COENZYME Q10

Q-FACTS™ (Updated May, 2007)

FREQUENTLY ASKED QUESTIONS

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What is coenzyme Q10 (CoQ10)?

CoQ10 is a vitamin-like nutrient that plays a vital role in cellular energy production. It is also known as ubiquinone because its chemical structure is that of a quinone and it is ubiquitously distributed in nature. The USP refers to CoQ10 as Ubidecarenone.

Who discovered CoQ10?

CoQ10 was discovered by Dr. Frederick L. Crane at the University of Wisconsin in the late 1950s during his research on the biochemistry of the mitochondrial electron transport chain, also known as the respiratory chain.[1] The pure substance isolated from beef heart mitochondria was sent to Dr. Karl Folkers at the pharmaceutical company Merck for identification and elucidation of its structure. It was designated coenzyme Q10 because of its quinone structure and the ten isoprene unit side chain. During the same time period, another group of scientists led by Dr. R. A. Morton in England isolated the same substance from mitochondria and named it ubiquinone because of its widespread occurrence in nature. The vital role of CoQ10 in the electron transport chain was first described by Dr. Peter Mitchell of England who was awarded the Nobel prize for his work.

What is the chemical nature of CoQ10?

The chemical structure of CoQ10, elucidated by Dr. Karl Folkers and his group, is 2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone.[2] The chemical identification number (called CAS #) assigned to ubiquinone is 303-98-0, and for ubiquinol (the reduced form of CoQ10) it is 992-78-9. The structures of ubiquinone and ubiquinol are shown below.

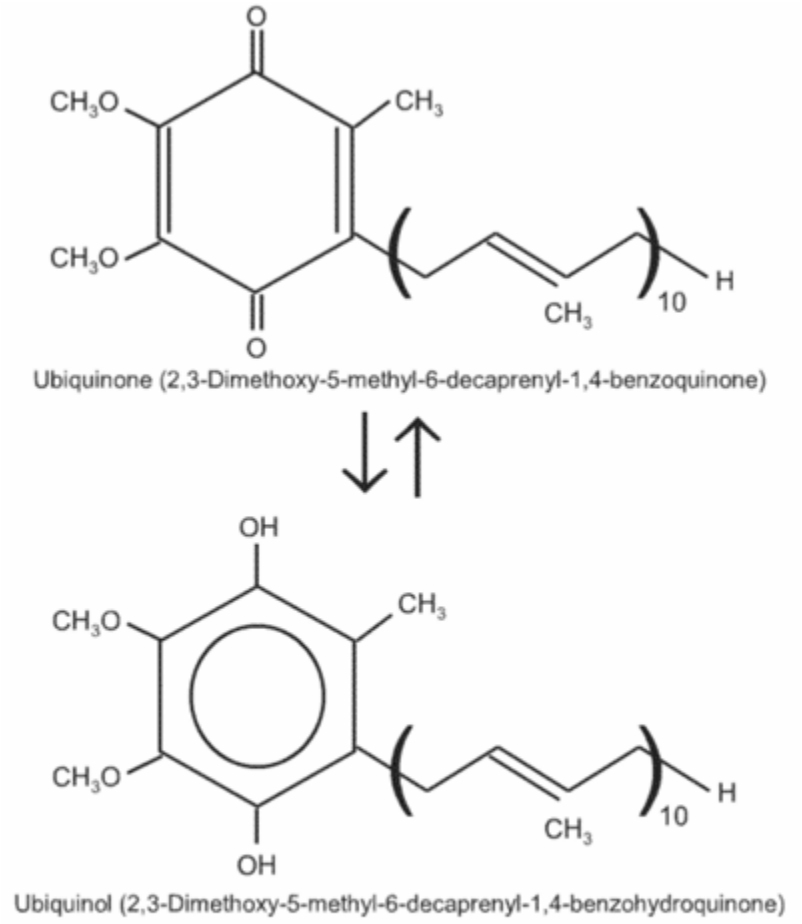


Figure 1 Structure of coenzyme Q10. Ubiquinone (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzoquinone) and ubiquinol (2,3-dimethoxy-5-methyl-6-decaprenyl-1,4-benzohydroquinone).

What are the properties of CoQ10?

The physicochemical characteristics of CoQ10 (Ubiquinone and Ubiquinol) are shown in Table 1(a) and 1(b).

Table1(a): Properties of Ubiquinone (CoQ10)
CAS Registry No: 303-98-0

Appearance	Orange crystals (at room temperature)
Empirical formula	$C_{59}H_{90}O_4$
Molecular weight	863.358
Melting point	49^0 C
Solubility	Insoluble in water Limited solubility in oils and fats Soluble in nonpolar solvents

Table 1(b): Properties of Ubiquinol (CoQ10 H_2)
CAS Registry No: 992-78-9

Appearance	White to very pale yellow crystalline powder
Empirical Formula	$C_{59}H_{92}O_4$
Molecular Weight	865.37
Melting Point	49.5°C
Solubility	Practically insoluble in water. Limited solubility in oils and fats. Soluble in nonpolar solvents.

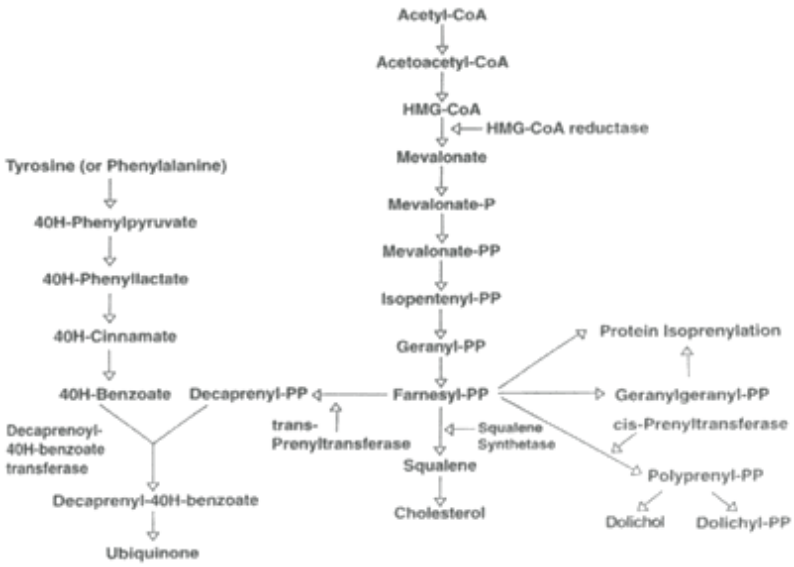
Where does CoQ10 occur in nature?

CoQ compounds are widely distributed in nature, from microorganisms to plants to animals including humans. In humans and several other species, the side chain is comprised of 10 isoprene units and hence the name CoQ10.
Animal products such as beef, pork and chicken are relatively good sources of CoQ10. Organ meats such as heart and muscle are the best sources. As a general rule, tissues with high energy demands contain relatively high amounts of CoQ10. Among foods of plant origin, broccoli and spinach contain significant amounts of CoQ10. Unrefined vegetable oils such as soybean oil and palm oil are also good sources of CoQ10.

How is CoQ10 synthesized in our body?

CoQ10 is present in almost all the cells in our body and also in circulation (in lipoproteins). Practically every cell has the ability to synthesize CoQ10. The endogenous synthesis of CoQ10 happens to be a very complex process requiring numerous vitamins such as vitamin B6, vitamin B12, folic acid, niacinamide, pantothenic acid and vitamin C, and also certain trace elements. The quinone ring structure is derived from the amino acid tyrosine, the methyl groups on the ring supplied by methionine, and the isoprenoid side chain coming from the mevalonate pathway (the same pathway shared by cholesterol). Thus the production of CoQ10 is dependent on an adequate supply of numerous precursors and cofactors, and a deficiency of one or more of these essential components can adversely affect the production of adequate amounts of CoQ10.

Figure 2: Synthesis of coenzyme Q10



How is CoQ10 produced commercially?

Commercial production of CoQ10 is largely by way of yeast fermentation, and to a smaller extent by bacterial fermentation. There is also a semisynthetic process for producing CoQ10 using solanesol, a tobacco byproduct, that provides the phytyl side chain, and the amino acid tyrosine for the ring structure. At this time, most of the world supply of CoQ10 comes from Japan, with smaller quantities coming from China, India, South Korea and Italy. In the US, natural CoQ10 is now being produced in a large plant in Pasadena, Texas.

What is the difference between “natural” and “synthetic” CoQ10?

CoQ10 occurs in two isomeric forms, namely the “trans” and the “cis” forms. The natural CoQ10 is in the trans form whereas the synthetic CoQ10 contains a mixture of both trans and cis isomers. The USP limits the presence of other CoQ analogs and the cis-isomer and related impurities to less than 1.5%.

How is CoQ10 absorbed in our body?

CoQ10 is a fat-soluble substance and therefore it is absorbed like any other fat in our diet. Digestion helps in the release of dietary CoQ10 from the food matrix. For CoQ10 supplements that are based on pure CoQ10, gastric digestion may not be necessary. In the small intestine, secretions from the pancreas and bile facilitate emulsification and micelle formation that are required for the absorption of fats along the small intestine. There is no “active” transport mechanism for the absorption of fats. Once CoQ10 is taken up by the intestinal mucosal cells, it is transported via the lymphatic system as part of the chylomicrons and eventually taken up by the liver for repackaging into lipoprotein particles and rereleased into the circulation.

How is CoQ10 distributed in the tissues?

CoQ10 is present in all tissues in our body. In blood it is associated with lipoproteins. The concentrations vary from tissue to tissue, and those with high rates of metabolic activity and high energy demands such as the heart, muscle, liver, kidney and brain contain relatively high concentrations of CoQ10.[3,4] The redox state of CoQ10 (oxidized vs. reduced, i.e. ubiquinone vs. ubiquinol) also varies from tissue to tissue, and those with high aerobic activity generally contain higher amounts of the oxidized form. In circulation, CoQ10 is present predominantly in the reduced form (as ubiquinol). The ratio of oxidized to the reduced form in blood may serve as a measure of in vivo oxidative stress[5]. Recent studies have shown that the level of circulating Ubiquinol tends to decline in certain disease conditions, such as diabetes, liver disease, down syndrome, etc. [48, 49, 50] with the result that the ratio of circulating Ubiquinol to total Coenzyme Q10 goes down.

How is the status of CoQ10 assessed?

In humans, plasma or serum CoQ10 concentrations will serve as a good indicator of status. The best way to assay CoQ10 is by HPLC (high pressure liquid chromatography) by UV or electrochemical detection. However, it should be noted that plasma CoQ10 may not always reflect tissue status. Localized deficiencies of CoQ10 may exist such as in the skeletal muscle or myocardial tissue while plasma concentrations may show “normal” values. If biopsy material is available, tissue CoQ10 analysis can yield more useful information.[7]

What are the pharmacokinetic parameters of CoQ10?

Normal serum/plasma CoQ10 concentrations (in healthy individuals) usually range from 0.5 µg to 1.0 µg per mL. The total body pool of CoQ10 is estimated to be between 1.5 - 2 gm in a healthy adult. Upon oral administration of CoQ10, plasma or serum concentrations reach a maximum (C_{max}) at about 6 hours (Tmax). The half-life (i.e. the time to reach half-maximum concentration ($T_{1/2}$) of CoQ10 is about 34 hours. With the ingestion of high doses of CoQ10, plasma CoQ10 levels have been found to plateau after a dose of 2400 mg a day.[8]

What does CoQ10 do in our body?

The primary function of CoQ10 in our body is in cellular energy production. It is a critical component of mitochondria that are present in practically every cell in our body. Mitochondria may in fact be considered as fuel cells where biological energy called ATP (adenosine triphosphate) is produced. CoQ10 is also a potent antioxidant and it helps protect the tissues and the cellular components in the body from free radical damage. In addition, CoQ10 has other important functions in the body.[4,9]

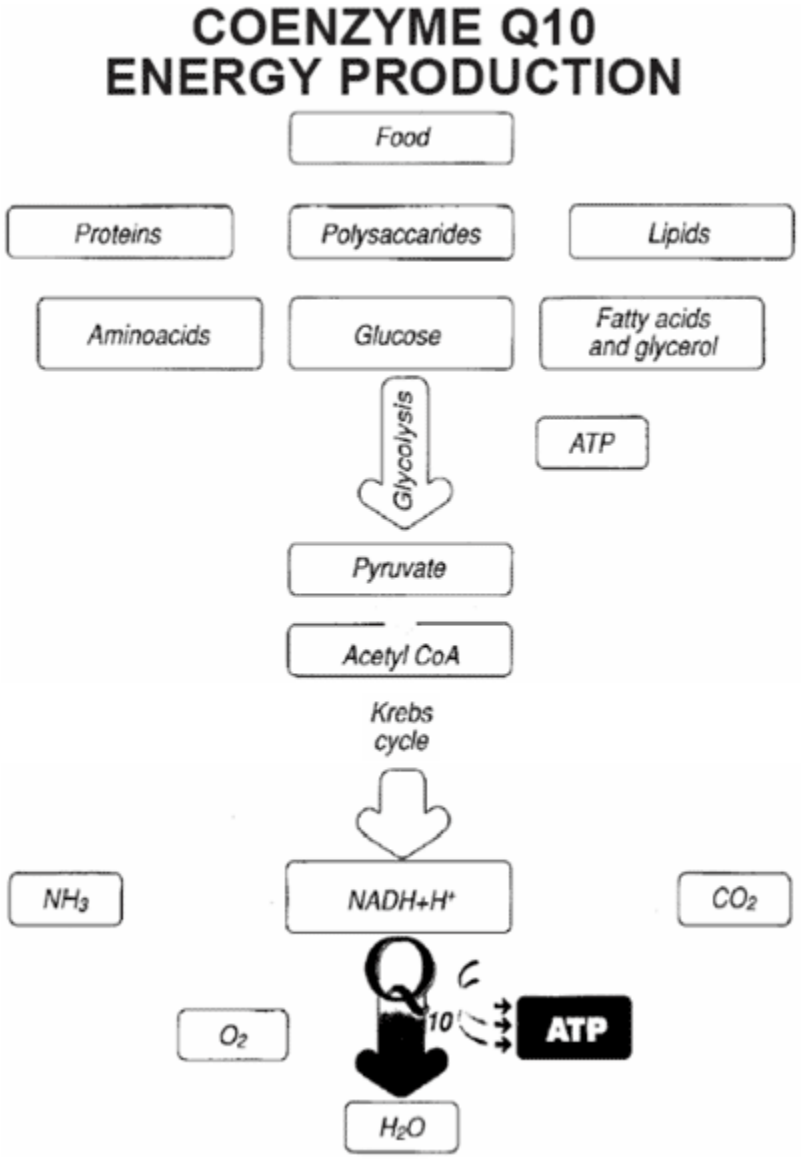
How does CoQ10 work in our body?

CoQ10 is a crucial component of the electron transport chain (respiratory chain) in the mitochondria where energy derived by a process called oxidative phosphorylation from the products of fatty acid, protein and carbohydrate metabolism is converted into biological energy called adenosine triphosphate (ATP) that drives cellular machinery and all biosynthetic processes. CoQ10

functions as an essential cofactor for the activities of the enzyme systems called complexes I, II and III in the electron transport chain. It shuttles electrons from complex I (nicotinamide adenine dinucleotide dehydrogenase) and Complex II (succinate dehydrogenase) to complex III (ubiquinone-cytochrome c reductase) by virtue of its redox (reduction-oxidation) properties. It is during this process of electron transfer along the electron transport chain that vital biological energy as ATP is generated (Figure 3). Thus, CoQ10 plays a critical role in cellular bioenergetics.[4,9,10,11]

CoQ10 is also an important fat-soluble antioxidant and as such, it helps protect vital structures from free radical damage from both endogenous and exogenous sources. CoQ10 has other important functions too in the body. It helps maintain membrane stability and has a role in cell signaling.[4,9]

Figure 3: CoQ10 and energy production



What is the role of CoQ10 in supporting our health?

Because of its fundamental role in cellular bioenergetics and also as an important antioxidant, CoQ10 plays a vital role in our well-being. Since it is involved in the pathophysiology of numerous disease states listed in the next section, assuring adequate CoQ10 status is essential for maintaining good health and preventing or reducing the risk for numerous chronic degenerative and metabolic diseases.

What are the clinical conditions and health benefits associated with CoQ10?

There is a large body of data on the beneficial effects of CoQ10 supplementation in various disease states.[12-19] The following list shows health problems that are associated with impaired CoQ10 status, and also numerous disease states and conditions where CoQ10 supplementation has been found to be beneficial.

Table 2: Potential Beneficial Effects of CoQ10 Supplementation

Cardiovascular disease
- Cardiomyopathy
- Congestive heart failure
- Angina pectoris
- Arrhythmias
- Mitral valve prolapse
- Hypertension
- Atherosclerosis
- Cardiotoxicity (drug-induced)

Neurodegenerative diseases
- Huntington's Disease
- Parkinson's Disease
- Alzheimer's Disease
- Amyotrophic lateral sclerosis (Lou Gehrig's Disease)

Neuromuscular diseases
Mitochondrial cytopathies (MELAS, MERRF, etc.)
Muscular dystrophy
Ataxias
Diabetes
Cancer
Chronic obstructive pulmonary disease
Asthma
Migraine
Immune disorders
HIV/AIDS
Periodontal disease
Chronic fatigue syndrome
Male infertility

Cardiovascular disease tops the list of disorders, and there is substantial evidence for the therapeutic role of CoQ10 supplementation in heart failure.

CoQ10 has also been found beneficial in various other conditions related to the heart and the cardiovascular system.[13-16,20-23] In addition to its basic function in cellular bioenergetics, CoQ10 has an important role as an antioxidant in maintaining cardiovascular health by way of protecting LDL from oxidation.[24,25] The role of CoQ10 in neurodegenerative diseases has received a great deal of attention in recent years.[18,26,27] Preliminary evidence for a beneficial effect of high doses of CoQ10 supplementation particularly in the case of Parkinson's and Huntington's diseases is indeed promising.[28,29] Animal data on the role of CoQ10 in amyotrophic lateral sclerosis is also provocative.[30] The importance of CoQ10 in the treatment of mitochondrial diseases that involve multisystem disorders is also well recognized.[31-34]

What are good sources of CoQ10?

Animal-based products and in particular organ meats such as heart are relatively good sources of CoQ10. But in reality, it is not likely that one could consume large quantities of any organ meat needed to obtain a reasonable amount of CoQ10 from dietary sources. CoQ10 supplements are therefore desirable and bioenhanced formulations of CoQ10 are available that can provide adequate amounts in a readily absorbable form.

Is CoQ10 a dietary essential?

CoQ10 is not considered a dietary essential because it is synthesized in our body. However, it could be called a "conditionally essential" nutrient because the endogenous production may not meet the requirements under certain conditions. There are several examples of conditionally essential nutrients such as Taurine, carnitine and choline. Furthermore, the production of CoQ10 is known to slow down as we age, starting from the 20s.[3,4]

Is there a "Recommended Dietary Intake" value assigned to CoQ10?

There is no RDI or DV for CoQ10 since it is not considered an essential dietary nutrient. However, it should be noted that under certain conditions, the endogenous production of CoQ10 may not be able to keep up with the body's demand, and in such situations supplemental CoQ10 is indicated.

Does our diet supply adequate amounts of CoQ10?

The average diet supplies only a small amount of CoQ10. It is estimated that a typical Western diet provides about 5 mg CoQ10 a day.[35] While CoQ10 supplementation may not be necessary for young adults, it is certainly desirable for physically active adults, and especially for the elderly as a group, since the production of CoQ10 declines with age.[3]

What is the relationship between CoQ10 and other nutrients in the body?

There is a great deal of synergy between CoQ10 and various other antioxidants and nutrients in the body. The antioxidants include both nonenzymatic and enzymatic defense systems. Among the nonenzymatic antioxidants that interact with CoQ10 either directly or indirectly are vitamin E, vitamin C, alpha lipoic acid,

and glutathione resulting in augmentation of overall antioxidant potential due to regeneration and recycling and this would translate into functional benefit.

What types of CoQ10 supplements are available on the market?

The commonly available supplements are all based on CoQ10 (Ubiquinone) powder in the form of tablets, two-piece capsules and oil based softgel (soft gelatin) capsules. A solubilized formulation of CoQ10 called Q-Gel® was introduced in 1996. Q-Gel® has been shown to possess superior bioavailability when compared with many other products on the market. More recently, a chewable tablet (ChewQ®) has been introduced which has also shown considerably enhanced bioavailability. A highly absorbable liposomal formulation called Liquid Q® (nano-dipersion) was also introduced recently. The marketed formulations of CoQ10 are all based on ubiquinone, the oxidized form. While CoQ10 also occurs in its reduced form as ubiquinol, it happens to be highly unstable. Tishcon Corporation overcame this problem and introduced for the first time a novel ubiquinol product as a solubilized and stabilized formulation (Q-Nol®, Li-Q-Nol®) several years ago. Recently Kaneka has introduced QH™ (Ubiquinol) in powder from which is now available in softgels.

Is there a difference in the bioavailability of CoQ10 supplements?

Yes. Most commonly available formulations of CoQ10 on the market are based on the powder, in the form of tablets, two-piece capsules, or softgel capsules containing an oil suspension. Pure CoQ10 is insoluble in water and has limited solubility in oils and fats. Because of this property, the powder based products show poor dissolution in aqueous media, and have shown relatively poor bioavailability in human testing. In order to improve the dissolution profile of CoQ10, a solubilized formulation of CoQ10 (Q-Gel®) was developed in 1996 that has shown superior bioavailability as compared with many other product forms. This enhanced bioavailability claim is based on both laboratory tests (dissolution test and cell culture studies using Caco-2 cells) and human and animal studies.[36-42] The relative bioavailability of CoQ10 in its reduced form as ubiquinol has been shown to be higher than that of CoQ10 in its oxidized form as ubiquinone in both animal and human studies.[39,40] In a recent trial with human subjects, the superior bioavailability profile of ubiquinol was clearly demonstrated when it was tested alone.[43]

Li-Q10® is a liquid preparation containing solubilized CoQ10 and it has also been shown to be superior to the other product forms in laboratory tests and in human bioavailability studies.[39,40] Li-Q10® thus represents an ideal formulation with enhanced bioavailability for patients requiring oral CoQ10 therapy such as infants, children, elderly, and those with difficulty swallowing. Anther product that is well-suited for individuals who do not wish to or are unable to swallow tablets or capsules is ChewQ®, a pleasant tasting chewable CoQ10 tablet formulation which has shown enhanced bioavailability via laboratory tests based on dissolution testing and cell culture studies involving CoQ10 uptake by Caco-2 cells.[42] The in vitro dissolution test is considered a good indicator of in vivo bioavailability. Dissolution test results of various product types are shown below.

Table 3: Typical Dissolution Data on Various Coenzyme Q10 Products

Product	Dissolution (%)
Compressed Tablets[1]	0-3
Hardshell Caps (powder-filled)[1]	0-3
Softgel Caps (oil suspension)[1]	0-3
Chewable wafers[1]	0-5
ChewQ® wafers[2]	75-80
Hydro-Q-Sorb® (powder)	75-100
Q-Gel® (softgel caps)[3]	90-100
Q-Nol® (softgel caps)[4]	90-100
Liquid Q® (Li-Q-sorb®) (aqueous nanodispersion)[5]	100

[1]Formulated with Coenzyme Q10, USP.
[2]Formulated with HydroQsorb®. US Patent No. 6,861,447
[3]Formulated via the Biosolv® process. US Patent No. 6,056,971
[4]Formulated via the Q-Nol® process. US Patent No. 6,740,338
[5]US Patent No. 6,455,072 ® Registered Trade Marks of Tishcon Corp.

Are daily divided doses of CoQ10 supplements better than a single dose?

Yes, and this is generally true of any dietary supplement ingested in high doses.

Is there a recommended way to take CoQ10 supplements?

Yes. As a general rule, dietary supplements should be taken with food. This assures better absorption and also minimizes or avoids any possible stomach discomfort.

Are there any contraindications for the use of CoQ10 supplements?

Yes. There are a couple of case reports indicating that high dose CoQ10 supplementation may interfere with anticoagulant (warfarin) therapy but this has not been verified in a controlled clinical trial. However, it is prudent that anyone on anticoagulant therapy consult with their health care provider before using CoQ10 supplements.[17]

Since there is no data on the safety of CoQ10 supplementation in pregnant or lactating women, its use is not recommended for these populations.

What are some of the adverse drug interactions with CoQ10?

The most significant ones to date are the adverse effects of cholesterol-lowering drugs (called statins) on CoQ10 status.[44] Since cholesterol and CoQ10 share the same biosynthetic pathway, inhibition of cholesterol production in the body also impairs CoQ10 synthesis. Beta-blockers have shown to decrease endogenous serum CoQ10 levels by inhibiting CoQ10-dependent enzymes.[17] Furthermore, CoQ10 supplementation has been reported to reduce insulin requirements in

diabetes mellitus. Additionally, some oral hypoglycemic agents including glyburide, acetohexamide, and tolazamide have also been shown to decrease endogenous CoQ10 levels. Therefore, diabetic patients taking CoQ10 may require dosage adjustments of hypoglycemic agents.[17]

Are there any adverse effects due to ingestion of high doses of CoQ10?

Documented side effects associated with the use of high doses of CoQ10 ranging anywhere from 30 mg to as high as 1,200 mg day in humans have been minor that are related to gastrointestinal problems.[14,20] They include epigastric discomfort, appetite suppression, nausea and diarrhea in a very small number of cases. One interesting observation is that ingestion of CoQ10 late in the evening might cause insomnia[15] and this may be due to increased energy levels.

Is the safety of high dose CoQ10 supplementation well-documented?

Yes. The safety of high doses of orally-ingested CoQ10 in the form of ubiquinone over long periods is very well documented in the literature.[14,23] The only side effects reported with a small number of subjects are mild gastrointestinal symptoms such as nausea and stomach upset.[14,17,23] In a recent study, doses as high as 3000 mg a day were found to be safe and tolerable in patients with Parkinson's disease.[8] According to Hathcock, et al[45] the observed safe level (OSL) of CoQ10 for chronic administration as a dietary supplement is 1200 mg/day. In a recent trial on the safety of CoQ10 in its reduced form as ubiquinol in human subjects, dosages of up to 300 mg daily for two months was found to be safe.[43] Higher dosages were not tested in this study.

Safety data on high dose CoQ10 ingestion are also available based upon animal studies. In one study with rats, long term ingestion of CoQ10 at doses up to 1200 mg/kg body weight was found to be safe and well tolerated.[46] In another study on the in vivo and in vitro mutagenic potential of CoQ10 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 S. typhimurium and E. coli.[47]

Are there any clinical trials on CoQ10 sponsored by the US Government?

There have been numerous studies on CoQ10 supported by the National Institutes of Health (USA) and carried out under INDs (Investigational New Drug). These have included Parkinson's and Huntington's diseases with promising results. Another multicenter clinical trial just getting started at the University of Florida (Principal Investigator: Dr. Peter Stacpoole) is on the efficacy of oral CoQ10 supplementation in patients with mitochondrial cytopathies *(Tishcon Corporation is providing the Liquid CoQ10 (Ubiquinol) active and placebo formulations for this study)*.

What is the regulatory status of CoQ10?

CoQ10 is available as a dietary supplement in the US and in several other countries. It is grandfathered under the Dietary Supplement Health and

Education Act (DSHEA) passed by the US Congress in1994. Coenzyme Q10 is official in the United States Pharmacopeia, European Pharmacopeia and the Japanese Pharmacopeia. Kaneka's CoQ10 has been self affirmed GRAS – opening the market for its use in foods.

CoQ10 has also been marketed as a drug for heart disease in Japan for many years.

Ubi-Q-Gel®, the solubilized formulation of CoQ10 (GelTec/Tishcon Corp.) has been awarded an Orphan Drug Designation by the US FDA for the treatment of mitochondrial cytopathies. Ubi-Q-Nol®, the stabilized reduced form of CoQ10 (GelTec/Tishcon Corp.) has also been awarded Orphan Drug Designations for the treatment of Huntington's Disease and Pediatric Congestive Heart Failure.

What are the significant milestones in CoQ10 research and in the evolution of CoQ10 products?

Table 4: CoQ10 timeline

1957	CoQ10 first isolated from beef heart mitochondria - Dr. Frederick L. Crane, University of Wisconsin.
1958	Chemical structure of CoQ10 determined - Dr. Karl Folkers and colleagues at Merck, Sharpe and Dohme.
1960s	Patients with CHF successfully treated with CoQ7 for the first time - Dr. Y. Yamamura in Japan.
1975	"Protonmotive Q cycle" in the mitochondrial electron transport chain proposed by Dr. P. Mitchell in England.
1978	Dr. P. Mitchell awarded the Nobel prize for elucidating its mechanism of action.
1980s	Renewed interest in the use of CoQ10 for heart disease. Several double-blind studies in the US and elsewhere (led by Dr. K. Folkers and his colleagues) documenting its efficacy. Exploration of the potential usefulness of CoQ10 for various other indications including mitochondrial cytopathies.
1987	Publication of the authoritative book on CoQ10 "The Miracle Nutrient Coenzyme Q10" by Dr. E. G. Bliznakov.
1990s	Increased awareness of the potential health benefits and soaring popularity of CoQ10 as a dietary supplement.
1994	Passage of Dietary Supplement Health and Education Act (DSHEA) by the US Congress. CoQ10 grandfathered as a dietary supplement.
1996	Introduction of Q-Gel®, the solubilized CoQ10 with enhanced bioavailability (GelTec/Tishcon Corp.).
1998-present	Numerous studies documenting the superior performance of Q-Gel® and other solubilized CoQ10 products. Publication of findings in several peer-reviewed journals and presentations at various scientific meetings.
1999	Orphan Drug Designation awarded by the FDA for CoQ10 (as Q-Gel®, Tishcon Corp.) for the treatment of mitochondrial cytopathies.

	Introduction of solubilized and stabilized ubiquinol (Q-Nol®, Li-Q-Nol®) by GelTec/Tishcon Corp.
2001	Publication of USP monographs on CoQ10.
2003	Two additional Orphan Drug designations awarded by the FDA for CoQ10 as ubiquinol (Q-Nol®, Tishcon Corp.) for the treatment of Huntington's Disease and Pediatric Congestive Heart Failure.
2004	Introduction of CoQ10-cyclodextrin complex as HydroQSorb® (Tishcon Corp.) with superior bioavailability for solid dosage form applications.
2005	Introduction of Liquid Q® (Tishcon) a nanodispersion of CoQ10 in water – with superior bioavailability.
2006	Introduction of Ubiquinol QH™ by Kaneka.

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