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Te Mana Kounga Kai – Ahitereiria me Aotearoa

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[5-10]

APPLICATION A1015
ETHYL LAUROYL ARGINATE AS A FOOD ADDITIVE
1st REVIEW REPORT

Executive Summary

On 30 October 2009, the Australia and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Application A1015. This Application seeks to amend Standard 1.3.1 – Food Additives of the *Australia New Zealand Food Standards Code* (the Code) to include a new food preservative, Ethyl Lauroyl Arginate (ELA). FSANZ was required to review the decision by 30 January 2010.

The grounds for the review were that the draft Standard –

- did not protect public health and safety
- placed an unreasonable cost burden on industry or consumers
- was difficult to enforce or comply with in both practical or resource terms.

Within these grounds, the key issues addressed by FSANZ were:

- Chemical safety issues. Toxicological relevance of adverse findings in the rat forestomach and delayed onset of puberty in rat pups. Effects on rat forestomach are usually not considered to be toxicologically relevant for a hazard assessment because there is no equivalent organ in humans. Delayed onset of puberty in rat pups was considered relevant and the ADI was based on this effect.

- Side effects of arginine in humans. Arginine, being an integral part of the human diet, is unlikely to elicit an adverse response at the levels likely to be consumed through the use of ELA as a food preservative.

- Consumption data based on 1995 National Nutrition Survey (NNS). At the time the Approval Report was prepared, dietary modelling based on 1995 or 1997 NNS food consumption data provided the best estimate of dietary exposure to ELA. FSANZ believes that use of the older intake data does not invalidate the safety assessment, but in fact provides a more conservative estimation of intake. The dietary exposure assessment incorporated key findings of the 2007 Children's Nutrition and Physical Activity Survey. The data indicated that dietary exposures to ELA estimated using the 2007 food consumption data may be somewhat lower than that estimated using the 1995 food consumption data.

- The relationship between the levels proposed in the Code and the general permitted levels in the USA. The proposed levels in the Code vary with different food types and are based on technological needs. This approach resulted in lower levels being proposed in some food types and higher levels in others, depending on the technical need that was demonstrated for the individual food types.

- Use of unpublished scientific data for pre-market approval of ELA. It is conventional practice by all regulatory agencies around the world to consider and evaluate all available scientific data for pre-market approval of drugs, pesticides, food additives and processing aids. Relevant published and unpublished data which considered the safety of ELA has been evaluated in the FSANZ risk assessment.

- Limited cost-benefit analysis. The cost-benefit analysis did not identify medium to significant additional competitive impacts or compliance costs and therefore a detailed, quantitative cost-benefit analysis was not required under the Regulatory Impact Statement requirements. The analysis therefore met the requirements of the Office of Best Practice Regulation, who confirmed that permission to use the proposed additive appeared to be of a minor nature.

- Absence of suitable ELA analysis method. While it is agreed that there is no published method, an effective method was provided by the Applicant and should be within the capability of most accredited laboratories. The method is available upon request from FSANZ.

FSANZ has considered the grounds raised by the Ministerial Council in relation to Application A1015 – Ethyl Lauroyl Arginate as a Food Additive. The preferred option is to re-affirm the approval of the draft variations to Standard 1.3.1 and Standard 1.2.4 as notified to the Ministerial Council.

Decision

To re-affirm the variations to Standard 1.3.1, Schedule 1 – Food Additives and Standard 1.2.4, to include permissions for ethyl lauroyl arginate in the specified food types at the specified maximum limits for the active ingredient, ethyl-N^{α}-lauroyl-L-arginate·HCl.

Reasons for Decision

- The questions posed by the Ministerial Council in relation to the risk assessment of ELA did not yield any specific public health and safety concerns.

- The regulatory impact assessment indicates that there are no significant additional costs associated with this Application (as this is a voluntary permission). The use of ELA as a preservative could have potential benefits to industry and consumers by increasing choice and the shelf life of products.

- FSANZ considers the method of analysis provided by the Applicant and available for the enforcement of the new standard is practical and the procedure for the extraction in the different food types provided by the Applicant should be within the capabilities of most accredited analytical laboratories.

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1. Introduction

On 30 October 2009, the Australian and New Zealand Food Regulation Ministerial Council (Ministerial Council) requested a First Review of Application A1015. This Application seeks to amend Standard 1.3.1 – Food Additives of the *Australia New Zealand Food Standards Code* (the Code) to include a new food preservative, Ethyl Lauroyl Arginate (ELA).

FSANZ approved the addition of this preservative to the food types at specified maximum permitted levels (MPL) of the active ingredient in a range of food types.

FSANZ was required to review the decision by 30 January 2010.

2. Objectives of Review

The objective of this Review is to reconsider the draft variation to Standards 1.3.1 and 1.2.4 in light of the Ministerial Council's grounds for review as outlined in Section 3 below.

3. Grounds for Review requested by the Ministerial Council

The Ministerial Council requested that FSANZ review the decision to approve the draft variations for Application A1015, for a range of food types, on the grounds that the draft standard –

- did not protect public health and safety
- placed an unreasonable cost burden on industry or consumers
- was difficult to enforce or comply with in both practical or resource terms.

4. Background

FSANZ received an Application from Laboratarios Miret SA (LAMIRSA) on 28 August 2008. This Application seeks to amend Standard 1.3.1 – Food Additives of the *Australia New Zealand Food Standards Code* (the Code) to include a new food preservative, ELA.

ELA is a new synthetic chemical preservative that is currently not permitted as a food additive in Standard 1.3.1 or Standard 1.2.4. Its active component, ethyl-N^{α}-lauroyl-L-arginate·HCl, is a cationic surfactant[1], which is able to disrupt the integrity of cell membranes of a broad spectrum of bacteria, yeast and moulds. The active ingredient is typically present at a concentration between 85% and 95%. ELA is intended to be used to protect food against microbial growth and thus spoilage and it is proposed to be used in a wide range of food groups.

Based on a comprehensive risk assessment, FSANZ concluded that there was no public health and safety concern for ELA when used as a food additive at the maximum levels proposed by the Applicant (see Section 5.3 in the Approval Report). ELA has been shown to be an effective preservative against a broad range of micro-organisms in the food types proposed and it is stable during storage (see Section 5.5 in the Approval Report).

[1] Surfactants are wetting agents that lower the surface tension of a liquid, allowing easier spreading, and lower the interfacial tension between two liquids.

ELA has Generally Recognised As Safe (GRAS) status in the USA (2005). In April 2007, the European Food Safety Authority (EFSA) issued the opinion of the Scientific Committee on ELA as a new food preservative for use in a range of food categories. An Acceptable Daily Intake (ADI) of 0-0.5 mg/kg body weight (bw) based on the ELA preparation was established by EFSA. Most recently, in June 2008, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) considered ELA as a food additive and allocated an ADI of 0-4 mg/kg bw for the active ingredient, ethyl-N^{α}-lauroyl-L-arginate·HCl. The large difference in the ADIs established by EFSA and JECFA is due to a difference in the interpretation of haematology data obtained in animal toxicity studies.

Based on the availability of an adequate range of suitable studies, FSANZ independently completed a safety assessment for ELA and established an ADI of 0-5 mg/kg bw[2], equivalent to the ADI set by JECFA for the active ingredient. The safety assessment reported that only minimal amounts of unchanged ELA enter the bloodstream because the compound is rapidly metabolised by enzymes in the upper intestine before substantial absorption can occur. In the intestine, ELA is rapidly degraded to compounds normally present in the diet such as the amino acid L-arginine and the fatty acid lauric acid.

Based on the conservative assumptions in the dietary exposure calculations, FSANZ concluded that there are no public health and safety concerns for ELA when used as a food additive at the maximum levels proposed by the Applicant.

5. Conclusion from the Approval Report

The FSANZ Board approved the proposed draft variations to Standards 1.2.4 and 1.3.1 to include permissions for ethyl lauroyl arginate in the food types at the specified maximum limits for the active ingredient, ethyl-N^{α}-lauroyl-L-arginate·HCl, as summarised in Table 1 of this Review Report.

6. Issues addressed in the First Review[3]

6.1 Public Health and Safety

6.1.1 Chemical safety issues

6.1.1.1 Risk assessment of rodent forestomach study

Ministerial Council statement: 'It is noted *ELA had a slight local irritant effect on the rat forestomach probably due to its surfactant activity. However, the rodent forestomach is not protected by mucus and has no anatomical equivalent in humans. The forestomach findings were therefore not considered to be relevant for a risk assessment in humans (page 5 of the Approval Report).* It is considered that more evidence is needed rather than making an assumption'.

Response: FSANZ acknowledges that the mechanism of forestomach irritation due to ELA has not been specifically investigated. However, establishing the mechanism of the local irritant effect of ELA on the rat forestomach is not considered necessary for safety assessment.

[2] The ADI of 0-4 mg/kg bw published by JECFA was derived from the same study as assessed by FSANZ, however JECFA applied a correction factor for the content of active ingredient in the batch used in the study (88%) to arrive at an ADI expressed as the active ingredient, ethyl-N^{α}-lauroyl-L-arginate·HCl. On the other hand, FSANZ established an ADI of 0-5 mg/kg bw expressed as ELA.

[3] The quotations used in this section are quotes of statements from the Request for Review Report while the italics within the quotation marks are quotes by the Ministerial Councils from the Approval Report.

The relevant points are: (i) humans do not possess a forestomach; (ii) the human stomach is lined by a protective layer of mucus; (iii) the rat stomach, which is also protected by mucus, did not show signs of irritation by ELA, and (iv) organs histologically similar to the forestomach, but with contact periods comparable to analogous human tissues such as the oral cavity, pharynx and oesophagus also did not show irritation in the rat studies. This can be explained by the short contact time with these organs relative to the much longer residence time applicable for the forestomach. There is no evidence of irritation of tissues analogous to human GI tract tissues where residence time is also analogous. Consequently, in view of the point made above and taking a weight of evidence approach, the finding of slight local irritation of the rat forestomach in isolation is not relevant for a human health and safety assessment and does not represent a risk to humans. This approach represents the usual practice which would be followed by the other (international) food regulatory agencies.

Mode of action studies may be justified in some cases, for example when a chemical exhibits carcinogenic activity in animal studies. Indeed, the relevance of chemically induced forestomach tumours to human safety assessment has been recently reviewed with a focus on the unique aspects of the rodent forestomach and the use of information on mode of action (Proctor et al., 2007). The review concluded that forestomach tumours associated with chronic irritation of the forestomach epithelium, particularly those induced by repeated oral gavage dosing, should not form the basis for carcinogenic classification or quantitative cancer potency estimates for humans. This highlights that even a severe adverse finding in animal studies may be of limited relevance to human safety assessment when other relevant information is considered.

6.1.1.2 Research on the reproductive and developmental toxicity studies

Ministerial Council statement: 'It is also noted *In reproductive and developmental toxicity studies the only notable and consistent finding was delayed onset of puberty in female rats. There was no information to indicate that this effect may not be relevant to humans* (page 5 of the Approval Report). Accordingly it would appear further research needs to be initiated on this issue'.

Response: As FSANZ was unable to conclude that the delayed onset of puberty observed in female rat pups was not relevant for a human risk assessment this endpoint was used as a conservative basis to derive a human health standard. The ADI, which in turn was used to derive the limits on levels of ELA permitted in food. If the resulting health standard was too low to permit ELA to be used in a range of human foods then it would be the responsibility of the sponsor to provide additional data to demonstrate that this endpoint observed in rats was not relevant for a human risk assessment. Dietary exposure estimates for ELA in a wide range of foods indicates that this health standard (ADI) will not be exceeded when ELA is used at levels specified in the code.

6.1.1.3 Arginine, the metabolites and breakdown products of ELA

Ministerial Council statements: 'It is noted that ethyl lauroyl arginate can rapidly metabolise to N^{α}-lauroyl-L-arginine (LAS) and arginine. It is also the case that arginine can pose serious side effects.' and 'Drugs containing arginine have been found to cause adverse reactions in diabetes and kidney disease sufferers and stomach irritation in other persons. The FSANZ risk assessment has not addressed these matters sufficiently.'

Response: Arginine is present in food predominantly as a component of proteins and also as the free amino acid and is therefore a normal component of the human diet. The typical dietary intake of arginine for an individual is several grams per day.

Arginine plays an essential role in human physiology and metabolism and there is extensive published scientific literature on the potential therapeutic benefits of arginine supplementation (recently reviewed by Wu *et al.*, 2009). Very large oral doses of supplementary arginine administered in clinical trials to test for adverse effects have sometimes been shown to be associated with adverse effects such as nausea, vomiting and diarrhoea (Grimble, 2007). Most side effects of arginine occurred at single doses greater than 9 g in adults often when part of a regime of 30 g per day. Adverse effects seemed dependent on the dosage regime and disappeared if divided doses were ingested. A more recent analysis of published clinical trial data suggests that a safe level for arginine supplementation is up to 20 g per day (Shao and Hathcock, 2008).

The estimated additional exposure to arginine resulting from consumption of ELA at 5 mg/kg bw (the upper limit of the ADI) is approximately 100 mg for a 60 kg person. This additional exposure is very small relative to the amount of arginine consumed from eating a typical diet and raises no health or safety concerns.

6.1.1.4 Dietary intake in view of cumulative impact from a variety of foods

Ministerial Council statement: *Further dietary modelling work is required in view of the wide range of foods for which the use of ELA would be permitted. The cumulative impact of ELA intake from a variety of foods could mean that some people will consume a dose that is much higher than their acceptable daily intake.*

Response: The dietary exposure assessment that was conducted for the Approval Report incorporated all food types for which the Applicant requested ELA permissions and at the Maximum Permitted Level requested. This assessment included where a food containing ELA was consumed on its own (e.g. cheese eaten as a piece of cheese) and where a food containing ELA was consumed as an ingredient in another food (e.g. cheese on a pizza, the cheese in cheese sauce). Therefore, the dietary exposure assessment already considers the cumulative impact of exposure from a variety of foods using very conservative assumptions.

When conducting a dietary exposure assessment using NNS food consumption data, each individual's exposure to ELA is calculated using his or her individual food records from the NNS. The modelling is based on the total amount of ELA from all foods consumed summed for each individual. Population statistics (mean and 90th percentile consumer exposures) are then derived from the individuals' ranked dietary exposures.

FSANZ considers that the 90th percentile of dietary exposure is the best estimate of long term high exposure to a food chemical when only a single day of food consumption data is available for individuals. The 90th percentile dietary exposure to ELA is estimated to be well below the ADI for all population groups assessed. FSANZ considers that actual dietary exposure to ELA would be even lower as it is unlikely that all foods permitted to contain ELA would in fact contain it, or that all food manufacturers would use the Maximum Permitted Level of this preservative. FSANZ considers it is highly unlikely that individuals would have regular dietary exposure to ELA at a level higher than the ADI.

Therefore FSANZ concluded that further dietary modelling is not required.

6.1.1.5 Consumption data

Ministerial Council statement: 'The Approval Report continues to rely heavily on out-of date data where approximately 14 years has elapsed since the 1995 Australian National Nutrition Survey (NNS) and the assumptions may not represent current nutritional intakes. It is noted that the Approval Report states *it should be noted that limitations exist within the NNS data.*

These limitations relate to the age of the data and the changes in eating patterns that may have occurred since the data were collected '

Response: At the time the Approval Report was written, dietary modelling based on 1995 or 1997 NNS food consumption data provided the best estimate of actual consumption of a food and the resulting estimated dietary exposure to a food additive for the population or sub-groups of the population. There were no other more recent data sets that detailed food consumption data on an individual basis in the required format in FSANZ's dietary modelling computer program (DIAMOND). Although the consumption data for Australia's 2007 Children's Nutrition and Physical Activity Survey had been uploaded into DIAMOND at the time of the Approval Report, additional data sets needed to be developed for food additive dietary exposure assessments to be conducted.

The Approval Report examined the issue of possible changes in consumption by Australian children of major ELA-contributing foods (fruit and vegetable juices, cordials and comminuted meat products) between 1995 and 2007. This indicated that potential dietary exposures estimated using the 2007 food consumption data may be somewhat lower than that estimated using the 1995 food consumption data. The dietary modelling was done on highly conservative assumptions that all foods with this permission would contain it at the maximum level.

Therefore FSANZ believes that use of the older intake data does not invalidate the safety assessment, but in fact provides a more conservative estimation of intake.

6.1.1.6 UK dietary modelling results

Ministerial Council statement: 'Dietary modelling for ELA in the UK indicated that some children had up to 170% of the acceptable daily intake for ELA. There may be valid reasons why these results would not be replicated in Australia. However, this issue is not canvassed in the FSANZ report.'

Response: Dietary exposure assessments conducted by FSANZ are specific for the Australian and New Zealand populations, using food consumption data for our two countries and the proposed food additive use levels that are the subject of the application or proposal under consideration.

The major reason why estimated mean dietary exposures to ELA are much higher for UK children as a percentage of the ADI is that the UK exposure assessment used an ADI (0.5 mg/kg bw/day) that is one tenth of that used by FSANZ (5 mg/kg bw/day). The reasons for the different ADIs derived by EFSA and JECFA/FSANZ are considered in 6.1.3.1.

6.1.2 Efficacy and stability

6.1.2.1 Efficacy and stability of the different physical forms of ELA

Ministerial Council statement*: '*There are references in the Approval Report to ELA as a powdered substance as well as in an aqueous solution. As the report appears to mainly refer to ELA in the powder form, there are questions as to its suitability and efficacy in an aqueous solution*.'* and *'*Nearly all the scientific data relied upon is taken from studies of ELA as a compound rather than in the various solution forms. It is not clear whether conclusions drawn from the compound studies are applicable to the solution form of ELA.'

Response: ELA is effective in either solid or liquid form, depending on its application on the product.

ELA is a white solid powder after its synthesis and purification. According to the Applicant, the application of this substance in its solid form presents technical difficulties due to the need to apply ELA homogenously and it being used at a low dosage in food products. The food industry prefers liquid product over solids. Therefore most of the ELA commercial products are sold in solution, in which ELA is dissolved in appropriate food-grade solvents such as water, propylene glycol, glycerine or ethanol. Examples of these commercial products with their respective solvents (in brackets) are: Mirenat-N (propylene glycol), Mirenat-G (glycerine) and Mirenat-ET (ethanol and water). A few of the ELA products are sold in solid form mixed with maltodextrin or salt.

The Applicant tested the stability and efficacy of ELA in the media appropriate for each food product to ensure that the stated amount of active ingredient is present through the stated shelf life of the product. The level of the active ingredient of ELA, ethyl-N^{α}-lauroyl-L-arginate·HCl, stated in the studies, is the actual amount of the compound required for preserving the food product over the desired length of storage irrespective of its physical forms. For example, ELA dissolved in propylene glycol (10% w/w) added to refrigerated soups at 200 mg/kg inhibited growth of aerobic mesophiles for at least 31 days. Another example showed that ELA dissolved in glycerine (20% w/w) used at 200 mg/kg suppressed growth of aerobic and enteric bacteria in a ready-to-eat salad for at least 30 days.

6.1.2.2 Evidence on the stability and efficacy of ELA in the various solutions and in specific food types stored under different environmental conditions

Ministerial Council statement: 'It is noted *While the data submitted by the Applicant demonstrates the inhibition of specific micro-organisms in a wide variety of food types, empirical laboratory data would need to be gathered to confirm efficacy in specific food products and under different environmental conditions.'* and 'There is insufficient evidence in the FSANZ report or in the literature on the stability of ELA in the various solutions to perform effectively as an antimicrobial in foods. Some foods may cause ELA to break down and thus render it ineffective as a preservative. This could potentially lead to food borne illness in consumers.'

Response: As it is not feasible to test the efficacy of ELA in every food product, FSANZ required the Applicant to demonstrate the efficacy of ELA in a food representative of each food type including storage under appropriate conditions.

Food types in the initial list of intended uses provided by the Applicant were removed from the initial list if no evidence of efficacy and stability was given in relevant storage studies. Examples of food types from the initial list removed as a result of the FSANZ assessment were: chewing gum, oil emulsions, ice confection, low joule jam, bakery products, tabletop sweeteners, liquid egg products, vegetable protein products, infant formula, formulated supplementary sports drinks, alcoholic beverages, tea, herbal infusions and beverages in mixed food types.

Thirty five laboratory reports were provided by the Applicant that demonstrated the inhibition of specific microorganisms in the approved food types over the desired shelf life. Many of these tests were done in collaboration with the Applicant's potential customers, i.e. food manufacturers.

FSANZ confirmed ELA performed its stated technological function (i.e. retard or prevent the deterioration of foods by microorganisms) when applied to foods at the required concentrations and stored under test conditions. As was noted by the Ministerial Council, approval for use of ELA in any food types not listed in the current list would need to be assessed for its efficacy in the specific food types and under appropriate environmental conditions prior to its use. This would require a new application and assessment.

6.1.2.3 Proposed ELA limits compared to the USA proposed levels

Ministerial Council statement: 'We also noted in the Approval Report that ELA is being proposed to be added to some foods well in excess of the 200mg/kg (e.g. up to 400 mg/kg in semi preserved fish and fish products and dairy and fat based desserts, dips and snacks).'

Response: Different levels of ELA are set out in the regulations of different countries for certain food types, to ensure that sufficient ELA is used to perform its technological function in those particular foods, without resulting in dietary exposures exceeding the ADI. Each country sets limits that reflect the ADI and the food consumption patterns of their countries.

A general level of 200 mg ethyl-Nα-lauroyl-L-arginate.HCl/kg in the permitted range of food types has been permitted by some countries.

However, FSANZ proposes specific usage levels depending on the type of food, e.g. 50 mg/kg for juices and drinks. A higher level, 400 mg/kg, is proposed in certain foods such as fish and dairy based products because ELA interacts with proteins and therefore these high protein foods require a higher level for effective preservation.

6.1.2.4 Review by independent microbiologist

Ministerial Council statement: 'The Approval Report does not adequately address the issue of a review by independent food microbiologists relative to the microbial effectiveness of ELA.'

Response: The usual practice in FSANZ is to obtain independent expert reviews where an issue is particularly complex – or contentious. In this case the microbiological aspects of the risk assessment were relatively routine and therefore there was no need for an independent review.

Laboratory studies provided by the Applicant were reviewed by food technologists and microbiologists in FSANZ to confirm that ELA performed its stated technological function (i.e. to retard or prevent the deterioration of foods by micro-organisms) when applied to specific food types. In a number of cases, further information and/or clarification on particular studies was sought from the Applicant. This included providing further details on the properties of the food to which ELA was being applied, as well as justification of the study duration with respect to the expected shelf-life of the product.

As with any preservative, the extent of inhibition will vary depending on the physical and chemical nature of the food, type of micro-organism, and the conditions of application including the environment (e.g. temperature of storage). Only food types with studies that demonstrated satisfactory results were included in the proposed intended uses of ELA.

6.1.3 Other aspects

6.1.3.1 The reason for the differing ADIs derived by EFSA and JECFA/FSANZ

Discussion of the differing ADIs derived by EFSA (0.5 mg/kg bw/day) and JECFA/FSANZ (5 mg/kg bw/day) was provided in the Assessment Report and the Approval Report. Since completion of the FSANZ Approval Report, EFSA has considered the opinions of three experts on white blood cell data obtained in a series of animal toxicity studies with ELA (EFSA 2009). These expert opinions were considered as part of the FSANZ (and JECFA) assessments. EFSA stated that each of these experts concluded that the haematological findings are toxicologically not significant.

However, EFSA concluded that scientific evidence of a plausible mechanism for the alterations in white blood cell counts has not been provided and that their original concerns and uncertainties have therefore not been addressed by these expert opinions. The original ADI derived by EFSA therefore remains unchanged.

Although FSANZ acknowledges that EFSA has used a more conservative toxicological endpoint, usual international best practice is to take a weight of evidence approach. In this case such a conservative endpoint would not be considered to conform with agreed practice – which is reflected in the different end point agreed by JECFA. FSANZ's conclusions are consistent with those of both the EU Scientific Committee on Cosmetic Products Intended for Consumers (SCCP) and of JECFA.

FSANZ is of the opinion that the haematological findings are unlikely to be toxicologically significant and therefore not an appropriate end-point for defining the ADI. As discussed in the Assessment Report, the white blood cell findings did not show a clear dose-effect relationship, varied depending on the rat strain and sex, and were inconsistent both within and between studies. In addition, there were no effects on normal myeloid cell production, bone marrow, lymphoid tissues or any other adverse histology findings.

Professor Brian Priestly was requested to review the toxicological assessment and concluded that on balance the totality of the information available is more consistent with the conclusions of JECFA and FSANZ than with those of EFSA. Therefore FSANZ reiterates its decision to base its risk characterisation on an ADI of 5 mg/kg bw/day.

6.1.3.2 Unpublished technical data

Ministerial Council statement: *'*The FSANZ review acknowledges throughout the document that the available data set is suboptimal. This is evidenced by *Unpublished laboratory data...';* and *'*Under *References* shown in Supporting Document 1 – Hazard Assessment Report there are 41 referred to publications – 35 have the words *Unpublished report* beside them.'

Response: FSANZ does not acknowledge that the available data set is suboptimal. While the available data on ELA consists primarily of unpublished reports, FSANZ is not of the opinion that this constitutes a suboptimal data set.

Applications to amend the Code were and must be supported by the provision of an adequate and robust data package which is frequently a combination of published journal articles and unpublished studies. All food regulators and other regulatory agencies, e.g. pharmaceutical regulators consider both published and unpublished student in their risk assessments. While there is a perception that a peer-reviewed article in a scientific journal has greater authority for a safety assessment, published journal articles also have some limitations. Published articles are often limited in length and this has the inevitable consequence of data being presented almost exclusively in summary or minimal form. Many of the important technical details or supporting observations are not included and the 'pathway' to the conclusions is not always transparent. In some instances, the paucity of important technical detail can prevent validation of the conclusions.

The peer review process which selects the articles appropriate for publication is usually based on whether the material is worthy of dissemination to other scientists. For example, it describes significant advances in the understanding of a biological process, proposes and tests or refutes hypotheses, or describes potentially useful new test methods or materials. These articles also provide a very valuable forum for the discussion of the findings in relation to other publications.

Consequently investigations, such as safety studies, which may reveal no adverse findings, are frequently not submitted for publication because they fail to meet the selection criteria for publication.

A limitation of unpublished studies can be that the results are usually discussed only within the context of that particular study and do not refer to other companion studies. The nature of these studies also sometimes necessitates that they are evaluated as 'commercial-in-confidence' but this does not devalue the quality of the data.

In undertaking a risk assessment, FSANZ evaluators consider all available data. The strength or weighting of individual studies (published or unpublished) depends on whether the evaluator has access to all the data or only an abridged summary from which to make an independent evaluation and interpretation. The same issues exist for the evaluation of drugs for human or veterinary use or the use of agricultural chemicals in Australia, Europe, North America and Japan.

Both published and unpublished studies have perceived limitations and benefits but all such studies are essential in establishing standards to protect public health. FSANZ needs to be able to consider the scientific merit of all available data in order to base its decisions on 'the best available evidence'. FSANZ was assured by its review of the studies that the data set was sufficient to substantiate the safety of the ELA.

6.1.3.3 US Food and Drug Administration (FDA) GRAS statement

The Ministerial Council stated that the Approval Report contained conflicting statements regarding the GRAS notices in which maximum levels were quoted as 200 mg ethyl-N^{α}-lauroyl-L-arginate·HCl /kg and 225 mg ELA/kg.

Response: There is no conflict in these levels because 200 mg/kg of the active ingredient (ethyl-N^{α}-lauroyl-L-arginate·HCl) corresponds to 225 mg/kg of ELA commercial product containing the active ingredient at a concentration of approximately 90% w/w (i.e. the middle of the range of 85-95% as listed in the JECFA specifications). FSANZ accepts there would have been less confusion if the same units and only one of either the active form or the commercial preparation of ELA had been used in the report.

6.1.3.4 Cosmetic use studies by the Scientific Committee on Cosmetic Products Intended for Consumers (SCCP)

M**inisterial Council statement***:* 'It is noted *the SCCP considered that ELA was considered safe for consumers, when used up to a maximum concentration of 0.4% as a preservative in cosmetic products but excluding products for the lips, oral hygiene products and spray products.* There is no explanation given why products for the lips, oral hygiene products and spray products were excluded*.'* and 'It is also noted *The SCCP opinion was based on the use of ELA in the specified cosmetic products only and took no account of other sources of exposure.'*

Response: FSANZ agrees that the SCCP report does not state the reason(s) for excluding products for the lips, oral hygiene products and spray products. The SCCP was considering a permission for the addition of 4000 mg/kg of cosmetic product compared to the proposed food use of 200 mg/kg of food. As irritation is a concentration and contact time dependent effect, a conclusion that irritation of mucous membranes is a potential risk at a level of 4000 mg/kg in a cosmetic or oral care product, is not inconsistent with a conclusion that a level of 200 mg/kg in a food does not present such a risk. The latter conclusion is entirely consistent with the results of the rat oral study which demonstrated no irritation in rat tissues relevant for human risk assessment.

The lack of explanatory detail in the SCCP report does not compromise the validity of the FSANZ safety assessment which also considered the potential additional oral exposure to ELA from the use of cosmetics and personal care products, in addition to dietary exposure.

6.2 Cost burden on industry or consumers

Ministerial Council statement: 'The cost-benefit analysis provides so little detail that it is impossible to know how the conclusion was reached by FSANZ', and 'FSANZ is requested to provide advice on how costs associated with the enforcement by jurisdictions were determined and how these costs were agreed upon in regard to this Application'.

Response: According to the FSANZ Act and the Council of Australian Government (COAG) guidelines, FSANZ's Regulatory Impact Statement (including cost-benefit analyses) considers the impact of various options on all sectors of the community, including consumers, the food industry and governments in Australia and New Zealand.

The Regulatory Impact Statement relies on input from stakeholders where relevant and is subject to clearance from the Office of Best Practice Regulation (OBPR), which promotes the Government's objective of improving the effectiveness and efficiency of regulation.

The OBPR Best Practice Regulation guidelines suggest that for proposals with no or low compliance costs, no further analysis is required4.

Where medium to significant competitive impacts or compliance costs are likely, FSANZ consults further with stakeholders and OBPR to estimate compliance costs of regulation. The level of analysis is commensurate to the issue and the regulatory impacts of the application or proposal.

In relation to this Application, a Best Practice Regulation Preliminary assessment did not identify any significant additional costs or issues for affected parties. This was approved by OBPR (OBPR Ref 10222), and they confirmed that the permission to use the proposed additive would appear to be of a minor or machinery of government nature and to not substantially alter existing regulatory arrangements. Therefore detailed or quantitative estimates of costs and benefits were not required and this Application did not seek input from stakeholders. However, although quantification of costs was not required, if this information had been provided voluntarily by submitters it would have been included in the Approval Report.

No further quantitative estimates, including additional enforcement costs from any jurisdictions, were provided by way of submission during the consultation period. Any costs incurred by manufacturers would be voluntary and determined by market forces rather than regulatory pressures.

As there were no public health and safety issues identified, and use of this preservative would be voluntary thereby increasing choice and potentially the shelf life of products, FSANZ's Cost Benefit Analysis concluded that there could be a net benefit from this Application.

[4] Best Practice Regulation Handbook, Pg 18.
http://www.finance.gov.au/obpr/docs/handbook.pdf

6.3 Enforcement and compliance issues

6.3.1 Analytical methods

6.3.1.1 Analytical methods for a range of foods

Ministerial Council statement: 'From a laboratory perspective, it is an on-going concern that FSANZ continues to develop standards where there are no or few analytical procedures to enable jurisdictions to monitor industry compliance with the new standards.' and 'There does not appear to be any peer reviewed or published analytical method that can reliably extract and determine the levels of ELA added to the range of foods proposed by the applicant. As a result, it will not be possible to enforce the new standard.'

Response: As was noted in the Approval Report, ELA is a novel food additive and therefore there are limited published methods for the use of this new preservative.

The analytical method suggested by the Applicant for quantifying the content of the active compound is reverse-phase high performance liquid chromatography (RP-HPLC). Despite the range of foods to be analysed being broad, the equipment, reagents and chromatographic conditions would be the same for the different food types; they differ only in method of extraction of the active ingredient from each sample.

The Applicant's proposed extraction method involves the use of slightly different but routine sample preparation techniques, depending on the type of food matrix to be analysed. Two of the techniques are suitable for solid and semi-solid food matrices and a third technique is suitable for liquid food matrices. The Application provided examples of different food matrices from which the ELA has been successfully extracted.

These methods are routine laboratory procedures, with slight variations on the RP-HPLC running conditions (e.g. temperatures, solutions and rates of elution). They are available in the Application A1015 Public Register file or from FSANZ by request if the enforcement agencies wish to consider these methods.

6.3.1.2 Methods for determining arginine and lauric acid

Ministerial Council statement: 'It should be noted that the extraction and determination of ELA is especially difficult in foods with high protein and fat levels, such as meat and cheeses as these naturally contain arginine and lauric acid, the metabolites of ELA.'

Response: The proposed method measures the active ingredient of ELA, ethyl-N^{α}-lauroyl-L-arginate·HCl. The presence of arginate and lauric acid does not interfere with the analysis.

6.3.1.3 Number of submitted internal studies

Ministerial Council noted a discrepancy regarding the number of studies submitted by the Applicant.

Response: There were 35 internal laboratory reports submitted by the Applicant (as stated on page 16 of the Approval Report). However, Experiment #33 was split into Part A and Part B. As a result, it was correctly reported as 36 studies being submitted (on page 7 of the Approval Report).

6.3.2 Drafting clarity

6.3.2.1 Propylene glycol is proposed as a solvent for ELA but it is not permitted to be used in fresh cut fruits and vegetables

Ministerial Council statement: *'*Under a different part of the Code, propylene glycol is not permitted to be added to certain foods such as cut fresh fruit and vegetables, fruit and vegetable juices and certain kinds of preserved fish. However, the proposed new standard would appear to permit the use of ELA soluble in propylene glycol as a preservative in these foods. It is not clear whether this general permission is intended to override the prohibition on the use of propylene glycol in certain foods elsewhere in the Code.' and 'It is noted that the product is to be sold in a solution form with ELA dissolved in appropriate carriers such as water, propylene glycol, glycerine or ethanol. The draft standard is not clear on this issue.'

Response: Propylene glycol, water, glycerin and ethanol are generally permitted processing aids in clause 3 of Standard 1.3.3. The use of these substances as carriers, solvents or diluents for ELA would therefore be permitted.

Additives in Schedule 2 of Standard 1.3.1, including propylene glycol, are permitted in a range of foods including peeled and/cut fruit and vegetables, and semi-preserved fish and fish products (food type 4.1.3 and food type 9.3, respectively, in Schedule 1 of Standard 1.3.1).

7. Review Options

There are three options proposed for consideration under this Review:

1. re-affirm approval of the draft variations to Standard 1.3.1 and Standard 1.2.4 of the Code as notified to the Ministerial Council; or

2. re-affirm approval of the draft variations to Standard 1.3.1 and Standard 1.2.4 subject to any amendments FSANZ considers necessary; or

3. withdraw approval of the draft variations to Standard 1.3.1 and Standard 1.2.4 as notified to the Council.

8. Decision

Decision

To re-affirm the variations to Standard 1.3.1, Schedule 1 – Food Additives and Standard 1.2.4, to include permissions for ethyl lauroyl arginate in the specified food types at the specified maximum limits for the active ingredient, ethyl-N$^{\alpha}$-lauroyl-L-arginate·HCl.

The specified maximum limits for the active ingredient, ethyl-N$^{\alpha}$-lauroyl-L-arginate·HCl, in the permitted food types are listed in Table 1.

Table 1: Intended uses of ethyl lauroyl arginate

Food types		Ethyl lauroyl arginate* (mg/kg; maximum)
0.1	Preparations of food additives	200
1.6	Cheese - soft/cream/processed and mozzarella	400 except for mozzarella at 200

Food types		Ethyl lauroyl arginate* (mg/kg; maximum)
1.6	Cheese – Hard/Semi-hard	1 mg/cm^2 of surface area of cheese (taken to a depth of 3 mm and not more than 5 mm)
4.1.3	Peeled and/or cut fruits and vegetables	200
4.3.8	Processed fruits and vegetables—rehydrated legumes only	200
6.3	Processed cereal and meal products-cooked rice only	200
6.4	Flour products (including noodles and pasta) – cooked pasta and noodles only	200
8.2	Processed meat, poultry and meat products in whole cuts or pieces	200
8.3	Processed comminuted meat and poultry products	315
9.3	Semi preserved fish and fish products	400
14.1.2	Fruit and vegetable juices and fruit and vegetable juice products	50
14.1.3	Water based flavoured drinks	50
20.2	Savoury toppings or fillings - essentially sauces such as tomato paste used in ready to eat pizzas, etc.	200
20.2	Dairy and fat based desserts, dips and snacks	400

* Ethyl lauroyl arginate is the name given to the commercially available product which contains 85-95% w/w of the active ingredient ethyl-N$^{\alpha}$-lauroyl-L-arginate·HCl, as indicated in the JECFA specifications. The values in Table 1 are the maximum permitted levels of the active ingredient.

8.1 Reasons for Decision

- The questions posed by the Ministerial Council in relation to the risk assessment of ELA did not yield any specific public health and safety concerns.

- The regulatory impact assessment indicates that there are no significant additional costs associated with this Application (as this is a voluntary permission). The use of ELA as a preservative could have potential benefits to industry and consumers by increasing choice and the shelf life of products.

- FSANZ considers the method of analysis provided by the Applicant and available for the enforcement of the new standard is practical and the procedure for the extraction in the different food types provided by the Applicant should be within the capabilities of most accredited analytical laboratories.

9. Implementation and Review

The draft variations to Standards 1.3.1 and 1.2.4 will come into effect on the date of gazettal.

10. References

European Food Safety Authority (EFSA). (2007) Opinion of the Scientific Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food on a request from the Commission related to an application on the use of ethyl lauroyl arginate as a food additive; Question number EFSA-Q-2006-035. The EFSA Journal, 511:1-27.

European Food Safety Authority EFSA) (2009) Statement on the evaluation of the new information provided on the food additive ethyl lauroyl arginate. The EFSA Journal, 7(10):1333. http://www.efsa.europa.eu/en/scdocs/doc/ans_ej1333_Ethyl_lauroyl_arginate_st_en.pdf

Grimble GK (2007) Adverse gastrointestinal effects of arginine and related amino acids. *J. Nutr.*, 137(6 Suppl 2):1693S-1701S.

Proctor DM, Gatto NM, Hong SJ, Allamneni KP (2007) Mode-of-action framework for evaluating the relevance of rodent forestomach tumors in cancer risk assessment.*Toxicol. Sci.*, 98(2):313-326.

Shao A, Hathcock JN (2008) Risk assessment for the amino acids taurine, L-glutamine and L-arginine. *Regul Toxicol Pharmacol.*, 50(3):376-399.

Wu G, Bazer FW, Davis TA, Kim SW, Li P, Marc Rhoads J, Carey Satterfield M, Smith SB, Spencer TE, Yin Y (2009) Arginine metabolism and nutrition in growth, health and disease. *Amino Acids*, 37(1):153-168.

ATTACHMENT

Draft variations to the *Australia New Zealand Food Standards Code*

Attachment 1

Draft Variations to the *Australia New Zealand Food Standards Code*

Section 87(8) of the FSANZ Act provides that standards or variations to standards are legislative instruments, but are not subject to disallowance or sunsetting

To commence on gazettal:

[1] ***Standard 1.2.4*** *of the Australia New Zealand Food Standards Code is varied by –*

[1.1] *inserting in* Part 1 *of* Schedule 2 –

Ethyl lauroyl arginate	243

[1.2] *inserting in* Part 2 *of* Schedule 2 –

Ethyl lauroyl arginate	243

[2] ***Standard 1.3.1*** *of the Australia New Zealand Food Standards Code is varied by –*

[2.1] *inserting in subclause 5(2) –*

ethyl lauroyl arginate shall be calculated as ethyl-N^{α}-lauroyl-L-arginate·HCl

[2.2] *inserting in* Schedule 1, *under item* 0.1 Preparations of food additives –

243	Ethyl lauroyl arginate	200	mg/kg	

[2.3] *inserting in* Schedule 1*, under item* 1.6 Cheese and cheese products, *immediately following the last additive entry –*

1.6.1 Soft cheese, cream cheese and processed cheese

243	Ethyl lauroyl arginate	400	mg/kg	

Mozzarella cheese

243	Ethyl lauroyl arginate	200	mg/kg	

1.6.2 Hard cheese and semi-hard cheese

243	Ethyl lauroyl arginate	1	mg/cm^2	applied to the surface of food; maximum level determined in a surface sample taken to a depth of not less than 3 mm and not more than 5 mm.

[2.4] *inserting in* Schedule 1*, under item* 4.1.3 Peeled and/or cut fruits and vegetables –

243	Ethyl lauroyl arginate	200	mg/kg

[2.5] *inserting in* Schedule 1*, under item* 4.3.8 Other fruit and vegetable based products* –

Rehydrated legumes

243	Ethyl lauroyl arginate	200	mg/kg	

[2.6] *inserting in* Schedule 1*, under item* 6.3 Processed cereal and meal products, *immediately following the last additive entry* –

6.3.1 Cooked rice

243	Ethyl lauroyl arginate	200	mg/kg	

[2.7] *inserting in* Schedule 1*, under item* 6.4 Flour products (including noodles and pasta)* –

243	Ethyl lauroyl arginate	200	mg/kg	cooked pasta and noodles only

[2.8] *inserting in* Schedule 1*, under item* 8.2 Processed meat, poultry and meat products in whole cuts or pieces –

243	Ethyl lauroyl arginate	200	mg/kg

[2.9] *inserting in* Schedule 1*, under item* 8.3 Processed comminuted meat, poultry and game products –

243	Ethyl lauroyl arginate	315	mg/kg

[2.10] *inserting in* Schedule 1*, under item* 9.3 Semi preserved fish and fish products –

243	Ethyl lauroyl arginate	400	mg/kg

[2.11] *inserting in* Schedule 1*, under item* 14.1.2 Fruit and vegetable juices and fruit and vegetable juice products* –

243	Ethyl lauroyl arginate	50	mg/kg

[2.12] *inserting in* Schedule 1*, under item* 14.1.3 Water based flavoured drinks* –

243	Ethyl lauroyl arginate	50	mg/kg

[2.13] *inserting in* Schedule 1*, under item* 20.2 Food other than beverages*, *sub-item* dairy and fat based desserts, dips and snacks –

243	Ethyl lauroyl arginate	400	mg/kg

[2.14] *inserting in* Schedule 1*, under item* 20.2 Food other than beverages*, *sub-item* sauces and toppings (including mayonnaises and salad dressings) –

243	Ethyl lauroyl arginate	200	mg/kg