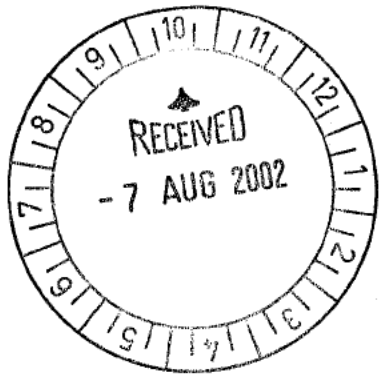
# Bioresco

*Bioresearch Management and Consulting Ltd.*

DHL




[redacted]
Product Standards Program
ANZFA
PO Box 7186
Canberra MC ACT 2610

Basel, November 23, 2001

**Proposal P236**

On behalf Lonza Ltd., Basel, Switzerland, we wish to make the following submission in reference to Proposal P236 "Development of Joint Food Regulation for Sports Foods". Our submission concerns the use of L-carnitine L-tartrate in Formulated Supplementary Sports Foods (Standard 2.9.4). According to Division 1, Section 2(c) of this Standard, formulated supplementary sports foods may contain L-carnitine at levels of not more than 100 mg per one-day quantity.

The first purpose of this submission is to ensure that the term "L-carnitine" as used in the Standard is understood to be a generic term which encompasses the different forms in which L-carnitine is commercially available [i.e., L-carnitine (free base), L-carnitine chloride, L-carnitine L-tartrate, L-carnitine magnesium citrate].

Another purpose of this submission is to request an increase of the acceptable maximum daily intake of L-carnitine from 100 mg/day to at least 1000 mg/d (calculated as the free base).

I trust that the information provided is satisfactory for your evaluation. However, should you have any questions or require further information, please let us know. We look forward to your favourable consideration and response.

With best regards

Bioresco Ltd.

[redacted]

[redacted]

Bioresco

Bioresearch Management and Consulting Ltd.

# L-Carnitine

Submission on behalf of Lonza Ltd., Basel, Switzerland in Reference to Proposal P236 "Development of Joint Food Regulation for Sports Foods" concerning the definition and maximum level of use of L-carnitine in Formulated Supplementary Sports Foods (Standard 2.9.4)

[redacted]

Date: November 15, 2001

## 1. Information on the Applicant

Petitioner: Lonza Ltd.
Münchensteinerstrasse 38
CH-4002 Basel

*represented by:*

Bioresco Ltd.
Bundesstrasse 29
CH-4054 Basel

Manufacturer: Lonza Ltd.
Münchensteinerstrasse 38
CH-4002 Basel

Responsible persons:

for Lonza Ltd.:

[redacted]

for Bioresco Ltd.

[redacted]

## 2. Information on the Application

L-Carnitine is a natural, vitamin-like nutrient which plays an important role in the metabolism of human and animal tissues. It is an essential factor in the transport system that shuttles fatty acids into the mitochondria for beta-oxidation.

### 2.1 Commercial forms of L-carnitine

L-Carnitine is sold in four different forms produced by different suppliers, namely:

- L-Carnitine (free base) is the basic form of L-carnitine. Specifications of this product are laid down in USP XXIII and the European Pharmacopeia (Suppl. 1999).

  In this form, L-carnitine is a white, extremely hygroscopic, crystalline powder. Because of its high hygroscopicity, this form is not recommended for use in solid (dry) food formulations.

- L-Carnitine chloride (syn.: L-carnitine hydrochloride) is the salt of L-carnitine with hydrochloric acid. Stoichiometrically the product consists of about 82% L-carnitine and 18% hydrochloric acid.

- L-Carnitine L-tartrate is the salt of L-carnitine with L-tartaric acid. Stoichiometrically the product consists of 68% L-carnitine and 32% L-tartaric acid. This salt is a crystalline, free flowing and not hygroscopic powder with ideal properties for use in capsules, tablets, bars and other solid foods. The product is odourless, has a pleasant taste and a high long-term stability.

- L-Carnitine magnesium citrate is the mixed salt of L-carnitine with magnesium citrate. Stoichiometrically it consists of 43% L-carnitine, 51% citric acid, and 6% magnesium ions. It forms a white granulated powder which is recommended for use in effervescent tablets and powder drink mixtures.

Official specifications do not exist for the different salts of L-carnitine. However, the products comply to the specifications of L-carnitine (for the L-carnitine portion of the product) and the specifications of the adjoining acids, i.e., hydrochloric, tartaric or citric acid (for the acid portion of the product).

## 2.2 Level of use

L-Carnitine is a vital factor in the production of acetyl-CoA from fatty acids in human and animal tissues. By mediating the transport of fatty acids across the inner mitochondrial membrane, it affects the rate at which fatty acids are oxidized (Müller et al., 2001). Another function of carnitine is to regulate the intramitochondrial ratio of acyl-CoA to free CoA. This function is important because it allows to remove excessive (and potentially toxic) short- and medium-chain fatty acids from the mitochondrion, and because it maintains sufficient free CoA within the mitochondrion to support energy metabolism.

L-Carnitine in the human body is derived from both dietary sources and endogenous biosynthesis. Under normal conditions, there is no absolute dietary requirement for L-carnitine. However, where a metabolic abnormality exists which either inhibits the endogenous biosynthesis of L-carnitine, interferes with its use, or increases its catabolism or excretion, symptoms of deficiency may develop. Therefore, L-Carnitine is regarded to be a "conditionally essential nutrient".

In metabolically healthy people, an insufficient dietary supply of L-carnitine may lead to blood L-carnitine levels below the normal range (subclinical secondary L-carnitine deficiency). It has been observed, for example, that triathletes who consumed a vegetarian diet, had L-carnitine levels of about 29 mmol/l which is well below the normal range of 40-50 mmol/l (Föhrenbach et al., 1993). Under these conditions, an increased dietary supply of L-carnitine is indicated.

The average non-vegetarian American diet provides about 100-300 mg L-carnitine daily (Feller & Rudman, 1988). However, the consumption of an additional 500 g meat (spread over the different meals of a day) may increase the total daily L-carnitine intake to 750-1000 mg (Harmeyer, 2000).

Considering that about 30-40% of ingested L-carnitine is absorbed (while the rest is excreted with the feces), and further considering that the body of an adult person contains between 15-20 g L-carnitine, a daily intake of 1 g results in a supply of absorbed L-carnitine that corresponds to not more than 2.3% of the normal body pool (Harmeyer, 2000).

## 3. Safety

The safety of L-carnitine has been assessed by a panel of independent experts qualified by scientific training and experience to evaluate the safety of substances added to food (Lonza's GRAS panel) (Blumenthal et al., 1993) (Annex 1). Based on a review of acute, subacute and chronic toxicity studies as well as reproductive and developmental studies of L-carnitine chloride, the panel concluded that the proposed uses which would result in an estimated total L-carnitine intake of 20 mg/kg bw/day (1200 mg/person/d) would not present a foreseeable risk to human health (The toxicological studies are presented in Annex 2 and Annex 3). The panel considered that intakes above this level might result in gastrointestinal disturbances. However, the panel did not specify the study which led it to believe that gastrointestinal disturbances might occur at higher intakes.

The physiological effects of L-carnitine have been examined in a number of human studies. The reports of these studies indicate that intakes of up to 15 g/d were usually tolerated without intestinal side-effects. Only in a few isolated cases, mild laxative effects were observed (Borum & Fisher, 1983; Sufeng et al., 1997; Lurz & Fischer, 1998; Brass, 2000).

In an addendum to the GRAS panel's report on L-carnitine, one member of the panel stated that the panel's conclusion would be fully applicable also to L-carnitine L-tartrate because this salt dissociates readily on dissolution yielding free L-carnitine and tartaric acid (Blumenthal et al., 1993).

There also is direct evidence for the safety of L-carnitine L-tartrate. In an acute oral toxicity test, male and female Wistar rats received a single oral dose of L-carnitine L-tartrate (5 g/kg bw). No signs of toxicity were observed upon dosing and during a 14-day post-treatment period. No gross pathological changes were observed at necropsy (Kaufmann, 1991).

In Ames tests with S. typhimurium (strains TA 1535, TA 1537, TA 1538, TA 98, TA 100) with and without metabolic activation with S9 mix, mutagenic activity was not observed in any of the tester strains (Hillmann, 1991).

In a human tolerance study, the ingestion of L-carnitine L-tartrate at a dose of 3 g/day for 3 weeks was not associated with changes of standard hematological and clinico-chemical parameters. Markers of hepatic and renal function were not affected by the treatment. Gastrointestinal side-effects were not observed (Rubin et al., 2001).

## 4. Bio-equivalence of L-carnitine base and its different salts (chloride, tartrate)

Two lines of evidence demonstrate the bio-equivalence of the different commercial forms of L-carnitine (free base, chloride, tartrate).

First, it has been shown by measurement of the optical rotation and conductivity as well as by ion chromatography that L-carnitine L-tartrate fully dissociates in its components, i.e., L-carnitine (base) and L-tartaric acid, upon dissolution (Schmidbaur et al., 1998; Schmidbaur, 2001).

Second, it has been shown that the intake of L-carnitine (2 g bolus dose) produces a similar increase of serum L-carnitine regardless of whether it is administered in the form of the free base or as the L-tartrate salt (Sewell and Böhles, 2000).

## 5. Purpose and level of use of L-carnitine in formulated supplementary sports foods

The fact that L-carnitine fulfils an essential function in the metabolism of fatty acids coupled with the observation that about 98% of the body's L-carnitine pool is located in muscle tissue, has stimulated research on the role of L-carnitine in exercise metabolism and its potential effects on athletic performance. The result of this research has been the subject of several reviews (Cerretelli & Marconi, 1990; Wagenmakers, 1991; Brass, 2000).

Although in some studies L-carnitine (typically given at doses of 2-5 g/day) has been shown during exercise to reduce lactate accumulation (Siliprandi et al., 1990; Vecchiet et al., 1990) reduce the heart rate (Soop et al., 1988; Natali et al., 1993), increase maximal oxygen consumption (Dragan et al., 1989; Marconi et al., 1985; Vecchiet et al., 1990), and improve force production (Dubelaar et al., 1991 a, b), these favourable effects could not always be reproduced. Therefore, definitive conclusions about the potential benefits of high doses of L-carnitine on athletic performance cannot yet be drawn (Brass, 2000).

However, there is an emerging picture that L-carnitine might play a more important role in the prevention of exercise-induced tissue damage and the recovery of muscle tissue after exercise rather than the enhancement of performance (Kraemer & Volek, 2000, 2001). It has been demonstrated, for example, that L-carnitine (3 g/d) led to a significant reduction in muscle pain, weakness and cellular damage following exertion (Giamberadino et al., 1996; Volek et al., 2002).

It is conceivable that extra-muscular effects on endothelial cells, vasodilation and blood flow are implicated in the protective effect of L-carnitine (Hülsmann & Dubelaar, 1988; Dubelaar et al., 1991a).

Pursuing a conservative approach and considering that intensive exercise may increase the demand for L-carnitine to an extent which cannot be completely compensated by an increased endogenous biosynthesis, it would be prudent to permit the addition of L-carnitine to supplementary sports food in amounts of up to 1000 mg per one-day quantity. This amount corresponds to the intake of L-carnitine with a diet in which meat represents the main source of protein (Harmeyer, 2000).

The safety and tolerance of L-carnitine would allow the addition of higher doses of L-carnitine (2-3 g/day, or more). However, considering the maximum use levels of many nutrients listed in the Standard for Supplementary Sports Foods, it appears that these levels are based more on the intakes that would be achieved with an "ideal" diet for sports people and on the perceived need rather than on the upper safe limit of use (Vitamin C and E with maximum permitted amounts of 80 and 20 mg, respectively, may serve as examples). Applying this rationale, a maximum amount of 1 g/d would be indicated for L-carnitine.

On the other hand, it is interesting to note that for creatin a maximum amount of 3 g/d is authorized according to the new Standard for Supplementary Sports Foods. Presumably, this value was derived from studies which have shown that the ingestion of 3 g/d creatine over a period of 1 month increases the total creatin content in human muscle by 15-20% (Hultman et al., 1996) and that creatine supplementation may improve performance in certain types of (anaerobic) exercise (Terjung et al., 2000).

Corresponding results exist for L-carnitine. The administration of 2 g L-carnitine per day for a period of 28 days led to increased levels of free and total L-carnitine in muscle tissue of sprinters (Huertas et al., 1992). Increases of muscular L-carnitine subsequent to long-term dietary supplementation of L-carnitine (2 g/d for 6 months) also have been observed by others (Arenas et al., 1991). As in the case of creatine, performance enhancing effects also were observed with L-carnitine under certain conditions. However, as indicated above, dietary supplementation of L-carnitine may be more important for protecting muscle tissue from exercise-induced damage than for enhancing performance. The intake of 3 g/d L-carnitine for 3 weeks prior to exhaustive exercise proved to be effective in this regard (Giamberadino et al., 1996). Applying this rationale and following the example of creatine, the maximum permitted amount of L-carnitine in supplementary sports foods would have to be set at 3 g/d.

## 6. References


Arenas J., Ricoy J.R., Encinas A.R., Pola P., D'Iddio S., Zeviani M., Didonato S. and Corsi M. (1991). Carnitine in muscle, serum, and urine of nonprofessional athletes: effects of physical exercise, training, and L-carnitine administration. Muscle & Nerve 14: 598-604.

Blumenthal H., Borzelleca J.F. and Filer L.J. (1993). Evaluation of L-carnitine for GRAS status. Report for Lonza Inc. USA.

Borum P.R. and Fisher K.D. (1983). Health effects of dietary carnitine. Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Md.

Brass E.P. (2000). Supplemental carnitine and exercise. Am. J. Clin. Nutr. 72 (Suppl.): S618-S623.

Cerretelli P. and Marconi C. (1990). L-Carnitine supplementation in humans: the effects on physical performance. Int. J. Sports Med. 11 (1): 1-14.

Dragan G.I., Vasiliu A., Georgescu E. and Eremia N. (1989). Studies concerning chronic and acute effects of L-carnitina in elite athletes. Rev. Roum. Morphol. Embryol. Physiol., Physiologie 26 (2): 111-129.

Dubelaar M.-L., Lucas C.M.H.B. and Hülsmann W.C. (1991a). Acute effect of L-carnitine on skeletal muscle force tests in dogs. Am. J. Physiol. 260: E189-E193.

Dubelaar M.-L., Lucas C.M.H.B. and Hülsmann W.C. (1991b). The effects of L-carnitine on force development of the latissimus dorsi muscle in dogs. J. Card. Surg. 6: 270-275.

Feller A.G. and Rudman D. (1988). Role of carnitine in human nutrition. J. Nutr. 118 (5): 541-547.

Föhrenbach R., März W., Lohrer H., Siekmeier R., Evangeliou A. and Böhles H.-J. (1993). Der Einfluss von L-Carnitin auf den Lipidstoffwechsel von Hochleistungssportlern. Dtsch. Z. Sportmed. 44 (8): 349-356.

Giamberardino M.A., Dragani L., Valente R., Di Lisa F., Saggini R. and Vecchiet L. (1996). Effects of prolonged L-carnitine administration on delayed muscle pain and CK release after eccentric effort. Int. J. Sports Med. 17 (5): 320-324.

Harmeyer J. (2000). Assessment of alimentary carnitine uptake. Expert Opinion for Lonza AG.

Hillmann E. (1991). Salmonella / Microsome test (Ames test) of P5497. Unpublished report of IBR Forschungs GmbH for Lonza AG.

Huertas R., Campos Y., Diaz E., Esteban J., Vechietti L., Montanari G., D'Iddio S., Corsi M. and Arenas J. (1992). Respiratory chain enzymes in muscle of endurance athletes: effect of L-carnitine. Biochem. Biophys. Res. Commun. 188 (1): 102-107.

Hülsmann W.C. and Dubelaar M.L. (1988). Aspects of fatty acid metabolism in vascular endothelial cells. Biochimie 70: 681-686.

Hultman E., Söderlund K., Timmons J.A., Cederblad G. and Greenhaff P.L. (1996). Muscle creatine loading in men. J. Appl. Physiol. 81 (1): 232-237.

Kaufmann K. (1991). Acute oral toxicity test of P5497. Unpublished report of IBR Forschungs GmbH for Lonza AG.

Kraemer W.J. and Volek J.S. (2000). L-Carnitine supplementation for the athlete. A new perspective. Ann. Nutr. Metabol. 44: 88-89.

Kraemer W.J. and Volek J.S. (2001). L-Carnitin-Supplementierung beim Sportler. Schweiz. Zschr. GanzheitsMedizin 13 (5): 256-258.

Lurz R. and Fischer R. (1998). Carnitin zur Unterstützung der Gewichtsabnahme bei Adipositas. Ärztezeitschr. Naturheilverf. 39 (1): 12-15.

Marconi C., Sassi G., Carpinelli A. and Cerretelli P. (1985). Effects of L-carnitine loading on the aerobic and anaerobic performance of endurance athletes. Eur. J. Appl. Physiol. 54: 131-135.

Müller D.M., Richter T. and Seim H. (2001). Effects of oral L-carnitine supplementation on in vivo oxidation of 1-[$^{13}$C] palmitic acid in healthy adults. Abstract represented in "Carnitine Conference" Experimental Biology 2001.

Natali A., Santoro D., Brandi L.S., Faraggiana D., Ciociaro D., Pecori N., Buzzigoli G., and Ferrannini E. (1993). Effects of acute hypercarnitinemia during increased fatty substrate oxidation in man. Metabolism 42 (5): 594-600.

Rubin M.R., Volek J.S., Gómez A.L., Ratamess N.A., French D.N., Sharman M.J. and Kraemer W.J. (2001). Safety measures of L-carnitine L-tartrate supplementation in healthy men. J. Strength Cond. Res. 15 (4): 486-490.

Schmidbaur H. (2001). Expert Opinion for Lonza AG.

Schmidbaur H., Schier A. and Bayler A. (1998). The solution and solid state structure of L-carnitine L-tartrate. Z. Naturforsch. 53 b: 788-791.

Sewell A.C. and Böhles H.-J. (2000). The uptake of oral carnitine tartrate is equivalent to that of carnitine base. Unpublished report for Lonza GmbH.

Siliprandi N., Di Lisa F., Pieralisi G., Ripari P., Maccari F., Menabo R., Giamberardino M.A. and Vecchiet L. (1990). Metabolic changes induced by maximal exercisc in human subjects following L-carnitine administration. Biochim. Biophys. Acta 1034: 17-21.

Soop M., Björkman O., Cedarblad G., Hagenfeldt L. and Wahren J. (1988). Influence of carnitine supplementation on muscle substrate and carnitine metabolism during exercise. J. Appl. Physiol. 64: 2394-2399.

Sufeng Z., Zhichian H., Jianping L. and Hui S. (1997). L-Carnitine's effect on comprehensive weight loss program in obese adolescents. Acta Nutr. Sin. 19: 151-?.

Terjung R.L., Clarkson P., Eichner E.R., Greenhaff P., Hespel P.J., Israel R.G., Kraemer W., Meyer R.A., Spriet L.L., Tarnopolsky M., Wagenmakers A. and Williams M. (2000). Round Table: The physiological and health effects of oral creatine supplementation. Med. Sci. Sports Ex. 32: 706-717.

Vecchiet L., Di Lisa F., Pieralisi G., Ripari P., Menabo R., Giamberardino M.A. and Siliprandi N. (1990). Influence of L-carnitine administration on maximal physical exercise. Eur. J. Appl. Physiol. 61: 486-490.

Volek J.S., Kraemer W.J., Rubin M.R., Gómez A.L., Ratamess N.A. and Gaynor P. (2002). L-Carnitine L-tartrate supplementation favourably affects markers of recovery from exercise stress. Am. J. Physiol. Endocrinol. Metab. 282: in print.

Wagenmakers A.J.M. (1991). L-Carnitine supplementation and performance in man. In: "Advances in Nutrition and Top Sport" (F. Brouns ed.), Med. Sport Sci. 32: 110-127.