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Risk assessment of "other substances" – L-Carnitine and L-Carnitine-L-tartrate

Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

Report from the Norwegian Scientific Committee for Food Safety (VKM) 2015:24
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Risk assessment of "other substances" – L-Carnitine and L-Carnitine-L-tartrate

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Assessed and approved

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(Panel members in alphabetical order after chair of the panel)

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Competence of VKM experts

Persons working for VKM, either as appointed members of the Committee or as external experts, do this by virtue of their scientific expertise, not as representatives for their employers or third party interests. The Civil Services Act instructions on legal competence apply for all work prepared by VKM.

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Summary

The Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) has, at the request of the Norwegian Food Safety Authority (Mattilsynet; NFSA), assessed the risk of "other substances" in food supplements and energy drinks sold in Norway. VKM has assessed the risk of doses given by NFSA. These risk assessments will provide NFSA with the scientific basis while regulating the addition of other substances to food supplements and other foods.

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional and/or physiological effect*. It is added mainly to food supplements, but also to energy drinks and other foods. In this series of risk assessments of "other substances", VKM has not evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of L-carnitine and L-carnitine-L-tartrate, and it is based on previous risk assessments and/or articles retrieved from a literature search.

According to information from NFSA, L-carnitine and L-carnitine-L-tartrate are ingredients in food supplements sold in Norway. NFSA has requested a risk assessment of 1500 mg/day (21.4 mg/kg bw per day) of L-carnitine and 2250 mg/day (32.1 mg/kg bw per day) of L-carnitine-L-tartrate in food supplements.

Other sources of L-carnitine and L-carnitine-L-tartrate, such as e.g. cosmetics, have not been included in the present risk assessment.

L-carnitine is a quaternary ammonium salt naturally occurring in all animals and bacteria. It is essential in the fatty acid metabolism. L-carnitine-L-tartrate is the salt of the L-carnitine base with tartaric acid, and is synthesised commercially.

L-carnitine occurs naturally in foods, and the richest source is red meat. L-carnitine-L-tartrate does not occur naturally in foods. L-carnitine-L-tartrate dissociates into L-carnitine and L-tartaric acid in the gastrointestinal tract. L-carnitine is endogenously synthesised from lysine and methionine.

L-carnitine is widely distributed in all mammalian tissues and is abundant in muscular tissue. After ingestion, L-carnitine is absorbed in the small intestine, and the bioavailability declines with increasing dose. L-carnitine is excreted mainly via the kidneys with a highly efficient tubular reabsorption; only 2% of the ingested L-carnitine is excreted in the faeces. The amount of L-carnitine absorbed into the systemic circulation is similar whether L-carnitine-L-tartrate or L-carnitine is administered.

Neonates, infants and young children can be exposed to L-carnitine and L-carnitine-L-tartrate through foods for particular nutritional uses (including infant formulae and various baby foods). L-carnitine and L-carnitine-L-tartrate are used as supplements in animal food, and

they are listed as ingredients in various cosmetic products. L-tartaric acid occurs naturally in fruits and wine, and L-tartaric acid and its salts are approved as food additives (E 334).

Adverse effects of L-carnitine (-L-tartrate) are occasionally observed in vulnerable groups such as in patients with kidney disease and persons with high plasma values of trimethylamine (TMA) and trimethylamine-N-oxide (TMAO). High plasma L-carnitine levels in subjects with concurrently high TMAO levels have been associated with cardiovascular disease and adverse cardiac events in patients undergoing cardiac evaluation. Adverse effects are suspected in patients with inborn errors of metabolism. Further, interactions with certain types of drugs have been reported.

One study of L-carnitine on children (6-13 year old boys diagnosed with attention deficit hyperactivity disorder (ADHD), but otherwise healthy) was identified, which did not indicate that children were more sensitive to L-carnitine than adults. No studies were found on adverse effects of L-carnitine-L-tartrate or tartaric acid specifically in children. No studies were found on adverse effects of L-carnitine, L-carnitine-L-tartrate or tartaric acid specifically in adolescents. Based on the included literature there was no evidence indicating that age affects sensitivity towards L-carnitine, L-carnitine-L-tartrate or tartaric acid. Therefore, in this risk characterisation the same tolerance level as for adults was assumed for children and adolescents (adjusted for body weight).

EFSA established a human tolerance level of L-carnitine-L-tartrate up to 3 g/day (43 mg/kg bw per day), equivalent to 2 g/day (29 mg/kg bw per day) L-carnitine in healthy adults. A safety factor for interindividual variation was not included in the established value. Further, this value was based on few studies of which all but one was unavailable to VKM. Intake of 3 g of L-carnitine-L-tartrate would yield 1 g of tartaric acid (14 mg/kg bw per day) (values in parentheses apply to a 70 kg adult). An acceptable daily intake (ADI) based on animal studies is set for tartaric acid of 0-30 mg/kg bw per day. These values (29 mg/kg bw per day L-carnitine, 43 mg/kg bw per day L-carnitine-L-tartrate and 30 mg/kg bw per day tartaric acid) were compared with the estimated exposure in the risk characterisation.

Based on the daily intake of 1500 mg L-carnitine (equivalent to 2250 mg L-carnitine-L-tartrate) and the default body weights determined by EFSA, the estimated exposure is 34.6, 24.5 and 21.4 mg/kg bw per day for the age groups children (10 to <14 years), adolescents (14 to <18 years) and adults (≥ 18 years), respectively.

VKM concludes that a dose of 1500 mg of L-carnitine per day, which is equivalent to a dose of 2250 mg of L-carnitine-L-tartrate per day, is unlikely to cause adverse health effects in adolescents (14 to <18 years) and adults (≥ 18 years), whereas intake at this level in children (10 to <14 years) may represent a risk of adverse health effects. The tartaric acid exposure from this dose of L-carnitine-L-tartrate is unlikely to cause adverse health effects.

Short summary

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority (NFSA), assessed the risk of 1500 mg/day of L-carnitine and 2250 mg/day of L-carnitine-L-tartrate in food supplements. L-carnitine occurs naturally in foods and is endogenously synthesised. L-carnitine-L-tartrate is synthesised commercially, and it dissociates into L-carnitine and tartaric acid in the gastrointestinal tract.

Based on the included literature there was no evidence indicating that age affects sensitivity towards L-carnitine, L-carnitine-L-tartrate or tartaric acid. Therefore, in this risk characterisation the same tolerance level as for adults was assumed for children and adolescents (adjusted for body weight).

VKM concludes that a dose of 1500 mg of L-carnitine per day, which is equivalent to a dose of 2250 mg of L-carnitine-L-tartrate per day, is unlikely to cause adverse health effects in adolescents (14 to <18 years) and adults (≥ 18 years), whereas intake at this level in children (10 to <14 years) may represent a risk of adverse health effects. The tartaric acid exposure from this dose of L-carnitine-L-tartrate is unlikely to cause adverse health effects.

Key words: Adverse health effect, food supplement, L-carnitine, L-carnitine-L-tartrate, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, tartaric acid, VKM

Sammendrag på norsk

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved tilsetning av «andre stoffer» i kosttilskudd og energidrikk som selges i Norge. VKM har risikovurdert ulike bruksdoser oppgitt fra Mattilsynet. Disse risikovurderingene vil gi Mattilsynet vitenskapelige grunnlag for å regulere andre stoffer.

«Andre stoffer» er beskrevet i kosttilskuddsdirektivet 2002/46/EC *som stoffer som har en ernæringsmessig og/eller fysiologisk effekt, og som ikke er vitaminer og mineraler*. De tilsettes i hovedsak til kosttilskudd, men også til energidrikker og andre næringsmidler. I disse risikovurderingene har VKM ikke sett på påståtte gunstige helseeffekter, men kun vurdert mulige negative helseeffekter.

Denne rapporten er en risikovurdering av L-karnitin og L-karnitin-L-tartrat. Den er basert på tidligere risikovurderinger av L-karnitin og L-karnitin-L-tartrat og artikler som er funnet ved et litteratursøk.

Ifølge informasjon fra Mattilsynet er L-karnitin og L-karnitin-L-tartrat ingredienser i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere 1500 mg per dag (21,4 mg/kg kroppsvekt per dag) av L-karnitin og 2250 mg per dag (32,1 mg/kg kroppsvekt per dag) av L-karnitin-L-tartrat i kosttilskudd.

Andre kilder til L-karnitin og L-karnitin-L-tartrat, som for eksempel kosmetikk, er ikke inkludert i denne risikovurderingen.

L-karnitin er et kvartært ammoniumsalt som finnes i alle dyr og bakterier. Stoffet har en sentral rolle i fettsyremetabolismen i levende celler. L-karnitin-L-tartrat er saltet av basen L-karnitin med tartarsyre, og stoffet syntetiseres kommersielt.

L-karnitin forekommer naturlig i mat, og mest finnes i rødt kjøtt. L-karnitin-L-tartrat, derimot, forekommer ikke naturlig i mat. Denne forbindelsen dissosieres til L-karnitin og L-tartarsyre i tarmen. L-karnitin blir endogent syntetisert fra lysin og metionin.

L-karnitin er vidt fordelt i alle vev hos pattedyr og forekommer særlig rikelig i muskelvev. L-karnitin blir absorbert i tynntarmen etter inntak, og biotilgjengeligheten minker ved økende dose. Ekskresjon av karnitin skjer primært gjennom nyrene, og den tubulære reabsorpsjonen er svært effektiv. Bare ca. 2% av inntatt L-karnitin skiller ut via feces. Mengden L-karnitin som blir absorbert til den systemiske sirkulasjonen blir den samme om karnitin gis som L-karnitin eller L-karnitin-L-tartrat.

Nyfødte, spedbarn og småbarn kan få i seg L-karnitin og L-karnitin-L-tartrat gjennom næringsmidler som er beregnet til bruk ved spesielle ernæringsmessige behov (inkludert morsmelkerstatning og ulike typer babymat). Videre brukes L-karnitin og L-karnitin-L-tartrat som tilskudd i dyrefor, og stoffene er også oppført som ingredienser i ulike kosmetiske

produkter. L-tartarsyre forekommer naturlig i frukt og vin, og både L-tartarsyre og salter av L-tartarsyre er godkjente tilsetningsstoffer i mat (E nummer 334).

Det er av og til observert bivirkninger av L-karnitin (-L-tartrat) hos sårbare grupper som f.eks. hos pasienter med nyresykdommer og personer som har høye plasmaverdier av trimetylamin (TMA) og trimetylamin-*N*-oksid (TMAO). Høye plasmanivåer av L-karnitin kombinert med høye nivåer av TMAO har blitt satt i sammenheng med kardiovaskulær sykdom og uønskede kardiale hendelser hos pasienter som er under hjertemedisinsk utredning. Det er mistanke om at det forekommer bivirkninger av L-karnitin hos personer med visse medfødte metabolske sykdommer. Interaksjoner av karnitin med visse typer legemidler har blitt rapportert.

En studie av L-karnitin i barn (6-13 år gamle gutter diagnostisert med hyperkinetisk forstyrrelse/ADHD («attention deficit hyperactivity disorder») og som ellers var friske) ble funnet. Denne studien tydet ikke på at barn er mer følsomme for dette stoffet enn voksne. Ingen studier ble funnet spesifikt for barn (10 to <14 år) eksponert for L-karnitin-L-tartrat eller tartarsyre. Ingen studier ble funnet spesifikt for ungdom (14 to <18 år) eksponert for L-karnitin, L-karnitin-L-tartrat eller tartarsyre. Ut i fra den inkluderte litteraturen var det ikke grunn til å anta at alder påvirker følsomhet for L-karnitin, L-karnitin-L-tartrat eller tartarsyre. Derfor ble samme toleransenivå som for voksne brukt for barn og ungdom (justert for kroppsvekt).

EFSA har etablert et toleransenivå for voksne av L-karnitin-L-tartrat på inntil 3 g/dag (43 mg/kg kroppsvekt per dag), tilsvarende 2 g/dag (29 mg/kg kroppsvekt per dag) av L-karnitin. Det er ikke lagt inn noen sikkerhetsmargin for individuell variasjon i denne verdien. Toleransenivået fremkom på grunnlag av få studier hvorav alle med unntak av én var utilgjengelig for VKM. Inntak av 3 g L-karnitin-L-tartrat gir 1 g L-tartarsyre (14 mg/kg kroppsvekt per dag) (verdier i parentes gjelder for en voksen som veier 70 kg). Det er satt et akseptabelt daglig inntak (ADI) på 0-30 mg/kg kroppsvekt per dag for tartarsyre basert på dyrestudier. Disse verdiene (29 mg/kg kroppsvekt per dag av L-karnitin, 43 mg/kg kroppsvekt per dag av L-karnitin-L-tartrat og 30 mg/kg kroppsvekt per dag av tartarsyre) ble sammenlignet med den estimerte eksponeringen i risikokarakteriseringen.

Ved inntak av en daglig dose på 1500 mg L-karnitin (tilsvarende 2250 mg L-karnitin-L-tartrat) blir den estimerte eksponeringen henholdsvis 34,6 mg/kg kroppsvekt per dag for barn (10 to <14 år), 24,5 mg/kg kroppsvekt per dag for ungdom (14 to <18 år) og 21,4 mg/kg kroppsvekt per dag for voksne (≥18 år).

VKM konkluderer at det er usannsynlig at en daglig dose på 1500 mg L-karnitin, som tilsvarer en L-karnitin-L-tartrat-dose på 2250 mg per dag, forårsaker negative helseeffekter hos ungdom (14 to <18 år) og voksne (≥18 år), mens denne dosen hos barn (10 to <14 år) vil kunne representere en risiko for negative helseeffekter. Det er usannsynlig at eksponeringen for tartarsyre fra dosen av L-karnitin-L-tartrat vil medføre en helserisiko.

Kort sammendrag

På oppdrag for Mattilsynet har Vitenskapskomiteen for mattrygghet (VKM) vurdert risiko ved inntak av 1500 mg/dag av L-karnitin og 2250 mg/dag av L-karnitin-L-tartrat i kosttilskudd. L-karnitin forekommer naturlig i mat og dannes endogent i kroppen. L-karnitin-L-tartrat syntetiseres kommersielt, og stoffet spaltes til L-karnitin og tartarsyre i tarmen.

Ut fra litteraturen som ble gjennomgått var det ikke grunn til å anta at alder påvirker følsomhet for L-karnitin, L-karnitin-L-tartrat eller tartarsyre, og derfor ble samme toleransenivå som for voksne brukt for barn og ungdom (justert for kroppsvekt).

VKM konkluderer at det er usannsynlig at en dose på 1500 mg L-karnitin per dag, som tilsvarer en L-karnitin-L-tartrat-dose på 2250 mg per dag, forårsaker negative helseeffekter hos ungdom (14 to <18 år) og voksne (≥ 18 år), mens inntaket hos barn (10 to <14 år) vil kunne representere en risiko for negative helseeffekter. Det er usannsynlig at eksponeringen for tartarsyre fra disse dosene av L-karnitin og L-karnitin-L-tartrat vil medføre en helserisiko.

Abbreviations and glossary

Abbreviations

ADI	- acceptable daily intake
ADHD	-attention deficit hyperactivity disorder
ADME	- absorption, distribution, metabolism, excretion
AESAN	- Spanish Agency for Food Safety and Nutrition
ALAT	- alanine aminotransferase
ASAT	- aspartate aminotransferase
EC	- European Commission
EFSA	- European Food Safety Authority
FMO3	- flavin-containing monooxygenase 3
GGT	- gamma-glutamyltransferase
IEM	- inborn errors of metabolism
NFSA	- Norwegian Food Safety Authority [<i>Norw.</i> : Mattilsynet]
OECD	- Organisation for Economic Co-operation and Development
RCT	- randomised, controlled trial
SCF	- Scientific Committee for Food
TA	- toxin/antitoxin
TMA	- trimethylamine
TMAO	- trimethylamine- <i>N</i> -oxide
VKM	- Norwegian Scientific Committee for Food Safety [<i>Norw.</i> : Vitenskapskomiteen for Mattrygghet]
WHO	- World Health Organization

Glossary

"Other substances": a substance other than a vitamin or mineral that has a nutritional or physiological effect (The European Parliament and the Council of the European Union, 2006).

"Negative health effect" and "adverse health effect" are broad terms. VKM uses the definition established by World Health Organization (WHO) for "adverse effect": a change in morphology, physiology, growth, development, reproduction or life span of an organism, system or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences (WHO, 1994).

Background as provided by the Norwegian Food Safety Authority

«Other substances» are substances other than vitamins and minerals, with a nutritional and/or physiological effect on the body. "Other substances" are mainly added to food supplements, but these may also be added to foods and beverages, such as sports products and energy drinks. Ingestion of these substances in high amounts presents a potential risk for consumers.

In Norway, a former practice of classification of medicines had constituted an effective barrier against the sale of potentially harmful "other substances". Ever since this practice was changed in 2009, it has become challenging to regulate and supervise foods with added "other substances". Meanwhile, in the recent years, the Norwegian market has witnessed a marked growth in the sales of products containing "other substances". In 2011, food supplements containing "other substances" constituted more than 50% of the market share.

While within the European Economic Area, these substances fall under the scope of the European Regulation (EC) No. 1925/2006 on the addition of vitamins, minerals and certain other substances to foods and the European Regulation (EC) No 258/97 concerning novel foods and novel food ingredients, "other substances" remain largely unregulated. In order to ensure safe use of "other substances" many countries have regulated their use at a national level. For example, Denmark regulates these substances in a positive list i.e. a list of substances with maximal daily doses, permitted for use in food supplements and other foods (FVM, 2014).

The Norwegian Food Safety Authority (NFSA) is working on the establishment of a regulation on the addition of "other substances" to foods at a national level. The regulation will include a list of substances with permitted maximal doses, based on the substances and doses found in products on the Norwegian market. In preparation for a regulation, NFSA has therefore requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of "other substances" found on the Norwegian market. NFSA, in consultation with the industry, has compiled a list of "other substances" found in products marketed in Norway. Only substances with a purity of minimum 50% or concentrated 40 times or more have been included in the list. Substances regulated by other legislations like those for novel foods, food additives, flavourings, foods for special medical purposes, etc. have been excluded from the list.

Terms of reference as provided by the Norwegian Food Safety Authority

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of L-carnitine and L-carnitine-L-tartrate in food supplements at the following doses: 1500 mg/day and 2250 mg/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance to the guidance document developed in Phase 2) at the doses specified (Phase 3). Safety assessments of "other substances" present in food supplements shall be carried out for the general population, ages 10 years and above.

Assessment

1 Introduction

"Other substances" are described in the food supplement directive 2002/46/EC as *substances other than vitamins or minerals that have a nutritional and/or physiological effect*, and may be added to food supplements or e.g. energy drinks (WHO, 1994).

This risk assessment regards the substances L-carnitine and L-carnitine-L-tartrate per se, and no specific products.

In this series of risk assessments of "other substances", VKM has not evaluated documentation of any potential beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway. Thus, potential high intake consumer groups of the substance may not be identified and therefore not included in this assessment.

According to information from the NFSA, L-carnitine and L-carnitine-L-tartrate are ingredients in food supplements purchased in Norway. NFSA has requested a risk assessment of the following doses of L-carnitine and L-carnitine-L-tartrate in food supplements: 1500 mg/day and 2250 mg/day, respectively. The total exposure to L-carnitine and L-carnitine-L-tartrate from other sources than energy drinks, such as foods and cosmetic products, is not included in the risk assessment.

L-carnitine (CAS no. 541-15-1) is a quaternary ammonium salt naturally occurring in all animals and bacteria as well as in foods, and the richest source is red meat. The average non-vegetarian diet provides up to 100 mg L-carnitine daily, or up to 300 mg in high meat eaters' diet (EFSA, 2003). Thus, in meat eaters the largest contribution comes from foods and to a lesser degree from endogenous synthesis from the amino acids methionine and lysine. In strict vegetarians, the largest contribution is of endogenous origin (EFSA, 2003). L-carnitine is essential in the transport of long-chain fatty acids from the cytosol into the mitochondria to facilitate the β -oxidation process in the cells, and it is also involved in other processes such as the reversible acetylation of coenzyme A (EFSA, 2012a; Nasser et al., 2012). (Acetyl-)L-carnitine is involved in the acetylation of tubulin, which plays an important role in neuronal protection (Hershman et al., 2013). L-carnitine can also be commercially synthesised (EFSA, 2012a). The total body pool of L-carnitine is 15-20 g, and the rate of L-carnitine biosynthesis (in vegetarians) has been estimated to be 1.2 $\mu\text{mol/kg}$ bw per day (193.4 $\mu\text{g/kg}$ bw per day) (Lombard et al., 1989). In this risk assessment, the concentration of L-carnitine used in food supplements is 1500 mg/day.

L-carnitine-L-tartrate (CAS no. 36687-82-8) is the salt of the L-carnitine base with tartaric acid. It does not occur naturally in foods, but is commercially manufactured from food origins and used as a source of L-carnitine. L-carnitine-L-tartrate dissociates into L-carnitine

and L-tartaric acid in the gastrointestinal tract (EFSA, 2003). In this risk assessment, the concentration of L-carnitine-L-tartrate used in food supplements is 2250 mg/day, which is equivalent to 1550 mg/day of L-carnitine. **L-tartaric acid** (CAS no. 87-69-4) occurs naturally in fruits and wine (120-180 mg/100 ml) and L-tartaric acid and its salts are approved as food additives (E334; typically used in baking powder, biscuits and jam) (EFSA, 2003).

L-carnitine and certain chemically related substances including L-carnitine-L-tartrate, used as sources of L-carnitine, are approved for use in food supplements and foods for particular nutritional uses (EFSA, 2003). Examples of such foods are infant formulae (for neonates and infants); cereal-based food and other baby foods (for infants and young children (toddlers)); foods for athletes; food for energy restricted diets; supplements given in diets to patients with L-carnitine deficiencies (e.g. primary systemic carnitine deficiency, secondary carnitine deficiency related to hemodialysis (Stanley, 2004)). L-carnitine is also approved for use in animal food (EFSA, 2012a). L-carnitine is an ingredient in some energy drinks (not reported to be on the Norwegian market) and both carnitine compounds are used in cosmetic products (CosIng, 2015).

2 Hazard identification and characterisation

2.1 Literature

The present risk assessment is based on previous risk assessments of L-carnitine and L-carnitine-L-tartrate and articles retrieved from a literature search.

2.1.1 Previous risk assessments

Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (AFC) on a request from the Commission related to L-carnitine-L-tartrate for use in foods for particular nutritional uses. The European Food Safety Authority (EFSA, 2003).

The Panel evaluated L-carnitine-L-tartrate as a source of L-carnitine for use in the manufacture of foods for particular nutritional uses that might result in intakes of L-carnitine-L-tartrate of 1.5-3.0 g/day in adults. A human study was referred to confirming the bioavailability of L-carnitine from L-carnitine-L-tartrate to be similar to L-carnitine given as the free base. Acute oral toxicity test in rats and gene mutation test in *Salmonella* (ser.) *Typhimurium* strains toxin/antitoxin (TA) 1535, TA 1537, TA 1538, TA 98 and TA 100 revealed no effects at the highest dose (5000 mg/kg bw per day and 5000 µg/plate, respectively).

According to the EFSA Panel, human tolerance of L-carnitine-L-tartrate up to 3 g/day has been established in adults with respect to gastrointestinal symptoms, haematology and clinical chemistry, including markers of liver and kidney function; this is equivalent to 2 g/day L-carnitine and 1 g/day of tartaric acid. For tartaric acid, this is equivalent to an intake of 16 mg tartaric acid/kg bw per day for a 60 kg adult (14 mg/kg bw per day for a 70 kg adult), which is around half the Acceptable Daily Intake (ADI) for tartaric acid of 0-30 mg/kg bw. The ADI was set based on lack of toxicity at the highest dose level tested (about 3 g/kg bw per day) in a chronic toxicity/carcinogenicity study in rats, with the application of a 100-fold safety factor. The EFSA Panel reports that in human tolerance studies on L-carnitine given as the free base gastrointestinal distress has only been reported after consumption of 4-6 g/day. Based on the proposed levels of use (1.5-3.0 g/day) and the dissociation of L-carnitine-L-tartrate into L-carnitine and L-tartaric acid, the EFSA Panel concluded that L-carnitine-L-tartrate is not of concern from the safety point of view as a source of L-carnitine for use in foods for particular nutritional uses, provided the ADI for tartaric acid from all sources in the diet is not regularly exceeded. The human tolerance level of 2 g/day of L-carnitine and 3 g/day of L-carnitine-L-tartrate was set by EFSA without application of a safety factor.

Four studies of human tolerance of L-carnitine were referred to of which three were cited as “original not seen” by the EFSA Panel. The fourth study was absent from the reference list. These studies were all provided to EFSA by the industry. One human tolerance study of L-carnitine-L-tartrate (Rubin et al., 2001) was referred to by the EFSA Panel.

Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements – 1. Spain (AESAN, 2012).

AESAN made an assessment of the proposal to authorise 49 substances other than vitamins and minerals in the manufacture of food supplements. The Committee endorsed the assessment of EFSA (2003) as regards research on tolerance in humans: Intakes of up to 15 g L-carnitine/day are usually well tolerated, although in some people it causes gastrointestinal upsets and diarrhea. In the case of L-carnitine-L-tartrate, the Committee also referred to a randomised double-blind crossover study with a 1 week wash-out period, in which the administration of 3 g/day of L-carnitine-L-tartrate for 3 weeks did not affect the biochemical and haematological parameters or the liver and kidney functions, but that doses of 4-6 g/day may have caused gastrointestinal upsets and diarrhea. The AESAN Scientific Committee concluded that a maximum daily amount of 2 g of L-carnitine, using L-carnitine or L-carnitine hydrochloride as sources, and of 3 g L-carnitine-L-tartrate, is acceptable from the safety point of view for use as a food supplement.

Scientific Opinion on the safety and efficacy of L-carnitine and L-carnitine-L-tartrate as feed additives for all animal species based on a dossier submitted by Lonza Benelux BV. The European Food Safety Authority (EFSA, 2012a).

This opinion was based upon a request from the EC regarding the safety and efficacy of L-carnitine and L-carnitine-L-tartrate as additives in feed and drinking water for drinking for all animal species. L-Carnitine and L-carnitine-L-tartrate were assessed as safe for the target species. Further, it was claimed that very little information was available on the toxicology of L-carnitine. Nevertheless, based on residue data obtained from multi-fold doses of the typical use levels, EFSA concluded that typical supplementation of feed with L-carnitine or L-carnitine L-tartrate would not substantially increase human exposure to carnitine from food of animal origin. As the absorption rate declines with increasing L-carnitine intake, the endogenous carnitine pool may not significantly increase. Therefore, EFSA considered that the use of L-carnitine and L-carnitine L-tartrate as additives in animal nutrition is safe for the human consumer. L-Carnitine and L-carnitine-L-tartrate are not irritating to skin or eyes nor are they skin sensitisers. L-carnitine and L-carnitine-L-tartrate showed limited dust formation. As inhalation toxicity studies were not available, adverse effects in the respiratory tract could not be fully excluded.

2.1.2 Literature search

2.1.2.1 Search strategy

Literature searches were performed in MEDLINE, EMBASE, Global Health and Web of Science in order to retrieve publications on adverse effects caused by L-carnitine and L-carnitine-L-tartrate.

These databases were chosen to ensure comprehensive study retrieval. The literature searches were performed by a librarian in February 2015. The strategy for the search is included in Appendix 1.

2.1.2.2 Publication selection

The literature search identified 378 articles. In the primary screening titles and abstracts of all publications retrieved, after duplicates were removed, were independently screened against the inclusion criteria checklist.

Inclusion criteria checklist:

- Adverse effects in relation to the substance alone are addressed
- Route of exposure for humans is oral
- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetic is equal to oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal absorption and metabolism of the assessed substance.
- Animal model studies address adverse effects relevant to human health

The inclusion criteria checklist was developed by members of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics and the Panel on Nutrition, Dietetic Products, Novel Food and Allergy. Articles that did not meet the inclusion criteria were excluded from further analysis. In situations where it was unclear whether the publication was of relevance to the study, it was retained for further screening. The primary screening was performed independently by two persons.

The full text of articles that passed the primary screening was retrieved for secondary screening. In this screening, the full text articles were reviewed and compared against the inclusion criteria checklist. The secondary screening was performed by one person.

The secondary screening resulted in 41 full text articles. Additionally, three studies from manual search/retrieval of relevant literature cited in the full-text papers have been identified and are included. A final total of seven publications was identified and included in the results in this report (see Figure 2.1.2.2-1).

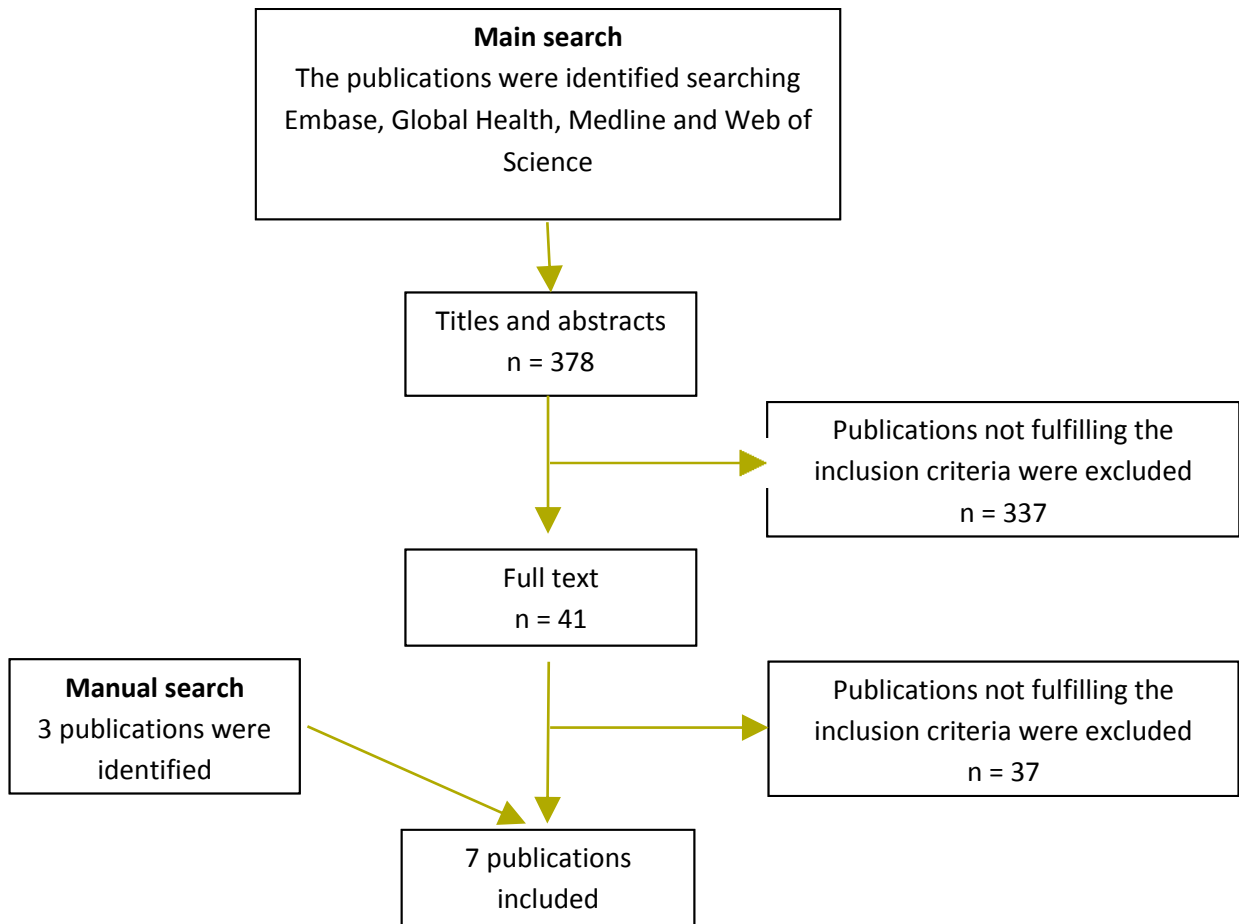


Figure 2.1.2.2-1 Flowchart for the literature search for L-carnitine and L-carnitine-L-tartrate and the subsequent publication selection.

2.2 General information

2.2.1 Chemistry

L-carnitine (CAS no. 541-15-1; EINECS no. 208-768-0) has the molecular formula $C_7H_{15}NO_3$ and a molecular weight of 161.19 g/mol. It has the chemical name β -hydroxy- γ -trimethyl aminobutyric acid; IUPAC name (3R)-3-hydroxy-4-(trimethylazaniumyl) butanoate, and a synonym is β -hydroxy- γ -trimethyl aminobutyric acid. L-carnitine is readily soluble in water (1–2.7 g/mL at 20–25 °C) (EFSA, 2012a). The structural formula of L-carnitine is shown in figure 2.2.1-1.

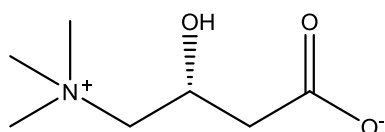


Fig. 2.2.1-1 The structural formula of L-carnitine (Ill. by Ida S. R. Stenhagen).

L-carnitine-L-tartrate (CAS no. 36687-82-8) is the salt of L-carnitine base with tartaric acid. L-carnitine-L-tartrate has the molecular formula $C_{18}H_{36}N_2O_{12}$ and a molecular weight of 472.49 g/mol. It has the IUPAC name 1-propanaminium, 3-carboxy-2-hydroxy-N,N,N-trimethyl-, (R)-, salt with (R-(R*,R*)-2,3-dihydroxybutanedioic acid (2:1) and synonyms β -hydroxy- γ -trimethyl aminobutyrate, L-tartrate, L-carnitine L-tartrate (2:1). L-carnitine-L-tartrate is highly soluble in water (>1 g/mL at 20 °C) (EFSA, 2003; EFSA, 2012a). The structural formula of L-carnitine-L-tartrate is shown in figure 2.2.1-2.

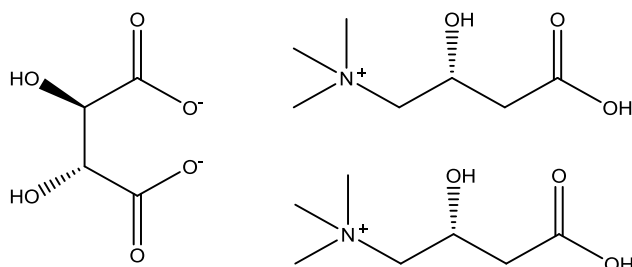


Fig. 2.2.1-2 The structural formula of L-carnitine-L-tartrate (Ill. by Ida S. R. Stenhagen).

L-tartaric acid (CAS no. 87-69-4; EINECS no. 201-766-0) has the molecular formula $C_4H_6O_6$. Salts of tartaric acid are known as tartrates. The molecular weight is 150.09 g/mol. It has the IUPAC name 2,3-dihydroxybutanedioic acid. The structural formula of L-tartaric acid is shown in figure 2.2.1-3.

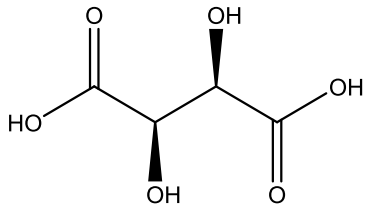


Fig. 2.2.1-3 The structural formula of L-tartaric acid (Ill. by Ida S. R. Stenhagen).

2.2.2 Occurrence

L-carnitine is present in the human diet in a variety of food sources. The richest source of dietary L-carnitine is red meat. The average non-vegetarian diet provides up to 100 mg L-carnitine daily, whereas high meat eater's diet may provide up to 300 mg per day (EFSA, 2003). L-carnitine is endogenously synthesised from the amino acids lysine and methionine (which is a methyl group donor)(EFSA, 2012a).

L-carnitine-L-tartrate does not occur naturally in foods, but is used as a source of L-carnitine as it dissociates completely into L-carnitine and L-tartaric acid in the gastrointestinal tract. Tartaric acid occurs naturally in fruits and wine and is, together with its salts, approved as a food additive (E334) (EFSA 2003, 2012b).

L-carnitine and L-carnitine-L-tartrate are used in foods for particular nutritional uses, such as infant formulae and processed foods for infants and young children, as well as in food supplements (EFSA 2003).

2.3 Absorption, distribution, metabolism and excretion (ADME)

2.3.1 In humans

After ingestion, L-carnitine is absorbed in the small intestine. The bioavailability of dietary L-carnitine is dependent on the L-carnitine content (intake up to 300 mg/day), and reported to be in the range of 30-87% in humans (EFSA, 2003; EFSA, 2012a). According to a pharmacokinetic study on humans, the bioavailability of non-dietary L-carnitine was about 16% and 5% after oral administration of a single dose of 2 and 6 g L-carnitine, respectively (EFSA, 2012a). L-carnitine can also be synthesised endogenously. The major portion of all carnitine in the body is found in the skeletal muscle where it is required for the metabolism of fatty acids. Studies with labelled L-carnitine suggest that carnitine is not metabolised to a great extent; however, carnitine might be converted, for example to β -methyl choline, during stress and disease or depending on the dietary or physiological conditions. Carnitine is excreted mainly via the kidneys with a highly efficient tubular reabsorption of about 90–99% at normal dietary intakes, only 2% of the ingested L-carnitine is excreted in the faeces (EFSA, 2003; EFSA, 2012a).

Carnitine homeostasis is maintained by absorption from dietary sources, endogenous biosynthesis (1.2 $\mu\text{mol/kg}$ bw per day (193.4 $\mu\text{g/kg}$ bw per day) in vegetarians (Lombard 1989)) and reabsorption of carnitine in the kidneys (EFSA, 2003).

L-carnitine-L-tartrate dissociates into L-carnitine and L-tartaric acid in the gastrointestinal tract. Bioequivalence of L-carnitine-L-tartrate to L-carnitine can be assumed from the complete dissociation of L-carnitine-L-tartrate upon dissolution. Intake of L-carnitine as a 2 g bolus dose produces a similar increase in serum L-carnitine whether administered as the free base (L-carnitine) or as the L-tartrate salt (L-carnitine-L-tartrate) (EFSA, 2003).

Tartaric acid

There are large differences in absorption, distribution, metabolism and excretion of tartaric acid between species. In humans, studies suggest that about 18% of an orally ingested tartrate dose was absorbed by the gastrointestinal tract. Following absorption, 14% and 4% of the originally ingested dose was excreted in the urine and metabolized in the tissues, respectively. Unabsorbed tartrate is likely to undergo metabolism by the intestinal microflora (77% of originally ingested dose). A small part of the unabsorbed tartrate (5%) is excreted in the faeces (EFSA, 2015).

2.3.2 Animal studies

The above chapter on ADME applies to all animal species (EFSA, 2012a).

2.4 Toxicological data/Adverse effects

L-carnitine is well tolerated by humans and all animal species, possibly because of its decreasing bioavailability with increasing dietary L-carnitine concentrations.

2.4.1 Human studies

An overview of human studies investigating L-carnitine or L-carnitine-L-tartrate and adverse health effects is given in Table 2.4.1-1.

Table 2.4.1-1 An overview of human studies investigating L-carnitine or L-carnitine-L-tartrate and adverse health effects.

Reference	Study design /Participant characteristics	Country	Number in treatment group		Dose	Main endpoints	Total study length	Adverse effect
			L-carnitine or L-carnitine-L-tartrate	Control/ placebo				
Villani et al. (2000)	Randomized, double-blind, placebo-controlled study/36 moderately overweight premenopausal women	Australia	18	18 placebo	4 g/day, L-carnitine, oral intake for 8 weeks	Weight loss efficacy: mean total body mass, fat mass, lipid utilization, resting energy expenditure	8 weeks	A percentage of 28 (5 of 18 in the treatment group) reported nausea and diarrhea and withdrew from the study
Rubin et al. (2001)	Randomised, double-blind, cross-over design/10 healthy, active men	USA	10: L-carnitine -L-tartrate – washout – placebo (and vice versa)	Own control	3 g/day L-carnitine-L-tartrate, oral intake (equivalent to 2 g/day of L-carnitine) for 3 weeks	Serum markers of kidney and liver function, metabolic screening profile and complete blood count with differential count	7 weeks	There were no gastrointestinal effects and no significant differences in the clinical parameters between exposed and placebo group

Reference	Study design /Participant characteristics	Country	Number in treatment group		Dose	Main endpoints	Total study length	Adverse effect
			L-carnitine or L-carnitine-L-tartrate	Control/ placebo				
Van Oudheusden and Scholte (2002)	Randomised, double-blind, placebo-controlled, crossover trial/ 26 boys diagnosed with ADHD (6-13 years).	The Netherlands	13: L-carnitine - placebo – L-carnitine	13: placebo – L-carnitine -placebo	100 mg/kg bw per day L-carnitine (maximum: 4 g), oral intake. Three treatment periods of 8 weeks each (maximum 16 weeks of intake)	Child Behavioural Check List, Conners teacher-rating score, hematological parameters, serum kidney and liver markers and free and acetyl carnitine, physical examination	24 weeks	One participant fainted during the placebo period following carnitine; one participant had reversible elevated plasma creatinine level during the last placebo period; one participant had unpleasant body odor during treatment with carnitine. Physical examination at the end of the trial showed no abnormalities
Galloway et al. (2011)	Case study, single blind, crossover, ordered (placebo first, carnitine last), 16 lean and overweight/obese men (18-36 years)	UK	8 lean, 8 overweight/ obese	Own placebo control	3 g/day L-carnitine-L-tartrate, oral intake, for 2 weeks following placebo for 2 weeks	Glucose sensitivity indices, glucose disposal and any change in these parameters' influence on glucagonlike peptide-1	5-6 weeks (total)	In the overweight/obese group, the timing of peak glucose response was delayed and the glucose concentration was higher after 90 min compared to the group of lean men (normal glucose levels)

Reference	Study design /Participant characteristics	Country	Number in treatment group		Dose	Main endpoints	Total study length	Adverse effect
			L-carnitine or L-carnitine-L-tartrate	Control/ placebo				
Hathcock and Shao (2006)	Risk assessment, based on 10 human clinical studies including both sexes, children and a variety of diseases	USA	10-431	11-215	Range of 0.050 g to 7 g of L-carnitine, acetyl-L-carnitine or propionyl-L-carnitine, oral intake and combined with intravenous	Various (see original publications)	2 months-1 year	Reported side effects of L-carnitine were unpleasant body odour and gastrointestinal distress

Randomised controlled studies

In a double-blind, placebo-controlled Australian study of the impact of aerobic training on weight loss in moderately obese premenopausal women, L-carnitine oral intake was 4 g/day for 8 weeks. Endpoints were mean total body mass, fat mass, lipid utilization and resting energy expenditure. A percentage of 28 (5 of 18 in the treatment group) reported nausea and diarrhea and withdrew from the study (Villani et al., 2000).

In a tolerance U.S. study using randomised, double-blind, cross-over design and placebo controls, L-carnitine-L-tartrate was given in a dose of 3 g/day (equivalent to 2 g/day of L-carnitine) for 3 weeks to 10 healthy male volunteers (mean age 23.7, SE=0.7). Serum markers of kidney and liver function as well as complete blood count were examined. It was concluded that there were no gastrointestinal effects, no changes in standard haematological or clinical chemistry parameters and no effects on markers of hepatic or renal function (Rubin et al., 2001).

In a randomised, double-blind, placebo-controlled, crossover Dutch trial by Van Oudheusden and Scholte (2002), including a total of 26 participants (boys, 6-13 years old, diagnosed with attention deficit hyperactivity disorder (ADHD), otherwise healthy), 100 mg/kg bw per day of L-carnitine (equivalent to 7000 mg/day in a 70 kg adult), up to a maximum of 4 g, was given. There were two groups of 13 boys, one group received placebo–carnitine–placebo and the other group carnitine–placebo–carnitine. The three treatment periods were 8 weeks each. Laboratory tests were done at screening, in week 8, 16 and 24 for hemoglobin, hematocrit, red blood cell count, white cell count, white cell differential count, platelet count and the plasma levels of urea, creatinine, sodium, potassium, aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT), gamma-glutamyltransferase (GGT), alkaline phosphatase and free and acetyl carnitine. Physical examination was done at screening and in week 24. Adverse events reported included a short unexplained period of fainting a few days after the onset of the placebo period following carnitine (one participant, no explanation was found), and an elevated plasma creatinine level during the last placebo period (one participant, 2 weeks after the trial a normal level was found). Physical examination of all boys by the pediatrician at the end of the three trial periods showed no abnormalities. One patient observed an unpleasant body odor during treatment with carnitine, a well-known side effect, likely due to the formation of trimethylamine. In this study, intake exceeded the tolerance level of 2 g L-carnitine/day, corresponding to 29 mg/kg bw per day for adults. This study did not indicate that children were more sensitive to adverse effects of L-carnitine than adults.

Case control study

In a case, placebo-controlled, single-blinded, crossover, ordered trial from the UK, glucose handling/disposal response to 3 g/day of oral L-carnitine-L-tartrate for 2 weeks was different between lean (n=8; age: 18.9-29.1 years) and overweight/obese men (n=8; age: 22.2-35.8 years). Main endpoints were glucose sensitivity indices, glucose disposal and any change in these parameters' influence on glucagonlike peptide-1. In the overweight/obese group, the

timing of peak glucose response was delayed and the glucose concentration was higher after 90 min. compared to the group of lean men. The glucose levels of both groups were within the normal range (Galloway et al., 2011).

Risk assessment

Hathcock and Shao (2006) performed a risk assessment of L-carnitine and two other available forms, acetyl-L-carnitine and propionyl-L-carnitine. Their assessment was based on several human clinical studies with doses in the range of 50-7000 mg (100 mg/kg bw per day), most of which were benefit studies and studies including patients with a variety of diseases. A lack of adequate toxicological animal data was recognised. According to the authors: "The hypothetical possibility exists of a carcinogenic effect of LCAR [L-carnitine, *ed. note*] through nitrosation of the LCAR metabolites TMA and TMAO to the carcinogen *N*-nitrosodimethylamine" (Bain et al., 2005). However, there is no current [2006, *ed. note*] evidence for carcinogenicity of LCAR through this or any other mechanism". Reported side effects of L-carnitine were unpleasant body odor and gastrointestinal distress from which no NOAEL could be established. The "observed safe levels" risk assessment method used by the authors indicated that "the evidence of safety was strong at intakes up to 2000 mg/day of L-carnitine equivalents for chronic supplementation". Further, it was concluded that due to lack of well-conducted long-term studies with high intakes the current "data for intakes above 2000 mg/day were not sufficient for a confident conclusion of long-term safety".

2.4.1.1 Interactions

In a randomized, double-blind, placebo-controlled U.S. trial, 3000 mg/day of (acetyl-) L-carnitine was given to women (≥ 18 years) undergoing adjuvant breast cancer therapy for the prevention of taxane-induced neuropathy for 24 weeks. An increase in chemotherapy-induced peripheral neuropathy was found in the group given L-carnitine (n=208) compared with the placebo group (n=201)(Hershman et al., 2013).

The carnitine system is dependent of several membrane transporters and enzymes. Some commonly used drugs (e.g. cardiovascular, antibiotic, antiviral, anti-tumour and nervous system) were found to interact with different carnitine transporters which caused alteration of the transport function by displacing the substrate from the binding site or by irreversible inactivation of the transporters and further, disturbances in the carnitine homeostasis (Indiveri C et al., 2010). Certain drugs, especially valproic acid and pivalic acid prodrugs (Hathcock and Shao, 2006; Rebouche, 1995), have been reported to negatively affect human carnitine status (causing deficiency).

In a randomized, double-blind, placebo-controlled 6 month Italian trial of adult women (n=50) on thyroid stimulating hormone-suppressive doses of L-thyroxine were given L-carnitine doses of 2 and 4 g/day (n=40). L-carnitine reversed and prevented symptoms of hyperthyroidism. Two patients reported nausea and gastralgia. The authors refer to previous

work where L-carnitine was considered to be a peripheral antagonist of thyroid hormone action (Benvenga et al., 2001).

TMA with the characteristic odour of rotting fish may be derived from the diet by enterobacterial generation from food rich in L-carnitine. Following absorption, TMA is metabolized by the enzyme flavin-containing monooxygenase 3 (FMO3) in the liver to form trimethylamine-*N*-oxide (TMAO). Individuals with decreased FMO3 activity develop trimethylaminuria characterised by body malodour and distressing psychosocial reactions (Bain et al., 2006b).

According to a monograph prepared as a guide to industry for the preparation of Product License Applications and labels for natural health product market authorisation by Health Canada (2013), patients with liver disease, kidney disease, or a seizure disorder should consult a health care practitioner prior to use of carnitine supplements.

2.4.1.2 Allergic sensitisation (including adjuvant effects)

No reports or studies of sensitisation after skin contact or oral intake have been found. Two studies reported unspecific rash (no information of sensitisation) as an adverse event in benefit studies in patient groups with various conditions:

Unspecific rash was reported in four of 643 paediatric patients with diverse conditions associated with carnitine deficiency treated with carnitine (no information as to type of carnitine) in dosages of 100 mg/kg bw per day or in the range 200-800 mg/kg bw per day in a U.S. study (non-refereed report in (De Vivo DC and Tein I, 1990). These doses exceeded the tolerance limits set for both L-carnitine and L-carnitine-L-tartrate. Rash (no further description) was reported as an adverse event in one person and was the reason for study withdrawal in a longitudinal, double-blind, placebo-controlled, parallel-group U.S. study of patients with probable Alzheimer's disease treated with 3 g acetyl L-carnitine/day for 12 months (carnitine: 216 patients/placebo: 215 patients) (Brooks et al., 1998).

2.4.2 Animal studies

L-carnitine

In a study of 32 healthy one day old, mixed-sex Black Neck ostrich chicks fed a diet supplemented with 0-600 mg/kg feed of L-carnitine for 60 days, a suppressive effect of growth response was observed for the highest L-carnitine concentration. The birds which were fed the highest dose of L-carnitine had the lowest live weight and weight gain as well as the highest feed conversion ratio (kg feed/kg weight gain) after the end of the study period indicating a suppressive effect of the supplement (Hajibabaei and Casey, 2012).

Atherosclerosis (significantly higher number of aortic lesions) in female mice (apolipoprotein E-knockout on C57BL/6J background) accelerated after oral intake of 1.3% (g/g) L-carnitine in drinking water for 10 weeks (n=72). This effect was attributed to intestinal breakdown of

L-carnitine to TMA and TMAO of which the latter is proatherogenic and associated with cardiovascular risk in a human study (Koeth et al., 2014) (see 2.4.5). According to Bremer (1983), "TMAO has been proposed to induce upregulation of macrophage scavenger receptors and thereby potentially contribute to enhanced "forward cholesterol transport". " No direct relationship between TMA or TMAO and the occurrence of atherosclerosis in humans has been proven.

L-carnitine-L-tartrate

An acute oral gavage toxicity test with L-carnitine-L-tartrate in rats showed no effects at a dose of 5000 mg/kg bw per day (EFSA, 2003; EFSA, 2012a).

EFSA (2012a) concluded that L-carnitine and L-carnitine-L-tartrate were not irritant to skin and eyes. No information was available on inhalation toxicity.

2.4.2.1 Interactions

In a 28 days *in vivo* study of adult, female rats, a dose of 300 mg/kg bw per day of L-carnitine (given intraperitoneally) was found to interfere with the antitumour effect of tamoxifen (Ibrahim et al., 2014).

L-carnitine, given male mice at doses of 8 and 16 mmol/kg (intraperitoneally) was shown to increase toxicity of paraquat (a herbicide) in a dose-dependent manner (Miguez et al., 1998).

Whether oral intake will have the same effect as that administered intraperitoneally is not known.

2.4.2.2 Allergic sensitisation (including adjuvant effects)

L-carnitine: Buehler test for skin sensitisations (OECD guideline 406) was performed on 20 guinea pigs exposed to up to 75% L-carnitine (w/w) (no further dose description was given) (10 guinea pigs served as controls). No skin reaction was observed after topical challenge (EFSA, 2012a).

L-carnitine-L-tartrate: A local lymph node assay (OECD guideline 429) for skin sensitisation was performed on five female CBA strain mice up to 50% L-carnitine-L-tartrate (no further dose description was given) by open application on the ears. It was concluded that skin sensitisation did not occur.

No reports have been found of sensitisation after oral intake in the included literature.

2.4.3 *In vitro* studies

A gene mutation test with L-carnitine-L-tartrate in *Salmonella* (ser.) *typhimurium* strains TA 1535, TA 1537, TA 1538, TA 98 and TA 100 in the concentration range 1.6-5000.0 µg/plate, with and without metabolic activation using rat liver S9 mix, showed no evidence of gene mutation (EFSA, 2003).

2.4.4 Mode of action for adverse effects

No mechanisms for adverse effects are reported in the included literature.

2.4.5 Vulnerable groups

Increased protein oxidation and decreased nitrogen balance was found in preterm, low-birth-weight neonates (n=12) fed total parenteral nutrition with supplementation of 48 mg/kg bw per day of L-carnitine on days 4-7 compared to a group without L-carnitine supplement (n=12) in a Dutch study (Sulkers et al., 1990). The dose exceeded the tolerance level of 29 mg/kg bw per day.

L-carnitine has been identified as a dietary source of gut microbe-dependent formation of TMA and TMAO, described in e.g. Koeth et al. (2013). In patients with severely compromised renal function, TMA and TMAO will accumulate due to poorly functioning kidneys. TMA and TMAO have the potential to form the carcinogen *N*-nitrosodimethylamine, and they are associated with abnormal neurological symptoms in patients with end-stage renal disease (Bain et al., 2006a).

An L-carnitine oral dose of 100 mg/kg bw per day was given to females with Rett syndrome aged 4-35 years (the majority below 20 years) in a placebo-controlled, double-blind crossover Australian trial with L-carnitine exposure for 8 weeks (n=35). Three patients reported fishy body or urine odor (Ellaway et al., 1999). The dose exceeded the tolerance level of 29 mg/kg bw per day.

In a Cochrane review of infants, children and adult patients with inborn errors of metabolism (IEM), the authors concluded that there were no published or ongoing randomized, controlled trials relevant to the review question. Thus, conclusions could not be made regarding efficacy and safety on the use of carnitine supplementation in patients with IEM. Doubts have been raised on the safety of carnitine supplementation in some people with certain IEMs (e.g. long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (Nasser et al., 2012)).

According to a monograph prepared as a guide to industry for the preparation of Product License Applications and labels for natural health product market authorisation by Health Canada (2013), patients with liver disease, kidney disease or a seizure disorder should consult a health care practitioner prior to use of carnitine supplements.

Fasting plasma L-carnitine levels (median 46.8 μM) predicted increased risks for prevalent cardiovascular disease and incident major adverse cardiac events in a mixed-sex cohort aged 53-72 years with concurrently high TMAO levels (median 4.6 μM) ($n = 2595$) in a U.S. study. The patients were undergoing elective cardiac evaluation. Exposure to carnitine was neither controlled nor was carnitine administration part of the study outline. Significant dose-dependent associations between plasma carnitine concentrations and risks of prevalent coronary artery disease, peripheral artery disease and overall cardiovascular disease were observed (all statistically significant). The associations remained significant after corrections of traditional cardiovascular risk factors (Koeth et al., 2013) (see also 2.4.2. Animal studies). The authors commented that their "results suggest that TMAO, rather than carnitine, is the primary driver of the association of carnitine with cardiovascular risks".

No reports have been found of the use L-carnitine or L-carnitine-L-tartrate in pregnant or lactating women.

2.5 Summary of hazard identification and characterisation

L-carnitine-L-tartrate dissociates into L-carnitine and L-tartaric acid in the gastrointestinal tract.

The available data indicated that L-carnitine-L-tartrate was not mutagenic.

A human tolerance level of L-carnitine-L-tartrate up to 3 g/day has been established in adults with respect to gastrointestinal symptoms, haematology and clinical chemistry, including markers of liver and kidney function. This is equivalent to 2 g/day L-carnitine (EFSA, 2003). No tolerance value is set specifically for L-carnitine or L-carnitine-L-tartrate for children and adolescents.

The upper value of 3 g for intake of L-carnitine-L-tartrate would yield 1 g of tartaric acid (the dissociation product from L-carnitine-L-tartrate). An ADI is set for tartaric acid of 0-30 mg/kg bw per day based on a chronic toxicity/carcinogenicity study in rats (SCF, 2003). A general intake, e.g. from supplements of L-carnitine-L-tartrate, will increase the level of tartaric acid. No tolerance value for tartaric acid is set specifically for children and adolescents.

After L-carnitine exposure of 4 g/day gastrointestinal symptoms occurred as well as occasional unpleasant body odour (Villani et al., 2000, Van Oudheusden and Scholte, 2002). These effects were described in the studies of exposure to L-carnitine equivalents of 0.050-7 g reported in the risk assessment by Hathcock and Shao (2006). After exposure to 3 g L-carnitine L-tartrate overweight/obese men showed delayed peak glucose response and their glucose concentration was higher 90 min after exposure compared to that of lean men given the same dose (Galloway et al., 2011). Studies performed after the publication of the EFSA report in 2003 (e.g. Galloway et al., 2011, Koeth et al., 2013) indicate that certain groups, including overweight men, may be more vulnerable to L-carnitine. However, there are too few studies available of sufficient quality studying adverse effects (rather than benefits) to

change the tolerance level set by EFSA (2003). The data basis for the human tolerance level in EFSA (2003) is weak.

Adverse effects of L-carnitine (-L-tartrate) are occasionally observed in vulnerable groups such as in patients with kidney disease and persons with high plasma values of TMA and TMAO. High plasma L-carnitine levels in subjects with concurrently high TMAO levels have been associated with cardiovascular disease and adverse cardiac events in patients undergoing cardiac evaluation. Adverse effects are suspected in patients with IEM. Further, interactions with certain types of drugs have been reported.

In the present risk assessment, the values for comparison with the estimated exposure used in the risk characterisation of L-carnitine and L-carnitine-L-tartrate are based on the human tolerance levels described by EFSA (2003). The human tolerance levels do not express any safety factor for interindividual variation. For L-carnitine the comparison value is 2 g/day (corresponding to 29 mg/kg bw per day). For L-carnitine-L-tartrate the comparison value is 3 g/day (corresponding to 43 mg/kg bw per day). Both values apply to adults (values in parentheses are for a 70 kg adult). For tartaric acid, the value for comparison used in the risk characterisation is the ADI of 0-30 mg/kg bw per day (SCF (2003)).

3 Exposure / Intake

Exposure to L-carnitine and L-carnitine-L-tartrate from the intake of food supplements was estimated for children (10 years and above), adolescents and adults.

3.1 Food supplements

NFSA requested VKM to perform a risk assessment of 1500 mg/day of **L-carnitine** and 2250 mg/day of **L-carnitine-L-tartrate** as food supplement for children (10 to <14 years), adolescents (14 to <18 years) and adults (≥18 years). The default body weights (bw) for these groups as determined by EFSA were used: 3 to <10 years; 23.1 kg, 10 to <14 years; 43.4 kg, 14 to <18 years; 61.3 kg and adults (≥18 years); 70.0 kg (EFSA, 2012b).

Based on the daily intake of 1500 mg **L-carnitine** and the default body weights determined by EFSA, the exposure is 34.6, 24.5 and 21.4 mg/kg bw per day for the age groups 10 to <14 years, 14 to <18 years and adults (≥18 years), respectively (Table 3.1-1).

Table 3.1-1 Estimated daily exposure from a daily intake of 1500 mg L-carnitine (mg/kg bw per day) from food supplements.

Age (years)	Children (10 to <14 years)	Adolescents (14 to <18 years)	Adults (≥18 years)
Body weight (kg)	43.4	61.3	70.0
Dose (mg/kg bw per day)	34.6	24.5	21.4

Based on the daily intake of 2250 mg **L-carnitine-L-tartrate** and the default body weights determined by EFSA, the exposure is 51.8, 36.7 and 32.1 mg/kg bw per day for the age groups 10 to <14 years, 14 to <18 years and adults (≥18 years), respectively (Table 3.1-2). Intake of 2250 mg L-carnitine-L-tartrate yields 1500 mg L-carnitine (as assessed above) and 750 mg tartaric acid (as assessed below).

Table 3.1-2 Estimated exposure from a daily intake of 2250 mg L-carnitine-L-tartrate (mg/kg bw per day) from food supplements.

Age (years)	Children (10 to <14 years)	Adolescents (14 to <18 years)	Adults (≥18 years)
Body weight (kg)	43.4	61.3	70.0
Dose (mg/kg bw per day)	51.8	36.7	32.1

Based on the daily intake of 750 mg **tartaric acid** and the default body weights determined by EFSA, the exposure is 17.3, 12.2 and 10.7 mg/kg bw per day for the age groups 10 to <14 years, 14 to <18 years and adults (≥18 years), respectively (Table 3.1-3).

Table 3.1-3 Estimated exposure from a daily intake of 750 mg tartaric acid (mg/kg bw per day) from food supplements.

Age (years)	Children	Adolescents	Adults
	(10 to <14 years)	(14 to <18 years)	(≥18 years)
Body weight (kg)	43.4	61.3	70.0
Dose (mg/kg bw per day)	17.3	12.2	10.7

3.2 Other sources

L-carnitine: Mean intake from food (not feed-supplemented animals) is 100-300 mg/day (Feller and Rudman, 1988 in EFSA, 2003). The highest intake is for high meat consumption. A newer range for human dietary intake has been provided by Rebouche (2004): <0.2 to 2.4 mg/kg bw per day (14–168 mg/day for a 70 kg adult). L-carnitine is endogenously synthesised from the amino acids lysine and methionine.

Although **L-carnitine** and **L-carnitine-L-tartrate** are used as supplements in animal food, EFSA concluded that typical supplementation of feed would not substantially increase human exposure to carnitine from food of animal origin (EFSA, 2012a). Further, EFSA (2012a) concluded that as the absorption rate declines with increasing L-carnitine intake, the endogenous carnitine pool may not significantly increase.

L-carnitine (equivalents) and **L-carnitine-L-tartrate** are listed as ingredients in various cosmetic products, such as e.g. hair conditioners (CosIng, 2015). Adolescents and adults are likely to be exposed.

Tartaric acid: L-tartaric acid occurs naturally in fruits and wine (120-180 mg/100 ml) and L-tartaric acid and its salts are approved as food additives (typically used in baking powder, biscuits and jam) (EFSA, 2003).

Neonates, infants and young children can be exposed to L-carnitine and L-carnitine-L-tartrate through foods for particular nutritional uses. Examples of such foods are infant formulae milk (for neonates and infants); follow-on formulae milk (infants); cereal-based food and other baby foods (for infants and young children (toddlers)) (EFSA, 2003).

4 Risk characterisation

NFSA requested VKM to perform a risk assessment of 1500 mg/day of L-carnitine and 2250 mg/day of L-carnitine-L-tartrate (which yields 1500 mg/day of L-carnitine and 750 mg tartaric acid) as food supplement for children (10 to <14 years old), adolescents (14 to <18 years) and adults (≥ 18 years).

One study of L-carnitine on children (6-13 years) was identified (Van Oudheusden and Scholte, 2002). The children were boys diagnosed with ADHD, who were otherwise healthy. A study of L-carnitine in girls with Rett syndrome, mainly younger than 20 years old (Ellaway et al., 1999), was categorised under the chapter "vulnerable groups" (see chapter 2.4.5.) due to the severity of the condition. Neither of the studies indicated that children were more sensitive to L-carnitine than adults. No studies were found on adverse effects of L-carnitine-L-tartrate or tartaric acid specifically in children. No studies were found on adverse effects of L-carnitine, L-carnitine-L-tartrate or tartaric acid specifically in adolescents. Safe levels of these substances specifically for children and adolescents based on studies performed in these age groups could, therefore, not be established. In this risk assessment, the same tolerance level as for adults, were assumed for children and adolescents (adjusted for body weight) for L-carnitine, L-carnitine-L-tartrate and tartaric acid.

In the present risk assessment, the values for comparison used in the risk characterisation of L-carnitine and L-carnitine-L-tartrate are based on the human tolerance levels described by EFSA (2003). The human tolerance levels do not express any safety factor for interindividual variation. Further, this value was based on few studies of which all but one was unavailable to VKM. For L-carnitine the comparison value is 2 g/day (corresponding to 29 mg/kg bw per day for a 70 kg adult). For L-carnitine-L-tartrate the comparison value is 3 g/day (corresponding to 43 mg/kg bw per day for a 70 kg adult).

The risk characterisation of tartaric acid is based on the acceptable daily intake (ADI) of 0-30 mg/kg bw per day from a chronic toxicity/carcinogenicity rat study established by SCF (2003) (the ADI was set with the application of a 100-fold safety factor, of which a factor 10 is for extrapolation from rats to humans and a factor 10 is for interindividual human variation).

The few studies that included children and adolescents were of relatively short duration, and have accordingly inherent uncertainty in extrapolating to long-term supplementation in these age groups. No tolerance level is set for L-carnitine or L-carnitine-L-tartrate specifically for children or adolescents. Assuming similar tolerance level for these age groups as for adults, it is unlikely that doses below 29 mg/kg bw per day of L-carnitine and 43 mg/kg bw per day of L-carnitine-L-tartrate cause adverse health effects in children and adolescents.

L-carnitine: A dose of 1500 mg/day in food supplements will give intakes of 34.6, 24.5 and 21.4 mg/kg bw per day for the age groups 10 to <14 years, 14 to <18 years and adults (≥ 18 years), respectively (Table 3.1-1). For 10 to <14 year old children, the intake will

slightly exceed 29 mg/kg bw per day. For the 14 to <18 year old adolescents and the adults (≥18 years), the intake is below 29 mg/kg bw per day.

L-carnitine-L-tartrate: A dose of 2250 mg/day yields 1500 mg/day of L-carnitine, and the risk characterisation of this dose of L-carnitine is performed in the paragraph above.

Tartaric acid: A dose of 2250 mg/day in food supplements of L-carnitine-L-tartrate will yield 750 mg/day of tartaric acid. An intake of 750 mg/day of tartaric acid from food supplements will give intakes of 17.3, 12.2 and 10.7 mg/kg bw per day for the age groups 10 to <14 years, 14 to <18 years and adults (≥18 years), respectively (Table 3.1-3). For all age groups, the tartaric acid exposure will be below the ADI of 0-30 mg/kg bw per day.

5 Uncertainties

5.1 Hazard identification and characterisation

Type of human studies available

Several of the human studies referred to are RCT studies, specifically designed to investigate the positive effects (such as in patients with deficiencies) and not negative effects of L-carnitine and L-carnitine-L-tartrate. Adverse effects may not always be recorded and if they are, they may not be properly diagnosed.

Both benefit studies and the few studies on negative health effects related to L-carnitine and L-carnitine-L-tartrate in adults have high heterogeneity both in design and participant characteristics.

The described relationship between carnitine, the concurrently high presence of its metabolite TMAO and the increased risk for prevalent cardiovascular disease (Koeth et al., 2013) cannot be taken as evidence for a direct relationship between carnitine and cardiovascular risk.

Uncertainty regarding children and adolescents

The only study of L-carnitine that included healthy children with ADHD (Van Oudheusden and Scholte, 2002) was of relatively short duration and of small size, and it is accordingly difficult to extrapolate to long-term supplementation in this age group. However, the above-mentioned study did not indicate that children were more sensitive to L-carnitine than adults. No studies were found specifically on adolescents.

Therefore, a safe level specifically for children and adolescents based on studies performed in these age groups was not established. Similar tolerance for these age groups as for adults was assumed.

Uncertainty of the value for comparison used in the risk characterisation

The reference doses for both L-carnitine and L-carnitine-L-tartrate were based on studies in human adults. The EFSA Opinion on L-carnitine-L-tartrate (EFSA, 2003) (see 2.1.1.) referred to five human tolerance studies of L-carnitine and L-carnitine-L-tartrate. Only one of these studies (Rubin et al., 2001) was described in some detail and was available to VKM. However, the study size was small (n=10) and the duration was short (3 weeks).

The ADI for tartaric acid was based on the highest dose tested in a chronic toxicity/carcinogenicity rat study. Therefore, there is a possibility that the actual ADI is higher than 0-30 mg/kg bw per day and that a risk assessment based on the ADI may be too conservative.

5.2 Uncertainty in exposure

The risk assessment is based on default body weights determined by EFSA. These values are somewhat lower than the body weights reported in Norwegian dietary surveys resulting in more conservative estimates in the current risk assessment.

With use of the default (mean) body weight of an age (population) group, the variance in all individuals in the group will not be covered.

5.3 Uncertainty in risk characterisation

The human tolerance levels for L-carnitine or L-carnitine-L-tartrate do not express any safety factor for interindividual variation.

6 Conclusions with answers to the terms of reference

The Norwegian Scientific Committee for Food Safety (VKM) has, at the request of the Norwegian Food Safety Authority (NFSA), assessed the risk of L-carnitine (1500 mg/day) and L-carnitine-L-tartrate (2250 mg/day) in food supplements. The present risk assessment is based on previous risk assessments and a literature search.

Human tolerance of L-carnitine-L-tartrate up to 3 g/day, equivalent to 2 g/day L-carnitine, has been established in adults (EFSA, 2003). The upper value of 3 g for intake of L-carnitine-L-tartrate would yield 1 g of tartaric acid (the dissociation product from L-carnitine-L-tartrate).

One study of L-carnitine on healthy children (6-13 years) with ADHD was identified (Van Oudheusden and Scholte, 2002), and this study did not indicate that children were more sensitive to L-carnitine than adults. No studies were found on adverse effects of L-carnitine-L-tartrate or tartaric acid specifically in children. No studies were found on adverse effects of L-carnitine, L-carnitine-L-tartrate or tartaric acid specifically in adolescents. Safe levels of these substances specifically for children and adolescents based on studies performed in these age groups could, therefore, not be established. In this risk assessment, the same tolerance level as for adults were assumed for children and adolescents (adjusted for body weight) for L-carnitine, L-carnitine-L-tartrate and tartaric acid.

VKM concludes that a dose of 1500 mg of L-carnitine per day, which is equivalent to a dose of 2250 mg of L-carnitine-L-tartrate per day, is unlikely to cause adverse health effects in adolescents (14 to <18 years old) and adults (≥ 18 years), whereas intake at this level in children (10 to <14 years) may represent a risk of adverse health effects. The tartaric acid exposure from this dose of L-carnitine-L-tartrate is unlikely to cause adverse health effects.

Adverse effects of L-carnitine or L-carnitine-L-tartrate are occasionally observed in vulnerable groups such as in patients with kidney disease and persons with high plasma values of TMA and TMAO. High plasma L-carnitine levels in subjects with concurrently high TMAO levels have been associated with cardiovascular disease and adverse cardiac events in patients undergoing cardiac evaluation. Adverse effects are suspected in patients with inborn errors of metabolism. Further, interactions with certain types of drugs have been reported.

An overview of the conclusions is given in Table 6-1. Estimated exposures unlikely to cause adverse health effects (below the value for comparison) is shown in green, whereas estimated exposures that may represent a risk of adverse health effects (above the value for comparison) is shown in red.

Table 6-1 An overview of the the conclusions. Green: estimated exposure unlikely to cause adverse health effects. Red: estimated exposure that may represent a risk of adverse health effects.

Food supplement	L-Carnitine	L-Carnitine-L-tartrate	Tartartic acid
	1500 mg/day	2250 mg/day (equivalent to 1500 mg carnitine/day)	750 mg/day
Age groups			
Children (10 to <14 years)			
Adolescents (14 to <18 years)			
Adults (≥18 years)			

7 Data gaps

- There is lack of acute, sub-chronic and chronic toxicity studies of L-carnitine in animals.
- There is lack of acute, sub-chronic and chronic toxicity studies of L-carnitine-L-tartrate in animals.
- There are few human studies on adverse health effects related to L-carnitine and L-carnitine-L-tartrate, especially in children and adolescents.
- No studies are found on effects of these substances in lactating or pregnant women.

8 References

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9 Appendix

Search Strategy Medline, Embase, Global Health:

1. l-carnitine* or carnitine* or l-carnitine-l-tartrate*).ti. (15403)
2. ((l-carnitine* or carnitine* or l-carnitine-l-tartrate*) adj3 (risk* or safety or adverse or reaction* or side-effect*1 or hazard* or harm* or negative or contraindicat* or contra-indicat* or interact* or consequence* or toxicity or toxic)).tw. (589)
3. 1 and 2 (488)
4. (conference abstract* or letter* or editorial*).pt. (3483123)
5. 3 not 4 (473)
6. remove duplicates from 5 (255)

Search strategy Web of Science:

3

266

#2 AND #1

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

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2

372

TS=(("l-carnitine*" or carnitine* or "l-carnitine-l-tartrate*") NEAR/3 (risk* or safety or adverse or reaction* or "side-effect*" or hazard* or harm* or negative or contraindicat* or "contra-indicat*" or interact* or consequence* or toxicity or toxic))

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

<https://images.webofknowledge.com/WOKRS5161B5/images/spacer.gif>

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4,581

(TI=("l-carnitine*" or carnitine* or "l-carnitine-l-tartrate*")) AND DOCUMENT TYPES: (Article OR Book OR Book Chapter OR Proceedings Paper OR Review)

Indexes=SCI-EXPANDED, SSCI, A&HCI Timespan=All years

After removal of the duplicates, the number of references retrieved was 378.