

Memorandum

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Date: MAR 8 2005

From: Consumer Safety Officer, Division of Dietary Supplement Programs, Office of Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305

Subject of the Notification: Kaneka QH™ brand of ubiquinol
Firm: CANTOX for Kaneka Corporation
Date Received by FDA: Dec. 3, 2004
90-Day Date: March 3, 2005

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Victoria Lutwak

1995S-0316

RPT266



Food and Drug Administration
5100 Paint Branch Parkway
College Park, Maryland 20740

FEB 10 2005

Dr. David H. Bechtel
Senior Scientific Consultant
CANTOX U.S. Inc.
1011 U.S. Highway 22, Suite 200
Bridgewater, NJ 08807

Dear Dr. Bechtel:

This is to inform you that the notification you submitted, dated December 2, 2004, on behalf of your client, Kaneka Corporation, pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on December 3, 2004. Your notification concerns the substance called "Kaneka QHTM brand of ubiquinol" that you intend to market as a new dietary ingredient.

The notification informs FDA that Kaneka Corporation intends to market the new dietary ingredient, "Kaneka QHTM brand of ubiquinol", in softgel capsules. The notification states that "each serving of the dietary supplement will contain 50 mg of Kaneka QHTM". For directions of use, the notification states that "consumption of up to 6 servings per day will be suggested or recommended in the label directions, resulting in a maximum daily consumption of up to 300 mg Kaneka QHTM".

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement that contains a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is deemed to be adulterated under 21 U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

FDA has carefully considered the information in your submission, and the agency has concerns about the evidence on which you rely to support your conclusion that a dietary supplement containing "Kaneka QHTM brand of ubiquinol" will reasonably be expected to be safe.

Your notification fails to clearly identify the new dietary ingredient that you call "Kaneka QHTM brand of ubiquinol". The notification fails to clearly identify the composition and manufacturing process for your new dietary ingredient, "Kaneka QHTM brand of ubiquinol". Information about your method of manufacture may have helped FDA to identify your new dietary ingredient.

For the reasons discussed above, the information in your submission does not provide an adequate basis to conclude that "Kaneka QHTM brand of ubiquinol", when used under the conditions recommended or suggested in the labeling of your product, will reasonably be expected to be safe. Therefore, your product may be adulterated under 21 U.S.C. 342(f)(1)(B) as a dietary supplement that contains a new dietary ingredient for which there is inadequate information to provide reasonable assurance that such ingredient does not present a significant or unreasonable risk of illness or injury. Introduction of such a product into interstate commerce is prohibited under 21 U.S.C. 331(a) and (v).

Your notification will be kept confidential for 90 days after the filing date of December 3, 2004. After the 90-day date, the notification will be placed on public display at FDA's Docket Management Branch in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any questions concerning this matter, please contact Linda Pellicore, Ph.D. at (301) 436-2375.

Sincerely yours,



for

Susan J. Walker, M.D.
Director
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements
Center for Food Safety
and Applied Nutrition

CANTOX

HEALTH SCIENCES INTERNATIONAL

1011 U.S. Hwy 22 West, Suite 200
Bridgewater, New Jersey 08807-2950
Phone: (908) 429-9202
Fax: (908) 429-9260

December 2, 2004

Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-820)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Pkwy
College Park, MD 20740

DEC 03 2004
OAB/FDA

RE: New Dietary Ingredient Notification

Dear Sir or Madam,

In accordance with the provisions of Section 413(a) of the Federal Food, Drug and Cosmetic Act, CANTOX U.S. Inc., on behalf of Kaneka Corporation, submits the attached information to the Food and Drug Administration, in support of marketing of a dietary supplement, containing the new dietary ingredient Kaneka QH™ brand of ubiquinol. It is Kaneka Corporation's intention to incorporate the ingredient Kaneka QH™ into a dietary supplement in the form of capsules. Pursuant to the applicable provisions of the DSHEA, 21 U.S.C. § 350b (a) (2), Kaneka Corporation will not introduce the ingredient or deliver it for introduction into interstate commerce until at least 75 days after the date on which FDA receives this notification.

Respectfully submitted,



David H. Bechtel, Ph.D., DABT
Senior Scientific Consultant

Enclosure

CANTOX

HEALTH SCIENCES INTERNATIONAL

New Dietary Ingredient Notification for Kaneka QH™

Submitted by: CANTOX HEALTH SCIENCES
INTERNATIONAL
1011 U.S. Highway 22 West, Suite 200
Bridgewater, New Jersey
08807

On behalf of: Kaneka Corporation
Functional Foods Development Division
3-2-4, Nakanoshima, Kita-Ku
Osaka 530-8288, Japan

December 2, 2004

CANTOX Offices:

Mississauga
905-542-2900

Vancouver
604-688-8255

New Jersey
908-429-9202

SECTION 1

The name and complete address of the manufacturer or distributor of the dietary supplement that contains a new dietary ingredient, or of the new dietary ingredient.

The manufacturer of the new dietary ingredient is:

Kaneka Corporation
Functional Foods Development Division
3-2-4, Nakanoshima, Kita-Ku
Osaka 530-8288, Japan

Direct correspondence to:

David H. Bechtel, Ph.D., DABT
Senior Scientific Consultant
CANTOX U.S. Inc.
1011 U.S. Highway 22, Suite 200
Bridgewater, NJ 08807
Phone: 908-429-9202
Fax: 908-429-9260

SECTION 2

The name of the new dietary ingredient.

KANEKA QH™ brand of ubiquinol.

SECTION 3

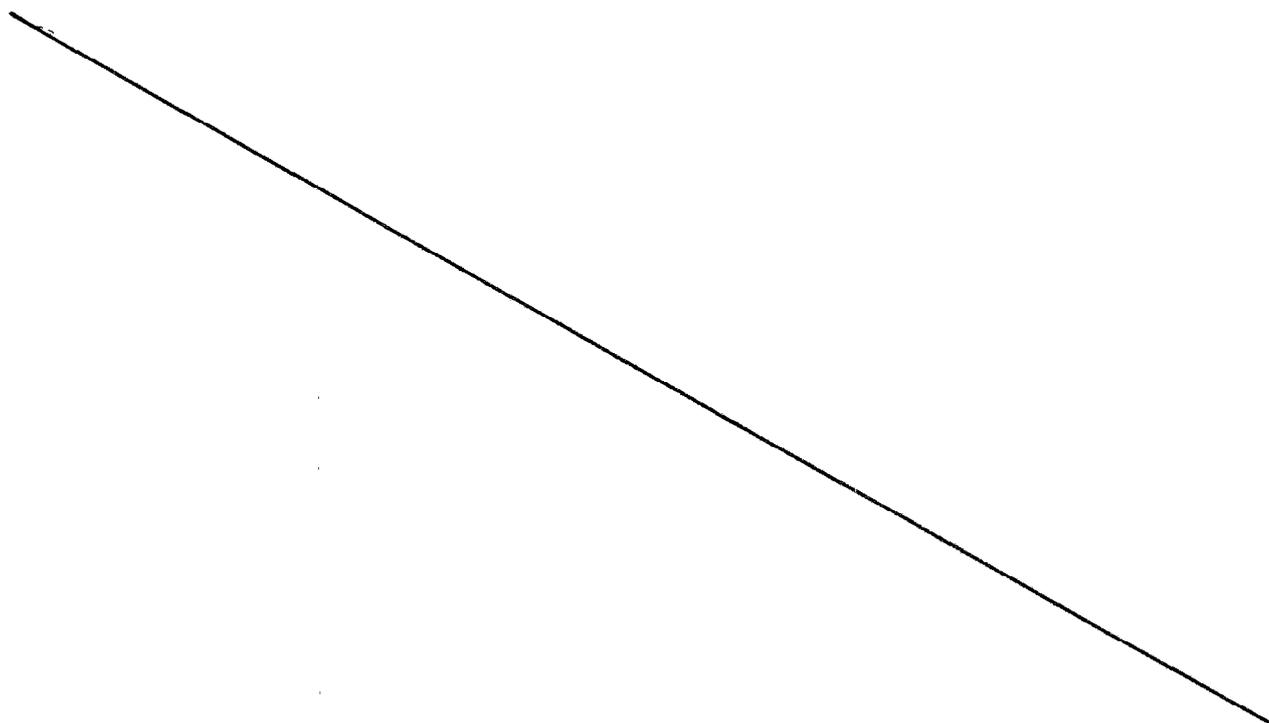
Description of the dietary supplement or dietary supplements that contain the dietary ingredient including (i) the level of the dietary ingredient in the dietary supplement, and (ii) the conditions of use recommended or suggested in the labeling of the dietary supplement, or if no conditions of use are recommended or suggested in the labeling of the dietary supplement, the ordinary conditions of use of the supplement.

The dietary supplement containing KANEKA QH™ will be in softgel capsule form. The KANEKA QH™ softgel capsules will be clearly labeled and promoted as a dietary supplement. A description of the number of softgel capsules per serving size will appear on the label, and each serving of the dietary supplement will contain 50 mg of KANEKA QH™. Consumption of up to 6 servings per day will be suggested or recommended in the label directions, resulting in a maximum daily consumption of up to 300 mg KANEKA QH™ (equivalent to 6 mg/kg/day for a 50 kg body weight person).

SECTION 4

The history of use or other evidence of safety establishing that the dietary ingredient, when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe, including any citation to published articles or other evidence that is the basis on which the distributor or manufacturer has concluded that the dietary supplement will reasonably be expected to be safe.

4.1 MANUFACTURE OF KANEKA QH™



4.2 BIOCHEMICAL CONSIDERATIONS AND BIOAVAILABILITY

4.2.1 Biochemical Considerations

4.2.1.1 Occurrence

4.2.1.1.1 Occurrence in Humans

Ubiquinol is the two-electron reduction product of coenzyme Q₁₀ (CoQ₁₀), a naturally-occurring, lipid-soluble nutrient (Frei *et al.*, 1990; Schoepp, 1997; Pepping, 1999). The term CoQ refers to a class of homologous benzoquinones that have been identified in all plants and animals, as well as in a majority of microorganisms (Budavari *et al.*, 1996; Nohl *et al.*, 1998). Benzoquinone

homologs consist of a redox active quinoid moiety, and a hydrophobic side chain comprised of 6 to 10 isoprenoid units, depending on the species (Ibrahim *et al.*, 2000; Matthews *et al.*, 1998; Lenaz, 2001). In humans and most mammals, the predominant form of coenzyme Q is coenzyme Q₁₀ (CoQ₁₀), which consists of 10 isoprenoid units in the side chain. In rats and mice the primary form is coenzyme Q₉, which contains 9 isoprenoid units, however, low levels of coenzyme Q₁₀ have also been reported (Battino *et al.*, 1992). Coenzyme Q₁₀ and its reduced form are also referred to as ubiquinone (or ubiquinone-10) and ubiquinol (or ubiquinol-10), respectively.

Coenzyme Q₁₀ is located in the hydrophobic interior of nearly every cellular membrane, and to varying degrees in all tissues (Lass and Sohal, 1999; Nohl *et al.*, 1998). Since its discovery in 1957 by Crane and colleagues (Bertelli and Ronca, 1990), coenzyme Q₁₀ has been extensively studied for its key role in mitochondrial energy production, where it acts as both an electron carrier and proton translocator during cellular respiration and adenosine triphosphate (ATP) production (Hughes *et al.*, 2002; Nohl *et al.*, 2001; Nohl *et al.*, 1998). Apart from its involvement in mitochondrial energy coupling, coenzyme Q₁₀ has also been shown to function in its reduced form (*i.e.*, ubiquinol) as an antioxidant in both mitochondria and lipid membranes (Forsmark-Andree *et al.*, 1997; Noack *et al.*, 1994). In addition, ubiquinol, like coenzyme Q₁₀, has been shown to be an integral part of virtually all living cells (Frei *et al.*, 1990).

Although coenzyme Q₁₀ becomes oxidized as a result of its antioxidant function, a substantial amount is maintained in its reduced state in the plasma membrane and endomembranes (Takahashi *et al.*, 1993), as well as in lipoproteins (Stocker and Frei, 1991). In the plasma membrane, reduction of coenzyme Q₁₀ is achieved through the involvement of several CoQ-reductases (*e.g.*, DT-diaphorase and NADPH-CoQ reductase) that may be either integral membrane proteins or cytosolic enzymes (Arroyo *et al.*, 2000). Stocker and Suarna (1993) also reported that natural ubiquinones are readily reduced after dietary uptake. While it is generally accepted that oxidized coenzyme Q₁₀ is the final product of its biosynthetic pathway, some authors (Stocker and Suarna, 1993; Schultz *et al.*, 1996) have proposed that the *de novo* synthesis of the hydroquinone also contributes, at least in part, to the high levels of ubiquinol observed *in vivo*. In fact, ubiquinol is the most common form of coenzyme Q₁₀ *in vivo* (Frei *et al.*, 1990), and represents more than 80% of the total ubiquinol-10 + coenzyme Q₁₀ pool in human plasma, intestine and liver (Edlund, 1988; Okamoto *et al.*, 1989; Åberg *et al.*, 1992). In the plasma of healthy adults, ubiquinol-10 accounts for approximately 95% of the total concentration, while ubiquinone-10 accounts for only 5% (Yamashita and Yamamoto, 1997); in human urine, ubiquinol-10 accounts for approximately 59% of the total ubiquinone-10 concentration (Okamoto *et al.*, 1989). Åberg *et al.* (1992) reported that high levels of reduction (70 to 100%) were also observed in human tissues including, the liver, pancreas, and intestine. Only in the brain and lung was most of the ubiquinone (approximately 80%) in the oxidized state. In contrast, the degree of ubiquinone reduction in all rat tissues was less than in corresponding human tissues.

Several authors have examined plasma concentrations of ubiquinol in human volunteers. For example, Kontush *et al.* (1997) reported that concentrations of ubiquinol-10 in plasma of young and aged controls were 0.66 and 0.77 μM , respectively, (0.57 $\mu\text{g/mL}$ and 0.67 $\mu\text{g/mL}$, respectively) while the percentage of total ubiquinol-10 + ubiquinone-10 was 85.7 and 83.1% in young and aged controls, respectively. Similarly, Miles *et al.* (2003) reported the plasma concentration of ubiquinol-10 in healthy adults was 1.07 $\mu\text{mol/L}$ (0.93 $\mu\text{g/mL}$), and Kaikkonen *et al.* (1999) reported values ranging from 0.5 to 2.0 $\mu\text{mol/L}$ (0.43 to 1.73 $\mu\text{g/mL}$). Since ubiquinol-10 can be rapidly recycled from its oxidized form by various electron transfer systems (Crane *et al.*, 1993), Stocker and Suarna (1993) suggested that the reduction of ubiquinone-10 to ubiquinol-10 by the liver plays an important role in maintaining its level in plasma.

Dietary supplementation with coenzyme Q₁₀ (100 to 300 mg/day) has been shown to increase concentrations of ubiquinol-10 in plasma and all of its lipoproteins (Mohr *et al.*, 1992). For example, in low-density lipoproteins (LDL), maximal supplementation is achieved following 4 to 5 days continuous coenzyme Q₁₀ supplementation, and at this time a 4 to 5-fold increase is also observed in LDL's ubiquinol-10 concentration [from 0.5 to 0.8, to 2.0 to 3.0 ubiquinol-10 molecules per LDL] (Thomas *et al.*, 1996; Mohr *et al.*, 1992). It is noteworthy that coenzyme Q₁₀ supplementation does not alter the ratio of ubiquinol-10 to ubiquinone-10 in LDL or plasma; the ratio remains constant with as much as 95% of the total coenzyme Q present as ubiquinol-10 (Mohr *et al.*, 1992). As such, Thomas *et al.* (1999) suggested that this finding was an indication that sufficient reducing potential is available to keep circulating coenzyme Q in the reduced form. Similarly, Takahashi *et al.* (1993) reported that a high ratio of ubiquinol to total ubiquinone (approximately 85%) was maintained even when serum concentrations of total ubiquinone were enhanced through oral supplementation with the oxidized form of ubiquinone. The authors suggested that this finding was an indication that the oxidized form of ubiquinone, when taken orally, is reduced to ubiquinol at the expense of reducing equivalents including, ND(P)H.

Several authors (Kontush *et al.*, 1997; Yamamoto and Yamashita, 1997, 1999; Lagendijk *et al.*, 1997; Wittenstein *et al.*, 2002) examined plasma ubiquinol and ubiquinone concentrations in patients with various pathological conditions (*e.g.*, hyperlipidemia, hepatitis, cirrhosis, hepatoma, coronary artery disease [CAD], diabetes mellitus), and reported that the ratio of ubiquinol to ubiquinone was decreased in these patients compared to healthy subjects. For example, Lagendijk *et al.* (1997) presented the following comparison of coenzyme Q₁₀ parameters between patients with CAD (n=40; mean age = 52.6) and controls (n=40; mean age = 52.6):

Parameter	CAD Patients (Mean)	Controls (Mean)
Ubiquinol (nmol/L)	1137.0	1145.1
Ubiquinone (nmol/L)	46.4	40.3
Ubiquinol/ubiquinone ratio	26.5	30.2

4.2.1.1.2 Occurrence in Animals

Aside from those investigations conducted in human volunteers, several authors have examined the concentration of ubiquinol, as well as the ratio of ubiquinol to ubiquinone, in rodents. In mice, tissues involved in detoxification, such as the liver and kidney were shown to have high levels of ubiquinol, which may, as Podda *et al.* (1996) and Tang *et al.* (2004) suggested, protect them from radicals escaping the P450 enzyme system. For example, according to Podda *et al.* (1996), concentrations of ubiquinol-9 and ubiquinol-10 in the liver and kidney were respectively, 42 and 81 nmol/g tissue, and 1.7 and 11 nmol/g tissue, compared to ubiquinol-9 and ubiquinol-10 concentrations of 1.6 and 0.6 nmol/g tissue in the brain, and 19 and 2.8 nmol/g tissue in the heart.

Tang *et al.* (2004) reported that mouse heart [mean (n=10): 897.5 nmol/g protein] and liver [mean (n=10): 281.3 nmol/g protein] contained appreciable concentrations of ubiquinol-9 compared to skeletal muscle [mean (n=10): 154 nmol/g protein] and brain [mean (n=10): 92.2 nmol/g protein]. For ubiquinol-10, mouse heart [mean (n=10): 83.8 nmol/g protein] reportedly contained a relatively appreciable amount, compared to the liver [mean (n=10): 4.6 nmol/g protein], skeletal muscle [mean (n=10): 6.5 nmol/g protein] and brain [mean (n=10): 26.7 nmol/g protein]. In addition, the authors reported that percentages of ubiquinol-9 in total CoQ₉ (TQ₉) were 85.5% in the liver, 60% in the heart, 58.7% in the muscle, and 31.2% in the brain; percentages of ubiquinol-10 in TQ₁₀ were 88.6% in the liver, 60.9% in the heart, 57.9% in the muscle, and 35.3% in the brain. Tang *et al.* (2004) noted that according to Podda *et al.* (1996) the percentages of ubiquinol-9 in brain, heart and liver were approximately 14%, 7%, and 48%, respectively, while the percentages of ubiquinol-10 were 15% in brain and 12% in heart (due to the sensitivity of the ultraviolet (UV) detector, Podda *et al.* (1996) did not measure ubiquinone-10 in liver). Recognizing the percentages of ubiquinol that they observed in mouse heart and liver were greater than those observed by Podda *et al.* (1996), Tang *et al.* (2004) suggested that such differences were the result of variations in sampling, extraction and analytical methods.

As mentioned previously, differences in the ratio of ubiquinol to ubiquinone have been reported in patients with various pathological conditions compared to healthy subjects. Similarly, variations in the ratio of ubiquinol to ubiquinone have also been shown to exist among different species. For example, in general, the reduced fraction (ubiquinol) has been reported to be higher in human than rat (Table 1).

Table 1 Coenzyme Q Concentration, Type and Extent of Reduction in Human and Rat Tissues

Tissue	Rat			Human		
	CoQ ₉	CoQ ₁₀	% Reduced	CoQ ₉	CoQ ₁₀	% Reduced
Heart	202	17	22	3	114	47
Kidney	124	22	42	3	67	73
Liver	131	21	87	2	55	95
Muscle	43	3	40	1	40	60
Brain	37	19	27	1	13	23
Pancreas	37	3	62	2	33	100
Spleen	23	9	18	1	25	87
Lung	17	2	12	1	8	24
Thyroid	44	7	45	1	25	68
Testis	32	5	49	1	11	78
Intestine	51	19	67	1	12	93
Colon	48	8	52	1	11	83
Ventricle	56	5	52	---	12	59

The values are presented in µg/g tissue. Data is taken from Åberg *et al.* (1992) and Runquist *et al.* (1995).

Takahashi *et al.* (1993) examined the concentrations of oxidized and reduced forms of ubiquinone homologues in rat tissues and subcellular fractions to clarify their distribution and physiological role. Concentrations (n=4 to 8) in tissues are shown in Table 2; the values are means, µg/g wet tissues or mL plasma.

Table 2 Concentrations of Oxidized and Reduced Forms of Ubiquinone in Rat Tissues and Subcellular Fractions

Tissue	Ubiquinone (UQ) Homologues Detected	t-UQ ^a Content	UQ _{red} Content	UQ _{red} (% of t-UQ) ^b
Plasma	UQ-9	0.48	0.39	82.1
	UQ-10	0.12	0.09	75.9
Liver	UQ-9	105.1	78	74.5
	UQ-10	18.8	12.7	67.4
Heart	UQ-9	188.4	17.4	9.3
	UQ-10	21.6	1.88	8.8
Kidney	UQ-9	122.6	19.9	16.2
	UQ-10	31.8	4.89	15.3
Spleen	UQ-9	75.9	22.4	29.8
	UQ-10	39.6	9.77	24.7

^a The sum of oxidized form of UQ (UQ_{ox}) and reduced form of UQ (ubiquinol) (UQ_{red}) of each of the homologues.

^b $\frac{[UQ_{red}]}{[UQ_{ox}] + [UQ_{red}]} \times 100$

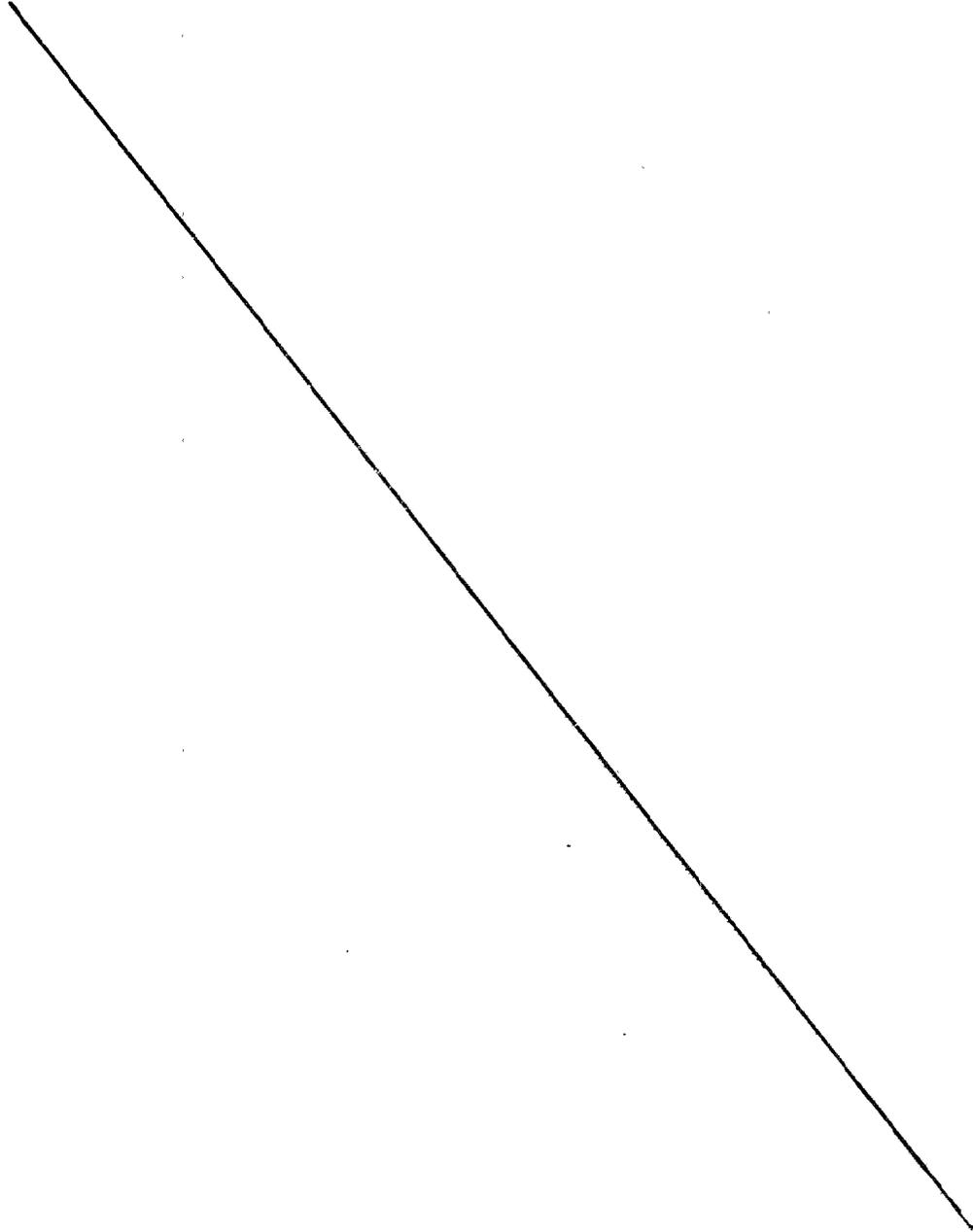
Similarly, UQ-9 and UQ-10 were detected in all blood cells isolated (*i.e.*, erythrocytes, ghost cells, endosomes, leukocytes, and platelets). Leukocytes and platelets, which have mitochondria, possessed higher concentrations of t-UQ-9 and t-UQ-10 than did erythrocytes, which do not have mitochondria. The UQ_{red} forms were below 10% of the t-UQ in erythrocytes and leukocytes, and they were not detected in platelets. With respect to subcellular distribution of UQ_{ox} and UQ_{red} homologues in rat liver and kidney, all fractions tested (*i.e.*, nuclei, mitochondria, crude lysosomes, crude microsomes, cytosol, plasma membranes) contained significant amounts of UQ-9 and UQ-10. The levels of the UQ_{red} forms reached 60-70% of

those of the t-UQ homologs in a majority of subcellular fractions of the liver, and accounted for approximately 25% of those in kidney.

Based on these findings, Takahashi *et al.* (1993) concluded that all rat tissues and subcellular fractions isolated from the liver and kidney contain significant amount of ubiquinone. In addition, the authors noted that 70 to 80% of the total amounts of each UQ_{ox} and UQ_{red} homologue in the liver and plasma, as well as 20 to 30% of those in other tissues, exist as the reduced hydroquinone form.

4.2.1.1.3 Occurrence in Foods

Table 3b Total Coenzyme Q₁₀, Ubiquinone and Ubiquinol Contents in Fish



4.2.1.2 Physiological Functions

Ubiquinol-10, the reduced and most common form of coenzyme Q₁₀ *in vivo*, has been shown to be a potent lipophilic antioxidant for protection of lipids in a number of biological and model systems (Frei *et al.*, 1990; Ernster and Forsmark-Andree, 1993). Furthermore, according to Ernster and Dallner (1995), ubiquinol is the only known lipid-soluble antioxidant that animals can synthesize *de novo*, and for which there exist mechanisms that can regenerate it from its oxidized product formed as a result of its antioxidant activity.

4.2.2 Bioavailability

4.2.2.1 Bioavailability of Ubiquinol Compared to Ubiquinone

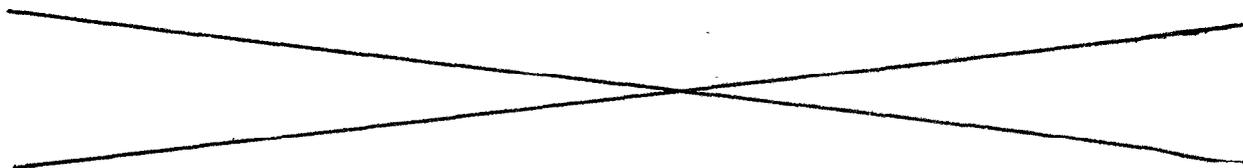
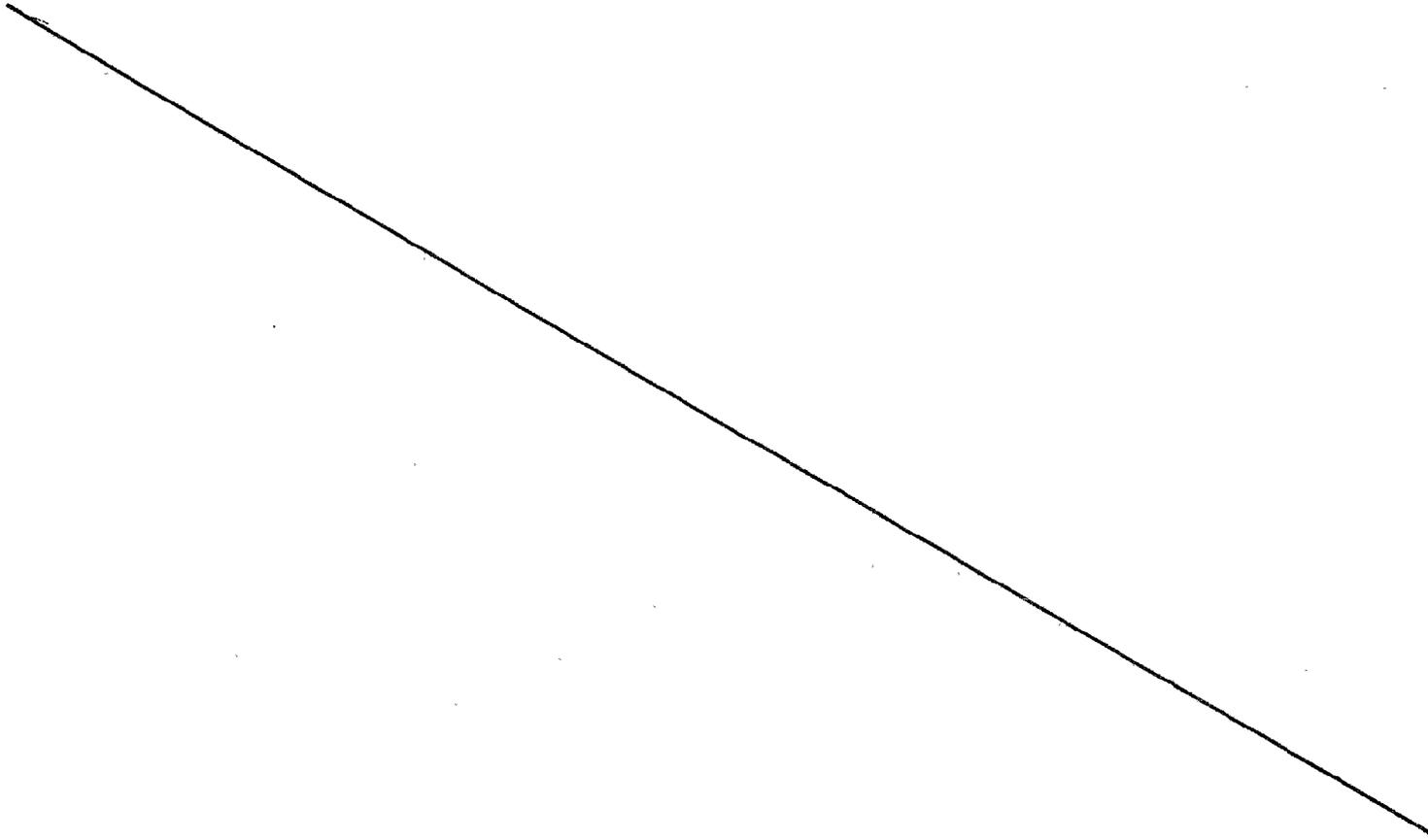
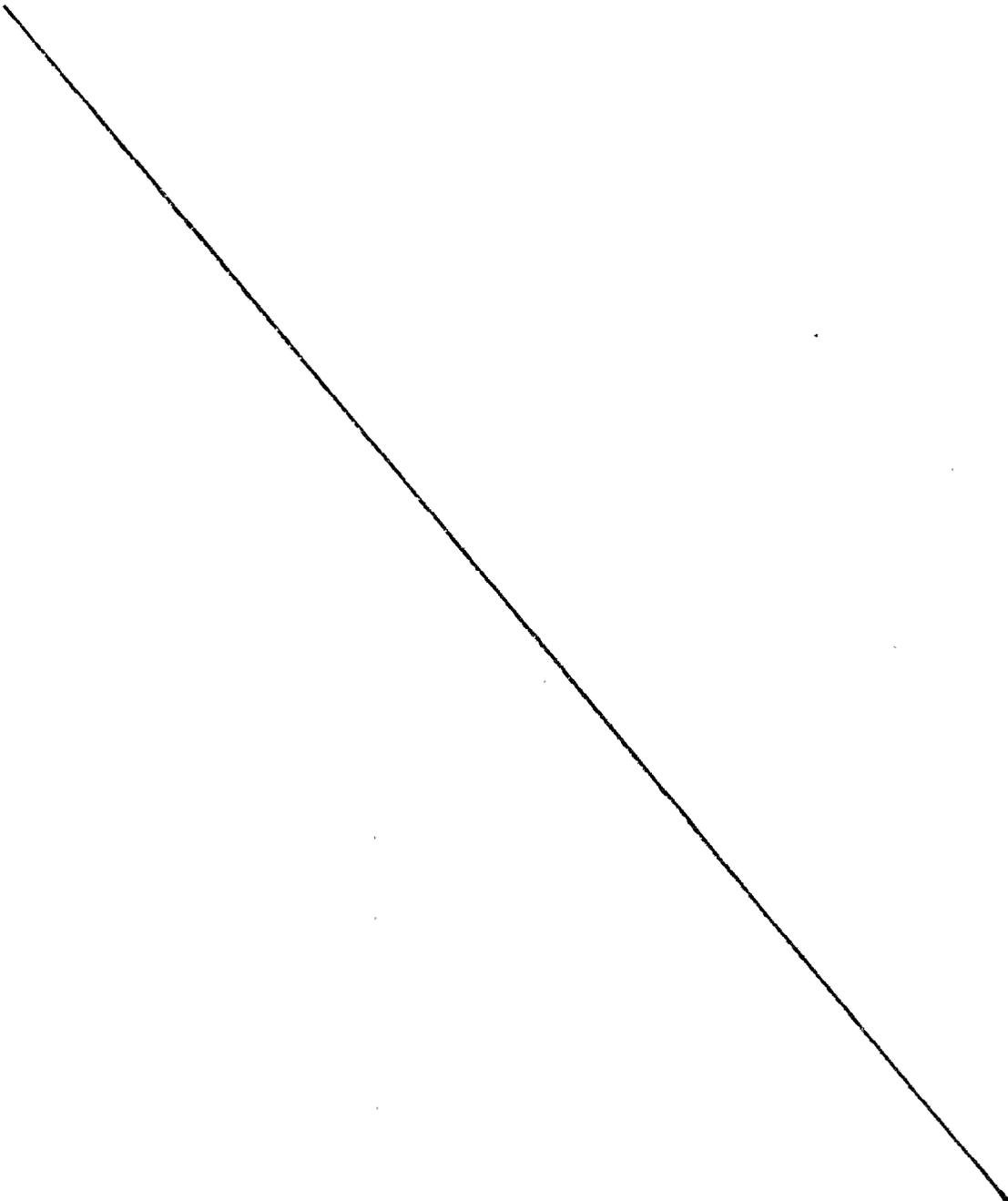


Figure 1 Comparison of Ubiquinol and Ubiquinone Bioavailability



4.2.2.2

Toxicokinetic Studies Conducted by Kaneka



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INFORMATION

4.2.2.3 Published Bioavailability Data in Humans

Mohr *et al.* (1992) examined the effects of coenzyme Q₁₀ supplementation on plasma and lipoprotein ubiquinol-10 concentrations. Within 6 hours of consumption of a single oral dose of 100 or 200 mg coenzyme Q₁₀, total plasma coenzyme Q₁₀ content was increased by 80% or 150%, respectively, in a single subject. Long-term supplementation, consisting of oral doses of 100 mg coenzyme Q₁₀ three times daily for 11 days resulted in a 4-fold increase of ubiquinol (CoQH₂) in the plasma and LDL of 3 normolipidemic male subjects. The proportion of coenzyme Q₁₀ in the reduced state [percent CoQH₂ = 100 CoQH₂ / (coenzyme Q₁₀ + CoQH₂)] was reportedly unchanged by treatment and remained constant throughout the monitored period, with approximately 80% of the coenzyme present as CoQH₂. The authors suggested that this finding indicated that efficient reduction of coenzyme Q₁₀ to CoQH₂ must occur either during absorption or rapidly after the appearance of coenzyme Q₁₀ in the blood (Mohr *et al.*, 1992).

In light of the approximate 4-fold increase in CoQH₂ and the potential role of CoQH₂ as an LDL antioxidant, Mohr *et al.* (1992) also examined whether *in vivo* supplemented LDL was correspondingly less susceptible to radical oxidation. The authors reported that incubation of LDL (isolated from a single subject before and after long-term supplementation) with 2,2'-azobis(2-amidinopropane hydrochloride) [AAPH, 20 or 40 μL of 100 mM in 0.156 M NaCl] resulted in immediate formation of lipid hydroperoxides; formation initially occurred at very low rates, however, a marked increase in the rate of lipid oxidation was noted with the disappearance of 80 to 90% CoQH₂. Results also demonstrated that the cumulative radical dose required to reach a "break point" in lipid hydroperoxide formation (*i.e.*, on a radical/LDL particle basis, ROO[•]/LDL ≈ 3 for non-supplemented versus ≈ 11 for the supplemented LDL) was nearly proportional to the 4-fold increase observed in LDL-[CoQH₂]. On this basis, Mohr *et al.* (1992) concluded that oral supplementation with coenzyme Q₁₀ increases CoQH₂ in the plasma and all lipoproteins, thereby increasing the resistance of LDL to radical oxidation.

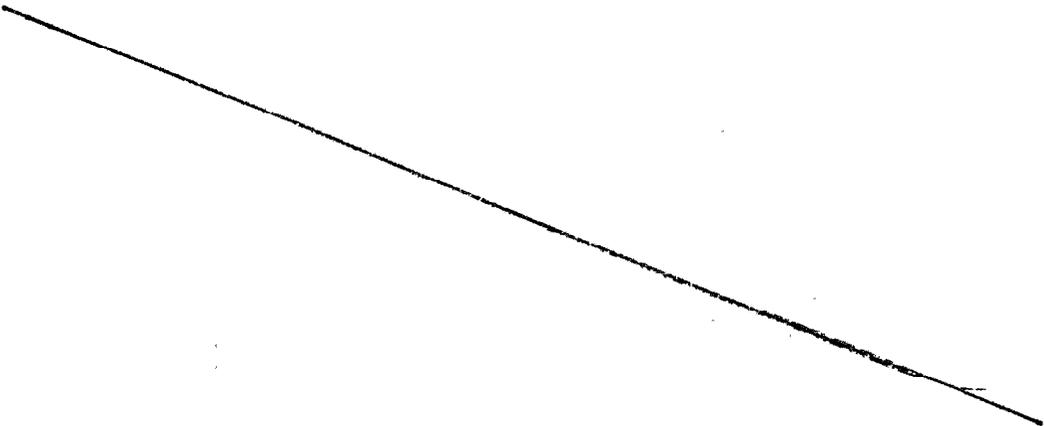
4.3 SAFETY OF UBIQUINOL

4.3.1 Non-clinical and Genotoxicity Studies Conducted with KANEKA QH™

4.3.1.1 Acute Toxicity

4.3.1.2 Subchronic Toxicity

4.3.1.2.1 *13-Week Study in Male and Female Dogs*

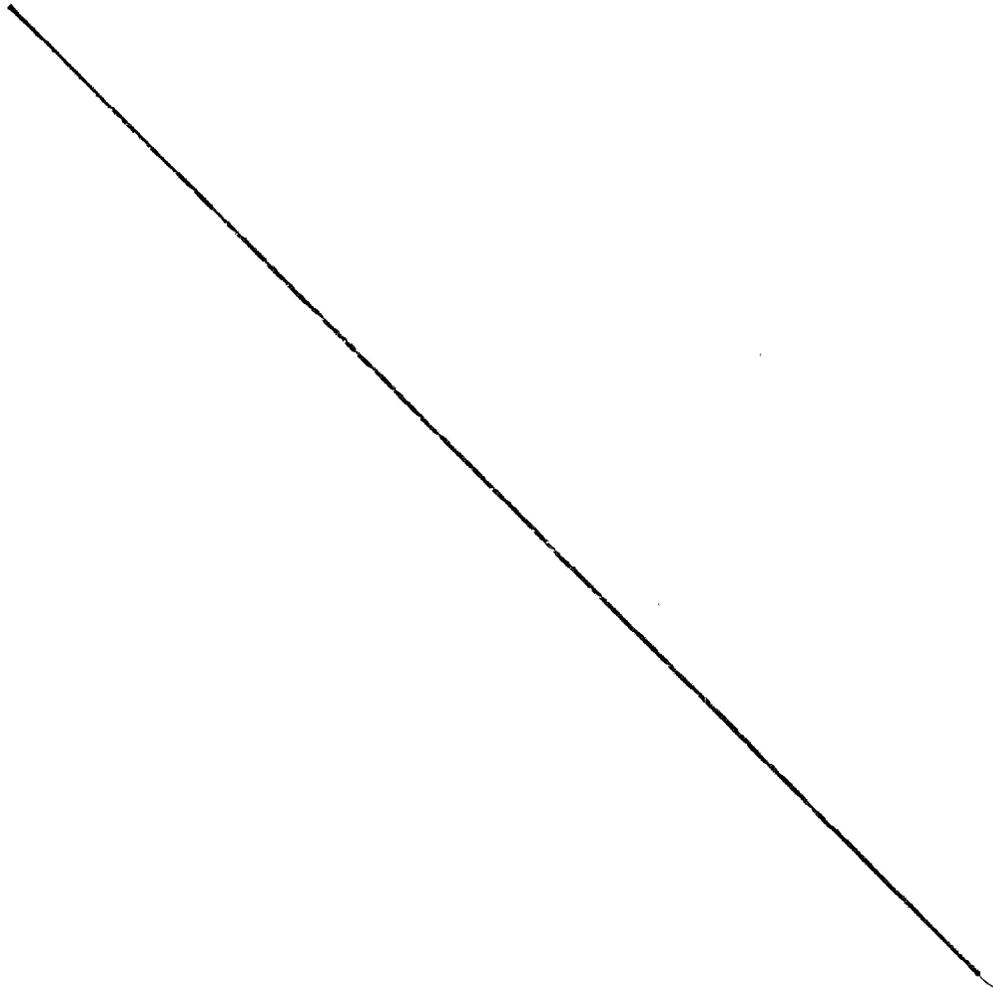


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4.3.1.2.2

13-Week Study in Male and Female Rats



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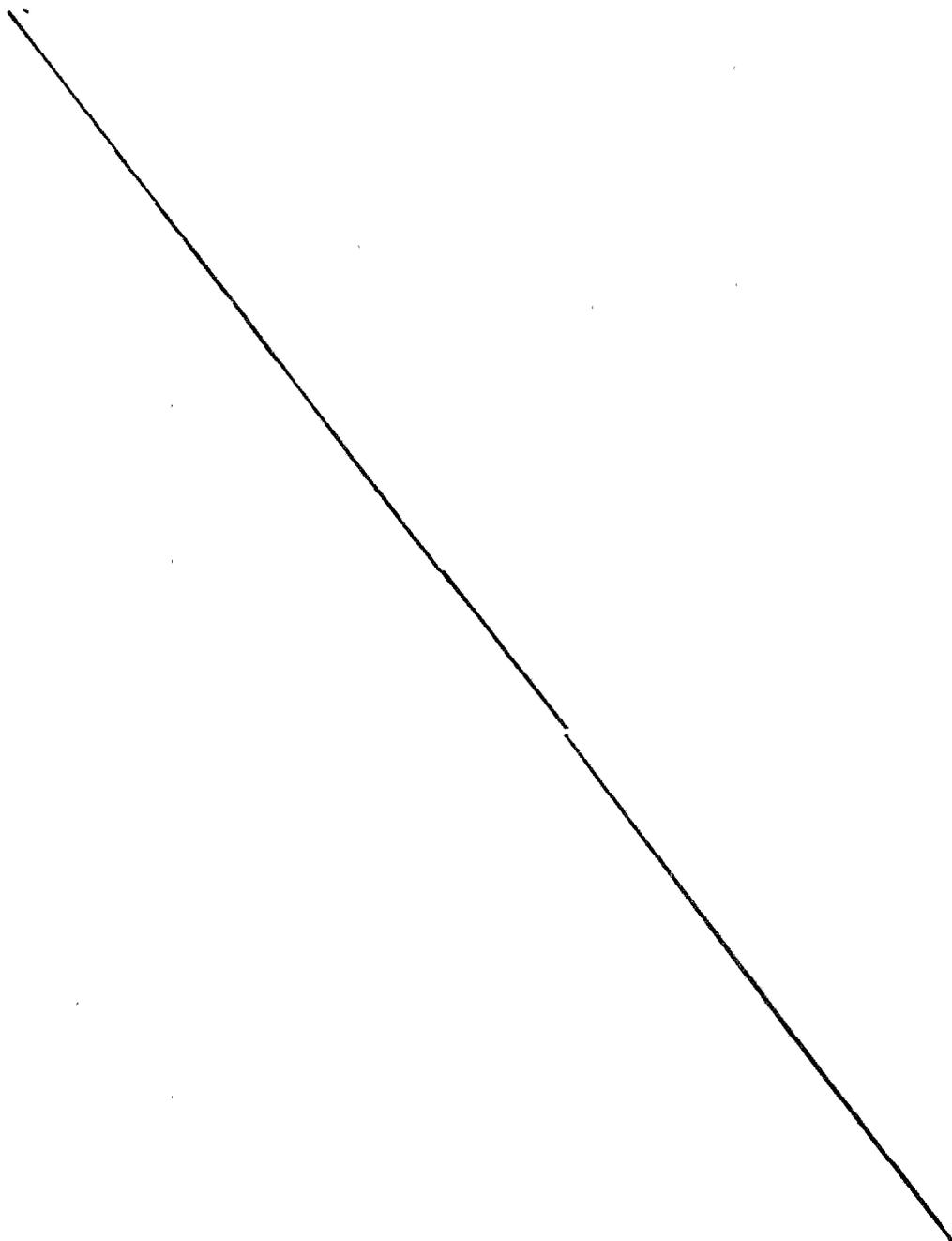
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4.3.1.2.3 *Follow up 13-Week Oral Toxicity Study with Ubiquinol in Female Rats*

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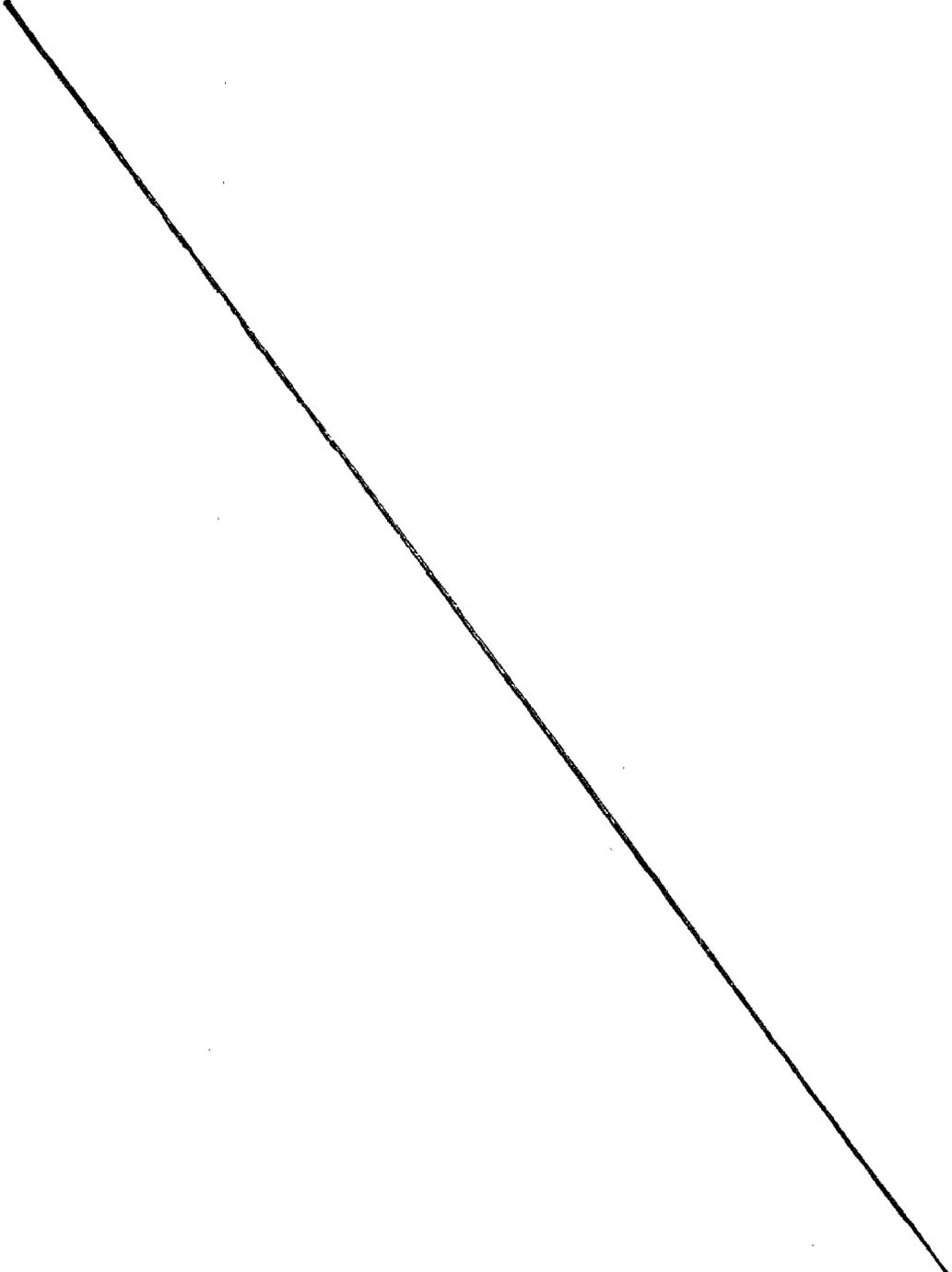
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4.3.1.3 Genotoxicity



4.3.2 Non-clinical and Genotoxicity Studies Conducted with Degraded KANEKA QH™





4.3.3 Clinical Safety

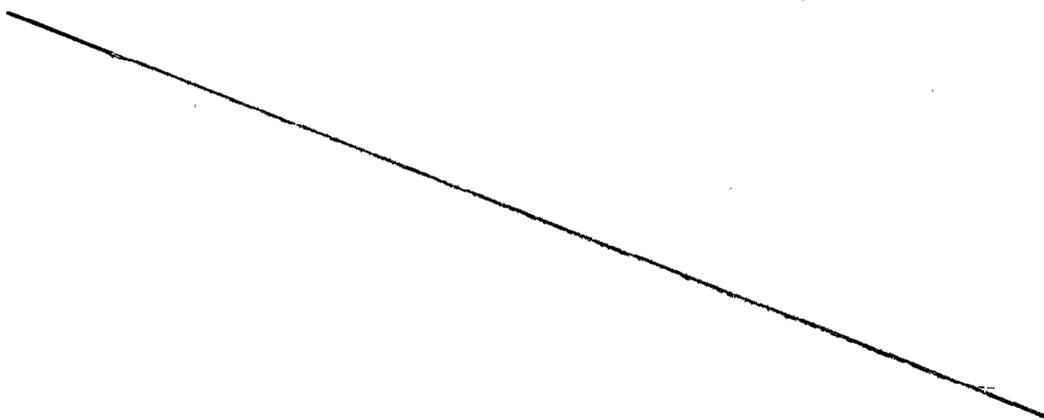
Weber *et al.* (1994) investigated the effect of coenzyme Q₁₀ supplementation on antioxidative status by exposing healthy subjects (n=22) to coenzyme Q₁₀ supplementation before and after induction of oxidative stress by fish oil supplementation, and subsequently monitoring markers of plasma oxidative status [levels of antioxidants (α -tocopherol, ascorbic acid), lipid peroxidation products (thiobarbituric acid reacting substances; TBARS), and the total amount and redox status of coenzyme Q₁₀]. Subjects consumed 90 mg/day of coenzyme Q₁₀ for 6 weeks; during weeks 3 and 4, α -tocopherol (10 mg/day) was added to the treatment regimen, while during weeks 5 and 6, subjects also consumed 3 g/day fish oil (in capsules furnishing 1.1 g/day EPA, 0.8 g/day DHA, and 10 mg/day vitamin E) to increase oxidative stress. Results pertaining to the effect of coenzyme Q₁₀ supplementation on antioxidant plasma levels and TBARS are not discussed herein since they were considered outside the scope of the current document; results pertaining to the effect of coenzyme Q₁₀ supplementation on the total amount and redox status of coenzyme Q₁₀ are summarized below.

The level of total coenzyme Q₁₀ increased significantly after coenzyme Q₁₀ supplementation and remained constant throughout the supplementation period. In addition, the redox status of coenzyme Q₁₀ (reduced coenzyme Q₁₀/total coenzyme Q₁₀) was unchanged by coenzyme Q₁₀ supplementation. The authors suggested that this finding indicated that exogenously supplied coenzyme Q₁₀ is reduced when appearing in plasma. Furthermore, Weber *et al.* (1994) suggested that the constant redox status implies the existence of a reducing capacity for coenzyme Q₁₀ large enough to maintain the majority of plasma coenzyme Q₁₀ in the reduced form, even when the total coenzyme Q₁₀ level increased 2-fold. With respect to the effect of increased oxidative stress, the redox level of coenzyme Q₁₀ was reportedly unaffected by the addition of fish oil to the treatment regimen (Weber *et al.*, 1994).

4.3.4 Supporting Safety Studies Conducted With Coenzyme Q₁₀

Mohr *et al.* (1992) and Weber *et al.* (1994) reported that following dietary supplementation with coenzyme Q₁₀, efficient reduction of coenzyme Q₁₀ to ubiquinol (CoQH₂) occurs either during absorption or rapidly after the appearance of coenzyme Q₁₀ in the blood. Furthermore, ubiquinol-10 has been identified as the most common form of coenzyme Q₁₀ *in vivo* (Frei *et al.*, 1990), representing more than 80% of the total ubiquinol-10 + coenzyme Q₁₀ pool in human plasma, intestine and liver (Edlund, 1988; Okamoto *et al.*, 1989; Åberg *et al.*, 1992). On this basis, studies examining the safety of coenzyme Q₁₀ were considered supportive of ubiquinol safety, and a brief summary of the available safety data for coenzyme Q₁₀ is provided below.

4.3.4.1 Non-Clinical Safety of Coenzyme Q₁₀



4.3.4.2 Clinical Safety of Coenzyme Q₁₀

Coenzyme Q₁₀ deficiency has been reported in patients with various cardiovascular diseases (e.g., congestive heart failure, angina pectoris, coronary artery disease, cardiomyopathy, hypertension, mitral valve prolapse), therefore, much of the available clinical data for coenzyme Q₁₀ was obtained from studies examining its possible therapeutic effect in these conditions. Although in most instances the safety of coenzyme Q₁₀ supplementation was not the focus of clinical trials, the absence of major adverse effects in subjects, as reported by several authors (Shults *et al.*, 2002, The Huntington Study Group, 2001, Baggio *et al.*, 1994; Hofman-Bang *et al.*, 1995; Langsjoen *et al.*, 1990), does offer support for safety. Adverse effects associated with coenzyme Q₁₀ therapy were reportedly rare and included nausea (0.16%), decreased appetite (0.23%), epigastric discomfort (0.39%), vomiting (rare), and diarrhea (0.12%). Increased lactic dehydrogenase and serum glutamic oxalotransferase levels have also been observed in rare instances, at coenzyme Q₁₀ doses above 300 mg/day; however, serious hepatotoxicity has not been reported (Singh *et al.*, 1998; Tran *et al.*, 2001). The use of coenzyme Q₁₀ is not recommended in patients with renal insufficiency, or during pregnancy and lactation (Micromedex, undated; Tran *et al.*, 2001).

4.3.5 Proposed Daily Intake

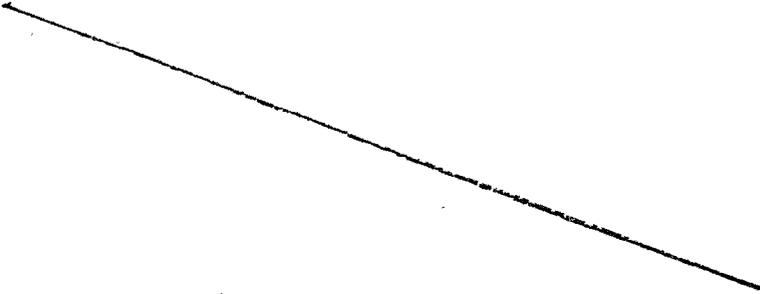
As mentioned in Section 3 of the current document, label directions of the dietary supplement containing KANEKA QH™ will suggest or recommend consumption of up to 6 servings per day, resulting in a maximum daily consumption of up to 300 mg KANEKA QH™ (equivalent to 6 mg/kg/day for a 50 kg body weight person).

Shapiro *et al.* (1995) and Mugford and Kedderis (1998) suggested that exaggerated gender differences in rat drug metabolism might hinder extrapolation to other species, including humans, in which gender-related differences are generally subtler.

Aside from gender-dependent differences noted in female rats, the selection of an appropriate experimental animal model was influenced by reported species-dependent differences. Specifically, as mentioned in Section 4.2.1.1.1, coenzyme Q homologs consist of a redox active quinoid moiety, and a hydrophobic side chain comprised of 6 to 10 isoprenoid units, depending on the species (Ibrahim *et al.*, 2000; Matthews *et al.*, 1998; Lenaz, 2001). In humans, as well as dogs, the predominant form of coenzyme Q is coenzyme Q₁₀ (CoQ₁₀), which consists of 10 isoprenoid units in the side chain. In rats and mice the primary form is coenzyme Q₉, which contains 9 isoprenoid units (Battino *et al.*, 1992).

CONCLUSION

Kaneka's conclusion that the use of KANEKA QH™ in dietary supplements at a level of up to 300 mg KANEKA QH™ (equivalent to 6 mg/kg/day for a 50 kg body weight person), will be reasonably expected to be safe is based on the following:

- (i) The chemical composition of KANEKA QH™ is well characterized, and the manufacturing process yields a product demonstrated to reproducibly meet compositional specifications.
- (ii) 
- (iii) 
- (iv) Numerous studies in the scientific literature have demonstrated the safety of coenzyme Q₁₀. Given that efficient reduction of coenzyme Q₁₀ to ubiquinol (CoQH₂) occurs either during absorption or rapidly after the appearance of coenzyme Q₁₀ in the blood, studies conducted with coenzyme Q₁₀ were considered supportive of the safety of KANEKA QH™.
- (v) Small quantities of KANEKA QH™ will be consumed as dietary supplements.
- (vi) Ubiquinol is a vital nutritive substance naturally present in human tissues and a common component of the human diet.

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