Expertise on a new formulation of Q1O (Contox®3) as an oral spray with high bioavailability and efficacy

Introduction:

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 all cells giving fuel to mitochondria for sufficient functioning (1).

Mode of action of Q10

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 (1). 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 (2) (1). 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. There they are 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 (3). Q10 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. Thus, CoQ10 can be considered the key player in cellular bioenergetics.

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 (4). 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 (5).

Difference in bioavailability of CoQ10 formulations

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. However, 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, resulting in relatively poor bioavailability in human testing. In order to improve the dissolution profile of CoQ10, solubilised formulation of CoQ10 (Q-Gel®) were developed that have shown superior bioavailability as compared with many other product forms. Such enhanced bioavailability claim is based on both laboratory tests (dissolution test and cell culture studies using Caco-2 cells) and human and animal studies (6) (7) (8) (9). On the other hand, 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. (7) (10). In a recent trial with human subjects, the superior bioavailability profile of ubiquinol was demonstrated when it was tested alone (11).

CAS Registry No:	303-98-0

Appearance	Orange crystals (at room temperature)
Empirical formula	C59H90O4
Molecular weight	863.358
Melting point	49° C
Solubility	Insoluble in water
Limited solubility	in oils and fats
Soluble	in nonpolar solvents

Table
Physicochemical properties of Ubiquinone (CoQ10)

CoQ10 has a biphasic absorption following oral dosing with an initial peak in plasma concentration at 5 to 6 hours, then a second peak at 24 hours. The second peak is believed to reflect tissue redistribution (from the liver) back into the circulation. Using lipid formulations and taking CoQ with food both increase absorption. The half-life of CoQ is approximately 30-50 hours, meaning that the time to pharmacological steady state is fairly prolonged (1-2 weeks). Clearances in adults have ranged from 0.0647-1.3062 L/hr. It has been suggested that CoQ may have nonlinear absorption with increasing doses absorbed to a lesser degree (12).

Commonly used liquid preparations of Q10 with high bioavailability – a note of caution

Li-Q10® is a liquid preparation containing solubilised CoQ10 and it has been shown to be superior to the other capsules in laboratory tests and in human bioavailability

studies (7), (10). 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. Another product that is suited for individuals who do not wish to or are unable to swallow tablets or capsules is ChewQ®, a 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 (9).

Product	**Dissolution in water (%)**
Compressed Tablets1	0-3
Hardshell Caps (powder-filled)	0-3
Softgel Caps (oil suspension)	0-3
Chewable wafers	0-5
ChewQ® wafers	75-80
Hydro-Q-Sorb® (powder)	75-100
Q-Gel® (softgel caps)	90-100
Q-Nol® (softgel caps)	90-100
Liquid Q® (Liquisorb®) (aqueous nanodispersion)	100

Table 2

Typical dissolution profiles of various coenzyme Q10 products. Adapted from (9)

As seen in table 2 there is a major drawback in commonly used Q10 formulation capsules, the poor dissolution, resulting in a low level of bioavailability. This is because a capsule, even in an oil suspension within, cannot readily

traverse by the inner intestinal mucous layer of the intestine. Being covered by a thin aqueous film, the mucous layers of the intestine wall are unable to let a potentially water insoluble agent pass through, thus reaching the systemic circulation. Such disadvantage can be circumvented by using a nanodispersion where practically all of Q10, because of their minute seize, are able to pass through the tight junction of intestinal cell walls, thus penetrating the diffusion barrier, and resulting in a nearly 100% absorption as demonstrated in table 2.

However, regular use of Q10-nanodispersion has to be considered with caution. This is because previous in vitro studies with pulmonary cells being exposed to industrial nanoparticles (nanosize particle include anything 300 nanometers or smaller) have demonstrated a cytotoxic effect. Aside from a change in the physicochemical properties of the original molecule, nanoparticles practically are able to penetrate though all lipid barriers resulting in a downregulation of cellular growth with apoptotic changes, a reaction that is independent of concentration (13). One striking finding was that particle solubility strongly influenced toxicity. For instance, low concentrations of soluble zinc oxide particles, for example, triggered a sharp drop in cell metabolism and proliferation. However, at higher concentrations, toxicity actually dropped, likely because zinc oxide particles clump together at the higher concentrations tested. In contrast, insoluble metal oxide particles showed virtually no effect on cell function at any concentration, and uncoated iron oxide particles were particularly toxic regardless of concentration.

Thus, safety of nano Q10-particles, for instance such as, PureSorb Q40™ (Nisshin Pharma) is questionable because new studies revealed that nonotechnology are being used in everything from beer to baby drinks, despite a lack of safety information (14). While the U.S. Food and

Drug Administration (FDA) currently does not specifically require nanoparticles to be proved safe but does require manufacturers to provide tests showing that the food goods employing them—be it beer, baby or vitamin products—are not harmful. To date, there are few published industry, government or scientific studies on the health and environmental impacts of nanoparticles although they are known to be more chemically reactive and more bioactive.

Also, co-administration of Q10 with a known solvent such as polysobate 20 (Poloxamer®) or other solvents being used to increase solubilisation does not solve the problem of reduced bioavailability. This is because the additional agents in cultured human epidermal cells and animal studies have shown to result in toxicity to mitochondria and a cellular destruction which is due to a disintegration of cellular membranes, ensuing apoptosis or preprogrammed cell death (15) (16) (17)

Contox®3 Spray – a unique Q10 preparation

Contox® in the other hand is a formulation, which consists of three natural ingredients (Vit. E, evening primrose oil and **u**biquinone Q10) using no artificial additive or solvent in order to increase solubilisation. Water solubility of Contox® is achieved by a unique formulation developed by the Sedamed Company in Switzerland. Contrary to in-vitro testing (9), the putative high bioavailability of Contox®3 was tested in humans. Data being derived in patients with myocardial insufficiency demonstrate a low level of Q10 before use of oral mucosal administration. Following mucosal administration of the Q10 preparation via a spray the median plasma concentration of Q10 which was < 1.4 mg/L in the control period resulted in an increase in plasma levels reaching a mean value > 1,7 mg/l after 1 hour (fig. 1).

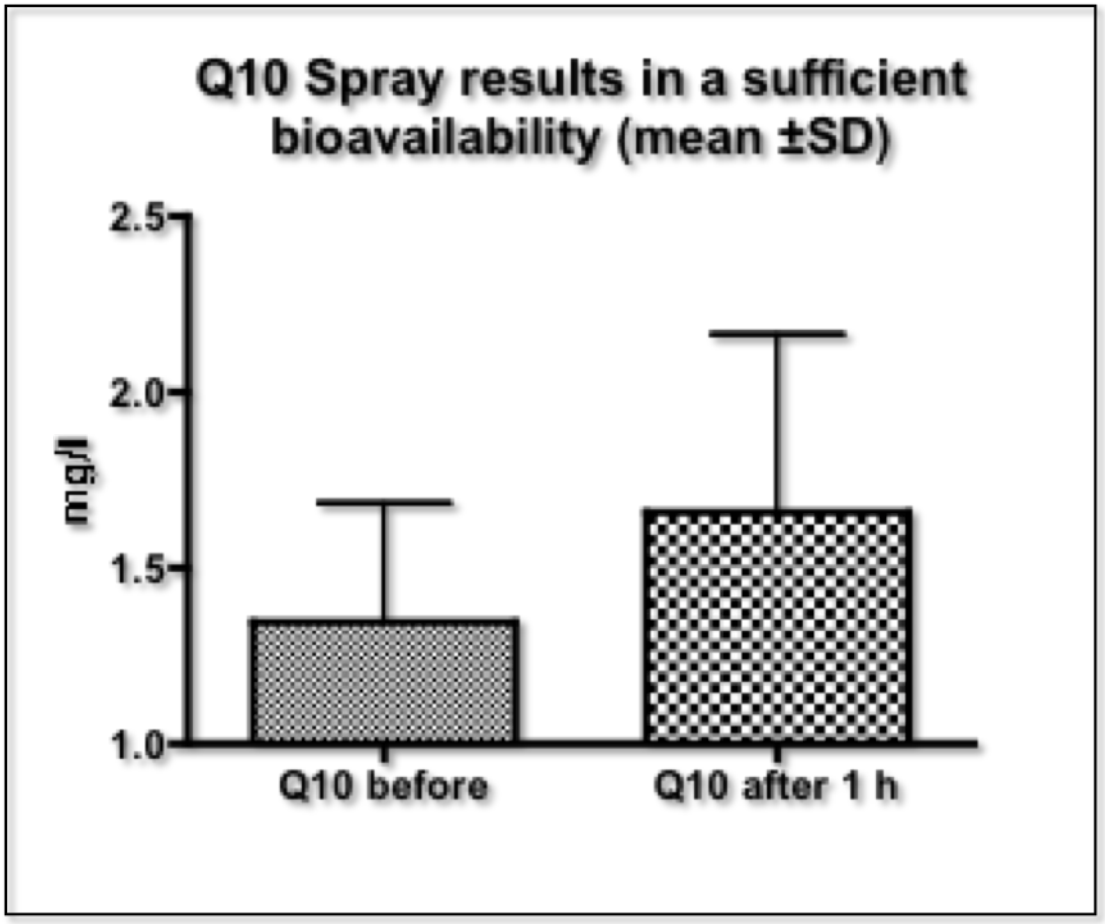

Fig. 1
Q10 plasma concentrations (mg/L) in patients with myocardial insufficiency (n=10; mean ±SD) before and after absorption of Contox®3 through mucous membranes within the oral cavity

Such data demonstrate rapid absorption of Q10 through the oral cavity resulting in high bioavailability within one hour after application with a 30% increase above control values.

Activation of neuronal activity within the CNS
Aside from demonstrating a sufficient bioavailability and absorption though mucous membranes of the oral cavity by use of a spray, the product incorporates another important advantage. This is by-passing of the liver, which normally would metabolize part of the Q10 being

reabsorbed from the intestine. In another study, not only rapid take-up but also an increase in efficacy following the application of Contox®3 spray was demonstrated in volunteers. This is nicely verified in changes of power spectra within the electroencephalogram (EEG).
Following a run-in period of 30 minutes EEG, power spectra were taken from ten individuals seated in a relaxed position with their eyes closed. EEG potentials were picked up from Ag/AgCl stick-on electrodes attached to the scalp at position Fp1-A1 with grounding at FpZ (18). EEG weaves were fed into a microprocessor controlled EEG recording machine (Lifecscan®, Diatek, San Diego/USA), which performed Fast Fourier Transformation over a time epoch of 60 sec yielding power spectra in the different power bands, delta (05-3 Hz), theta (3-7 Hz), alpha (7-13 Hz) and beta (13-30 Hz). As a results of Contox®3 Q10 and compared to the control situation (fig. 2), there is a highly significant increase of power in the fast frequency domain beta (13-30 Hz) after 1 hour (fig. 3, 4).

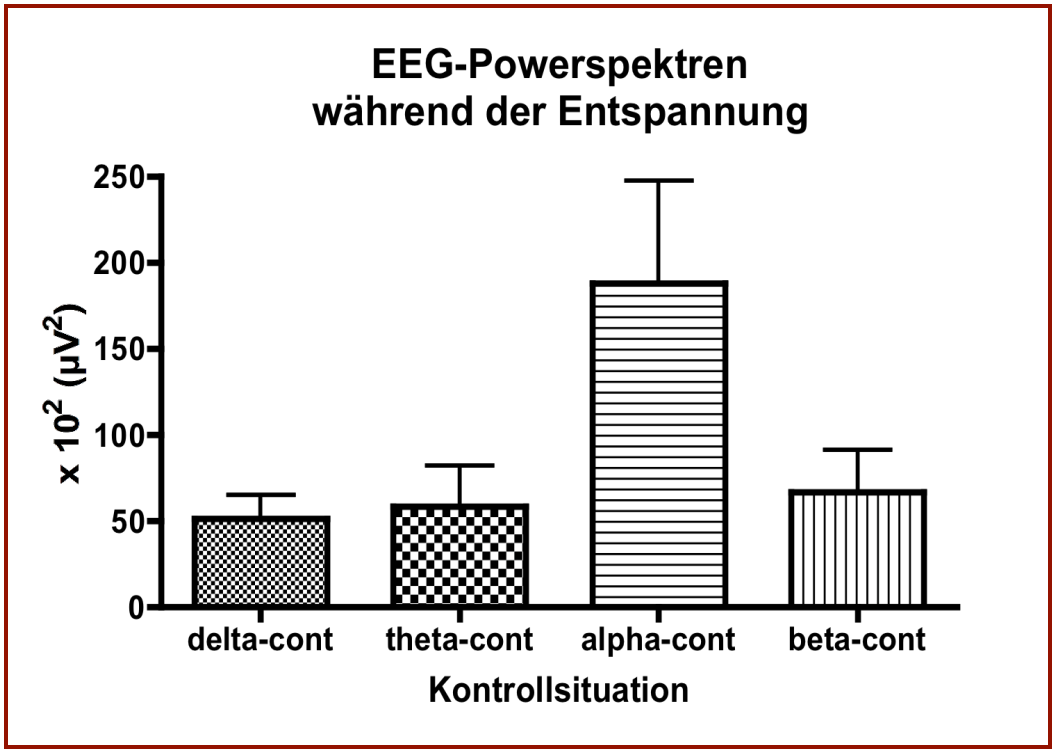

Fig. 2
Grand mean of EEG power spectra of 10 volunteers seated in a relaxed and noise-free environment. Note the high activity within the alpha-band (7-13 H7) reflecting a sedative state

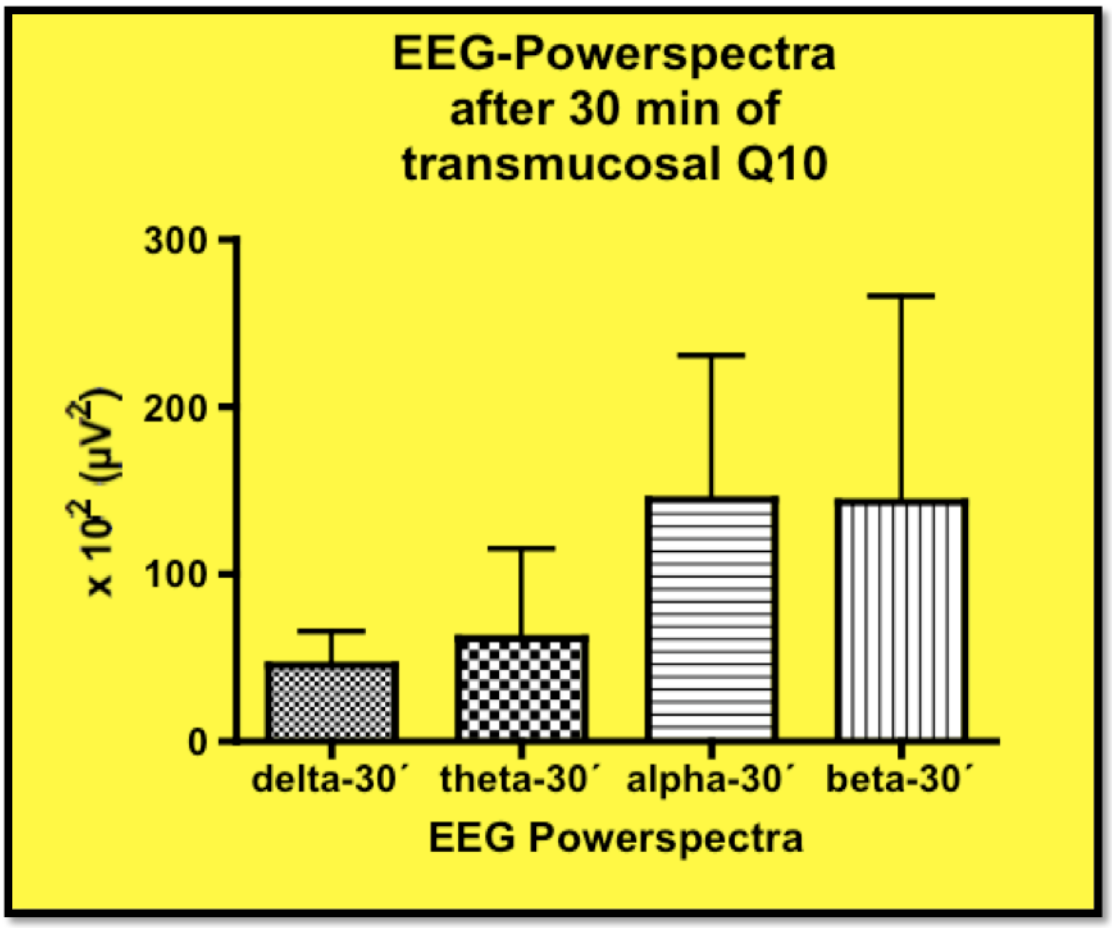

Fig.3
Gradual change of the grand mean of power within different EEG spectra to a higher frequency range as a result of Contox®3 intake, depicting by a shift to the right fast spectrum

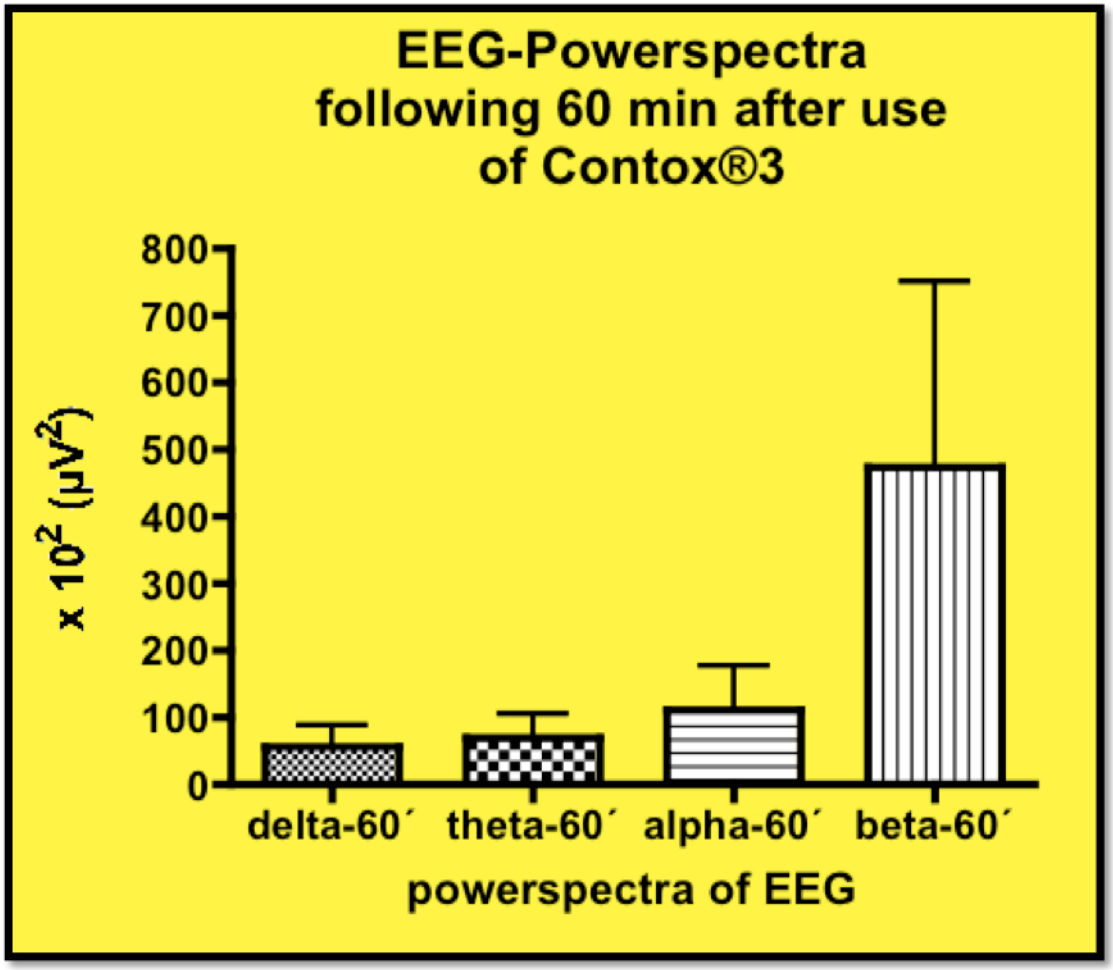

Fig.4
Further increase in EEG power spectra to the right demonstrating a highly significant increase in the fast beta- domain ($p < 0.001$) when compared to the control situation, following 1 hour after intake

The EEG data clearly demonstrate that following use of Contox®3 beta-activity within the EEG is increased by **616 % (!)** when compared to the control situation. Such data indicate a highly significant increase in the level of vigilance and alertness when using the transmucosal Q10 preparation.

Discussion and conclusion

The present data following use of Q10 Spray (Contox®3) suggest that within the allotted time, sufficient aliquots of Q10 traverse through a natural barricade, the BBB (blood brain barrier) resulting in an accumulation of satisfactory amounts of Q10 within the central nervous system, which is followed by an increase in energy formation. This is reflected in a desynchronization of EEG waves and high activity within the beta-band of the EEG, representing an increase in attention and vigilance.

These results are in contrast to studies with other preparations of Q10 where in spite a change in CoQ plasma concentration, the net effect on functioning of cells had not been indicated. With other Q10 preparations it appears that prolonged dosing will be needed. For instance rats given doses of 200-500 mg/kg/day, 1-2 months of supplementation was needed to see a significant increase in brain CoQ concentrations (i.e., 10-30%). In addition, plasma concentrations may not adequately correlated with brain or other cell function.

By using Contox®3 in human volunteers and by demonstrating efficacy in the EEG it can be concluded:

a. Sufficient amounts of Q10 reach the central nervous system resulting in an subsequent activation of neuronal cells
b. The mode of action of Q10 at neuronal cells results in an increase of power within the fast beta domain (13-39 Hz) of the EEG.
c. The increase in fast activity of the EEG corresponds with an increase of vigilance reaching max levels within 60 minutes. This is in marked contrast to the usual 4-5 hours with all other oral formulations.
d. Activation of central nervous activity may be of advantage in a situation of tiredness or in attention deficit when a burst of awareness is of advantage or even mandatory.

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