight (kg)	Exposure (mg/kg bw per day)
Children (10 to <14 years)	100	43.4	2.3
Adolescents (14 to <18 years)	100	61.3	1.6
Adults ((≥18 years)	100	70.0	1.4

3.2 Other sources

Meat and fish are the richest natural food sources of CoQ10. The richest vegetable sources are the oils, and concentrations were found ranging from 100 to 280 mg/kg in soybean, corn and olive oil. Nuts and cereals also contain CoQ10 but in lower quantities (Pravst et al., 2010). CoQ10 obtained from the diet ranges between 3 and 6 mg/day in developed countries (AESAN, 2012).

CoQ10 is used in several cosmetic products, i.e. in various anti-aging skin creams allegedly due to its antioxidant activity (CosIng, 2015).

4 Risk characterisation

4.1 Food supplements

The values used for comparison with the estimated exposure in the risk characterization are 900 mg/day (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) based on human studies (4 weeks) and the NOAEL of 1200 mg/kg bw per day based on a chronic toxicity study in rats (52 weeks).

NFSA requested VKM to perform a risk assessment of a dose of 100 mg/day of CoQ10 in food supplements for a general population, ages 10 years and above.

4.1.1 Comparing the NOAEL from a rat study with the estimated exposure

A NOAEL of 1200 mg/kg bw per day was determined in a chronic toxicity study in rats (52 weeks).The risk characterization is based on the Margin of Exposure (MOE) approach; the ratio of the NOAEL to the exposure. The calculated MOE values are used to determine human health risk. An acceptable MOE value for a NOAEL-based assessment of CoQ10 based on an animal study is ≥100, which includes a factor 10 for extrapolation from animals to humans, and a factor 10 for interindividual human variation (EPA, 2012). A MOE below 100 may also be acceptable; however, such assessment must be based on supporting scientific literature and expert judgement.

From a daily dose of 100 mg CoQ10, the daily exposure is 2.3 mg/kg bw for children (10 to <14 years), 1.6 mg/kg bw for adolescents (14 to <18 years), and 1.4 mg/kg bw for adults (Table 3.1-1). Using the MOE approach, for a daily intake of 100 mg CoQ10 from food supplements and a NOAEL of 1200 mg/kg bw per day from a rat study, the margins of exposure are 522, 750 and 857 for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years), respectively (Table 4.1.1-1). Thus, for a daily intake of 100 mg CoQ10, the margin is above 100 for all age groups.

Table 4.1.1-1 The calculated MOE values for the various age groups exposed to CoQ10 from food supplements.

Age groups	Margin of safety for 100 mg/day CoQ10
Children (10 to <14 years)	522
Adolescents (14 to <18 years)	750
Adults ((≥18 years)	857

4.1.2 Comparing the well tolerated dose from human studies with the estimated exposure

No studies on children (10 to <14 years) and adolescents (14 to <18 years) were identified. Based on the included literature there was no evidence indicating that children or

adolescents are more vulnerable than adults to CoQ10. Therefore, in this risk characterisation a tolerance as for adults, based on body weight, was assumed for these age groups, in the comparison with human data.

The well tolerated dose of 900 mg/day derived from human studies (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) is compared directly with the estimated intake from food supplements. From a daily dose of 100 mg CoQ10, the daily exposure is 2.3 mg/kg bw for children (10 to <14 years), 1.6 mg/kg bw for adolescents (14 to <18 years), and 1.4 mg/kg bw for adults (Table 3.1-1). Thus, the intakes are below this value for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

4.1.3 Summary of the risk characterization – food supplement

From the results of the comparison of the well tolerated dose from human studies (4 weeks) or the NOAEL from a chronic toxicity study in rats (52 weeks) with the exposure, VKM concludes that it is unlikely that 100 mg CoQ10 per day in food supplements causes adverse effects in any of the age groups.

5 Uncertainties

5.1 Exposure

With use of the default (mean) body weight of an age (population) group, the variance in all individuals in the group will not be covered.

5.2 Risk characterization

The exposure was compared directly with a safe level from a human study on adults, without using an uncertainty factor of 10 for human interindividual variation. No studies on children and adolescents were identified. A tolerance as for adults, based on body weight, was assumed for these age groups, which may underestimate the risk for children and adolescents.

The human studies were of short duration (4 weeks).

6 Conclusions with answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority, assessed the risk of coenzyme Q10 (CoQ10) (100 mg/day) in food supplements. The present risk assessment is based on previous risk assessments and a literature search.

Several studies of CoQ10 (both oxidized and reduced form) have been performed in adult humans and animals, showing fairly similar results. The tolerance of doses up to 900 mg orally ingested CoQ10 per day over periods up to one month was documented in adult humans. The adverse effects reported in a small number of subjects in human studies were generally limited to mild gastrointestinal symptoms such as nausea and stomach upset. With regard to animal studies, there was a lack of adverse effects of CoQ10 from doses up to 1200 mg/kg per day in long-term toxicity studies.

No studies on children and adolescents were identified. Based on the included literature there was no evidence indicating that age affects tolerance for CoQ10. Therefore, a tolerance as for adults, based on body weight, was assumed for these age groups, in the comparison of human data.

For the risk characterization, the values used for comparison with the estimated exposure are 900 mg/day (corresponding to 12.9 mg/kg bw per day in a 70 kg adult) based on human studies (4 weeks) and the no observed adverse effect level (NOAEL) of 1200 mg/kg bw per day based on a long-term toxicity study in rats (52 weeks). The margin of exposure (MOE) approach is used for the rat study; that is the ratio of the NOAEL to the exposure.

Based on the MOE values when comparing the NOAEL from a long-term toxicity study with the estimated exposure, it is unlikely that a daily dose of 100 mg/day of CoQ10 causes adverse health effects for children above 10 years, adolescents and adults. Comparing the dose reported to be safe and well tolerated for healthy adults with the estimated exposure, it is unlikely that a daily dose of 100 mg/day of CoQ10 causes adverse health effects for children above 10 years, adolescents and adults.

VKM concludes that it is unlikely that a daily dose of 100 mg of CoQ10 from food supplements causes adverse health effects in children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years).

An overview of the conclusions is presented in Table 6.1. Estimated exposures unlikely to cause adverse health effects (below the value for comparison) are shown in green.

Table 6.1 An overview of the conclusions on CoQ10 (100 mg/day) in food supplements. Green: estimated exposure to CoQ10 is unlikely to cause adverse health effects.

Coenzyme Q10 (CoQ10)	
Food supplement / **Age groups**	**100 mg/day**
Children (10 to <14 years)	
Adolescents (14 to <18 years)	
Adults (≥18 years)	

7 Data gaps

No studies on adverse health effects of CoQ10 in children, adolescents, pregnant women or lactating women were identified.

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9 Appendix

Search Strategy Medline, Embase, Global Health

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