UBIQUINONE
and
UBIQUINOL
(Active forms of Coenzyme Q10)

a report prepared by | William V. Judy, Ph.D

UBIQUINONE and UBIQUINOL

(Active forms of Coenzyme Q10)

The market demand for CoQ10 products has increased in recent years. Currently, there is a wide variety of CoQ10 supplement forms from which to choose. This article will present an overview of the properties and metabolism of CoQ10 and compare the major forms, particularly the reduced form to the oxidized form.

Coenzyme Q10 (CoQ10) is found in all living cells of animals, plants, and microorganisms in three active forms: *oxidized (Ubiquinone), partially reduced (Semiubiquinone), and reduced (Ubiquinol)*. Ubiquinone was isolated from beef heart mitochondria in 1957 by Dr Fred Crane. The partially reduced and reduced CoQ10 is formed by the action of reducing agents on the oxidized form. These reducing agents are located in virtually all living cells. Humans and larger animals have the CoQ10 analog, while smaller animals (rodents) and plants have CoQ9. Most microorganisms, such as yeast and bacteria, have CoQ5-6, except for one known bacterium and yeast that produces CoQ10. Although the body's cells produce ubiquinone, it is rapidly converted to ubiquinol, which accounts for 90 to 95 percent of the total body CoQ10. Unlike commercially manufactured ubiquinol, ubiquinone, which entered the supplement market c. 1974, is very stable in the crystalline form.

Ubiquinone functions as cofactor stimulation for energy synthesis in the electron transport system. This process occurs in the inner membrane of the mitochondria. It is responsible for 95 percent of the energy produced in the cell by a process called *oxidative phosphorylation*. This energy is essential for life, as, without ubiquinone energy synthesis, life forms using oxygen in the metabolic process would cease to exist.

Semiubiquinone is an intermediary between ubiquinone and ubiquinol. Although unstable and not commercially available, it may be important to growth and development, establishment of cell membrane characteristics, control of membrane function, and intercellular communication. In addition, it may serve as a second messenger.

Ubiquinol, the fully reduced form of CoQ10, is a very important antioxidant that functions in the lymph, blood, and phospholipid membranes of cells and cell organelles. One of two lipid-soluble antioxidants produced by the body, ubiquinol is also found in many of the foods we eat. When functioning as an antioxidant, it cycles back to the ubiquinone form and gives up an electron to neutralize toxic superoxides and free radicals produced in metabolic

processes, as well as those present in foods and environmental pollutants. Because the body produces many antioxidants and obtains others from food, it is not known if ubiquinol is essential for life. However, its high level in lymph, circulating blood, cell and cell organelle membranes does suggest that it may be the primary lipid antioxidant responsible for preventing lipid peroxidation and destruction of these membranes. This functional capacity occurs in all age groups, but may be more prominent in those over 45 years of age. The greatest need for ubiquinol will be among the 5% of Caucasians, 25% of Mexicans, 23% of Indians, and 21% of Chinese who have a deficiency of the oxido-reductase enzyme. This enzyme production is controlled by the NQO-1 gene. Mutation of this gene results in less oxido-reductase enzyme and less conversion of ubiquinone to ubiquinol. To date, these groups have not been well defined, but it is known that the NQO-1 gene mutates. In societies with a high incidence of gene mutation, rapid aging and age-related degenerative diseases are also common. As these three forms of CoQ10 have uniquely different functions, no one form is more bioactive than the other. The important thing to note is that the three forms do not work independently, but are a part of what we called a *redox* (oxidation-reduction) mechanism. Essentially, one cannot exist without the other. In their respective functions, one recycles to the other and vice versa. For example, the body does not store large quantities of energy as adenosine triphosphate (ATP). To produce ATP rapidly, ubiquinone in the inner membrane of the mitochondria forms a complex with NADH called NADH-Ubiquinone Reductase. This enzyme stimulates NADH to *give up* an electron while stimulating ubiquinone to *take on* two electrons and become reduced. Ubiquinone also forms a complex with cytochrome C (Ubiquinone-Cytochrome C Reductase), which stimulates Cytochrome C to give up electrons and stimulates ubiquinone to take on electrons and become fully reduced. During this process, ubiquinol is formed and, in the presence of free radicals and superoxides produced in the metabolic processes, gives up electrons and is recycled back to ubiquinone.

The same redox relationship occurs when supplemental ubiquinone is absorbed in the intestines. Immediately after being absorbed, the oxidized CoQ10 is converted (in the presence of reducing agents) to the reduced CoQ10 so it can function as an antioxidant. Both forms of CoQ10 play vital roles within the body and both act as redox agents, freely recycling each other.

The entry of ubiquinol into the supplement market has created a controversy over which form is more bioactive and more bioavailable. Some marketers claim that ubiquinol has 800 percent greater absorption than the crystalline ubiquinone product. However, more recent absorption studies do not show that the claimed absorption of ubiquinol is superior to that of other oxidized liposomal, micellular, dissolved, or nanoparticle forms of CoQ10. The ubiquinol product is certainly not as absorbable as XYMOGEN®'s oxidized CoQmax CF™, which is approximately 960 times more absorbable than oxidized dry powder CoQ10. (See Figure 1)

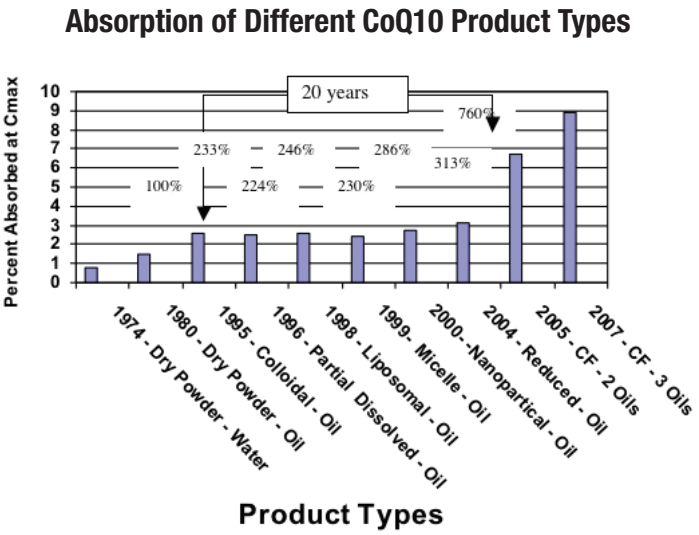

Figure 1: Absorption of different CoQ10 product types at Cmax as a percent of the ingested dose (100mg). The inserts above each product type represent the percentage of absorption above that of the Dry Powder control. Note the enhanced absorption of the crystal-free (CF) products presenting single molecules of CoQ10 and a lipid carrier to the absorption cells. Each study used the same protocol, the same laboratory, and a heterogeneous group of 10-20 male and female subjects who ate a controlled diet and did not take CoQ10 supplements prior to the study. Peak Absorption and Steady State Bioavailability of a New Coenzyme Q10 Product Types in Normal Volunteers Compared to Dry Powder CoQ10. *SIBR Research Internal study Oct. 5, 2006*

The inserts above each product shown in Figure 1 do not show the 800% relative absorption of the ubiquinol (reduced) product above that of the oxidized dry powder CoQ10, as claimed by the marketers of this product. The 313% greater absorption above dry powder CoQ10 suggests that the ubiquinol product is no better absorbed than a good lipid-based softgel product developed between 1995 and 2005. In fact, of the seven independent studies conducted with regard to the absorption of the ubiquinol product, not one has been able to reproduce the 800 % greater absorption claims of the ubiquinol marketers.

Ubiquinol, being an antioxidant, is characteristically unstable when exposed to air or to the gastric juice and contents of the intestines. Therefore, it should be converted to the ubiquinone (oxidized) form before being absorbed in the small intestines. To test the stability of ubiquinol in a simulated gastric fluid environment, SIBR Research analyzed the reduced and oxidized CoQ10 in samples taken from a slowly stirred ubiquinol in simulated gastric fluid at 30 minute intervals (Figure 2).

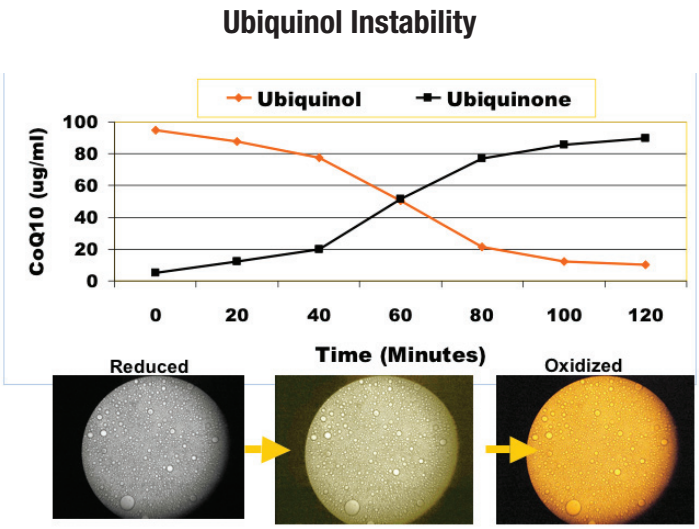

Figure2: Conversion of ubiquinol to ubiquinone when placed in a simulated gastric juice solution. Note that, after 80 minutes, the reduced form (dark gray) is almost completely converted to the oxidized form (orange). The conversion time makes absorption of ubiquinol in the small intestines as the reduced form virtually impossible.

In the initial sample (0 time), the reduced CoQ10 was 96 percent and the oxidized form was 4 percent of the CoQ10 in the gastric juice solution. With time, the proportion of reduced CoQ10 decreased to 10 percent, while the oxidized CoQ10 increased to 90 percent. Microphotography (see Figure 2) shows the conversion of the gray-white reduced liposomes to yellow-orange liposomes after 120 minutes. This data clearly illustrates the instability of ubiquinol when placed in a watery acid environment. Ubiquinol, always an antioxidant, is chemically unstable. The only patented form of ubiquinol in the USA turns to a liposome when placed in simulated gastric juice or in the intestines. With a time interval of 80 minutes for the ubiquinol to convert to ubiquinone, it is doubtful that a significant quantity of the CoQ10 is absorbed as ubiquinol. This conversion to ubiquinone may well be the reason for the similar 313% absorption (as shown in Figure 1) for ubiquinol product types. Thus, the claim of a higher absorption and bioavailability of the ubiquinol product is one that is vulnerable to challenge. It takes foods 60-80 minutes to move from the stomach into the small intestines, where they are absorbed.

The ubiquinol product has not been in the CoQ10 research arena long enough to effectively compare its benefits to those of ubiquinone. At this time, although we know that both CoQ10 forms are important to man, we also know that ubiquinone is the only form involved as a cofactor in the synthesis of energy in all cell mitochondria. While ubiquinol is important as an antioxidant, it is only one of many antioxidants that we ingest in our diets or manufacture in our bodies. Ubiquinone, whose only known function is to act as an energizer, is essential for life. Unfortunately, ubiquinone synthesis diminishes after 21 years of age, as does ubiquinol level. The proportion of ubiquinol in the body may also decrease in a select group of individuals after the age of 45 years. **These individuals have a general reduced conversion of ubiquinone to ubiquinol due to lower production of the oxireductase enzyme as a result of NQO-1 gene mutation.**

As mentioned above, the three forms of CoQ10 are part of a redox relationship that allows one form to be converted to the other in what is known as the CoQ10 cycle. While this may suggest that there are few structural differences between ubiquinone and ubiquinol, the functional characteristics of each are quite different. These differences are:

1. Ubiquinol is two hydrogen atoms larger (866 Daltons) than ubiquinone (864 Daltons).
2. Ninety-five percent of the CoQ10 outside the mitochondria is the ubiquinol form.
3. Ubiquinone is significantly more stable than ubiquinol.
4. Ubiquinone is essential for energy synthesis; ubiquinol is not directly involved in the synthesis of energy.
5. Ubiquinol is an antioxidant that neutralizes superoxides and free radicals, protecting all body cell membranes from lipid peroxidation.
6. Ubiquinone is an electron acceptor, while ubiquinol is an electron donor.
7. Ubiquinone is synthesized in the mitochondria; ubiquinol is converted from ubiquinone by an oxireductase enzyme.
8. All three CoQ10 forms are part of a redox relationship in which the three forms can be converted from one form to another in what is known as the CoQ10 cycle.

UBIQUINONE and UBIQUINOL

(Active forms of Coenzyme Q10)

The major point of this comparison is that there is no obvious advantage in selecting the reduced form of CoQ10 for supplementation. This is because the oxidized form is rapidly converted to the reduced form *in vivo*. The absorption of the reduced form is not higher, is less stable, and costs approximately three times as much as the oxidized form, which has been clinically proven to raise blood levels to a greater extent that the reduced form.