



Scientific Committee on Consumer Safety
SCCS

ADDENDUM to the
SCCS Opinion on
Ethyl lauroyl arginate HCl - SCCS/1519/13
COLIPA n° P95

The SCCS adopted this opinion at its 8th plenary meeting
on 16 December 2014

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Safety (SCCS), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Agency (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCCS

The Committee shall provide opinions on questions concerning all types of health and safety risks (notably chemical, biological, mechanical and other physical risks) of non-food consumer products (for example: cosmetic products and their ingredients, toys, textiles, clothing, personal care and household products such as detergents, etc.) and services (for example: tattooing, artificial sun tanning, etc.).

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http://ec.europa.eu/health/scientific_committees/consumer_safety/index_en.htm

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This opinion has been subject to a commenting period of at least four weeks after its initial publication. Comments received during this time have been considered by the SCCS and discussed in the subsequent plenary meeting. Where appropriate, the text of the relevant sections of the opinion has been modified or explanations have been added. In the cases where the SCCS after consideration and discussion of the comments, has decided to maintain its initial views, the opinion (or the section concerned) has remained unchanged. Revised opinions carry the date of revision.

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1. BACKGROUND

Ethyl Lauroyl Arginate HCl (ELA) CAS n. 60372-77-2 was evaluated by the SCCP in 2004 (SCCP/0837/04) and in 2007 (SCCP/1106/07) and by the SCCS in 2011 (SCCS/1415/11, revised 14 Dec 2011).

Ethyl Lauroyl Arginate HCl (ELA) CAS n. 60372-77-2 is currently authorized as preservative under the Cosmetic Regulation n. 1223/2009 – Annex V/58 at maximum concentration of 0.4% in all cosmetic products except lip products, oral products and spray products. Ethyl Lauroyl Arginate HCl (ELA) is also regulated under Annex III/197 of Cosmetic Regulation n. 1223/2009 to be used for purposes other than inhibiting the development of micro-organisms exclusively in soap, anti-dandruff shampoos and deodorants (not in form of spray) at maximum concentration of 0.8%.

The SCCS adopted the fourth opinion (SCCS/1519/13) on Ethyl Lauroyl Arginate HCl (ELA) at its 3th plenary meeting of 19 September 2013 (revised in December 2013) with the following conclusion:

The SCCS considers Ethyl lauroyl arginate HCl safe for use as a preservative, when used up to a maximum concentration of 0.15% in mouthwashes, though not in oral cosmetic products as a whole. As no human data concerning local toxicity of Ethyl lauroyl arginate HCl in toothpaste are available, the safety of Ethyl lauroyl arginate HCl in toothpaste cannot be assessed.

In February 2014 the Commission received a document on Ethyl Lauroyl Arginate HCl (ELA) from the applicant Lamirsa that draws the attention on the EFSA assessment on ELA as food preservative and consequently on the total exposure of it used both in food and cosmetic products.

2. TERMS OF REFERENCE

1) *In the light of the data provided, does the SCCS consider that Ethyl Lauroyl Arginate HCl is still safe for the consumers at current use in all cosmetic product including oral products, considering the exposure from other sources, such as food?*

2) *In particular does the SCCS consider that Ethyl Lauroyl Arginate HCl is safe considering the specific age groups who might be particularly susceptible to the effects of total exposure to Ethyl Lauroyl Arginate HCl, used in both cosmetic and food products?*

3) *Does the SCCS have any further scientific concerns with regard to the use of Ethyl Lauroyl Arginate HCl in cosmetic products?*

3. OPINION

3.1. Chemical and Physical Specifications

3.1.1. Chemical identity

3.1.1.1. Primary name and/or INCI name

Ethyl lauroyl arginate HCl (INCI name)

3.1.1.2. Chemical names

Ethyl-N^o-dodecanoyl-L-arginate hydrochloride (IUPAC)
Monohydrochloride of L-arginine, N^a-lauroyl-ethylester

3.1.1.3. Trade names and abbreviations

LAE-P abbreviation for pure compound

LAE

Lauric arginate

Mirenat-N

Aminat

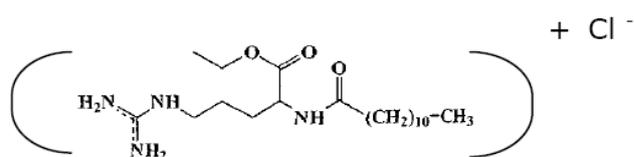
Lauramide arginine ethyl ester

3.1.1.4. CAS / EC number

CAS: 60372-77-2

EC: 434-630-6

3.1.1.5. Structural formula



3.1.1.6. Empirical formula

Formula: C₂₀H₄₁N₄O₃Cl

3.1.2. Physical form

White solid

3.1.3. Molecular weight

421.02 g/mol

3.1.4. Purity, composition and substance codes

Ethyl lauroyl arginate HCl is the active ingredient in the commercial product, LAE. In the crude technical product the aqueous paste contains 74-84% Ethyl lauroyl arginate HCl. LAE is the dehydrated crude product containing 85-95% Ethyl lauroyl arginate HCl (Table 1).

Table 1: Specifications from submission II

	Ethyl lauroyl arginate HCl Content	Physical form	Comments
Crude Technical product	74-84%	White solid. H ₂ O Content: 14-22%	Obtained at the end of the synthesis of Ethyl-N ^o -dodecanoyl-L-arginate HCl
LAE (Dehydrated commercial product)	85-95%	White solid. H ₂ O Content: 0-1.5%	Obtained after drying the crude technical product
Ethyl lauroyl arginate HCl formulated			
MIRENAT-N AMINAT	20-20.4%	Liquid form Formulation of Ethyl lauroyl arginate HCl in propylene glycol	Both can be formulated from the Crude Technical or from LAE

According to the applicant, 'impurities in the commercially available products have no toxicological relevance. Ethyl lauroyl arginate HCl is rapidly hydrolysed to the naturally occurring amino acid (arginine) and to the corresponding carboxylic acid (lauric acid) in plasma. The impurities correspond to these metabolites or are esters thereof, which are rapidly hydrolysed. Arginine is further metabolised to ornithine and urea. Moreover, the impurities of Ethyl lauroyl arginate HCl are also implicitly assessed in the toxicological studies performed with Ethyl lauroyl arginate HCl as they form part of the test substance.'

Table 2 lists the Ethyl lauroyl arginate HCl content and accompanying contaminants of the batches used in the provided studies. The main impurities are N^o-lauroyl-L-arginine, lauric acid and ethyl laurate. It should be noted that Batch 5159 had a higher water content. It was stated in the submission that it was used in some of the older tests. However, it was only used in the embryo-foetal toxicity studies between 1998 and 1999. The batches used in the studies provided in submission II are included.

Table 2: Ethyl lauroyl arginate HCl content and accompanying contaminants of the batches used in the provided studies

Batch name/number	LAE-P	3036	5733	2625	5159	7446	10234	12547	LV090081*
	%	%	%	%	%	%	%	%	%
Ethyl lauroyl arginate HCl	99.0	93.2	90.3	90.1	69.1	88.2	88.2	91.87	86.6
Water		4.1	0.9	0.4	23.1	3.7	2.8	1.72	
Ethyl laurate		1.5	2.0	0.7	1.0	1.0	1.4	0.83	
Lauric acid		2.7	3.0	4.2	1.7	2.7	2.5	2.11	
N ^o -lauroyl-L-arginine (LAS)		1.5	2.1	3.3	1.0	1.9	1.6	1.83	
L-arginine ethyl ester		0.3	0.4	0.3	0.2				
L-arginine		0.3	0.3	0.2	0.2				
Arginate HCl						0.1	0.4	0.18	
Ethyl arginate 2HCl						<0.1	<0.1		
Salts (mostly NaCl)		0.7	0.9	0.8	1.6	1.5	0.8		
Ethanol					1.9				

*No other data provided

In the acute inhalation toxicity study dossier, the test substance was RGR 6895, LAE in ethanol, batch LI-531 (October 19, 2005); stated as "purity" of 0.63% LAE is the concentration. There was no further information. In the study dossier, Ethyl lauroyl arginate HCl and LAE seem to be considered equivalent.

Mirenat-N is reported to be a formulation of 21.6 – 22% (w/w) LAE. Details of the Ethyl lauroyl arginate HCl content and impurities of the batches used in the studies are in Table 3.

Table 3: Ethyl lauroyl arginate HCl content (%) and accompanying contaminants in Mirenat

Batch	0000001 4-12-95	0000003	12 June 1995	13 Dec 1995	3128
	% (w/w)	% (w/w)	% (w/w)	% (w/w)	% (w/w)
Ethyl lauroyl arginate HCl	20.2	20.3	20.4	20.4	20.0
N ^o -lauroyl-L-arginine	0.4	0.4	0.3	0.2	0.3
Lauric acid	0.7	0.6	0.7	0.7	0.6
Ethyl laurate	0.3	0.3	0.2	0.3	0.3
Water	3.8	3.4	3.5	76.9	3.8
Ethanol	0.3	0.2	0.2	0.2	0.2
Citric acid	1.2	1.2	1.2	1.2	1.2
Propylene glycol	73.0	73.5	73.3	0.2	73.7
LAE in formulation	21.6	21.6	21.6	21.6	21.2

There are some inconsistencies between the different submissions and the study reports. Batch 0000003 was given as 25% N-Lauroyl ethyl arginate monochlorohydrate.

Batch 13 Dec 1995 differs from the other batches of Mirenat since it is an aqueous formulation rather than a propylene glycol formulation as the other batches of Mirenat (~73% propylene glycol).

Aminat, in the summary description of eye irritation studies, is referred to as a dilution of Mirenat. However, elsewhere in the submission, it was indicated that Mirenat-N and Aminat were 20.0 –20.4% Ethyl lauroyl arginate HCl.

Submission II states that 'Mirenat-N and Aminat are trade names for a formulation of 21.2 – 21.6% LAE (which means 20-20.4% Ethyl lauroyl arginate HCl) in propylene glycol.' Mirenat is used for to preserve food products, while Aminat is the same formulation but proposed for cosmetics (Table 4).

Table 4: Mirenat-N and Aminat (20.0-20.4% Ethyl lauroyl arginate HCl)

Composition	Range w/w (%)
LAE	21.2-21.6
Propylene glycol	73-74
Water	3-4
Citric acid	1.1-1.3
Ethanol	0.1-0.3

Aminat 4%, in the mucous membrane irritation test from submission II, was prepared from Aminat, batch JMR-672. This was described as 20% LAE, Ethyl-N^o-dodecanoyl-L-arginate HCl on the certificate of analysis. No other information on the formulation of Aminat was provided. It is not stated whether batch JMR-672 was formulated in water or propylene glycol.

In Submission III, a new formulation, Aminat-G (INCI name: Glycerin and Ethyl lauroyl arginate HCl), was used in the gingival irritation studies. Aminat-G was described as 20% LAE in glycerin in the technical data sheet supplied on October 2011: no information on the solubility of LAE in glycerin was given.

In submission IV, the mouthwashes (0.10% and 0.15% Ethyl lauroyl arginate HCl) have been prepared from Aminat-G (batch number LV110050, 20.0 ± 0.5 % Ethyl lauroyl arginate HCl). The raw LAE employed to produce this batch was dehydrated technical LAE (85 - 95% Ethyl lauroyl arginate HCl, batch LT110001).

SCCS Comment

The SCCS notes that the nomenclature used is confusing and inconsistencies exist between the different submissions. See Annex.

3.1.5. Impurities / accompanying contaminants

The accompanying contaminants are listed in 3.1.4 for most batches of Ethyl lauroyl arginate used in the toxicological studies.

3.1.6. Solubility

In water, the solubility is greater than 247 g/l at 20°C. Information provided to JECFA (2008, Ref. 1) and FSANZ (2009, Ref. 2) indicates that Ethyl lauroyl arginate is soluble up to 20% in propylene glycol, glycerin and ethanol, but no substantiating data was provided to the SCCS. In dimethyl sulphoxide (DMSO), LAE solubility is approximately 236 mg/ml. However precipitation occurred in cell culture medium, when dosed at 1% in media, to as low as 118 mg/ml. Solutions of LAE from 15 mg/ml, 30 mg/ml and 59 mg/ml formed cloudy/milky suspensions in medium, whereas 7 mg/ml solutions and lower did not form visible precipitate in medium. No colour change was observed at any of the concentrations. In the acute inhalation toxicity study, the test substance was described as LAE in ethanol. According to the applicant, LAE is soluble in ethanol up to 30%, but no documentation was provided for this.

3.1.7. Partition coefficient (Log Pow)

Log P_{ow} : 1.43 at 20 °C

3.1.8. Additional physical and chemical specifications

In previous submissions, no specific characteristics were given for Ethyl lauroyl arginate HCl, only for LAE.

Melting point:	50.5 to 58.0 °C
Boiling point:	decomposition from 107 °C
Flash point:	/
Vapour pressure:	5.45×10^{-4} Pa at 25 °C
Density:	1.11
Viscosity:	/
pKa:	/
Refractive index:	/
pH:	/
Stability:	not specified but assumed to be 6 months at 4°C in the dark by study authors

Ethyl lauroyl arginate - additional physicochemical data

In the Ethyl lauroyl arginate Chemical and Technical Assessment (JECFA 2008, Ref. 1), the chemical characterisations of six Ethyl lauroyl arginate batches are included; four are in common with the earlier opinion SCCP/1106/07. There are some minor variations in the

composition of the batches. It also states that commercial products are formulated as 20-25% solutions in appropriate food-grade solvents.

The pH of 1% aqueous solution is in the range of 3.64 to 4.25 in 4 batches.

Ref: 1

In submission IV, additional specifications for Aminat-G are provided by the applicant:

Density: 1.22±0.02 g/cm³ (at 20°C)
 Viscosity: 4000-6500 cP (at 20°C)

Specifications for the mouthwashes containing 0.10% and 0.15% Ethyl lauroyl arginate HCl and for placebo mouthwash used in the clinical study of submission IV are listed in Table 5.

Table 5: Specifications of the mouthwashes used in the clinical study for long-term acceptability of Ethyl lauroyl arginate HCl.

	Ref.	batch	concentration LAE (% m/m)	pH	density (g/ml at 20°C)
PLACEBO	001	002	-	5.10	1.0163
	001	003	-	5.16	1.015
	001	004	-	5.11	1.016
AMINAT 0.10%	001	002	0.10	5.06	1.0174
	001	003	0.10	5.15	1.016
	001	004	0.10	5.13	1.017
AMINAT 0.15%	002	002	0.156	5.08	1.0180
	002	003	0.156	5.13	0.017
	002	004	0.152	5.16	1.017

SCCS comment

Aminat 0.15%, Ref. 002, batch 003 has a strongly deviating density (0.017 g/ml at 20°C). See Annex.

3.1.9. Homogeneity and Stability

Ethyl-N-lauroyl-L-arginate HCl present in Ethyl lauroyl arginate is stable for more than 2 years at room temperature when protected in a closed container. The aqueous stability of Ethyl lauroyl arginate has been evaluated under acid conditions and at varying temperatures. The acids employed to evaluate the stability were phosphoric, citric, tartaric, maleic and fumaric acids and the temperatures were 4, 25 and 50 °C. The results indicate that the stability of Ethyl lauroyl arginate decreases with increasing temperature and reducing pH. In general, the strong inorganic acids affected stability more than the organic acids studied.

Ref. 1

SCCS comment

In submission IV, no information on the stability of the mouthwashes is provided. All mouthwashes contain 0.9-0.11% (m/m) nipagin (methylparaben) and 0.054-0.066% (m/m) nipasol (propylparaben).

General Comments to physico-chemical characterisation

In the previous dossiers, Ethyl lauroyl arginate HCl and LAE[®] appear to be considered equivalent. For LAE[®] used in the *in vitro* irritation studies, only information on purity and metal content was available.

Whereas the chemistry of the pure chemical is well characterised, in many studies, there is uncertainty as to the purity, dilution and solvent used.

From submission I and II, it appears that the only formulation for cosmetics was Aminat, 20% Ethyl lauroyl arginate HCl in propylene glycol. However, according to information supplied in October 2011, Aminat®-G (20% LAE in glycerin) was the formulation used. In submission IV, Aminat®-G was used.

3.2. Function and uses

Ethyl lauroyl arginate HCl is a cationic surfactant, active against bacteria, algae and fungi by modifying the permeability of membranes. For Ethyl lauroyl arginate as a food additive EFSA (2007, Ref. 3) established an ADI of 0.5 mg/kg bw Ethyl lauroyl arginate for use in non-alcoholic drinks and fruit juices, salted fish, specified meat products, toppings and prepared salads. Commercial products are formulations comprising 20-25% solutions of Ethyl lauroyl arginate in appropriate foodgrade solvents. In an updated application, uses in dried and salted fish, heat-treated meat products, meat-based prepared salads and surface treatment of cheese are stated. Furthermore, EFSA issued a statement in July 2013 in which it concluded that the 95th percentile of the anticipated estimated exposure for all population groups from the uses requested by the applicant as a food additive is below the ADI. The EFSA statement took into consideration the exposure coming from the cosmetic uses approved at that time and estimated by the SCCS to be 0.0322 mg/kg bw/day, and concluded that the total exposure to Ethyl lauroyl arginate from all sources (including both food and cosmetic uses) would not lead to an exceedance of the ADI (EFSA 2013, Add. Ref. 1).

In cosmetic products Ethyl lauroyl arginate is used as a multi-functional component in the formulation, with claimed applications as an anti-static agent and a surfactant with antimicrobial properties in cosmetics and toiletry formulations. The concentration used in any product depends on the susceptibility to microbial contamination. In Submission II, the application was meant for inclusion of Ethyl lauroyl arginate HCl in annex VI as a preservative with a new maximum concentration of 0.4% in all cosmetic products, and in addition as an antimicrobial in soap, as anti-plaque in oral cosmetic products, as deodorant in deodorant products and antidandruff agent in shampoos up to a maximum concentration of 0.8%. Following SCCP opinion SCCP/1106/07, adopted in April 2008, these uses were introduced into the Cosmetics Directive, with the exclusion of use in lip products, oral cosmetic products and spray products. Submission IV intended to use 0.15% Ethyl lauroyl arginate HCl in mouthwash and toothpaste.

SCCS comment

The purpose of using Ethyl lauroyl arginate HCl in oral cosmetic products seems to be antimicrobial rather than as a preservative. Indicative is the use of parabens in the tested mouthwashes.

3.3 Summary of safety data on Ethyl lauroyl arginate HCl available in SCCNFP/0837/04, SCCP/1106/07 and SCCS/1415/11 (Ref. 4, 5 and 6)

Acute toxicity

In an **acute oral** study on LAE, the acute lethal dose to rats of Ethyl lauroyl arginate HCl was shown to be greater than 1800 mg of Ethyl lauroyl arginate HCl /kg bw. No deaths occurred in an acute oral study on Mirenat (21.6 – 22% (w/w) LAE).

Well-defined irritation (erythema and oedema) was noted in all rats in an **acute dermal** toxicity study. Irritation was resolved by day 9 in 8/10 animals, but persisted to day 12 or 14 in the other two rats. The acute lethal dermal dose to rats of LAE was shown to be greater than 1802 mg/kg bw Ethyl lauroyl arginate HCl.

An **acute inhalation** toxicity study suggested a **mild respiratory tract irritation** if exposure to the aerosol is sufficiently high. However, the exposure to the non-volatile LAE is difficult to assess since much appears to have been lost before reaching the breathing zone. The 4 h aerosol LC₅₀ is greater than 28150 mg/m³ for the volatile fraction and greater than 5883 mg/m³ for the aerosol fraction.

Irritation and corrosivity

The results of a **skin irritation** study indicate that the test item, 90.1% Ethyl lauroyl arginate HCl, has some irritant effect on the skin of the rabbit. The study authors concluded that incidence and severity of this reaction were not sufficient to require classification of the test item.

Several **mucous membrane irritation** studies on New Zealand albino rabbits were performed. In concentrations up to 20.4%, Ethyl lauroyl arginate HCl showed to have an irritating potential and would be classified as "an irritant" under EU labeling regulations. In a study with a concentration up to **0.8%** Ethyl lauroyl arginate HCl was considered as **non-irritant** to the eyes.

Skin sensitisation

Two Magnusson Kligman studies (OECD 406, EC. B6) were performed. The results indicate that 18% (first study) and 20.4% (second study) Ethyl lauroyl arginate HCl do not induce a sensitisation response in the guinea pig.

Dermal/percutaneous absorption

Out of two dermal absorption studies, the SCCS concluded that, according to the SCCS Notes of Guidance (7th revision, Ref. 7), **3.0%** (mean absorption of 2.1% +1 SD, 0.9) is used for the calculation of the MOS as a **preservative at 0.4%**, and **2.38%** (mean absorption of 0.82% +2 SD, 2 x 0.78, due to high variability) for use as an **active ingredient at 0.8%**.

Repeated dose toxicity

28 day, subchronic and chronic studies are available. Table 6 indicates the achieved doses of Ethyl lauroyl arginate HCl (mg/ kg bw/day) in diet and the NO(A)EL derived by the study authors.

Table 6: achieved doses of Ethyl lauroyl arginate HCl (mg/ kg bw/day) in diet and the derived NO(A)EL values

Study	Test substance	Strain	Sex	Low dose mg/ kg bw/ day	Mid dose mg/ kg bw/ day	High dose mg/ kg bw/ day	NOAEL mg/ kg bw/ day
28 day	LAE	Han, Wistar	M	2120	3098	3850	/
			F	2143	2999	4182	
	Mirenat	Sprague Dawley	M	68	283	1070	
			F	71	284	1187	
Sub- chronic*	LAE	Han, Wistar	M	346	1030	3346	346
			F	401	1159	3527	
	Mirenat	Sprague Dawley	M	44	183	671	183 (NOEL)
			F	53	216	793	

Revision of the Addendum to the SCCS Opinion on Ethyl lauroyl arginate HCl (SCCS/1519/13)

Chronic	LAE	Sprague Dawley	M	93.5	271	800	271
			F	131	393	1128	

The NOAEL of **271 mg/kg bw/day** from the chronic study is used for the calculation of the Margin of Safety.

*Remark: In the previous opinion of 15 April 2008, the result section of the sub-chronic study on Wistar Han rats states that "There was evidence of neurotoxicity during the weekly functional observational battery tests." This is not correct and changes the interpretation of the outcome of the study. Therefore the SCCS would like to note that the sentence should be "There was no clear evidence of neurotoxicity..."

Mutagenicity/genotoxicity

Ethyl lauroyl arginate HCl did not appear to have any mutagenic potential under the experimental conditions.

Carcinogenicity

No data submitted

Reproductive toxicity

The NOAEL values for **maternotoxicity** and **foetotoxicity** of Ethyl lauroyl arginate HCl were **207 mg/kg bw/day** and **691 mg/kg bw/day** respectively. No treatment related effects were seen in a two-generation reproduction toxicity study.

Toxicokinetics

Low systemic toxicity of Ethyl lauroyl arginate HCl is supported by its toxicokinetics. In the chronic rat study, the rate and extent of systemic exposure to Ethyl lauroyl arginate HCl and its metabolite LAS appeared to be characterised by dose-independent kinetics. High interindividual variation in plasma LAE concentrations was noted, but this was less marked in plasma LAS concentrations in both sexes.

In human volunteers, the oral pharmacokinetics of Ethyl lauroyl arginate HCl indicated rapid absorption and hydrolysis to LAS and arginine. The terminal half-life of ¹³C-LAS (range 2.2 to 3.3 hours) and ¹³C-arginine (range 1.6 to 4.0 hours) were similar. Plasma concentrations of ¹³C-arginine were generally considerably higher than those of ¹³C-LAS.

Thus, even assuming 100% absorption at 0.4% Ethyl lauroyl arginate HCl, it would suggest rapid hydrolysis of Ethyl lauroyl arginate HCl if absorbed through the skin. Therefore, systemic exposure to Ethyl lauroyl arginate HCl and Na-lauroyl-L-arginine *in vivo* is likely to be very short.

3.4. Specific concerns expressed in SCCS/1415/11 with respect to potential mucosal irritation of Ethyl lauroyl arginate HCl

3.4.1. Gingival irritation – in vitro reconstructed human gingival epithelium (3D)

Two *in vitro* studies (testing toothpaste and mouthwash) in which the irritation potential of Ethyl lauroyl arginate HCl was evaluated were provided by the applicant. The *in vitro* method Skinethic RHE, formally validated for human skin irritation (OECD 439, EC. B46) of substances, was applied and its use was extrapolated to study the effects of Ethyl lauroyl arginate HCl on human gingival epithelium.

60 µl/cm² of each test substance (solutions, formulations, negative and positive controls) was applied on three tissue replicates for 10 minutes (mouthwash) or 20 minutes (toothpaste) at room temperature (RT, between 18°C to 24°C). Cell viability was assessed by an MTT test. Sodium Dodecyl Sulphate (SDS 5%) and PBS treated epidermis were used as positive and negative controls, respectively.

The performing laboratory concluded that, on the basis of the obtained results, the analysed samples (both mouthwash and toothpaste) can be considered as non-irritant for the gingival epithelium under the assayed test conditions.

SCCS comments

Skinethic RHE has been formally validated for detecting skin irritation but not for gingival epithelium irritation. No proof was provided that this *in vitro* assay is suitable to assess the potential of chemical substances for mucous membrane irritation. Wurzbürger (2011, Ref. 8) reported that the application of reconstructed human gingival epithelium might be a useful screening test prior to human studies. The RhE assay and similar tests, however, are not designed to detect mild irritants. Furthermore, a single application on reconstituted human skin is not comparable to long-term repeated use of oral cosmetic products. Therefore the SCCS could not draw any conclusion from these tests that would be relevant for the safety assessment of Ethyl lauroyl arginate HCl used in oral cosmetic products.

3.4.2. Human data

Clinical and Antibacterial Effect of Toothpastes

The applicant submitted (submission III) information on three clinical studies with toothpaste and mouth rinse containing Ethyl lauroyl arginate HCl (Ref. 9, 10, 11). The reports of the studies were covered by confidentiality clauses. Published abstracts were available only for a toothpaste study and a mouth rinse study. In these studies, small groups of subjects (9-16) were selected based on rigorous inclusion and exclusion criteria (Ref. 9, 11). Assessment of possible adverse effects was not reported, indirectly suggesting overall excellent oral hygiene and health of the participants. The persons involved were exposed to the test product for periods between 4 and 10 days. These studies were designed to assess the efficacy of the antimicrobial effect of Ethyl lauroyl arginate HCl in formulations in comparison with similar marketed products. The focus of these studies was to evaluate plaque control. Scant information on the test formulations was provided (even in the study reports) and effects on gingival tissue after treatment were not provided.

SCCS comments

The human studies, designed to assess efficacy of plaque control, showed that Ethyl lauroyl arginate HCl reduced plaque significantly. A limitation of the studies was the rigorous inclusion and exclusion criteria of participants, resulting in selection of only participants with excellent oral health. In addition, the group sizes were small, the time frames (4-10 days) short and inadequate information on potentially negative effects, especially on the gingiva, was provided.

These short-term studies did not mirror long term consumer usage, which would consist of twice daily brushing of the teeth with toothpaste and possibly also similar daily usage with a mouthwash. In addition, the oral hygiene of a high percentage (>50%) of consumers would be considered poor in comparison with those having been selected to take part in these studies. Therefore, these studies did not provide reassurance that no local oral mucosal irritation, in particular of the gingiva, occurs, especially if it would already be compromised. This could be resolved by showing that there would be no local irritation of the oral mucosa and gingiva in long-term studies.

3.5. Submission IV applicant request

In submission IV dated 14 September 2012, the applicant considered that Ethyl lauroyl arginate HCl is safe for use as a preservative in oral cosmetic products up to a maximum concentration of 0.15% and requests an adaptation to Annex VI to Council Directive 76/768/EEC (which corresponds now with Annex V of regulation 1223/2009). This request is made on the basis of new oral care tolerance data obtained from human volunteers studies, along with the safe toxicological profile described in the previous dossiers (summarised under 3.3) and with a new risk assessment of Ethyl lauroyl arginate HCl.

3.5.1. Human data

Verification of the long term acceptability of two mouthwashes versus placebo under normal conditions of use. In-use test in humans controlled by an odontologist.

A study in a group of human volunteers was submitted by the applicant, in order to evaluate the tolerance of Ethyl lauroyl arginate HCl in a mouthwash (as an example of an oral cosmetic product) and to address the limitations identified by the SCCS in the previous submission (SCCS/1415/11).

Summary of the study

84 volunteers, of which 6 dropped out, mentioned as 'unconnected to the effect of the test substance' were distributed in three different test groups:

- Test group, sample A (placebo mouthwash): 26 subjects
- Test group, sample B (mouthwash with 0.15% Ethyl lauroyl arginate HCl): 25 subjects
- Test group, sample C (mouthwash with 0.10% Ethyl lauroyl arginate HCl): 27 subjects

A 14-day wash-out period (D-14 to D0) was foreseen, in which all subjects applied the same commercial neutral toothpaste at home under normal conditions of use, followed by a 6-month study (D0 to D168) in which twice daily, after using the commercial neutral toothpaste, all subjects rinsed their mouth with 15 ml of the mouthwash for 30 seconds.

The condition of volunteers' mouth (oral mucosa, gingiva and teeth) was examined by an odontologist on a double blind basis. At both dose levels of Ethyl lauroyl arginate HCl tested (0.15% and 0.10%), the percentage of subjects exhibiting clinical signs attributable to the test products was in all cases 0%.

In addition, an analysis of the sensation of discomfort was reported directly by the test subjects to the odontologist at the time of clinical examination and recorded in their daily logs. The test subjects, at home, had to complete a daily log for each of the 168 consecutive days of the study period, reporting any reaction observed and sensation of discomfort felt. The percentage of subjects reporting sensations of discomfort at the time of examination by the odontologist attributable to the presence of Ethyl lauroyl arginate HCl in the mouthwash (days D8, D14, D28, D56, D84, D112, D140 and D168) was also 0%. No increase in the clinical signs presenting at D0 were recorded in the daily log by any test subject over the duration of the study.

To complete the evaluation of tolerance, the odontologist calculated two inflammation indices that were based on clinical assessment of the gums. These indices were: the "Loë and Silness" index (to evaluate the degree of inflammation) and the gingival bleeding index (to evaluate the extent of any haemorrhage).

The "Loë and Silness" index considers qualitative changes in the gingiva, providing scores from 0-3. The criteria are:

0= Normal gingiva

1= Mild inflammation – slight change in color, slight oedema but no bleeding on probing;
 2= Moderate inflammation – redness, oedema and glazing, bleeding on probing;
 3= Severe inflammation – marked redness and oedema, ulceration, tendency to spontaneous bleeding.

The gingival bleeding index was calculated by dividing the number of bleeding areas by the total number of observed areas and multiplying by 100.

Ref. 12, 13, 14

In addition, an efficacy study was performed according to the same conditions as the tolerance study. To assess the effect of the mouthwash on the dental plaque of the volunteers, a coloration of dental plaque and a calculations of the O'Leary index were performed before and after 168 ± 8 consecutive days of product use (on days D0, D8, D14, D28 and D168) and results are present in the submission. Standardised photographs were taken on D0, D8, D14 and D28, which were included in the submission.

The applicant mentioned (related to efficacy and not to risk assessment) that product Sample B (mouthwash with 0.15% Ethyl lauroyl arginate HCl) and Sample C (mouthwash with 0.10% of Ethyl lauroyl arginate HCl) have a statistically significant effect on dental plaque after 8, 14, 28 and 168 days of treatment, under the experimental conditions adopted and differ from the placebo product Sample A (mouthwash with 0% Ethyl lauroyl arginate HCl), indicating an effect on dental plaque control by the active ingredient after 28 days of treatment.

Furthermore, Sample B (0.15% Ethyl lauroyl arginate HCl) differs in a statistically significant way from the product Sample A (0% Ethyl lauroyl arginate HCl) after 168 days of treatment, indicating a higher effect of reducing the dental plaque.

Ref. 14, 15

Conclusion by the applicant

No intolerance reaction was noted by the investigator and no sensation of discomfort was described after questioning the test subjects for the duration of the study. Subjects using Samples A (Placebo, 0% Ethyl lauroyl arginate HCl), B (0.15% Ethyl lauroyl arginate HCl) and C (0.10% Ethyl lauroyl arginate HCl) all tolerated the mouthwash well and experienced an improvement of mouth condition.

The maximum level of Ethyl lauroyl arginate HCl administered in a mouthwash under test was 0.15%. In view of the absence of any adverse effects demonstrated by the study at any level of administration, the applicant requests the inclusion of Ethyl lauroyl arginate HCl in Part I of Annex VI of Directive 76/768/EEC (Annex V in regulation 1223/2009) for use as a preservative in oral cosmetic products at levels up to 0.15%.

In terms of efficacy, 0.15% Ethyl lauroyl arginate HCl shows to have a statistically significant higher effect of reducing dental plaque than the placebo after 168 days.

Ref. 14, 15

SCCS comments

The values given for the "Loë and Silness" index and for the gingival bleeding index have a high standard deviation and no other statistical evaluation has been carried out. The measurements of the different samples seem to be of a similar order of magnitude.

No signs of irritancy were reported on a long-term period of 168 consecutive days on 25 subjects, using the mouthwash with 0.15% Ethyl lauroyl arginate HCl twice a day. The requested concentration as preservative in oral cosmetic products is 0.15%. Oral cosmetic products, however, not only consist of mouthwash but also of toothpaste. As in the human volunteer studies presented here, only the use of mouthwash at a concentration of 0.15% was evaluated, it is not possible to predict whether irritation would occur under combined

use of both mouthwash and twice daily use of toothpaste (once in the morning, once in the evening), containing both 0.15% Ethyl lauroyl arginate HCl as preservative.

3.6. New information on exposure from the applicant

Estimate of combined exposure from food and cosmetics uses

The anticipated intakes of Ethyl Lauroyl Arginate HCl from the foods included in the proposed Food Regulation, as estimated by EFSA and reported in its statement by population group, are presented in the following table. The values represent intakes by consumers only and are expressed in mg/kg bw/day. Data from a number of food consumption surveys from across the EU were used in their calculation and the ranges reflect the ranges in food consumption values reported survey by survey.

Table 7: Food exposure in the EU from different surveys

Age group	Toddlers	Children	Adolescents	Adults	The elderly
Mean exposure	0.024 - 0.133	0.016 - 0.131	0.017 - 0.086	0.017 - 0.088	0.025 - 0.055
Exposure 95 th percentile	0.165 - 0.354	0.100 - 0.442	0.104 - 0.329	0.073 - 0.237	0.070 - 0.182

In its recent opinion, in which it concluded that the use of Ethyl Lauroyl Arginate HCl in mouthwashes is safe, the SCCS made a new estimate of the Systemic Exposure Dosage (SED) to the substance. The calculation took into account the exposure from the cosmetic uses already approved plus the exposure from the new use under consideration (all oral cosmetic products at 0.15%, although the approval will be only for mouth washes) and the SED was estimated to be 0.0897 mg/kg bw/day.

There is no agreed methodology as to how to calculate the total exposure of a substance used both in food and as a cosmetics ingredient. In its statement, EFSA considered it not relevant to simply add the maximum estimates from both fields since the food intake estimates are based on the consumption of a small number of food categories by consumers only, and the SED for cosmetics uses is based on estimates of cosmetics use by adults. A simple addition of the two values arguably represents an unrealistically conservative scenario.

In order to capture the worst (i.e. the most conservative) case, the applicant has calculated the total exposure to Ethyl Lauroyl Arginate HCl by summing the 95% percentile exposure (consumers only) from food as estimated by EFSA, with the SCCS' most recent estimate of the SED of 0.0897 mg/kg bw/day from all evaluated cosmetics uses. Values, expressed in mg/kg bw/day for each population group, are presented in the following Table 7:

Table 7: Total exposure including cosmetics

Age group	Toddlers	Children	Adolescents	Adults	The elderly
Mean exposure	0.114 - 0.223	0.106 - 0.221	0.107 - 0.176	0.107 - 0.178	0.115 - 0.145
Exposure 95 th percentile	0.255 - 0.444	0.190 - 0.532	0.194 - 0.419	0.163 - 0.327	0.160 - 0.272

It can be seen that in one case (i.e. the 95th percentile exposure for children) the ADI of 0.5 mg/kg bw established by EFSA is marginally exceeded. The extremely conservative nature of this method of calculation (i.e. the simple addition of the highest estimates from food and adult cosmetic uses) should, however, be noted.

SCCS comment

The ADI of 0.5 mg/kg bw/day was established by EFSA based on a NOAEL of 47 and 56 mg/kg bw/day for males and females, respectively, from a 13-week oral toxicity study in rats. SCCP, however, used a NOAEL of 271 mg/kg bw/day in a chronic oral toxicity study in rats since the observed changes in white blood cell counts were judged to be local due to gastric mucosal lesion and therefore not relevant for cosmetic uses. However, at that time only dermal applications were considered by the SCCP (SCCP/1106/07). Later on, also the use as preservative up to 0.15 % Ethyl Lauroyl Arginate HCl in mouthwashes was considered safe (SCCS/1519/13). The exposure estimations provided by the applicant suggest that for the subgroup 'Children, 3 to 9 years old' the ADI may be exceeded when adding food exposure (using the 95th exposure percentile) and cosmetic exposure. However, the amounts stemming from dermal exposure should not be added when using the ADI based on the low NOAEL used by EFSA. To the maximum amount of 0.442 mg/kg bw/day (food exposure, 3 year old children, 12 kg body weight, 95th exposure percentile) only 0.29 mg/kg bw/day from oral exposure should be added, resulting in a total exposure of 0.73 mg/kg bw/day. In contrast, when considering 9 year old children (body weight 25 kg) the oral exposure from cosmetics would be 0.14 mg/kg bw/day and the sum would be 0.58 mg/kg bw/day. Both of these values (0.58 and 0.73 mg/kg bw/day) are not covered by the ADI. However, no continuous exposure of children to mouthwashes containing Ethyl Lauroyl Arginate is considered realistic by the SCCS.

3.7. Safety evaluation (including calculation of the MoS)

CALCULATION OF THE MARGIN OF SAFETY

Ethyl lauroyl arginate HCl, for a combined application of preservative and active ingredient

0.15% Ethyl lauroyl arginate HCl as a preservative in oral cosmetic products, 0.4% for other preservative uses and 0.8% as an active ingredient in soap, shampoo and non-spray deodorant

(i) SED for 0.8% Ethyl lauroyl arginate HCl as an active ingredient in soap, shampoo and non-spray deodorant:

Amount of the cosmetic product containing ethyl lauryl arginate as active ingredient (a.i.) applied daily (ref. 16):

Soap:	0.2 g/day
Deodorants:	1.5 g/day
Shampoo:	0.11g/day
TOTAL	1.81 g/day

Estimated daily exposure	A	= 1.81 g/day
Dermal absorption per treatment	DAp (%)	= 2.38% (Ref. 6)
Typical body weight of human		= 60 kg

SED	AxCxDApx1000/60kg	= 0.00574mg/kg bw/d
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(ii) SED for 0.15% Ethyl lauroyl arginate HCl as a preservative in oral cosmetic products

Estimated daily exposure	A	= 2.30 g/day
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Concentration	C	= 0.15%
Absorption per treatment	D_{Ap} (%)	= 100%
Typical body weight of human		= 60 kg
SED	AxCxD_{Ap}x1000/60kg	= 0.0575 mg/kg bw/d

(iii) SED for product categories where Ethyl lauroyl arginate HCl can be applied at 0.4% as a preservative

A	= 17.4 - (1.81_[cosmetics a.i.] + 2.36_[oral care & lipstick])	= 13.23 g/day
C		= 0.4%
D_{Ap} (%)		= 3% (Ref. 6)
Typical body weight of human		= 60 kg
SED	AxCxD_{Ap}x1000/60kg	= 0.02646 mg/kg bw/d

(iv) SED for combined preservative and active ingredient uses when oral cosmetic products at 0.15% are included:

$$\text{SED} = 0.0575 + 0.02646 + 0.00574 = 0.08970 \text{ mg/kg bw/d}$$

MoS for cosmetic uses of Ethyl lauroyl arginate HCl = $\frac{271 \text{ mg/kg bw/day}}{0.0897 \text{ mg/kg bw/day}} = 3021$
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(v) SED for 0.15% Ethyl lauroyl arginate HCl as a preservative in oral cosmetic products for children 3 years old (worst case, 12 kg body weight) and 9 years old (25 kg body weight)

Estimated daily exposure	A	= 2.30 g/day
Concentration	C	= 0.15%
Absorption per treatment	D_{Ap} (%)	= 100%
Typical body weight of 3 years old child		= 12 kg / 25 kg
SED _{12 kg bw}	AxCxD_{Ap}x1000/12kg	= 0.29 mg/kg bw/d
SED _{25 kg bw}	AxCxD_{Ap}x1000/25kg	= 0.14 mg/kg bw/d

3.7.1. Discussion

In the previous opinion, the SCCS stated that *the additional data provided on mucosal irritation does not alter its earlier opinion on Ethyl lauroyl arginate HCl. The concern that in the general population, regular use of toothpaste and possible additional use of a mouthwash containing Ethyl lauroyl arginate HCl could cause local mucosal irritation was not addressed by the submitted studies.*

In order to address the limitations in the previously submitted studies, the applicant presented a long-term current study of mouthwashes which contain 0.10% and 0.15% respectively of the substance under investigation. No intolerance reactions were noted during the study and no sensation of discomfort was described after questioning the test subjects for the duration of the study.

Since the study was indeed long term (168 days), and conducted on a varied population of male and female volunteers from 18 to 70 years, with all types of gums and all types of oral hygiene habits, it is reasonable to conclude that the mouthwashes containing 0.10% and 0.15% Ethyl lauroyl arginate HCl cause no local mucosal irritation. The SCCS, however, does not consider a mouthwash as a representative product for all oral cosmetic products.

Indeed, with this study it is not possible to predict whether irritation would occur under combined use of both mouthwash and twice daily use of toothpaste (once in the morning, once in the evening), containing both 0.15% Ethyl lauroyl arginate HCl as preservative. Neither can rinsing one's mouth be compared to the action of brushing one's teeth, the latter not only involving a longer duration of exposure than 30 seconds, but also possibly being more aggravating for the gum.

Systemic safety evaluation and MoS calculations for the use of Ethyl lauroyl arginate HCl as a preservative at 0.15% in oral cosmetic products and 0.4% in other cosmetic products, combined with its use as an active ingredient at 0.8% in soap, shampoo and non-spray deodorant, show that Ethyl lauroyl arginate HCl has a low systemic toxicity. However, since there is no human data concerning local toxicity for combined use of mouthwash and toothpaste at 0.15%, it can only be concluded that Ethyl lauroyl arginate HCl is safe for use in mouthwashes.

The SCCS points out that the use of Ethyl lauroyl arginate HCl in oral cosmetic products appears to be for another function than preservative as parabens were present in all tested formulations.

The ADI of 0.5 mg/kg bw/day was established by EFSA based on a NOAEL of 47 and 56 mg/kg bw/day for males and females, respectively, from a 13-week oral toxicity study in rats. SCCP, however, used a NOAEL of 271 mg/kg bw/day in a chronic oral toxicity study in rats since the observed changes in white blood cell counts were judged to be local due to gastric mucosal lesion and therefore not relevant for cosmetic uses. However, at that time only dermal applications were considered (SCCP/1106/07). Later on, also the use as preservative up to 0.15 % Ethyl Lauroyl Arginate HCl in mouthwashes was considered safe (SCCS/1519/13). The exposure estimations provided by the applicant suggest that for the subgroup 'Children' the ADI may be exceeded when adding food exposure (using the 95th exposure percentile) and cosmetic exposure.

However, the amounts stemming from dermal exposure should not be added when using the ADI based on the low NOAEL used by EFSA. To the maximum amount of 0.442 mg/kg bw/day (food exposure, 3 year old children, 12 kg body weight, 95th exposure percentile) only 0.29 mg/kg bw/day from oral exposure should be added resulting in a total exposure of 0.73 mg/kg bw/day. In contrast, when considering 9 year old children (body weight 25 kg) the oral exposure from cosmetics would be 0.14 mg/kg bw/day and the sum would be 0.58 mg/kg bw/day. Both of these values (0.58 and 0.73 mg/kg bw/day) are not covered by the ADI. The SCCS considers the use of Ethyl Lauroyl Arginate in mouthwashes for children at the concentration of 0.15% for longer time periods as not safe.

4. CONCLUSION

1) In the light of the data provided, does the SCCS consider that Ethyl Lauroyl Arginate HCl is still safe for the consumers at current use in all cosmetic product including oral products, considering the exposure from other sources, such as food?

The SCCS considers Ethyl lauroyl arginate HCl safe for use as a preservative, when used up to a maximum concentration of 0.15% in mouthwashes, though not in oral cosmetic products as a whole.

2) In particular does the SCCS consider that Ethyl Lauroyl Arginate HCl is safe considering the specific age groups who might be particularly susceptible to the effects of total exposure to Ethyl Lauroyl Arginate HCl, used in both cosmetic and food products?

The exposure estimations provided suggest that for the subgroup 'Children' the ADI may be exceeded when adding food exposure (using the 95th exposure percentile) and cosmetic exposure. However, the amounts stemming from dermal exposure should not be added when using the ADI based on the low NOAEL used by EFSA. To the maximum amount of

0.442 mg/kg bw/day (food exposure, 3 year old children, 12 kg body weight, 95th exposure percentile) only 0.29 mg/kg bw/day from oral exposure should be added resulting in a total exposure of 0.73 mg/kg bw/day. In contrast, when considering 9 year old children (body weight 25 kg) the oral exposure from cosmetics would be 0.14 mg/kg bw/day and the sum would be 0.58 mg/kg bw/day. Both of these values (0.58 and 0.73 mg/kg bw/day) are not covered by the ADI. The SCCS considers the use of Ethyl Lauroyl Arginate in mouthwashes for children at the concentration of 0.15% for longer time periods as not safe.

3) *Does the SCCS have any further scientific concerns with regard to the use of Ethyl Lauroyl Arginate HCl in cosmetic products?*

As no human data concerning local toxicity of Ethyl lauroyl arginate HCl in toothpaste are available, the safety of Ethyl lauroyl arginate HCl in toothpaste cannot be assessed.

5. MINORITY OPINION

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7. ANNEX

Concerning trade names of the Ethyl lauroyl arginate HCl, the following information has been provided by the applicant:

Mirenat-N: this is the trade name of a formulation containing c.a. 20% of Ethyl lauroyl arginate HCl in propylene glycol marketed for use by the food industry. Several toxicological studies have been performed with this product.

Mirenat-N water dispersed (13-12-95): this designation refers to a special batch of Mirenat-N consisting of Ethyl lauroyl arginate HCl c.a. 20% dispersed in water (without any propylene glycol). This special formulation was prepared in order to provide a propylene glycol-free comparator to the standard Mirenat-N for use in studying effects on eye irritation.

Aminat: this is the trade name of a formulation containing c.a. 20% of Ethyl lauroyl arginate HCl in propylene glycol marketed for use by the cosmetics industry. Several toxicological studies have been performed with this product. In some of the toxicological studies in which Aminat was used, the test product was diluted in water. In these cases the designation of the test product is given as Aminat X%, where X% indicates the proportion of Aminat (i.e. 20% Ethyl lauroyl arginate HCl in propylene glycol) in water. This is the case in several eye irritation studies.

Aminat-G: this is the trade name of a formulation containing c.a. 20% of Ethyllauroyl arginate HCl in glycerine marketed for use by the cosmetics industry.

Additional information provided by the applicant after the publication of this opinion is: Section 3.1.8: the deviating value of the density 0.017g/ml at 20°C should be 1.017g/ml.