

Risk assessment for coenzyme Q10 (Ubiquinone) [☆]

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Abstract

Coenzyme Q10 (CoQ10) widely occurs in organisms and tissues, and is produced and used as both a drug and dietary supplement. Increasing evidence of health benefits of orally administered CoQ10 are leading to daily consumption in larger amounts, and this increase justifies research and risk assessment to evaluate the safety. A large number of clinical trials have been conducted using a range of CoQ10 doses. 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. Systematic evaluation of the research designs and data do not provide a basis for risk assessment and the usual safe upper level of intake (UL) derived from it unless the newer methods described as the observed safe level (OSL) or highest observed intake (HOI) are utilized. The OSL risk assessment method indicates that the evidence of safety is strong at intakes up to 1200 mg/day, and this level is identified as the OSL. Much higher levels have been tested without adverse effects and may be safe, but the data for intakes above 1200 mg/day are not sufficient for a confident conclusion of safety.

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1. Introduction

Coenzyme Q is a biosynthesized quinone structure that occurs widely in living organisms such as yeasts, plants, and animals, and hence is also known as ubiquinone (ubiquitously occurring quinone) (Nohl et al., 1998). In higher organisms, including humans, this compound has 10 isoprenoid units in the side chain, and is thus named coenzyme Q10 (CoQ10) (Ernster, 1977).

CoQ10 has two major physiological activities: (a) mitochondrial electron-transport activity involved in the efficient production of high-energy phosphates necessary for muscle contraction and other cellular functions (Mitchell, 1976), and (b) an antioxidant activity (Lonnrot et al., 1996). The antioxidant activity occurs only with the reduced form (ubiquinol), which is produced physiologi-

cally from CoQ10. Its important function in the mitochondria may explain observed benefits related to diabetes (Hodgson et al., 2002; Lamson and Plaza, 2002; Watts et al., 2002; Hodgson and Watts, 2003; Chew and Watts, 2004; Chinnery et al., 2006) and neurodegenerative diseases (Shults et al., 1998, 2004; Shults, 2003; Beal, 2004; Damian et al., 2004). One or both of these functions may account for the reported benefits in persons with acute myocardial infarction (Chello et al., 1994, 1996; Singh et al., 1998a, 2003; Morin et al., 2001), or its use as an adjunct therapy in patients following cardiac surgery (Chello et al., 1994, 1996; Rosenfeldt et al., 2002a,b; Chung, 2004; Littarru and Tiano, 2005; Rosenfeldt et al., 2005). The antioxidant activity or improved immune function may explain CoQ10's potential anti-cancer effects observed in some studies (Lockwood et al., 1994).

CoQ10 is not considered an essential nutrient, and therefore is not recognized as a vitamin (Food and Nutrition Board. Institute of Medicine, 2000). However, it does possess some vitamin-like qualities, including benefits under some circumstances when ingested even though small quan-

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tities are synthesized in the tissues (Folkers, 1969). The potential benefits of oral intake have led to extensive interest in use of CoQ10 as a dietary supplement or as a drug. The widespread use of this ingredient in dietary supplements suggests a need to evaluate the safety of CoQ10 through quantitative risk assessment.

Most upper safe levels of nutrients and related substances are based on widely applicable upper level risk assessment models used by the US Food and Nutrition Board (FNB) in its Dietary Reference Intakes documents in 1997 and after (Food and Nutrition Board, Institute of Medicine, 1997, 1998b,a, 2000, 2001). The FNB method and reviews are a formalization and extension of the quantitative methods widely used earlier in risk assessment of other substances, and by the food and dietary supplement industries. Because of the systematic, comprehensive, and authoritative character of the FNB UL risk assessment method for nutrients, this approach has gathered widespread support and adoption by others such as the European Commission Scientific Committee on Food (SCF) (European Commission, 2001), the United Kingdom Expert Group on Vitamins and Minerals (EVM) (Food Standards Agency, 2003) and more recently by the Food and Agriculture Organization/World Health Organization project report *A Model for Establishing Upper Levels of Intake for Nutrients and Related Substances* (FAO, 2006) with some slight modifications. All these report reflect the concepts and procedures established much earlier for the risk assessment of non-carcinogenic chemicals, which include identification of a no observed adverse effect level (NOAEL) and adjustment for the degree of uncertainty (National Research Council, 1983).

2. Methods

The safety evaluation method applied to orally administered CoQ10 is from the Council for Responsible Nutrition (CRN) *Vitamin and Mineral Safety*, 2nd Edition (Hathcock, 2004), which contains the basic features of the FNB UL method and also the observed safe level (OSL) modification recently adopted as a highest observed intake (HOI) in the FAO/WHO report.

The criteria for selection of clinical trials should reflect the application of the UL identified to daily intake of indefinitely long duration by the general population of adults. Thus, the primary criteria for selection and assigning importance to the trials were randomized and controlled design, dosage level, duration, size, and adequacy of monitoring. Also, clinical trials and review articles were reviewed to determine whether adverse effects were produced at any CoQ10 intake.

Overall, this risk analysis was derived from the human clinical trial database through the following major steps:

1. Derive a safe upper level of intake (UL) if the data are appropriate:
 - a. Search for data that identify a hazard related to excessive intake
 - b. Assess the dose–response relationship for the identified hazard
 - c. Consider uncertainty and assign an uncertainty factor (UF)
 - d. Derive a UL from the no observed adverse intake level (NOAEL) or lowest observed adverse effect level (LOAEL), as $UL = NOAEL \div UF$.
2. If no data establish adverse effects in humans, the above procedure cannot be used. In these circumstances, identify the highest intake level with sufficient evidence of safety as a value named the OSL by CRN and the HOI by FAO/WHO.

We applied the first procedure to the CoQ10 human trial data and found no basis for a NOAEL or LOAEL, and thus could not derive a UL. Consequently, we applied the OSL procedure to the CoQ10 clinical trial data, with the results described in the sections below.

No efforts were made in any of the clinical trials to avoid dietary CoQ10, and therefore the subjects must have been consuming normal dietary levels of this substance. Also, the clinical trials involved subjects with a wide variety of diseases, which make it extremely implausible that there were uniform differences between the subjects and the general population in CoQ10 biosynthesis or resistance to potential adverse effects. Thus, the OSL value identified from the trials does not require correction for dietary intakes or endogenous synthesis, and the OSL can be identified as a safe upper level for supplements (ULS).

3. Clinical trial data

Several double-blind, placebo-controlled clinical trials have been conducted with CoQ10 using relatively high dosages, and no systematic pattern of adverse effects have been observed: 2400 mg/day in Parkinson's disease patients (Shults et al., 2004), 1200 mg/day in early Parkinson's disease patients (Shults et al., 2002), 900 mg/day in healthy adults (Ikematsu et al., 2006), 600 mg/day in Parkinson's disease patients (Shults et al., 1999), 600 mg/day in Parkinson's disease patients (Shults et al., 1998). There is also the absence of any pattern of adverse effects from a large number of clinical trials conducted using dosages from 390 mg/day down to 100 mg/day in subjects who were healthy or had a variety of disease conditions (Lucker et al., 1984; van Gaal et al., 1984; Folkers et al., 1985, 1991, 1993; Kamikawa et al., 1985; Langsjoen et al., 1985; Tomono et al., 1986; Yamagami et al., 1986; Goda et al., 1987; Zuliani et al., 1989; Langsjoen and Folkers, 1990; Amadio et al., 1991; Cerioli et al., 1991; Fiorella et al., 1991; Wilson et al., 1991; Zeppilli et al., 1991; Digiesi et al., 1992; Permanetter et al., 1992; Hanioka et al., 1993; McRee et al., 1993; Bargossi et al., 1994; Lockwood et al., 1994, 1995; Folkers and Simonsen, 1995; Hofman-Bang et al., 1995; Laaksonen et al., 1995; Porter et al., 1995; Lonrot et al., 1996; Andersen et al., 1997; Koroshetz et al., 1997; Malm et al., 1997; Mizuno et al., 1997; Serebruany et al., 1997; Chopra et al., 1998; Suzuki et al., 1998; Henriksen et al., 1999; Khatta et al., 2000; Singh et al., 1999, 2000, 2003; Burke et al., 2001; Engelsen et al., 2002; Hodgson et al., 2002; Niklowitz et al., 2002; Rozen et al., 2002; Watts et al., 2002; Balercia et al., 2004). The size, duration, observations made, and the overall quality and power of these studies varied considerably. Considered together, they provide strong evidence that there is no consistent pattern or incidence of nausea, related gastrointestinal effect, or other adverse effect of CoQ10 over a period of up to a few months. Higher doses, up to 3000 mg/day have been administered without adverse effects in three small groups of patients without control groups (Musumeci et al., 2001; Shults et al., 2004; Ferrante et al., 2005). The largest of these three trials (Ferrante et al., 2005) provides substantial but not conclusive evidence of safety at an oral intake of 3000 mg/day.

Some clinical trials with CoQ10 administration found CoQ10 treatment to possibly produce nausea, heartburn,

upset stomach or related effects at dosages of 1200 mg/day (Feigin et al., 1996) and 600 mg/day in Huntington's disease patients (Huntington, 2001) and 600 mg/day in myocardial infarction patients (Langsjoen et al., 1994). Similar effects have been observed at dosages of 180 mg/day (specifically 1.5 mg/kg) in patients with stable angina pectoris (Hiasa et al., 1984), at 150 mg/day in heart failure patients (Lampertico and Comis, 1993; Baggio et al., 1994), at 120 mg/day in acute myocardial infarction patients (Singh et al., 1998b, 2003), and as low as 60 mg/day in oligospermia subjects (Fujii et al., 1984).

The incidence of stomach upset with CoQ10 was similar to that with placebo in one study at 120 mg daily dosage (Burke et al., 2001) but greater with the same dosage of CoQ10 in another (Singh et al., 1998b). In a 16-month clinical trial involving 80 subjects, much higher doses of CoQ10 (300–1200 mg/day) did not produce significant nausea or other adverse effects (Shults et al., 2002).

Neither the incidence nor the severity of nausea increases with the dosage. No adverse impacts other than these mild and transient gastrointestinal effects have been reported. The recurrent pattern of nausea and related effects suggest causality by some component of the administered capsules, but there is no dose–response relationship to the CoQ10 content. Nausea has been reported in clinical trials with CoQ10 at dosages of 60, 120, 150, 180, 600, and 1200 mg/day, but its incidence and severity in the placebo group was just as great as in the treated group in most of the trials. No nausea or related gastrointestinal effect was reported in a much larger number of clinical trials in a dosage range up to 3000 mg/day, although one uncontrolled trial at 3000 mg/day was only 10 days and involved a small number of subjects (Shults et al., 2004) and the other uncontrolled trial at 3000 mg/day involved long-term administration but had no control group (Musumeci et al., 2001).

The absence of a dose–response relationship between CoQ10 and nausea strongly suggests that the capsule or oil vehicle, and not the CoQ10 itself, may have been responsible for the nausea effect. Also, concomitant pain in some of the disease conditions in some trial subjects, especially angina and myocardial infarction, might have predisposed these patients toward the occurrence of nausea.

A possible indirect adverse effect of oral CoQ10 would be decreased endogenous biosynthesis and decreased blood and tissue levels resulting in a “rebound” deficiency if the oral supply should be discontinued. There is no scientific evidence to support this hypothetical concern, and there is significant evidence, in both humans and animals, that this mechanism does not present a significant problem. A well-conducted human trial with oral intakes up to 900 mg/day included a multiple month follow up period that provided direct evidence that rebound deficiency did not occur (Ikematsu et al., 2006). More detailed metabolic evidence is available that shows endogenous synthesis of CoQ9 is not decreased in rats by an oral dose of 103 mg/kg (Zhang et al., 1995) or 20 mg/kg (Naini et al., 2003). Overall, the scientific

evidence strongly indicates that conditioned, rebound deficiency is not a problem with CoQ10.

Overall, the clinical trial database shows no adverse effects causally or plausibly related to CoQ10. Any effects that have occurred with CoQ10 also occurred with similar frequency in the placebo-group subjects in the same clinical trials.

4. Human NOAEL or OSL (HOI)

No adverse effect causally related to CoQ10 consumption by humans has been identified, and thus a NOAEL (or LOAEL) cannot be identified, and a UL cannot be derived. The dosages used in clinical trials are evaluated for adequacy to confidently determine a lack of adverse effect at that level of CoQ10 intake. Therefore, the clinical trial data were evaluated to identify an OSL that justifies a high level of confidence and the corresponding application of a UF of 1.0.

4.1. 3000 mg/day

This level of CoQ10 intake was evaluated in an open label study in 31 amyotrophic lateral sclerosis (ALS) patients (Ferrante et al., 2005) that were assessed with an extensive series of clinical and laboratory indices that might have shown any adverse effects, but the open label design of this trial limits the confidence in the finding of no adverse effects. Other data at this dosage level come from case reports on two groups of six subjects each (Musumeci et al., 2001; Shults et al., 2004). The lack of control groups and the small number of subjects precludes use of these data to identify a low uncertainty OSL for healthy adults.

4.2. 2400 mg/day

This level of CoQ10 intake was administered to 16 Parkinson's disease patients for 8 weeks without any adverse effect (Shults et al., 2004). The short duration and small cohort increase the uncertainty in the application of these data to healthy adults, although the data are consistent with this level being an OSL. Selection of this level as an OSL would require application of UF greater than unity to calculate a UL and ULS. The size of a UF for this calculation is not apparent from these data. These limitations do not allow the identification of this level of intake as a high-confidence OSL with no correction for uncertainty, i.e., allow a value of unity (1.0) to be assigned to the uncertainty.

4.3. 1200 mg/day

This level has been studied in a relatively large cohort ($n=80$) of early Parkinson's disease patients in a strongly designed clinical trial of 16 months duration that found no adverse effects (Shults et al., 2002). Another smaller clinical trial ($n=10$) of six months duration at this intake resulted

in “heartburn” possibly related to this level of CoQ10 administration (Feigin et al., 1996). Because there is no consistent pattern of this or related adverse effect with a dose–response relationship, this finding is judged not to establish an adverse effect of CoQ10 at this level of intake. The 16-month trial provides strong evidence of the lack of an adverse effect of this level of CoQ10. There is no known mechanism that suggests the Huntington’s disease or early Parkinson’s disease patients would be less susceptible to any adverse effect of CoQ10 than healthy adults, and therefore these data are judged appropriate to establish an OSL.

4.4. 900 mg/day

The absence of adverse effects in a well-conducted clinical trial in a healthy cohort ($n=88$) over a four week period (Ikematsu et al., 2006) is completely consistent with and supports the OSL of 1200 mg/day identified above. This trial found no adverse effects of CoQ10 on a spectrum of safety indices.

4.5. 600 mg/day and lower intakes

The only adverse effect reported (nausea) with CoQ10 intake is not consistent and has no apparent dose–response relationship, indicating that it is not causally related. Collectively, this large number of clinical trials provides strong evidence that is consistent with the OSL identified. Nothing in these reports contradicts the OSL identified.

5. Risk assessment

5.1. NOAEL and LOAEL

No toxicological basis was found.

5.2. OSL

The OSL identified came from a clinical trial with a substantial cohort of 80 and fairly long duration of 16 months (Shults et al., 2004) and a shorter, smaller clinical trial (Feigin et al., 1996). Plasma levels of CoQ10 in subjects consuming 3000 mg/day reach a plateau by 4 months (Ferrante et al., 2005), indicating that a bioaccumulation effect is not likely to precipitate chronic toxicity. Animal data (Zhang et al., 1995) and human data (Ikematsu et al., 2006) indicate that rebound deficiency after cessation of high CoQ10 intake is not detected. The complete absence of a significant pattern of adverse effects that are causally related to CoQ10 at higher and lower intakes provides confidence in the extrapolation of the data with Parkinson’s disease patients to healthy adults. OSL: 1200 mg/day.

The OSL was identified from data on subjects consuming a variety of diets and having *in vivo* synthesis of CoQ10. These additional sources of CoQ10 are already considered and do not need to be subtracted from the OSL to identify a ULS. Thus, a ULS based on the toxicological evidence in

human clinical trials is 1200 mg CoQ10 per day. ULS: 1200 mg/day.

6. Conclusions

The body of evidence supporting a beneficial effect of CoQ10 supplementation on a number of health outcomes continues to grow at a rapid pace. This pace is being matched by the increasing availability and appearance of this ingredient in dietary supplement products. The present review of the available published human clinical trial data involving CoQ10 supports a high level of confidence in this ingredient with respect to its safe use in dietary supplements. The absence of a well-defined critical effect precludes the selection of a NOAEL, and therefore required use of the observed safe level (OSL) or highest observed intake (HOI) approach established by FAO/WHO to conduct this risk assessment. Evidence from well-designed randomized, controlled human clinical trials indicates that the upper level for supplements (ULS) for CoQ10 is 1200 mg/day.

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