[14:00 - 14:40]

Safety, High Quality, Confidence of Kaneka CoQ10

Kenji Fujii (Kaneka Corporation)

Abstract

Kaneka Corporation (Kaneka) has been manufacturing CoQ10 under GMP regulation since 1977. Kaneka has a sophisticated quality control system and has been supplying high quality CoQ10 materials to the worldwide customers (Kaneka CoQ10) for about 30 years. Kaneka CoQ10 is characterized by a lot of safety data, which are derived from clinical trials with healthy volunteers (single-dose and 4-week multi-dose safety studies), animal studies (13-week sub-chronic study in dogs and 52-week chronic study in rats), three types of mutagenicity test, six type of skin irritation test (for cosmetics), and others.

The risk assessment of CoQ10 was performed by Council for Responsible Nutrition (USA). They reviewed many of available clinical data including clinical trials using Kaneka Q10, and concluded that the upper level for supplements (ULS) of CoQ10 is 1,200 mg/day (Hathcock and Shao. 2006, Regulatory Toxicology and Pharmacology, 45, 282 – 288).

Introduction

Coenzyme Q10 (CoQ10) is a popular ingredient as a dietary supplement in many countries. It has also been used as a drug and cosmetics. CoQ10 has two major functions; mitochondrial electron transport carrier (ATP production) and anti-oxidant activity. Many of clinical trial data indicate that CoQ10 has beneficial effects on heart disease, brain disease, fatigue,

hypertension, and diabetes, and others.

Because dietary supplements are supposed to be used for long periods without medical prescription, the safety data is very important for consumers. Indeed, a lot of side effects of other dietary supplement have been reported in Japan and other countries. It is very important that consumers are able to obtain such safety information easily to select the suitable dietary supplement. Kaneka has been making effort to supply such safety data for consumers.

Kaneka Corporation (Kaneka) has been manufacturing CoQ10 (Kaneka Q10) under GMP regulation since 1977. Kaneka has a sophisticated quality control system and has been supplying a high quality CoQ10 material to the worldwide customers (Kaneka CoQ10) for about 30 years.

Quality of Kaneka CoQ10

The specifications of Kaneka CoQ10 are more severe than those of USP, EP and JP. Kaneka supplies high quality CoQ10 for both medicine and food supplement. They are identical in terms of quality and manufacturing process. All impurities of Kaneka CoQ10 were controlled and identified.

To maintain the high quality, Kaneka established the quality control system based on FDA system. It consists of six items, which are material, plant, manufacture, package, analysis and quality control. Our quality control system is based on GMP (ICH Q7A).

Status of Kaneka CoQ10

Kaneka CoQ10 has a lot of statuses as follows;

- JGMP certificate from Japanese Government
- US self-affirmation GRAS
- PHARMACOPOEIA compliance (USP, EP, JP)

- GMO free (Microorganism & Raw Materials)
- KOSHER certificate
- BSE free
- DMF for European countries
- Import Drug License for China
- ISO 14001

Safety of Kaneka CoQ10

Kaneka CoQ10 is characterized by a lot of safety data, which are derived from clinical trials with healthy volunteers (single-dose and 4-week multi-dose safety studies), animal studies (13-week sub-chronic study in dogs and 52-week chronic study in rats), three types of mutagenicity test, six type of skin irritation test (for cosmetics), and others.

The safety profile of Kaneka CoQ10 at high doses for healthy subjects was assessed in a double blind, randomized, placebo-controlled study. Kaneka CoQ10 in capsule form was taken for 4 weeks at doses of 300, 600, and 900 mg/day by a total of eighty-eight adult volunteers.

No serious adverse events were observed in any group. Adverse events were reported in 16 volunteers with placebo, in 12 volunteers with the 300 mg dose, in 20 volunteers with the 600 mg, dose and in 16 volunteers with the 900 mg dose. The most commonly reported events included common cold symptoms and gastrointestinal effects such as abdominal pain and soft feces. These events exhibited no dose-dependency and were judged to have no relationship to Kaneka CoQ10.

Changes observed in hematology, blood biochemistry, and urinalysis were not dose-related and were judged not to be clinically significant.

Table 1 shows numbers of subjective symptoms. There were no severe

subjective symptoms observed after intake of Kaneka CoQ10 and no significantly change in frequency of symptoms.

Table 1. Numbers of subjective symptoms

	Number of subjective symptoms					
	Plausibly Related	Possibly Related	Total	Uncertain Relationship	Unrelated	Total
Placebo	0	1	(1)	8	7	(15)
300 mg	0	0	(0)	10	2	(12)
600 mg	0	0	(0)	9	11	(20)
900 mg	0	0	(0)	4	12	(16)

Plausibly Related: the source of the adverse event was probably the test material, as judged by the recognition of a clear temporal relationship to the administration of the test material. Possibly Related: Although a clear temporal relationship to administration was recognized, the possibility that the source of the adverse event could have been something other than the test material remained. Uncertain Relationship: No clear temporal relationship to administration of the test material was found, and it appeared likely that the source of the adverse event was something other than the test material.

The plasma CoQ10 concentration was increase as dose dependent manner and reached to plateau after 2 weeks in all dose groups (Fig. 1).

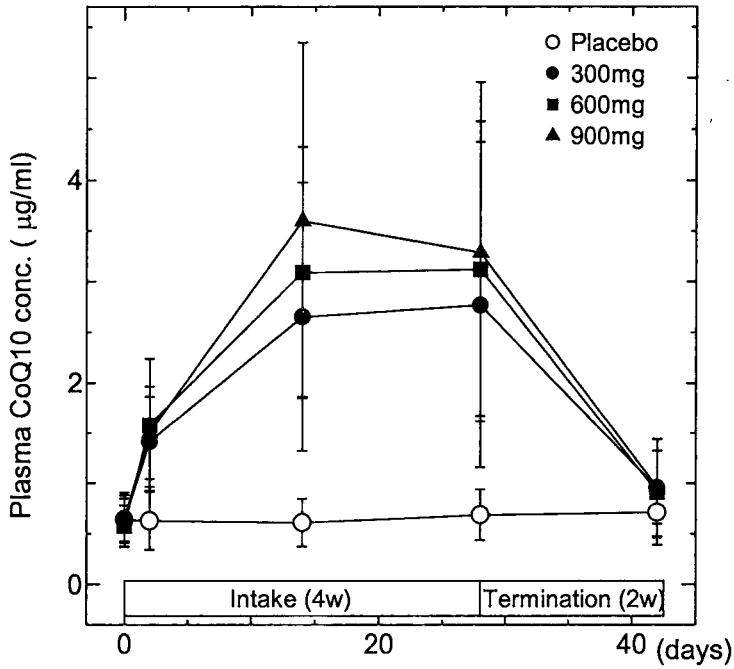


Fig. 1. Changes in plasma CoQ10 concentration during test periods. Values are Mean±SD in placebo (open circles), 300mg/day (closed circles), 600mg/day (closed squares) and 900mg/day (closed triangles) groups.

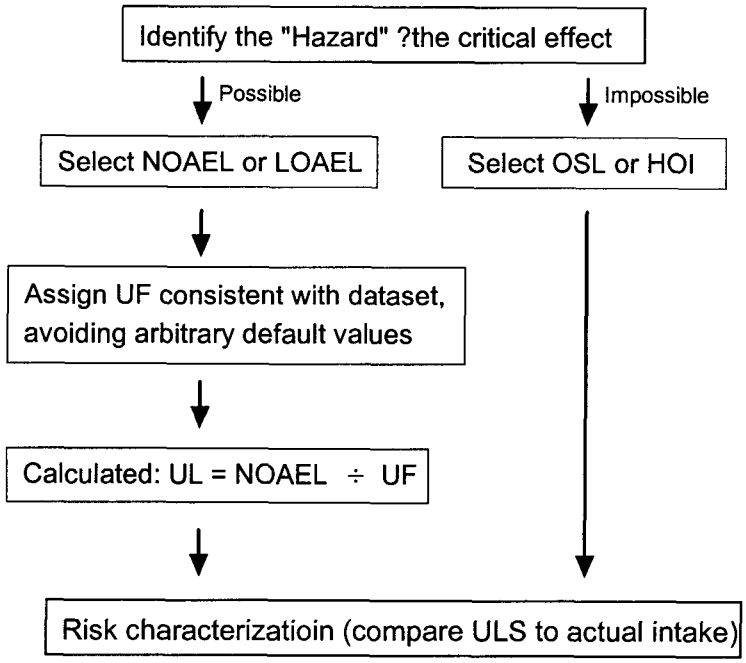
Plasma CoQ10 was reduced to the basal level after 2 weeks of termination. It suggested that CoQ10 was not accumulated in plasma. The plasma CoQ10 concentration after 8-month withdrawal was almost the same as that before administration. It might suggest that a large amount of CoQ10 intake did not affected to CoQ10 biosynthesis.

These findings showed that Kaneka CoQ10 was well tolerated and safe for healthy adults at intake of up to 900 mg/day.

Risk assessment of CoQ10

The risk assessment of CoQ10 was reported by Council for Responsible Nutrition (USA) (Hathcock, J. N., and Shao, A., 2006, Regulatory Toxicology and Pharmacology, 45, 282 – 288).

The step of risk assessment for functional food ingredients (UL method) is summarized in Fig. 2.



NOAEL: No oberved adverse effect level
LOAEL: Lowest oberved adverse effect level
OSL: Observed safe level
HOI: Highest observed intake
UF: Uncertainty factor
ULS: Upper level for supplements

Fg.2 UL Method for risk assessment of functional food ingredient

In this risk assessment, the comprehensive strong clinical trial (double blind placebo controlled trial etc.) were listed to identify the "Hazard" in high dose order, which was 3000, 2400, 1200, 900, and 600 mg/day. It was concluded that the upper level for supplements (ULS) of CoQ10 was 1200

mg/day. It should be noted that all high dose clinical trials listed in this assessment were using Kaneka CoQ10 as CoQ10. It is considered that ULS of Kaneka CoQ10 is 1200 mg/day.

Conclusion

Coenzyme Q10 is considered to be one of the most safe and useful ingredients for food supplement. Kaneka manufactures CoQ10 under the sophisticated quality control system and has a lot of safety data. The safe upper level of CoQ10 intake risk was assessed to 1200mg/day.