

**14 September 2017**  
**[24-17]**

## **Final consideration report – Urgent Proposal P1046**

### **L-amino acid acetate in food for special medical purposes**

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Food Standards Australia New Zealand (FSANZ) has approved a draft food regulatory measure after considering an urgent proposal to remove a negative effect on trade in food for special medical purposes by permitting L-arginine acetate in food for special medical purposes.

On 21 August 2017, FSANZ sought submissions on a draft variation and published an associated initial consideration report. FSANZ received 4 submissions.

FSANZ approved the draft variation on 14 September 2017.

This Report is provided pursuant to section 97 of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act).

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## Executive summary

This Proposal was prepared in response to a request from the New Zealand Ministry for Primary Industries (MPI) for urgent consideration of an amendment to the *Australia New Zealand Food Standards Code* (the Code) to permit the use of L-arginine acetate in food for special medical purposes (FSMP). The request was made to remove an unintended negative impact on trade to enable FSMP containing L-arginine acetate to be imported to address a medical need. This permission applies to all FSMP manufactured or imported into Australia New Zealand.

The Proposal was declared an urgent Proposal for the purposes of Division 4 of Part 3 of the *Food Standards Australia New Zealand Act 1991* (Cth) (the FSANZ Act).

Standard 2.9.5 and Schedule 29 of the Code currently permit L-lysine acetate as the only acetate form of single L-amino acids for use in FSMP.

Acetate is a common constituent in food. Following oral ingestion, acetate salts of L-amino acids will dissociate in the low pH of the stomach to the respective L-amino acids and acetic acid. If introduced directly to the small intestine, the amino acid-acetate compound will still dissociate freely in this aqueous environment allowing absorption to occur unhindered. Acetate is an endogenous human metabolite formed from glucose and fatty acid metabolism in the liver and is the chemical species present in blood. The risk assessment concluded that approval for the use of acetates of single L-amino acids would not present a public health and safety concern.

FSMP products are nearly always manufactured overseas and imported into Australia and New Zealand. There are no relevant international standards for the composition of FSMP for the general population, only for infants and young children.

To ensure the continued supply of FSMP to those who rely on these products, to avoid unnecessarily impeding the trade in FSMP and, given the safety of the acetate form, FSANZ has approved a draft variation to Schedules 3 and 29. The variation to Schedule 29 permits L-arginine acetate to be used in or added to any FSMP product. The variation to Schedule 3 sets a specification for L-arginine acetate.

The FSANZ Act provides that FSANZ must, within 12 months of notification of the approved draft variation, undertake a full assessment of that variation, call for public comment and either reaffirm its approval of the variation or prepare a proposal to amend, replace or revoke that variation.

# **1 Introduction**

## **1.1 The Proposal**

This Proposal was prepared in response to a request from the New Zealand Ministry for Primary Industries (MPI) for urgent consideration of an amendment to the *Australia New Zealand Food Standards Code* (the Code) to permit L-arginine acetate in FSMP. The request was made to remove an unintended negative impact on trade to enable FSMP containing L-arginine acetate to be locally available to address a medical need.

## **1.2 The current standard**

Standard 2.9.5 and Schedule 29 permit several L-amino acids and a limited range of their compounds to be used in FSMP. No permission is given for the acetate form of L-arginine. L-lysine acetate is the only single L-amino acid currently permitted in the acetate form. There are no specifications for L-Arginine acetate in the sources listed in Schedule 3 – Identity and Purity.

## **1.3 Reasons for preparing the Proposal**

The Proposal was prepared to consider amendment of the Code to permit the use of L-arginine acetate in FSMP.

## **1.4 Procedure for consideration**

The Proposal was considered as an Urgent Proposal. The Proposal was declared an Urgent Proposal for the purposes of Division 4 of Part 3 of the FSANZ Act.

## **1.5 Decision**

The draft variation as proposed following initial consideration was approved with three amendments. The amendments were to: include an additional variation to Schedule 3 of the Code to set a specification for L-arginine acetate; limit the new permission in Schedule 29 to L-arginine acetate; and provide for the variation's commencement on the date that public notice of the variation's approval is given in accordance with subsection 97(4) of the FSANZ Act. The permission for use of L-arginine acetate in FSMP applied to all such products manufactured or imported into Australia New Zealand.

The variation took effect on notification. The approved draft variation, as varied after consideration of submissions, is at Attachment A. The related explanatory statement is at Attachment B. An explanatory statement is required to accompany an instrument if it is lodged on the Federal Register of Legislation. The draft variation on which submissions were sought is at Attachment C.

The FSANZ Act provides that FSANZ must, within 12 months of notification of the approved draft variation, undertake a full assessment of that variation, call for public comment and either reaffirm its approval of the variation or prepare a proposal to amend, replace or revoke that variation.

# **2 Summary of the findings**

Four submissions were received. All except one supported the approval of L-arginine acetate for use in FSMP.

## 2.1 Summary of issues raised in submissions

**Table 1: Summary of issues**

Issue	Raised by	FSANZ response
Does not support inclusion of acetate forms of all L-amino acids for use in FSMP at this point of the Proposal despite their inclusion now having no adverse trade impacts and no adverse public health risk. Instead, it should only be considered at the next and final stage of assessment.	Victorian Departments of Health & Human Services and Economic Development, Jobs, Transport & Resources	The draft variation has been amended to apply to L-arginine acetate only. The potential to approve other relevant forms of L-amino acid acetate will be included at the next and final stage of the assessment.
Changes to the composition of foods for medical purposes must be evaluated to ensure safety and optimal health outcomes. The proposal should therefore be reviewed by medical and dietetic professionals from the Australasian Society for Inborn Errors of Metabolism.	Metabolic Dietary Disorders Association	Noted.  This approved draft variation increases to 3, the number of L-arginine forms available for voluntary use in FSMP. FSMP suitable for amino acid disorders are not affected.

## 3 Summary of the final consideration

### 3.1 Risk assessment

Acetate acts as a charge-neutralising anion in compounds with L-amino acids that possess an amino functional group in their side chain (L-arginine, L-histidine, L-lysine, and L-ornithine). L-lysine acetate is currently the only permitted acetate form of an L-amino acid listed in Schedule 29.

Acetate is a common constituent in food and is an endogenous human metabolite formed from glucose and fatty acid metabolism in the liver. The main dietary sources of acetate are acetate-containing foods (pickled foods, cheese and other dairy products, processed meats, bread, wine and beer) and dietary fibres such as resistant starches and other plant-derived polysaccharides (Schug et al. 2016). Acetic acid and acetate compounds are also added to some foods as emulsifiers, acidity regulators or preservatives.

Following oral ingestion, acetate salts of L-amino acids will dissociate in the low pH of the stomach to the respective L-amino acids and acetic acid. If introduced directly to the small intestine, the amino acid-acetate compound will still dissociate freely in this aqueous environment allowing absorption to occur unhindered. The rate of dissociation may vary somewhat between stomach and small intestine but this would not be expected to have any practical consequences.

Acetate, the deprotonated form of acetic acid, is the chemical species present in blood. Blood levels can vary markedly depending on the diet (Pomare et al. 1985). During fasting in humans, blood acetate concentrations have been shown to increase 3-fold, likely due to conversion of free fatty acids to acetate. Multi-gram quantities of acetate can be formed in the colon following fibre consumption and a substantial fraction of the acetate is systemically

absorbed from the colon resulting in markedly increased blood levels (Scheppach et al. 1991; Vogt and Wolever 2003). However, the largest increase in blood acetate concentration, by up to a factor of 20, has been observed following consumption of alcohol which is metabolised in the liver to acetaldehyde and then to acetate (Lundquist et al. 1962; Suokas et al. 1984).

There are few animal studies investigating the potential adverse effects from high dietary intake of acetate. A study in dogs showed no adverse effects when up to 5% of total dietary energy was provided by acetic acid (Naoum et al. 2002).

The European Scientific Committee for Food (SCF) has stated that, in evaluating the acceptance of acetate compounds as food additives, emphasis is placed on their established metabolic pathway and their consumption as normal constituents of the diet. The SCF considered that it was unnecessary to establish a numerical value for an acceptable daily intake (ADI) for acetate (i.e. an ADI “not specified” was established) (SCF 1990).

Human blood levels of acetate can vary considerably depending on direct dietary intake, fasting, endogenous production from glucose and fatty acids, and formation in the gut from dietary fibre. Large increases in acetate blood levels are handled metabolically without adverse effects. No medical conditions have been identified that would result in a health risk from the use of acetate forms of L-amino acids.

Based on these considerations, approval for the use in FSMPs of acetate forms of all single L-amino acids, including L-arginine acetate, would not present a public health and safety concern to those for whom L-arginine itself does not pose a risk to health.

### **3.2 Risk management**

Codex has not considered nutrient compounds for FSMP other than for infants and young children. Several L-amino acid compounds are listed in the *Codex Advisory List of Nutrient Compounds for Use in Foods for Special Dietary Use Intended for Infants and Young Children* (CAC/GL 10-1987). No acetate forms of single L-amino acids in FSMP are permitted in the European Union.

The Codex text formed the basis of the permitted forms of L-amino acids for use in FSMP in Schedule 29 of the Code. The Schedule includes many single L-amino acids and permits all of them to be used in the hydrochloride form and only L-lysine in the acetate form. L-amino acids for use in FSMP meet the definition of ‘use as a nutritive substance’ in the Code. Schedule 15 of the Code also permits a small number of food additives in the acetate form for use in FSMP in accordance with good manufacturing practice.

As mentioned in the reports prepared for Proposal P242 – Foods for Special Medical Purposes, FSMP products are nearly always manufactured overseas and imported into Australia and New Zealand. It is important that the Code enables the continued supply of FSMP to those who rely on these products and does not impede trade in FSMP unnecessarily.

FSANZ has approved a draft variation to permit the addition to FSMP of L-arginine acetate based on the risk assessment conclusion that it is safe. We also used available supplier and other information to establish a specification for L-arginine acetate. The identity and basic chemical elements of the specification are provided in Table 2.

**Table 2: Identity and chemical properties of L-arginine acetate**

Criteria	Details
Common chemical name	L-arginine acetate
Alternative names	L-arginine, acetate; L-arginine, monoacetate
Systematic chemical name	(2S)-2-amino-5-(diaminomethylideneamino)pentanoic acid acetate
Molecular Formula	C <sub>8</sub> H <sub>18</sub> N <sub>4</sub> O <sub>4</sub>
Molecular weight	234.256 g/mol
CAS <sup>1</sup> number	71173-62-1
Purity (assay, % on dried basis)	98.0–101.0

A full specification for L-arginine acetate has been set in Schedule 3 based on data in Table 2, purity, and maximum limits for arsenic and heavy metals: cadmium, lead, and mercury from relevant industry supplier data. The maximum limits are lower than those listed in section S3—4.

### 3.3 Risk communication

#### 3.3.1 Consultation

Consultation is a key part of FSANZ's standards development process. In relation to this urgent proposal, the call for submissions was notified through notification circulars, a media release and social media. FSANZ also prepared supporting materials for our existing information on food for special medical purposes web page to explain the nature of the Proposal. All interested parties were notified through FSANZ's regular notification processes (i.e. the notification circular).

FSANZ acknowledges the time taken by individuals and organisations to make submissions on this Proposal. Every submission on this proposal was considered by the FSANZ Board. All comments were valued and contribute to the rigour of our assessment.

### 3.4 FSANZ Act considerations

In addition to the submissions received, FSANZ had regard to the following matters when considering approving the draft variation.

#### 3.4.1 Whether the measure's costs may outweigh its benefits

The Proposal provided for an alternative form of L-arginine to be used in FSMP manufactured in or imported into Australia and New Zealand. This provided a potential net benefit for both industry and consumers who need or would benefit from products containing this compound. Given the small scope of the amendment, no additional costs to government were foreseen. Since this Proposal dealt with a deregulatory measure to permit an additional form of L-arginine as a nutritive substance, it has been exempted from a regulatory impact statement by the Office of Best Practice Regulation (OBPR, reference number 14943).

#### 3.4.2 Whether there are other more cost effective measures available

There were no other measures (whether available to FSANZ or not) that were more cost-effective than a food regulatory measure varied as a result of the Proposal.

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<sup>1</sup> CAS is the abbreviation for Chemical Abstract Service

### **3.4.3 Whether there are any relevant New Zealand standards**

Standard 2.9.5 and Schedules 3 and 29 apply in New Zealand. There were no other relevant New Zealand standards.

### **3.4.4 FSANZ's statutory objectives in standards development**

FSANZ also had regard to the three objectives in subsection 18(1) of the FSANZ Act during its initial consideration.

#### ***3.4.4.1 Protection of public health and safety***

Acetate forms of single L-amino acids were assessed as safe for consumers of FSMP. Amendment of the Code to permit L-arginine acetate in FSMP enabled the supply of FSMP containing L-arginine acetate to those who depend on or would benefit from these foods as a source of nutrition. A specification for L-arginine acetate was also written for inclusion in the Code.

#### ***3.4.4.2 The provision of adequate information relating to food to enable consumers to make informed choices***

This objective was met by the Code's existing labelling provisions for FSMP.

#### ***3.4.4.3 The prevention of misleading or deceptive conduct***

This objective was also met by the Code's existing provisions for FSMP.

### **3.4.5 Subsection 18(2) considerations**

FSANZ has also had regard to:

- the need for standards to be based on risk analysis using the best available scientific evidence
- the desirability of an efficient and internationally competitive food industry
- the promotion of fair trading in food
- any written policy guidelines formulated by the Forum on Food Regulation.

FSANZ noted that the approved draft variation removed the current negative impact on trade that was not envisaged when Standard 2.9.5 was made. The draft variation was consistent with the *Ministerial Policy Guideline on the Intent of Part 2.9 – Special Purpose Foods*.

## **4 Draft variation**

The draft variation to the Code is at Attachment A and takes effect on notification. A draft explanatory statement is at Attachment B. The draft variation at call for submissions is at Attachment C.

## **5 Review of the draft variation**

The approved draft variation was considered and approved as part of an Urgent Proposal under sections 95 to 97 of the FSANZ Act. As such, the FSANZ Act provides that FSANZ must now undertake a full assessment of the approved draft variation, call for public comment and then either reaffirm its approval of the variation or prepare a proposal to amend, replace or revoke that variation. This assessment may include considering the need



for permission of other relevant L-amino acids in the acetate form. This process must be completed within 12 months of notification of the approved draft variation.

## 6 References

Lundquist F, Tygstrup N, Winkler K, Mellempgaard K, Munck-Petersen S (1962) Ethanol metabolism and production of free acetate in the human liver. *J Clin Invest* 41(5):955–961

Naoum H, Van Nes JJ, Kappert HJ, Beynen AC (2002) Effect of acetic acid consumption on clinical laboratory values in the dog. *J Animal Phys Animal Nutr* 86:105–110

Pomare EW, Branch WJ, Cummings JH. Carbohydrate fermentation in the human colon and its relation to acetate concentrations in venous blood (1985) *J Clin Invest* 75(5):1448–1454

SCF (1990) Reports of the Scientific Committee for Food. Twenty-fifth series. First series of food additives of various technological functions. Commission of the European Communities.

Scheppach W, Pomare EW, Elia M, Cummings JH (1991) The contribution of the large intestine to blood acetate in man. *Clin Sci (Lond)* 80(2):177–182

Schug ZT, Vande Voorde J, Gottlieb E (2016) The metabolic fate of acetate in cancer. *Nature Reviews Cancer* 16:708–717

Suokas A, Forsander O, Lindros K (1984) Distribution and utilization of alcohol-derived acetate in the rat. *J Stud Alcohol* 45(5):381–5

Vogt JA, Wolever TM (2003) Fecal acetate is inversely related to acetate absorption from the human rectum and distal colon. *J Nutr* 133(10):3145–3148.

## Attachments

- A. Approved draft variation to the *Australia New Zealand Food Standards Code*
- B. Explanatory Statement
- C. Draft variation to the *Australia New Zealand Food Standards Code* (call for submissions)
- D. Request from the New Zealand Government

## **Attachment A – Approved draft variation to the *Australia New Zealand Food Standards Code***



### **Food Standards (Proposal P1046 – L-amino acid acetate in Food for Special Medical Purposes) Variation**

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The Board of Food Standards Australia New Zealand gives public notice of the approval of this variation under section 97 of the *Food Standards Australia New Zealand Act 1991*. The variation commences on the date specified in clause 3 of this variation.

Dated [To be completed by Standards Management Officer]

Standards Management Officer  
Delegate of the Board of Food Standards Australia New Zealand

**Note:**

Public notice of the approval of the variation will be given in the *Food Standards Australia New Zealand Notification Circular* Number 24-17 published and issued on 14 September 2017. This means that this date is the date of public notice for the purposes of clause 3 of the variation.

**1 Name**

This instrument is the *Food Standards (Proposal P1046 – L-amino acid acetate in Food for Special Medical Purposes) Variation*.

**2 Variation to standards in the Australia New Zealand Food Standards Code**

The Schedule varies Standards in the *Australia New Zealand Food Standards Code*.

**3 Commencement**

The variation commences on the date of public notice under subsection 97(4) of the *Food Standards Australia New Zealand Act 1991* of the approval of the variation.

**Schedule**

**[1] Schedule 3** is varied by

[1.1] inserting in the table to subsection S3—2(2) in alphabetical order

L-arginine acetate section S3—38

[1.2] inserting after section S3—37

**S3—38 Specification for L-arginine acetate**

For L-arginine acetate, the specifications are the following:

- (a) full chemical name—(2S)-2-amino-5-(diaminomethylideneamino) pentanoic acid acetate;
- (b) description—white crystalline powder;
- (c) chemical formula— $C_8H_{18}N_4O_4$ ;
- (d) CAS number—71173-62-1;
- (e) purity (assay, on dried basis)—98.0-101.0%;
- (f) loss on drying—maximum 0.5%;
- (g) lead—maximum 0.4 mg/kg;
- (h) arsenic—maximum 1 mg/kg;
- (i) cadmium—maximum 0.2 mg/kg;
- (j) mercury—maximum 0.4 mg/kg.

**[2] Schedule 29** is varied by omitting from the table to section S29—20

L-arginine

substituting

L-arginine

L-arginine acetate

## **Attachment B – Draft Explanatory Statement**

### **1. Authority**

Section 13 of the *Food Standards Australia New Zealand Act 1991* (the FSANZ Act) provides that the functions of Food Standards Australia New Zealand (the Authority) include the development of standards and variations of standards for inclusion in the *Australia New Zealand Food Standards Code* (the Code).

Division 2 of Part 3 of the FSANZ Act specifies that the Authority may prepare a proposal for the development or variation of food regulatory measures, including standards. This Division also stipulates the procedure for considering a proposal for the development or variation of food regulatory measures.

FSANZ prepared Proposal P1046 to permit the addition to Food for Special Medical Purposes of the acetate form of the single amino acids listed in section S29—20 of the Code.

Proposal P1046 was declared an Urgent Proposal for the purposes of Division 4 of Part 3 of the FSANZ Act.

The Authority considered the Proposal in accordance with sections 96 and 97 of the FSANZ Act and has approved a draft variation.

### **2. Purpose**

The approved draft variation's purpose is to amend Schedule 3 to set a specification for L-arginine acetate and to amend Schedule 29 in order to permit the addition to FSMP of L-arginine acetate.

### **3. Documents incorporated by reference**

The variations to food regulatory measures do not incorporate any documents by reference.

### **4. Consultation**

The Authority considered the Proposal in accordance with the procedure in Division 4 of Part 3 of the FSANZ Act. That consideration included one round of public consultation following an initial consideration and the preparation of a draft variation and associated assessment summary. After that public consultation, the Authority had regard to all submissions received and approved an amended version of the draft variation. The approved draft variation must be reviewed by the Authority within 12 months of its notification in accordance with Subdivision B of Division 4 of Part 3 of the FSANZ Act. Further public consultation is required as a part of that assessment.

A Regulation Impact Statement was not required because the approved draft variation is likely to have only a minor impact on business and individuals.

### **5. Statement of compatibility with human rights**

This instrument is exempt from the requirements for a statement of compatibility with human rights as it is a non-disallowable instrument under section 94 of the FSANZ Act.

### **6. Variation**

Item [1] varies Schedule 3.

Item [1.1] varies the table to subsection S3—2(2). The variation amends that table to include in it references to 'L-arginine acetate' and to new section S3—38. The effect is that subsection 1.1.1—15(2) of Standard 1.1.1 will require L-arginine acetate, when added to food or sold for use in food, to comply with the specifications listed for L-arginine acetate in the new section.

Item [1.2] inserts new section S3—38 into Schedule 3. New section S3—38 provides the specifications for L-arginine acetate.

Item [2] amends Schedule 29. The item inserts a reference to L-arginine acetate into Column 2 of the table to section S29—20. Paragraph 2.9.5—6(1)(a) of the Code will provide that the effect of this amendment is to permit L-arginine acetate to be added to Food for Special Medical Purposes.

## Attachment C – Draft variation to the *Australia New Zealand Food Standards Code* (call for submissions)



### Food Standards (Proposal P1046 – L-amino acid acetate in Food for Special Medical Purposes) Variation

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The Board of Food Standards Australia New Zealand gives notice of the making of this variation under section 92 of the *Food Standards Australia New Zealand Act 1991*. The variation commences on the date specified in clause 3 of this variation.

Dated [To be completed by Standards Management Officer]

Standards Management Officer  
Delegate of the Board of Food Standards Australia New Zealand

**Note:**

This variation will be published in the Commonwealth of Australia Gazette No. FSC **XX on XX Month 20XX**. This means that this date is the gazettal date for the purposes of clause 3 of the variation.

**1 Name**

This instrument is the *Food Standards (Proposal P1046 – L-amino acid acetate in Food for Special Medical Purposes) Variation*.

**2 Variation to a standard in the *Australia New Zealand Food Standards Code***

The Schedule varies a Standard in the *Australia New Zealand Food Standards Code*.

**3 Commencement**

The variation commences on the date of gazettal.

**Schedule**

**[1] Schedule 29** is varied by

[1.1] omitting from the table to section S29—20

Amino acids

Sodium, potassium, calcium, magnesium salts of single amino acids listed in this section

substituting

Amino acids

Sodium, potassium, calcium, magnesium salts of single amino acids listed in this section

Acetates of single amino acids listed in this section.

[1.2] omitting from the table to section S29—20

L-lysine acetate