



VKM Report 2017:13

# Risk assessment of "other substances" – beta-alanine

**Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of  
the Norwegian Scientific Committee for Food Safety**



Report from the Norwegian Scientific Committee for Food Safety (VKM) 2017: 13  
Risk assessment of "other substances" – beta-alanine

Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the  
Norwegian Scientific Committee for Food Safety  
05.10.2017

ISBN: 978-82-8259-270-3

ISSN 2535-4019

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Cover photo: iStock Photo

Suggested citation: VKM. (2017). Risk assessment of "other substances" – beta-alanine  
Opinion of the Panel on Nutrition, dietetic products, Novel Food an Allergy of the Norwegian  
Scientific Committee for Food Safety, ISBN: 978-82-8259-270-3, Oslo, Norway



## **Risk assessment of "other substances" - beta-alanine**

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

### **Acknowledgment**

The Panel on Nutrition, Dietetic Products, Novel Food and Allergy has answered the request from the Norwegian Food Safety Authority. Project leader from the VKM secretariat has been Bente Mangschou. Martinus Løvik is acknowledged for his valuable work on this opinion. Jan Alexander (the Scientific Steering Committee), Åshild Krogdahl (the Scientific Steering Committee) and Helle Margrete Meltzer (former member of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy) constituted a reference group and are acknowledged for their valuable comments and suggestions on this opinion.

### **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 "other substances" in food supplements.

"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" the VKM has not evaluated any claimed beneficial effects from these substances, only possible adverse effects.

The present report is a risk assessment of specified doses of beta-alanine in food supplements, and it is based on previous risk assessments and articles retrieved from literature searches.

According to information from NFSA, beta-alanine is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of beta-alanine: 1000, 1500 and 2000 mg/day from food supplements.

Beta-alanine is a non-essential, non-proteogenic naturally occurring beta amino acid. Beta-alanine is a component of the naturally occurring peptides carnosine, anserine and balenine. Supplementation with beta-alanine leads to an increased production of the peptide carnosine, which is found in high concentrations in the skeletal muscle of both vertebrates and non-vertebrates. Data suggest that beta-alanine functions as a small molecule neurotransmitter and should join the ranks of the other amino acid neurotransmitters.

The only observed adverse effect from beta-alanine supplementation in humans is transient (1-2 hours) paraesthesia and flushing. Paraesthesia is characterised by a stinging or prickling sensation in the skin. There is no evidence that the paraesthesia in the skin is harmful in any way. Long-term studies in humans were not found. Four small human clinical studies have been included in this risk assessment. The occurrence of paraesthesia apparently is dependent on the magnitude of the individual doses that the daily dose is split into. Single doses of beta-alanine of 10 mg/kg bw (700 mg in a 70 kg person) or more provoked transient paraesthesia. Symptom occurrence and severity increased with the dose. Repeated intakes of 5 mg beta-alanine/kg bw or less taken with >2 hours intervals did not induce

paraesthesia. Haematology and plasma clinical chemistry was found normal after daily doses of 2.8 g and 3.2 g for 4 weeks in healthy adults. Apart from occasional paraesthesia, a daily dose of 6.4 g for up to seven weeks did not induce any adverse clinical effects in healthy adults of 80 kg, corresponding to a dose of 5.6 g per day in a 70-kg person.

We are not aware of any data indicating that children and adolescents are more vulnerable than adults for supplementation with beta-alanine on a per kg bw basis.

No relevant animal studies were identified.

VKM concludes that:

- In adults ( $\geq 18$  years), the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.
- In adolescents (14 to  $< 18$  years) and children (10 to  $< 14$  years) the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.

Children younger than 10 years were not within the scope of the present risk assessment.

### **Short summary**

At the request of the Norwegian Food Safety Authority, the Norwegian Scientific Committee for Food Safety (VKM) has characterised the risk of specified doses of beta-alanine in food supplements. VKM concludes that:

- In adults ( $\geq 18$  years), the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.
- In adolescents (14 to  $< 18$  years) and children (10 to  $< 14$  years) the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.



**Key words:** Beta-alanine, food supplement, adverse health effect, negative health effect, Norwegian Food Safety Authority, Norwegian Scientific Committee for Food Safety, other substances, risk assessment, 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 vitenskapelig grunnlag for å regulere "andre stoffer" i kosttilskudd.

"Andre stoffer" er beskrevet i kosttilskudddirektivet (2002/46/EF) som stoffer som har en ernæringsmessig eller fysiologisk effekt, og som ikke er vitaminer og mineraler. De tilsettes i hovedsak i kosttilskudd, men også i energidrikker og andre næringsmidler. I disse risikovurderingene har VKM kun vurdert mulige negative helseeffekter, ikke potensielle gunstige helseeffekter.

Denne rapporten er en risikovurdering av beta-alanin, og den er basert på tidligere risikovurderinger og artikler hentet fra litteratursøk.

Ifølge informasjon fra Mattilsynet er betaalanin en ingrediens i kosttilskudd som selges i Norge. Oppdraget fra Mattilsynet var å risikovurdere inntak på 1000, 1500 og 2000 mg/dag betaalanin i kosttilskudd.

Betaalanin er en ikke-essensiell, ikke-proteogen naturlig forekommende beta-aminosyre. Betaalanin inngår i naturlig forekommende peptider som karnosin, anserin og balenin. Tilskudd av betaalanin fører til økt produksjon av peptidet karnosin. Karnosin fins i høye konsentrasjoner i skjelettmuskulatur hos både virveldyr og ikke-virveldyr. Data tyder på at betaalanin fungerer som neurotransmitter.

Det eneste negative helseeffekten som er observert hos mennesker ved tilskudd med betaalanin er forbigående parestesier og flushing, det vil si lokal rødhet og varmfølelse. Parestesier gir en stikkende og prikkende følelse i huden, som kan oppleves som ubehagelig når den er sterk. Det finnes ikke dokumentasjon for at parestesier er skadelig, ut over ubehaget.

Kun fire små kliniske studier er inkludert i denne risikovurderingen. Det er ikke funnet langtidsstudier. Inntak av enkeltdoser med betaalanin på 10 mg/kg kroppsvekt (700 mg i en 70 kg person) eller mer, førte til parestesier. Symptomgraden økte med dosen. Gjentatte inntak av 5 mg betaalanin per kg kroppsvekt tatt med mer enn 2 timers mellomrom fremkalte ikke parestesier. Hematologi og klinisk-kjemiske undersøkelser var normale etter daglige doser på henholdsvis 2,8 g og 3,2 g betaalanin i 4 uker hos friske voksne. En daglig dose på 6,4 g i inntil 7 uker til friske voksne på 80 kg, svarende til 5,6 g for en person på 70 kg, ga ikke andre negative kliniske effekter enn noen tilfeller av parestesi, som synes å

avhenge av i hvor store enkeltdoser dagsdosen deles opp. Vi har ikke funnet data som kan tyde på at barn og ungdom har lavere toleranse enn voksne for tilskudd med betaalanin dosert på basis av kroppsvekt.

Det ble ikke identifisert noen relevante dyrestudier.

Vitenskapskomiteen for mattrygghet (VKM) konkluderer med at:

- For voksne ( $\geq 18$  år) er det usannsynlig at de spesifiserte dosene på 1000, 1500 og 2000 mg/dag betaalanin i kosttilskudd vil forårsake negative helseeffekter, forutsatt at hvert inntak er maksimalt 5 mg/kg kroppsvekt og at varigheten mellom inntakene er minimum 2 timer.
- For ungdom (14 til  $< 18$  år) og barn (10 til  $< 14$  år) er det usannsynlig at de spesifiserte dosene på 1000, 1500 og 2000 mg/dag betaalanin i kosttilskudd vil forårsake negative helseeffekter, forutsatt at hvert inntak er maksimalt 5 mg/kg kroppsvekt og at varigheten mellom inntakene er minimum 2 timer.

Barn under 10 år inngår ikke i dette oppdraget.

### **Kort sammendrag**

Vitenskapskomiteen for mattrygghet (VKM) har på oppdrag for Mattilsynet vurdert risiko ved inntak spesifikke doser av betaalanin i kosttilskudd. VKM konkluderer med at:

- For voksne ( $\geq 18$  år) er det usannsynlig at de spesifiserte dosene på 1000, 1500 og 2000 mg/dag betaalanin i kosttilskudd vil forårsake negative helseeffekter, forutsatt at hvert inntak er maksimalt 5 mg/kg kroppsvekt og at varigheten mellom inntakene er minimum 2 timer.
- For ungdom (14 til  $< 18$  år) og barn (10 til  $< 14$  år) er det usannsynlig at de spesifiserte dosene på 1000, 1500 og 2000 mg/dag betaalanin i kosttilskudd vil forårsake negative helseeffekter, forutsatt at hvert inntak er maksimalt 5 mg/kg kroppsvekt og at varigheten mellom inntakene er minimum 2 timer.



# Abbreviations and glossary

## Abbreviations

AESAN	- Spanish Agency for Food Safety and Nutrition
bw	- body weight
EFSA	- European Food Safety Authority
IOM	- Institute of Medicine, USA
mrg	- mas-related gene
NFSA	- Norwegian Food Safety Authority [ <i>Norw.</i> : Mattilsynet]
UL	- tolerable upper intake level
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 (European Regulation (EC) No. 1925/2006, Article 2; <http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R1925&from=en>).

"Negative health effect" and "adverse health effect" are broad terms. The World Health Organization (WHO) has established the following definition of "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).

An adverse event is considered serious if it results in death, is life-threatening, requires or prolongs hospitalisation, is a congenital anomaly or birth defect, is a persistent or significant disability/incapacity, or is another serious or important medical event.

## 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 other 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, aromas, 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 beta-alanine in food supplements at the following doses: 1000, 1500 and 2000 mg/day.

NFSA requested VKM to assess the safety of "other substances" (in accordance with the guidance document developed in Phase 2) for the specified doses (Phase 3).

The safety assessments for "other substances" present in food supplements shall be carried out for the general population, age 10 years and older.

# 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.

This risk assessment regards the substance beta-alanine per se, and no specific products.

In this series of risk assessments of "other substances" the VKM has not evaluated any claimed beneficial effects from these substances, but merely possible adverse effects at specified doses used in Norway.

According to information from the Norwegian Food Safety Authority (NFSA), beta-alanine is an ingredient in food supplements sold in Norway. NFSA has requested a risk assessment of the intake of 1000, 1500 and 2000 mg beta-alanine per day from food supplements. The total beta-alanine exposure from other sources than food supplements is not included in the risk assessment.

Foods rich in beta-alanine are in particular those made from skeletal muscle of vertebrates as well as non-vertebrates. The amount of beta-alanine intake from food is unknown.

Beta-alanine is a naturally occurring amino acid, with the amino group at the beta-position from the carboxylate group. Beta-alanine is not used in the biosynthesis of any major proteins or enzymes and is therefore described as non-proteogenic. Beta-alanine is a component of the naturally occurring peptides carnosine (beta-alanyl-L-histidine), anserine (beta-alanyl-N(pi)-methyl-L-histidine) and balenine (beta-alanyl-N tau-methyl histidine) and is also a metabolite of pantothenic acid (vitamin B<sub>5</sub>). Moreover, beta-alanine is produced by breakdown of pyrimidine nucleotides. Beta-alanine is produced endogenously in the liver of many animals, but at varying rates. In humans, beta-alanine is mostly acquired through consumption of foods.

## 2 Hazard identification and characterisation

### 2.1 Literature

This risk assessment is based on previous risk assessments of beta-alanine, as well as scientific papers retrieved from systematic literature searches.

#### 2.1.1 Previous risk assessments

Risks related to beta-alanine have previously been evaluated by VKM in 2011 and the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) for use in food supplements in 2012.

##### ***VKM report on risk categorisation of amino acids. Norway, 2011***

In 2011, VKM conducted a risk categorisation of about 30 amino acids and amino acid compounds based on potential health risks related to high intakes of the amino acids (VKM, 2011).

According to the report, beta-alanine provided as gelatine capsules in single doses of > 10 mg/kg bw per day (> 700 mg in a 70 kg person) resulted in transient paraesthesia. Beta-alanine consumed from foods as carnosine (e.g. meats or chicken broth) up to 40 mg/kg bw per day did not induce adverse effects. Based on these results, which were retrieved from Harris et al. (2006), beta-alanine was grouped as a low risk amino acid. It was, however, emphasised that the VKM report from 2011 had several limitations and could only be regarded as an initial screening and not as risk assessment of the many amino acids.

##### ***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. Spain, 2012.***

In 2012, AESAN stated that doses of beta-alanine above 10 mg/kg bw have been observed to provoke adverse effects. The adverse effects are associated with its potential to induce paraesthesia, characterised by an increase in the sensitivity of the nociceptive neurons, the transmitters of neuropathic pain, causing a stinging sensation and redness on the skin

(Crozier et al., 2007; Harris et al., 2006; Sale et al., 2010). The studies by Harris et al (2006) (see section 2.4.1) are discussed.

The plasma kinetics and the incidence of symptoms similar to paraesthesia were monitored in a randomised, simple blinded test that involved gradual release over time of a beta-alanine supplement (Decombaz et al., 2012). Healthy adults (n = 11) received three treatments: 1.6 g of gradually-released beta-alanine orally, the same dose administered normally (bolus), and a placebo. Urine and plasma samples were taken during the 6 hours following the administration of each treatment and a questionnaire was given to the participants. The gradually-released beta-alanine caused lower and later plasma peaks, together with reduced loss through urine indicating a greater retention of beta-alanine. The standard form of administering beta-alanine led to paraesthesia, whereas the gradually-released dose and the placebo behaved similarly and triggered no symptoms. The authors concluded that higher doses (>10 mg/kg bw) of gradually-released beta-alanine can be taken without the risk of paraesthesia (Decombaz et al., 2012).

In conclusion, AESAN (2012) considers that the precautions to be adopted when beta-alanine is used as a food supplement are due to its potential to induce paraesthesia. High doses of beta-alanine (above 10 mg/kg bw per day) may produce paraesthesia. Moreover, individuals with a predisposition to paraesthesia should refrain from taking this food supplement.

## **2.1.2 Literature search**

Literature searches were performed in MEDLINE and EMBASE in order to retrieve publications on adverse effects caused by beta-alanine. Both databases were searched to ensure comprehensive study retrieval. The literature search for human studies was conducted on 13 September 2016, and the search for animal studies was conducted on 28 October 2016. The strategies for the searches are outlined in Appendix 1.

### ***2.1.2.1 Publication selection and data extraction***

The literature search for human studies identified 367 articles, and the literature search for animal studies identified 395 articles. In the primary screening, titles and abstracts of all unique publications retrieved were independently screened against the inclusion criteria.

Inclusion criteria:

- An adverse effect/adverse effects in relation to beta-alanine alone is addressed
- Route of exposure for humans is oral



- Route of exposure for animals is oral, in addition, subcutaneous exposure is included if the toxicokinetics are equal as by oral exposure
- Human studies are performed in apparently healthy individuals or patient groups assumed to have normal alanine absorption and metabolism
- Animal model studies address adverse effects relevant to human health

In vitro studies were not included.

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. Titles and abstracts that did not fulfil the inclusion criteria were excluded from further screening. In situations where it was unclear whether the publication was of relevance to the current risk assessment, it was retained for further screening. The primary screening was performed independently by two persons.

The papers that passed the primary screening were reviewed in full text against the same inclusion criteria by the author of this report.

In the search aimed at human studies, the screening of titles and abstracts resulted in 25 full text articles, while the full-text review resulted in 3 relevant articles. In addition, one publication from a manual search was identified and reviewed. In the literature search aimed at retrieving animal studies, no titles and abstracts passed the primary screening. Thus, in total, four human studies was found relevant and included in the results in this report (see Figure 2.1.2.1-1).

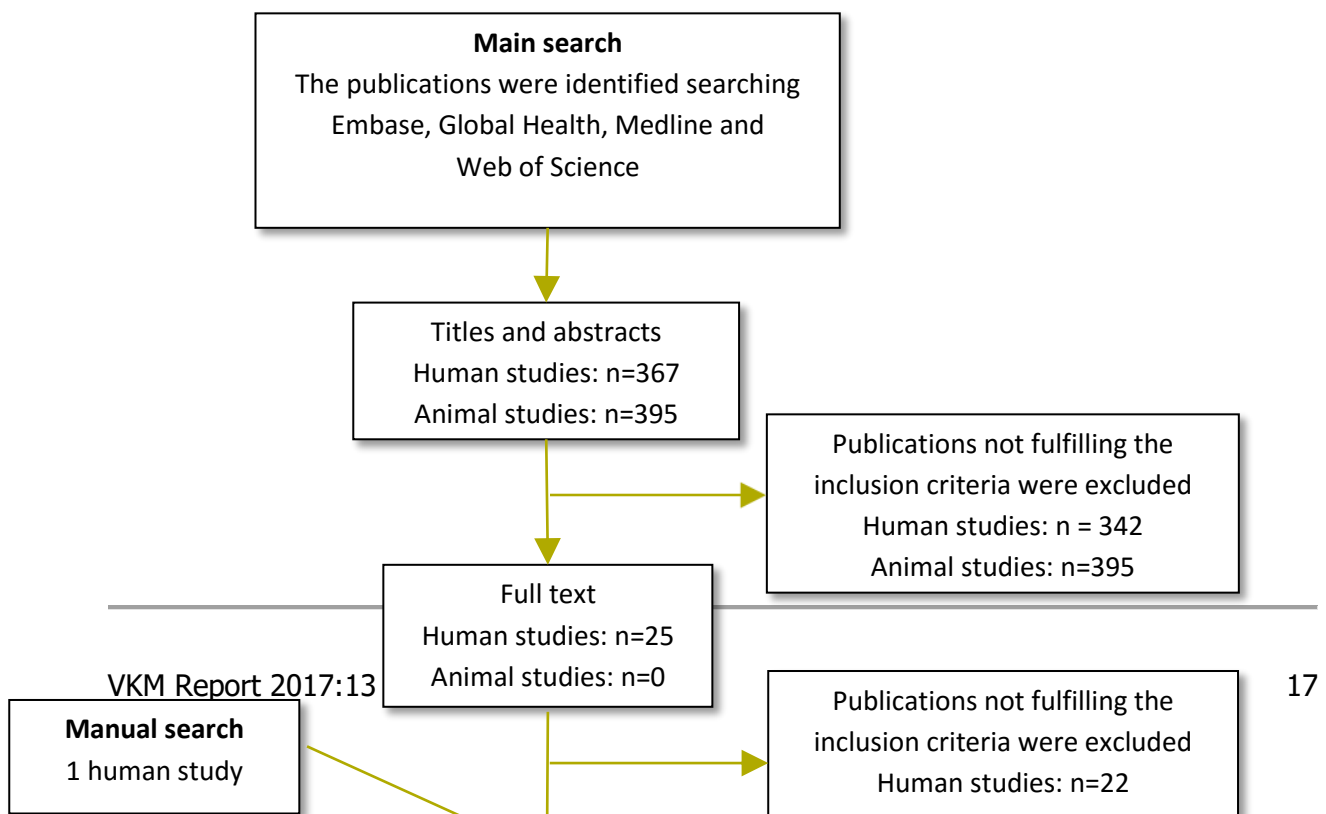




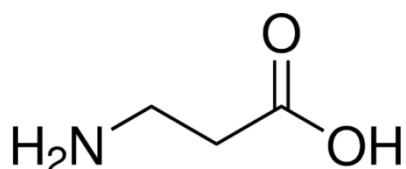
Figure 2.1.2.1-1: Flowchart for publication selection for beta-alanine.



## 2.2 General information

### 2.2.1 Chemistry

Beta-alanine is a non-essential amino acid that is formed by the degradation of dihydrouracil. It may also be formed by degradation of the dipeptides carnosine, anserine and balenine, where carnosine is the major source for beta-alanine in vivo. The molecular formula is  $C_3H_7NO_2$ , and the CAS number is 107-95-9. The structural formula is shown in figure 2.2.1-1.



**Figure 2.2.1-1:** Structural formula of beta-alanine.

### 2.2.2 Occurrence

Beta-alanine is a component of the naturally occurring peptides carnosine, anserine and balenine. Carnosine is found in high concentrations in the skeletal muscle of both vertebrates and non-vertebrates, where it is believed to function as a small molecule neurotransmitter. Meat and fish are rich food sources of beta-alanine.

## 2.3 Absorption, distribution, metabolism and excretion

### 2.3.1 In humans

Beta-alanine is a naturally occurring amino acid in which the amino group is at the beta-position from the carboxylate group. Beta-alanine is a component of the naturally occurring peptides carnosine (beta-alanyl-L-histidine), anserine (beta-alanyl-N(pi)-methyl-L-histidine) and balenine (beta-alanyl-N tau-methyl histidine) and also of pantothenic acid (vitamin B<sub>5</sub>), a component of coenzyme A. Carnosine is the most abundant beta-alanine containing peptide and is a cytoplasmic dipeptide found in high concentrations in skeletal muscle, as well as in the central nervous system (Sale et al., 2010). Beta-alanine is the rate-limiting precursor of carnosine synthesis (Sale et al., 2010). This means that endogenous carnosine levels are limited by the amount of available beta-alanine. Carnosine concentrations in human skeletal muscle is in the magnitude of 20 mmol/kg dry muscle (Mannion et al., 1992). Data suggest

that beta-alanine functions as a small molecule neurotransmitter and should join the ranks of the other amino acid neurotransmitters (Tiedje et al., 2010).

Under normal conditions, beta-alanine can undergo a transamination reaction with pyruvate to form malonate-semialdehyde and L-alanine. The malonate semialdehyde can then be converted into malonate via malonate-semialdehyde dehydrogenase. Malonate is then converted into malonyl-CoA and enter fatty acid biosynthesis.

Beta-alanine is produced endogenously in the liver of many animals, but at varying rates. Increasing beta-alanine concentration has been found to increase the concentration of carnosine in the skeletal muscle of both vertebrates and non-vertebrates. The species having the highest skeletal muscle beta-alanine containing dipeptide concentrations are those whose muscles are exposed to frequent bouts of hypoxia, such as diving whales, or those who depend upon anaerobic exercise for survival, such as hunting or escaping animals (Abe, 2000). High beta-alanine containing dipeptides have been shown in several species involved in athletic competition, such as horses, greyhounds, camels and, indeed, humans (Dunnett and Harris, 1997; Harris et al., 1990). Moreover, the distribution of beta-alanine containing carnosine varies in skeletal muscle across species and between different muscle fibre types in the same species. The beta-alanine containing peptide carnosine acts as an intracellular proton chelator and hence pH buffer (Severin et al., 1953) and a potent antioxidant (Kohen et al., 1988).

## **2.4 Toxicological data/Adverse effects**

The only adverse effect from beta-alanine reported in literature is paraesthesia (i.e. a tingling or prickling sensation) in the skin. The paraesthesia has mainly been experienced in the face, neck and back of hands, but also on the upper trunk and lower back. It may vary in severity from a light, almost pleasant tingling to a strongly uncomfortable feeling. Paraesthesia is commonly experienced in individuals consuming single doses of 10 mg beta-alanine/kg bw or more (Trexler et al., 2015). It appears to be dose-dependent both with regard to occurrence and severity (Harris et al., 2006; see also below). However, after an interval of 2-3 hrs or more, another dose can be taken without significantly increased risk of paraesthesia (Harris et al., 2006). Thus, two different safety issues emerge: one is the magnitude of the individual dose, the other is the magnitude of the total daily intake. Regarding the individual dose, for most individuals, a dose of 400 mg beta-alanine ingested acutely was symptom free, and this dose has frequently been used in various studies (e.g. (Baguet et al., 2009; Derave et al., 2007; Harris et al., 2006)). With 500 mg doses, no symptoms were reported and treatment identification was not different between verum and placebo (Van Thienen et al., 2009). With 800 mg doses (10 mg/kg bw), Harris et al. (2006)

acknowledged “mild symptoms of flushing” in about 25% of about 50 subjects, while Hill et al. (2007) report that symptoms were “infrequent and mild when they occurred”. With a 1.6-g dose, symptoms were recorded as “significant” in three of four subjects (Harris et al., 2006), and one third of 11 participants in the study reported by Decombaz et al. (2012) had moderate to low-intensity symptoms. Brisola et al. (2016) reported paraesthesia in three out of 11 study subjects. No symptoms were reported for this dose in other studies (Stout et al., 2007) although, as communicated later, about 20% of the subjects reported “tingling” sensations with beta-alanine in this study (J. Stout, personal communication, cited in: Décombaz et al., 2012). This illustrates that paraesthesia symptoms may be under-reported in some studies. When increasing beta-alanine doses to 2 g, Sweeney et al. (2010) reported “no side effects other than a mild prickling sensation” in the neck and the limbs, while Bellinger and Minahan (2016) reported paraesthesia in a study of eight cyclists, two of which found the feelings uncomfortable or unpleasant. Macphee et al. (2013) gave a dose of 3 g beta-alanine to 20 study subjects; no response rate is given, but the data presented indicate that at least 15 out of 20 participants experienced paraesthesia, and one third of them characterised their symptoms as extremely bothersome. With single beta-alanine doses of 3.2 g (40 mg/kg bw) and greater, side-effects were perceived as “unpleasant” (Harris et al., 2006). Thus, it appears that a single doses up to 500 mg will be well tolerated, while a dose of 800 mg frequently will provoke mild, transient paraesthesia symptoms, and with higher doses the incidence and severity of paraesthesia will increase progressively.

Another peculiarity is that after an interval of 2-3 hours since taking beta-alanine, plasma concentrations of beta-alanine have normalised, and a new dose will be tolerated. This may be repeated several times over the day (Harris et al., 2006). If paraesthesia is to be avoided, individual doses should therefore be 500 mg or lower for a 70 kg person. Higher daily doses should be split accordingly, and individual doses should be taken with 2-3 hour intervals. With slow-release preparations of beta-alanine, higher individual doses have been reported to be tolerated compared to the soluble powder form (Decombaz et al., 2012; Stellingwerff et al., 2012).

## 2.4.1 Human studies

Table 2.4.1-1 An overview of human studies investigating beta-alanine and adverse health effects.

Reference	Study design/ participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Length of follow-up eller duration of the study	Adverse effect
			Beta- alanine	Control				
Harris et al., 2006 (studies 1, 2, and 3)	Healthy male volunteers	UK, South Korea and USA				Circulating beta-alanine, muscle carnocine		

Reference	Study design/ participant characteristics	Country	Number in treatment group		Dose	Main endpoint	Length of follow-up or duration of the study	Adverse effect
			Beta- alanine	Control				
Study 1			n=6		0, 10, 20, 40 mg/kg bw		2 hours	10, 20 and 40 mg/kg bw transient paraesthesia (mild to unpleasant)
Study 2			n=6		10 mg /kg bw x 3 per day		2 weeks	Occasional flushing
Study 3 Pre-study  Main study			n=8  n = 5 n=5	n=8  n = 6	10 mg/kg bw x 4  Stepwise increase from 5 mg/kg bw x 6 plus 10 mg/kg bw x 2 to 10 mg/kg bw x 8	Haematology , clinical chemistry	4 weeks  4 weeks	Occasional mild flushing  Mild symptoms of flushing
Brisola et al., 2016	Randomised, double blind, parallel-group, placebo- controlled	Brazil	13 (11 analys. )	14 (11 analys.)	4.8 g/day (800 mg x 6) for 10 days, then 6.4 g/day (1600 mg x 4) for 18 days	Repeated sprint ability	28 days (18 days highest dose)	Paraesthesia in 4 subjects (3 in verum group, 1 in placebo group)
Hill et al., 2007	Randomised, placebo- controlled, double blind	Chichester, U.K.	13 – after week 4 n=6	12 – after week 4 n=6	400 mgx6 + 800 mgx2 first week, 400 mgx4 + 800 mgx4 for second week, 400 mgx2 + 800 mgx6 third week, 800 mgx8 for 7 weeks	Muscle carnosine accumulation ; high- intensity cycling capacity	10 weeks, 7 on the highest dose	Symptoms of paraesthesia infrequent and mild
Stellingwerff et al., 2012	Placebo- controlled, double-blind, randomised, parallel-design (3 arms), single center study	Switzerland	10 (high- low), 11 (low- low)	10	High-low: 3.2 g beta- alanine per day 4 weeks, 1.6 g beta- alanine 4 weeks Low-low: 1.6 g beta-alanine per day 8 weeks	Muscle carnosine synthesis	8 weeks + 8 weeks wash- out followed. Clin chem and hema- tology after 8 weeks intervention	Pre- screened for paraesthesia reactors

## **The absorption of orally supplied beta-alanine and its effect on muscle carnosine synthesis in human vastus lateralis. Harris et al., 2006.**

Harris et al. (2006) performed a study where the absorption of orally supplied beta-alanine in its free form, or as carnosine in chicken broth, was examined in the context of beta-alanine blood concentrations and muscle carnosine synthesis. VKM has only considered the data from beta-alanine consumed in free form in the present report.

Study 1: Six healthy male subjects with mean $\pm$ SD age of 33.5  $\pm$ 9.9 yrs and weighing 80.2  $\pm$  17.1 kg were recruited to this study where beta-alanine was administered at single doses of 0, 10, 20 and 40 mg/kg bw. Plasma beta-alanine peaked after 30-40 min and regained baseline at 2-3 hours after administration. Subjects given 40 mg/kg bw of beta-alanine quickly complained of symptoms of flushing (described variously as an irritation of the skin and prickly sensation) which began within 20 minutes and lasted up to one hour after administration. As a result, the two lower doses of 10 and 20 mg/kg bw were introduced and similar symptoms were evident at 20 mg/kg bw and followed a similar time course, but were judged to be less intense. Mild symptoms of flushing were experienced by 2 of the 4 subjects taking 10 mg/kg bw. Based on this study, two additional studies (studies 2 and 3) were conducted.

Study 2: The blood levels of beta-alanine were investigated in 6 males aged 28.3  $\pm$  2.7 years and weighing 83.2  $\pm$ 14.3 kg. Each subject was given three daily doses of 10 mg/kg bw beta-alanine at 0, 3 and 6 h over a period of 15 days. The plasma concentration of beta-alanine peaked within 30-40 minutes of the intake and returned to baseline before the next intake. Notably, this repeated dosing did not give rise to any negative health affects apart from the occasional report of mild symptoms of flushing.

Study 3: In the first part (pre-study), 8 male subjects for four weeks ingested four doses per day of 800 mg (10 mg/kg bw) beta-alanine in gelatine capsules (2 x 400 mg) at 9 am, 12 am, 3 pm and 6 pm, giving a dose of 3.2 g/day, while 8 male subjects had a corresponding intake of placebo capsules (n=16, 19.4  $\pm$  SD 1.6 yrs; 79.5  $\pm$  9.3 kg). The aim was to study effects of beta-alanine on haematology and clinical chemistry. It is stated that no clinically significant changes in 25 haematological and biochemical parameters were observed by the end of the 4-week period (results given, but statistical analysis not presented).

For the second (main) part, to measure effects on muscle, twenty-one males (26.1  $\pm$ 5.6 years; 79.5  $\pm$ 10.5 kg) were recruited. Of these, two groups (n=5) consumed beta-alanine 8 times a day for four weeks (9, 10, 11, 12 am, 3, 4, 5, 6 pm), while a third group (n=6) took placebo (maltodextrin). One of the verum groups took 800 mg beta-alanine 4 times per day (daily dose 3.2 g) for four weeks. The other verum group took beta-alanine as follows: In

week one the subjects consumed a daily dose of 4 g (400 mg x 6 plus 800 mg x 2). In week two the daily dose was increased to 4.8 g (400 mg x 4 plus 800 mg x 4). In week three the daily dose was increased to 5.6 g (400 mg x 2 plus 800 mg x 6) whereas in week four the daily dose was increased to 6.4 g (800 mg x 8). There were no clinically significant symptoms during the study, apart from mild symptoms of flushing in some subjects (4 subjects in week 2). One subject given the placebo also recorded mild symptoms of flushing. The authors stated that in later studies, involving about 50 subjects given 800 mg beta-alanine (about 10 mg/kg bw) per day, about 25% of subjects reported mild or very mild paraesthesia symptoms.

### **Influence of $\beta$ -alanine supplementation on skeletal muscle carnosine concentrations and high intensity cycling capacity. Hill et al., 2007**

Hill et al. (2007) report a randomised, double blind, parallel-group, placebo-controlled study (n=25) on beta-alanine supplementation, with muscle carnosine levels and high-intensity cycling capacity as the main outcome. Subjects took placebo or beta-alanine 5 mg/kg bw x 6 plus 10 mg/kg bw x 2 (daily dose 4.0 g) the first week, 5 mg/kg bw x 4 plus 10 mg/kg bw x 4 (daily dose 4.8 g) the second week, 5 mg/kg bw x 2 plus 10 mg/kg bw x 6 (daily dose 5.6 g) the third week, and 10 mg/kg bw x 8 (4.8 g/day) from week 4 through week 10 (7 weeks). Thirteen participants stopped the experiment after week 4 by design, while 6 participants taking verum and 6 taking placebo continued through week 10, i.e. for a total of 7 weeks with the highest dose of 6.4 g/day. By design any side effects were to be recorded. Side effect-relevant blood analyses were not performed. Symptoms of paraesthesia were 'infrequent and mild' when they occurred (number not given), no other adverse effects are reported.

### **Effects of four weeks of $\beta$ -alanine supplementation on repeated sprint ability in water polo players. Brisola et al., 2016**

Brisola et al. (2016) report a randomised, double blind, parallel-group, placebo-controlled study on beta-alanine supplementation, with repeated sprint ability in water polo players (n=27) as the main outcome. Subjects took beta-alanine 4.8 g/day (800 mg x 6) for 10 days, then 6.4 g/day (1600 mg x 4) for 18 days. In the placebo group 2 subjects were lost to follow-up (injured), and in the verum group 3 subjects were lost (1 injured, 2 left the team), so that in each group 11 subjects were included in the analyses. Side effects were to be reported by design. Side effect-relevant blood analyses were not performed. Paraesthesia occurred in 4 subjects (3 in verum group, 1 in placebo group), no other adverse effects are mentioned.



## **Effect of two $\beta$ -alanine dosing protocols on muscle carnosine synthesis and washout. Stellingwerff et al., 2012**

Stellingwerff et al. (2012) performed an eight-week placebo-controlled double-blind study in thirty-one young males randomised into three groups, receiving either 3.2 g (40 mg/kg bw) beta-alanine for four weeks followed by 1.6 g (20 mg/kg bw) beta-alanine for the next four weeks, 1.6 g beta-alanine for eight weeks, or placebo. Slow-release, 800-mg tablets were used. A wide range of haematology and clinical chemistry parameters were measured at baseline and at week 8. A questionnaire-based self-assessment of possible paraesthesia symptoms was conducted at weeks 0, 2, 4, and 8. A number of questionnaires were used, for body surface symptom score, profile of mood states, anxiety, and flushing symptoms. Participants had been pre-screened for re activity to a 400-mg dose (5 mg/kg bw) of a conventional beta-alanine preparation. Flushing symptoms and blood clinical chemistry findings were reported to be 'trivial' in all three groups in this pre-screened population, with no statistical differences. It should be noted that although plasma kinetics of beta-alanine and therefore presumably the risk of paraesthesia differs between conventional and slow-release preparations, the area under the curve has been reported to be similar with conventional and slow-release beta-alanine preparations (Decombaz et al., 2012). Hence, the doses used in the present study are relevant in the discussion of potential toxicity (apart from paraesthesia) of conventional beta-alanine preparations.

### **2.4.1.1 Interactions**

There was no information concerning interactions in the literature reviewed in the present risk assessment. The absence of information in the selected literature does not document an absence of interactions.

### **2.4.1.2 Allergic sensitisation (including adjuvant effects)**

There was no information concerning allergic sensitisation or allergy adjuvant effects in the literature reviewed in the present risk assessment. Beta-alanine per se would not be expected to behave as an allergen. The absence of information in the selected literature does not document an absence of allergic sensitisation or allergy adjuvant effects.

## **2.4.2 Animal studies**

VKM considers that the available animal data are insufficient for use in the present report as they rely on experiments where beta-alanine has not been given in a free form, but as carnosine or peptide solutions.



### **2.4.3 *In vitro* studies**

No *in vitro* studies of relevance were identified.

### **2.4.4 Mode of action for adverse effects**

Several possible mechanisms exist for the well-known side effect of paraesthesia, including beta-alanine activated strychnine-sensitive glycine receptor sites, associated with glutamate sensitive N-methyl-D-aspartate receptors in the brain and central nervous system (Mori et al., 2002; Tokutomi et al., 1989; Wang et al., 2003). Beta-alanine stimulation of nociceptive neurons is expected to be the transmitters of neuropathic pain. Moreover, it has been suggested that beta-alanine activates Mas-related genes (Mrg) or sensory neuron specific G-protein coupled receptors (Shinohara et al., 2004). Specifically, MrgD, which is expressed in the dorsal root ganglion, terminates in the skin (Crozier et al., 2007) and it is likely that activation of MrgD from beta-alanine results in paraesthesia only in the skin. However, there is no evidence that the paraesthesia in the skin is harmful in any way apart from the discomfort (Bellinger and Minahan, 2016; Trexler et al., 2015).

### **2.4.5. Vulnerable groups**

No vulnerable groups to excess doses of beta-alanine have been reported, apart from a preliminary study suggesting possible gender and ethnicity-dependent differences regarding paraesthesia (Macphee et al., 2013). There have been no reported studies involving children, elderly, pregnant women or lactating women.

## **2.5 Summary of hazard identification and characterisation**

The only observed adverse effect from beta-alanine supplementation in humans is short-lasting (60-120 min) paraesthesia (tingling, prickling, pin-and-needles sensation) that may be accompanied by flushing. There is no evidence that the paraesthesia and flushing in the skin is harmful (Bellinger and Minahan, 2016; Trexler et al., 2015), apart from the short-lasting discomfort. The incidence and intensity of the discomfort appears to be dose-dependent, and paraesthesia appears to occur rarely after a single dose smaller than 10 mg beta-alanine. This applies also if the dose is repeated after an interval of 2-3 hrs or more. The 10-mg dose of beta-alanine is frequently accompanied by mild paraesthesia. Higher doses may give stronger discomfort (Harris et al., 2006).

In their 2006 paper, Harris et al. presented data from three placebo-controlled studies of healthy subjects consuming beta-alanine according to specific dosing regimens. A dose of

800 mg in 80-kg subjects i.e. 10 mg/kg bw four times daily over four weeks induced occasional symptoms of flushing, but no biologically relevant changes in 25 haematological and biochemical parameters. With increased frequency of beta-alanine intakes (8 doses daily, 400 and 800 mg doses) and incremental increase in the daily doses from 4 g the first week up to a maximum of 6.4 g the fourth week, four weeks of beta-alanine supplementation still produced only occasional episodes of flushing.

In humans, paraesthesia may be provoked at intakes of beta-alanine of 10 mg/kg bw and higher. This implies that the individual dose of beta-alanine should not exceed 5 mg/kg bw (350 mg for a person of 70 kg bw), but this dose can be administered several times a day with 2-3 hour intervals as serum levels then have been normalised (Harris et al., 2006). If mild paraesthesia symptoms are seen as acceptable, single doses of 10 mg/kg bw taken with down to 1-hour intervals appear to be without other adverse health effects (Harris et al., 2006) (Study 3, second part).

The studies by Harris et al. (2006), Hill et al. (2007, and Brisola et al. (2016) indicate that given a proper splitting of the daily dose as discussed above, a daily dose of 6.4 g beta-alanine in an 80-kg person (corresponding to 5.6 g or 80 mg/kg bw for a 70-kg person) for up to 7 weeks is unlikely to trigger adverse effects. With regard to haematology and clinical chemistry, support for this conclusion - although with half the dose of beta-alanine - is provided by the studies of Stellingwerff et al. (2012) and Harris et al. (2006).

In summary, intake of individual doses of beta-alanine at 5 mg/kg bw or less is expected not to produce symptoms, whereas a dose of 10 mg/kg bw is associated with occasional mild symptoms of paraesthesia and flushing. Repeated intakes at 2-3 hour intervals of beta-alanine with maximum 5 mg/kg bw per intake and a maximum daily dose of 6.4 g of beta-alanine in an 80-kg person (corresponding to about 80 mg/kg bw per day, or 5.6 g in a 70 kg adult) can be consumed without significant adverse health effects. VKM will in the present report use 80 mg/kg bw per day as the value of comparison.

## 3 Exposure / Intake

Exposure to beta-alanine was estimated from the intake of food supplements. For food supplements, the intake was estimated for the age groups 10 to <14 years, 14 to <18 years and adults (≥18 years).

### 3.1 Food supplements

The Norwegian Food Safety Authority requested VKM to perform a risk assessment of 1000, 1500 and 200 mg/day of beta-alanine in food supplement for children (10 – 17 years) and adults. The default body weights for age groups determined by EFSA were used: 10 to <14 years = 43.4 kg, 14 to <18 years = 61.3 kg and adults = 70.0 kg. The exposures per kg bw are given in Table 3.1-1.

**Table 3.1-1** Estimated exposures of beta-alanine from specified doses in food supplements in children, adolescents and adults.

Groups	Beta-alanine, daily doses (mg)	Body weight (kg)	Exposures, (mg/kg bw per day)
<b>Children (10 to &lt;14 years)</b>	1000, 1500 and 2000	43.4	23.0, 34.6 and 46.1
<b>Adolescents (14 to &lt;18 years)</b>	1000, 1500 and 2000	61.3	16.3, 24.5 and 32.6
<b>Adults (≥18 years)</b>	1000, 1500 and 2000	70.0	14.3, 21.4 and 28.6

### 3.2 Other sources

Foods rich in beta-alanine are in particular those prepared from skeletal muscle from vertebrates or invertebrates.

## 4 Risk characterisation

The doses of beta-alanine in food supplement for which the Norwegian Food Safety Authority requested VKM to perform a risk assessment were 1000, 1500 and 2000 mg/day of for children (10 – 17 years) and adults. The default body weights for age groups determined by EFSA were used: 10 to <14 years = 43.4 kg, 14 to <18 years = 61.3 kg and adults = 70.0 kg.

Harris et al. (2006) gave 5 subjects (80 kg) stepwise increasing divided daily doses of 4.0 g, 4.8 g, 5.6 g and 6.4 g (highest dose corresponding to 5.6 g or 80 mg/kg bw for a 70 kg person) over four weeks, with no adverse clinical effects observed other than occasional flushing. No haematological or blood clinical chemistry analyses were done. In the study by Hill et al. (2007), 6 subjects took beta-alanine 4.0 g for one week, followed by daily doses of 4.8 g the second week and 5.6 g the third week. Thereafter, daily doses of 6.4 g (corresponding to 5.6 g or 80 mg/kg bw for a 70 kg person) were taken for 7 weeks. No adverse effects were noted other than symptoms of paraesthesia that were 'infrequent and mild when they occurred'. Brisola et al. (2016) gave 14 subjects beta-alanine 4.8 g per day in divided doses for 10 days, followed by 18 days with a daily dose of 6.4 g beta-alanine (corresponding to 80 mg/kg bw). In the 11 participants included in the analysis, no adverse effects were reported except for infrequent and mild paraesthesia, which appears to be dependent on the single dose rather than the total daily dose (see above).

Regarding laboratory parameters, in the study by Harris et al. (2006), beta-alanine 10 mg/kg bw x 4 per day (40 mg/kg bw or 2.8 g for a 70 kg person daily dose) for four weeks was found not to be associated with any significant change in haematology or clinical chemistry. There were no other signs and symptoms of any adverse effect, except for some cases of mild flushing (paraesthesia) that can be attributed to the magnitude of the individual doses. One other study can be considered as supportive with regard to haematology and clinical chemistry. Stellingwerff et al. (2012) with a slow-release preparation giving the same plasma level area-under-the-curve as regular soluble beta-alanine found that the dosage schemes of either 3.2 g beta-alanine per week for four weeks followed by 1.6 g beta-alanine for another four weeks or 1.6 g per day for 8 weeks gave no clinically relevant changes in haematological or clinical chemistry parameters.

No adverse effects other than paraesthesia have been reported after beta-alanine intake, and general considerations of the metabolism of beta-alanine do not indicate any particular risk of adverse effects. Based on the studies by Harris et al. (2006), Hill et al. (2007), Brisola et al. (2016) and supported by the study of Stellingwerff et al. (2012), VKM will in the

present report use 80 mg/kg bw per day (corresponding to 5.5 g for a 70 kg person) as the value of comparison (divided doses must be used, see above for magnitude of individual doses and dosing intervals).

Our literature review did not reveal any studies of beta-alanine in children or adolescents, and there were no studies in children 10 years or older included in previous risk assessments. There are no data indicating that children and adolescents are more vulnerable than adults for beta-alanine.

The margin of exposure (MOE-values) between 80 mg/kg bw per day and the exposures of beta-alanine from the specified food supplement doses, relevant for hypothetical adverse effects other than paraesthesia, are presented in Table 4-1.

**Table 4-1:** The calculated margins between the value for comparison (80 mg/kg bw per day) and the exposure to beta-alanine from food supplements (MOE-values) for the various age groups.

<b>Age groups</b>	<b>1000 mg/day</b>	<b>1500 mg/day</b>	<b>2000 mg/day</b>
<b>Children (10 to &lt;14 years) (43.4 kg)</b>	3.5	2.3	1.7
<b>Adolescents (14 to &lt;18 years) (61.3 kg)</b>	4.9	3.3	2.5
<b>Adults (≥18 years) (70 kg)</b>	5.6	3.7	2.8

The calculated MOE-values for data from the human studies ranged from 5.6 to 1.7 for a daily intake of 1000-2000 mg/day of supplemental beta-alanine.

MOE-values below 10 in Table 4-1 (for interindividual differences in humans) were regarded as acceptable since beta-alanine is not known to cause any adverse health effects apart from the paraesthesia that is avoided by taking individual doses not exceeding 5 mg/kg bw, and since beta-alanine also is produced by the body and several foods contain significant amounts of beta-alanine.



VKM finds that it is unlikely that the specified doses of 1000, 1500 and 2000 mg of beta-alanine in food supplements given to adults ( $\geq 18$  years), adolescents (14 to  $<18$  years) and children (10 to  $<14$  years) will cause adverse health effects (provided that beta-alanine is consumed with 5 mg/kg bw or less per intake and with a minimum of 2 hours between the intakes).

VKM considers that:

- In adults ( $\geq 18$  years), the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with 5 mg/kg bw per intake and preferably with 2 hours between the intakes.
- In adolescents (14 to  $<18$  years) and children (10 to  $<14$  years) the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with 5 mg/kg bw per intake and preferably with 2 hours between the intakes.



## 5 Uncertainties

The present risk assessment involves uncertainty related to:

- the lack of long-term studies in humans reporting on potential adverse health effects of long-term beta-alanine supplementation at or above 80 mg/kg bw per day
- Individual variation, as the quoted studies were small and mostly performed in males only, while some studies suggest gender and ethnic differences in susceptibility to paraesthesia
- the fact that clinical chemistry and haematology data are available only for doses about half the magnitude of that used for comparison in the present report
- the lack of studies on adolescents or children
- the lack of data from toxicological animal studies



## 6 Conclusions with answers to the terms of reference

The Norwegian Food Safety Authority (NFSA) requested the Norwegian Scientific Committee for Food Safety (VKM) to assess the safety of beta-alanine at the specified doses 1000, 1500 and 2000 mg/day in food supplements for the general population, ages 10 years and above.

Based on data from three human studies and one supplementary study, a total daily intake of maximally 5.6 g (corresponding to 80 mg/kg bw per day in a 70 kg adult) for as long as 7 weeks did not result in any adverse health effects.

No particular vulnerable groups for beta-alanine supplements have been identified.

VKM concludes that:

- In adults ( $\geq 18$  years), the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.
- In adolescents (14 to  $< 18$  years) and children (10 to  $< 14$  years) the specified doses 1000, 1500 and 2000 mg/day of beta-alanine in food supplements are unlikely to cause adverse health effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.

An overview of the conclusions is presented in Table 6-1.

**Table 6-1:** An overview of the conclusions for beta-alanine in food supplements.  
Green: Estimated exposures to beta-alanine are unlikely to cause adverse health effects. Note that



these exposures are considered to be without adverse effects provided that beta-alanine is consumed with maximum 5 mg/kg bw per intake and a minimum of 2 hours between the intakes.

Doses	<b>Beta-alanine</b>		
	1000 mg/day	1500 mg/day	2000 mg/day
Age groups			
Children (10 to <14 years)			
Adolescents (14 to <18 years)			
Adults (≥18 years)			



## 7 Data gaps

- There is a lack of studies focusing specifically on negative health effects related to beta-alanine taken over time in adults ( $\geq 18$  years), adolescents ( $< 18$  and  $> 10$  years) and children ( $> 10$  years)
- Studies using female subjects are essentially lacking
- No studies are found that include effects of beta-alanine in potentially vulnerable groups (e.g. the elderly, pregnant and lactating women)
- Relevant toxicological animal studies are lacking

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# Appendix 1

## Search strategies for this risk assessment

### Search strategy human studies

Database: Embase <1974 to 2016 September 13>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1. alanine\*.ti. (16574)
2. alanine aminotransferase.ti. (2565)
3. 1 not 2 (14009)
4. (risk\* or safety or adverse or side-effect\*1 or hazard\* or harm\* or negative or contraindicat\* or contra-indicat\* or interact\* or toxicity or toxic).tw. (10259252)
5. 3 and 4 (2308)
6. (conference abstract\* or letter\* or editorial\*).pt. (5171367)
7. 5 not 6 (2239)
8. limit 7 to (danish or english or norwegian or swedish) (2188)
9. limit 8 to human (580)
10. remove duplicates from 9 (367)

### Search strategy animal studies

Database: Embase <1974 to 2016 October 27>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1. alanine\*.ti. (16391)
2. alanine aminotransferase.ti. (2595)
3. 1 not 2 (13796)
4. (risk\* or safety or adverse or side-effect\*1 or hazard\* or harm\* or negative or contraindicat\* or contra-indicat\* or interact\* or toxicity or toxic).tw. (10393048)
5. 3 and 4 (2326)
6. (conference abstract\* or letter\* or editorial\*).pt. (5207647)
7. 5 not 6 (2256)
8. limit 7 to (danish or english or norwegian or swedish) (2205)
9. limit 8 to animals (555)
10. remove duplicates from 9 (395)