Article

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Safety Assessment of α-Amino Acids as Used in Cosmetics

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Abstract

The Cosmetic Ingredient Review Expert Panel (Panel) reviewed the safety of α-amino acids, which function primarily as hair- and skin-conditioning agents in cosmetic products. The safety of α-amino acids as direct food additives has been well established based on extensive research through acute and chronic dietary exposures. The Panel focused its review on dermal irritation and sensitization data relevant to the use of these ingredients in topical cosmetics. The Panel concluded that α-amino acids were safe as cosmetic ingredients in the practices of use and concentration of this safety assessment.

Keywords

cosmetics, α-amino acids, safety assessment

Introduction

Amino acids and their salts are widely used as cosmetic ingredients and function primarily as hair-conditioning agents and skin-conditioning agents (humectant and miscellaneous).

The 21 most common naturally occurring amino acids are building blocks of proteins. As such, amino acids are critical to life and metabolic function. Eight of these amino acids, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine, are essential and must be obtained through nutrients, as they cannot be synthesized by human cells. Because amino acids are present in all living organisms and their general biology is well characterized, they are not considered to pose any significant safety concern following oral exposure, except to individuals with certain genetic disorders. Accordingly, this safety assessment focuses on the basic chemistry, uses as cosmetic ingredients, and, because of the importance for products that will be applied to the skin, addresses all irritation and sensitization data available on these 21 amino acids and their simple salts. The full list of the ingredients in this report is found in Table 1.

The naturally occurring protein amino acids are all α-amino acids and, with the exception of glycine and methionine, have L-stereochemistry at the α-carbon. The "L-" amino acids are considered Generally Recognized as Safe (GRAS) direct food additives by the US Food and Drug Administration (FDA), thus oral toxicity was not a focus for these ingredients in this assessment.

Monosodium glutamate (MSG) has been reported to be associated with a human condition known as "MSG symptom complex" in which symptoms such as a burning sensation of the face, neck, and chest; headache; and nausea occur after consumption of large amounts of this amino acid salt in some foods.[1-3]

A rare genetic disorder, phenylketonuria, caused by a mutation in the gene that encodes phenylalanine hydroxylase, prevents affected individuals from converting phenylalanine to tyrosine.[4] If this disorder is not detected by blood testing during the first few days after birth and proper dietary management is not observed, irreversible neurological effects may occur.

Chemistry

The definition and structure of these ingredients are presented in Table 2, and available information on the physical and chemical properties of amino acids and their salts is presented in Table 3.

The generic term "amino acid" is commonly considered shorthand for α-amino acid. This designates a carboxylic acid

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Table 1. Amino Acids and Related Simple Salts.

Alanine	Histidine
Arginine	Histidine HCl
Arginine HCl	Isoleucine
Asparagine	Leucine
Aspartic acid	Lysine
Sodium aspartate	Lysine HCl
Potassium aspartate	Methionine
Dipotassium aspartate	Phenylalanine
Calcium aspartate	Proline
Magnesium aspartate	Serine
Cysteine	Threonine
Cysteine HCl	Tryptophan
Cystine	Tyrosine
Glutamic acid	Valine
Sodium glutamate	
Glutamine	
Glycine	
Sodium glycinate	
Calcium glycinate	
Magnesium glycinate	

with an amine group on the immediately adjacent (α) carbon as shown in Figure 1.

The ''natural'' amino acids present in proteins are all α-amino acids, with *S*-stereochemistry at the α-carbon, except glycine and cysteine. Glycine is achiral (no stereochemistry). L-Cysteine actually has *R* stereochemistry due to the effect of the sulfur atom on application of the Cahn-Ingold-Prelog rules used to define stereochemical configuration. The chirality of amino acids is commonly denoted by the prefixes ''D-'' and ''L-,'' which indicate stereochemistry analogous to the D and L forms of glyceraldehyde. According to this nomenclature, all of the ''natural'' α-amino acids have the L configuration. Exceptions are shown in Figure 2. Additionally, all of the natural amino acids contain primary amines (ie, acids with an NH_2 group pendant from the α carbon), except proline, also shown in Figure 2, which is a secondary amine.

Cysteine and cystine are related as thiol (reduced monomer) and the disulfide (oxidized dimer) forms of the same structure. These 2 molecules play major roles in reversible cellular redox chemistry as shown in Figure 3 and can serve a similar function in hairdressings, such as permanent waves.

Method of Manufacturing

The most common manufacture methodology for glutamine, histidine, leucine, isoleucine, proline, serine, arginine, tryptophan, phenylalanine, threonine, glutamic acid, and lysine is fermentation.[5] This method utilizes bacterial strains that overproduce and release, extracellularly, the desired amino acids during carbohydrate metabolism. Cell separation and crystallization of the amino acids remove any concern of residual organisms or proteins in the end product. For example, glutamate can be produced in a fermentation tank charged with a culture medium including sugar and a culture of *Corynebacterium glutamicum*. The extracellularly released glutamate is then separated from the biomass and crystallized.

Alanine, methionine, valine, and aspartic acid, on the other hand, are most commonly manufactured via enzymatic catalysis.[5] This method utilizes active cell components in continuously operating reactors. Often, these biocatalysts can be immobilized to provide more efficient separations. This methodology also involves separation techniques that negate any concern of organism or protein contamination in the end product. For example, methionine can be produced in an enzyme membrane reactor with an acylase from *Aspergillus oryzae* and easily crystallized from the reaction mixture.

Cystine (and cysteine by reduction of cystine), asparagine, and tyrosine, however, are primarily obtained by extraction from the complete hydrolysis of proteins.[5] Glycine, the achiral amino acid, is typically synthesized from chloroacetic acid and ammonia.

Impurities

A supplier to the cosmetics industry reported that D-glutamic acid has not more than 0.3% methanol.[6]

According to the Food Chemicals Codex, United States Pharmacopeia (USP)-grade amino acids (''DL-'' and ''L-'') must be at least 98% to 98.5% pure and contain no more than 5 mg/ kg lead.[7]

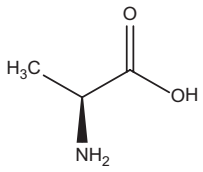
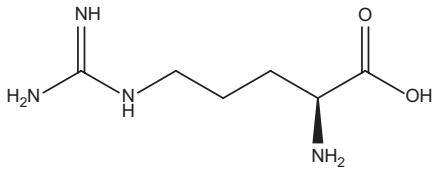
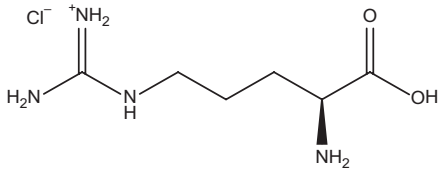
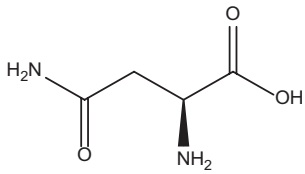
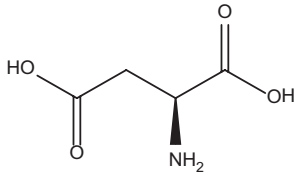
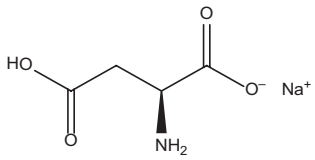
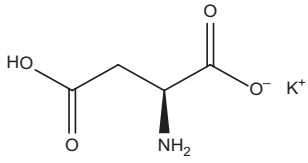
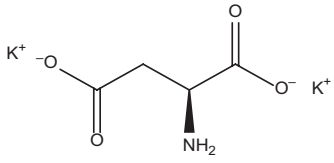
Use

Cosmetic

The amino acids and the salts discussed in this safety assessment function primarily as hair-conditioning agents and skin-conditioning agents (humectant and miscellaneous) in cosmetic formulations.[8] Additional functions may include the use as oral care agents (arginine), antioxidants (cysteine and cysteine HCl), hair waving/straightening agents (cysteine and cysteine HCl), reducing agents (cysteine and cysteine HCl), fragrance ingredients (cystine), buffering agents (glycine and its calcium and magnesium salts), and pH adjusters (glycine and its calcium and magnesium salts).

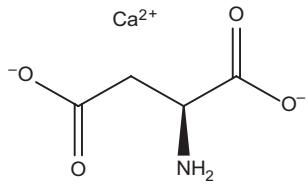
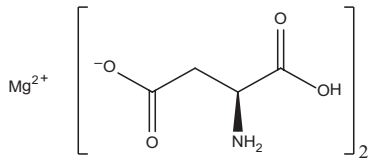
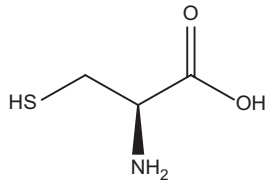
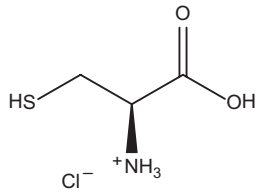
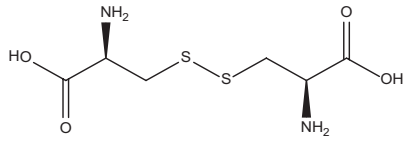
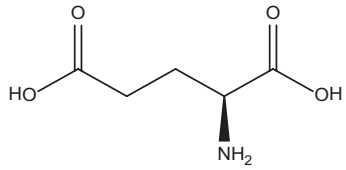
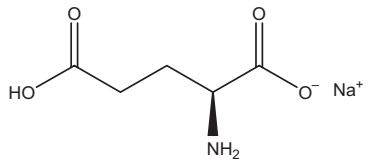
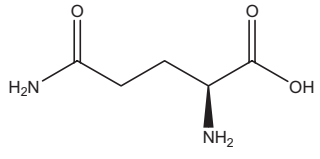
Table 4 presents the frequency and maximum use concentration ranges for amino acids.[9,10] According to information supplied to the FDA by industry as part of the Voluntary Cosmetic Registration Program (VCRP), arginine has the most reported uses in cosmetic and personal care products, with a total of 505 uses; 411 of those uses are in leave-on formulations.[9] Glycine has the second greatest number of overall uses reported, with a total of 364; 252 of those uses are in leave-on formulations. No uses were reported to the VCRP for sodium aspartate, dipotassium aspartate, calcium aspartate, calcium glycinate, or magnesium glycinate. In a recent survey of use concentrations, arginine had a maximum use concentration range of 2.0×10^{-5}% to 18%, with the 18% reported in paste masks and mud packs.[10] Glycine had a maximum use concentration range of 5.0×10^{-4}% to 4%, with the 4% reported in

Table 2. Definitions, Functions, and Idealized Structures of α-amino Acid Ingredients in This Safety Assessment.[a]

Ingredient CAS no.	Definition	Formula/structure
Alanine 56-41-7	Alanine is the amino acid that conforms to the formula. Alanine is the α-methyl-substituted amino acid of proteins	
Arginine 74-79-3	Arginine is the amino acid that conforms to the formula. Arginine is the α-guanidinylpropyl-substituted amino acid of proteins	
Arginine HCl 1119-34-2	Arginine HCl is the amino acid salt that conforms to the formula. Arginine HCl is the hydrochloride salt of arginine	
Asparagine 70-47-3, 5794-13-8 (monohydrate)	Asparagine is the amino acid that conforms to the formula. Asparagine is the α-acetamidyl-substituted amino acid of proteins	
Aspartic acid 56-84-8	Aspartic acid is the amino acid that conforms to the formula. Aspartic acid is the α-acetic acid-substituted amino acid of proteins	
Sodium aspartate 5598-53-8	Sodium aspartate is the sodium salt of aspartic acid that conforms to the formula. Sodium aspartate is the monosodium salt of aspartic acid	
Potassium aspartate 1115-63-5	Potassium aspartate is the potassium salt of aspartic acid that conforms to the formula. Potassium aspartate is the monopotassium salt of aspartic acid	
Dipotassium Aspartate 14007-45-5	Dipotassium aspartate is the dipotassium salt of aspartic acid	

(continued)

Table 2. (continued)

Ingredient CAS no.	Definition	Formula/structure
Calcium aspartate 21059-46-1	Calcium aspartate is the calcium salt of aspartic acid (q.v.) that conforms to the formula	
Magnesium aspartate 2068-80-6, 18962-61-3	Magnesium aspartate is the magnesium salt of aspartic acid (q.v.) that conforms to the formula	
Cysteine 52-90-4	Cysteine is the amino acid that conforms to the formula. Cysteine is the α-mercaptomethyl (α-thiomethyl)-substituted amino acid of proteins	
Cysteine HCl 52-89-1	Cysteine HCl is the hydrochloride of the amino acid that conforms to the formula. Cysteine HCl is the hydrochloride salt of cysteine	
Cystine 56-89-3	Cystine is the amino acid that conforms to the formula. Cystine is the disulfide (thiol dimer) of cysteine	
Glutamic acid 56-86-0	Glutamic acid is the organic acid that conforms to the formula. Glutamic acid is the α-propionic acid-substituted amino acid of proteins	
Sodium glutamate 16177-21-2, 142-47-26106-04-3 (hydrate)	Sodium glutamate is the monosodium salt of the L-form of glutamic acid. It conforms to the formula. Sodium glutamate (MSG) is the monosodium salt of glutamic acid	
Glutamine 56-85-9	Glutamine is the organic compound that conforms to the formula. Glutamine is the α-propanamidyl-substituted amino acid of proteins	

(continued)

Table 2. (continued)

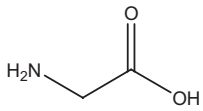
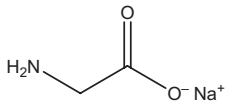
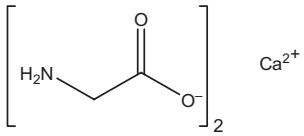
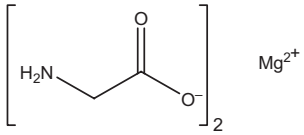
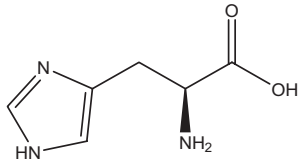
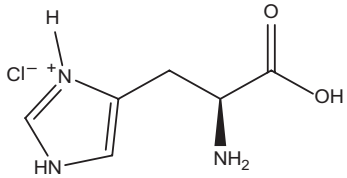
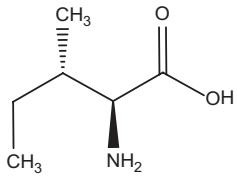
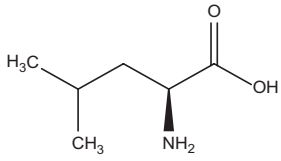
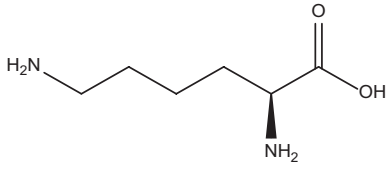
Ingredient CAS no.	Definition	Formula/structure
Glycine 56-40-6	Glycine is the amino acid that conforms to the formula. Glycine is the α-unsubstituted amino acid of proteins. Glycine is the only α-amino acid of proteins without a stereocenter	
Sodium glycinate 6000-44-8	Sodium glycinate is the sodium salt of glycine that conforms to the formula	
Calcium glycinate 35947-07-0	Calcium glycinate is the calcium salt of glycine that conforms to the formula	
Magnesium glycinate 14783-68-7	Magnesium glycinate is the magnesium salt of glycine that conforms to the formula	
Histidine 71-00-1	Histidine is the amino acid that conforms to the formula. Histidine is the α-imidazolemethyl-substituted amino acid of proteins	
Histidine HCl 645-35-2, 5934-29-2 (hydrate)	Histidine HCl is the amine salt that conforms to the formula. Histidine HCl is the hydrochloride salt of histidine	
Isoleucine 73-32-5	Isoleucine is the amino acid that conforms to the formula. Isoleucine is the α-((S)-sec-butyl)-substituted amino acid of proteins	
Leucine 61-90-5	Leucine is the amino acid that conforms to the formula. Leucine is the α-isobutyl-substituted amino acid of proteins	
Lysine 56-87-1	Lysine is the amino acid that conforms to the formula. Lysine is the α-(4-amino-n-butyl)-substituted amino acid of proteins	

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Table 2. (continued)

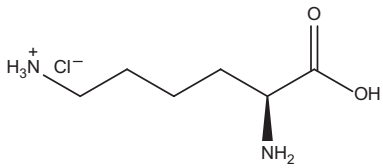
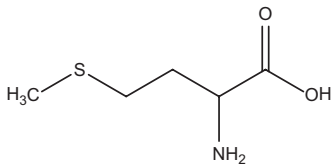
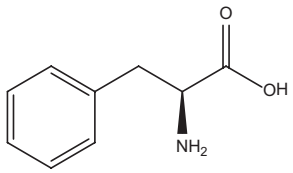
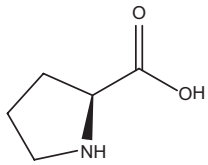
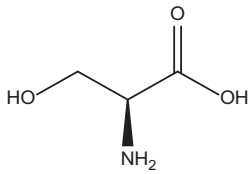
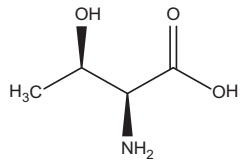
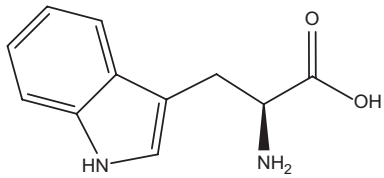
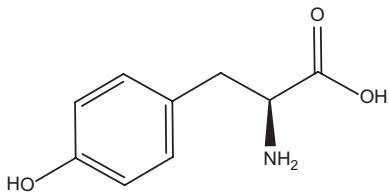
Ingredient CAS no.	Definition	Formula/structure
Lysine HCl 657-27-2, 10098-89-2	Lysine HCl is the amine salt that conforms to the formula. Lysine HCl is the hydrochloride salt of Lysine	
Methionine 59-51-8 (DL), 63-68-3	Methionine is the amino acid that conforms to the formula. Methionine is the α-methylmercaptopropyl (α-methylthiopropyl)-substituted amino acid of proteins	
Phenylalanine 63-91-2, 62056-68-2	Phenylalanine is the amino acid that conforms to the formula. Phenylalanine is the α-benzyl-substituted amino acid of proteins	
Proline 147-85-3	Proline is the amino acid that conforms to the formula. Proline is the α-pyrrolidine-substituted amino acid of proteins. Proline is the only α-amino acid of proteins wherein the α-amine is secondary	
Serine 56-45-1	Serine is the amino acid that conforms to the formula. Serine is the α-hydroxymethyl-substituted amino acid of proteins	
Threonine 72-19-5	Threonine is the amino acid that conforms to the formula. Threonine is the α-((R)-1-hydroxy-1-ethyl)-substituted amino acid of proteins	 (2*S*,3*R*)-2-amino-3-hydroxybutanoic acid
Tryptophan 73-22-3	Tryptophan is the amino acid that conforms to the formula. Tryptophan is the α-indolemethyl-substituted amino acid of proteins	
Tyrosine 60-18-4	Tyrosine is the amino acid that conforms to the formula. Tyrosine is the α-(p-hydroxybenzyl)-substituted amino acid of proteins	

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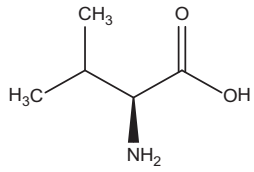
Table 2. (continued)

Ingredient CAS no.	Definition	Formula/structure
Valine 72-18-4	Valine is the amino acid that conforms to the formula. Valine is the α-isopropyl-substituted amino acid of proteins	

Abbreviation: CAS, chemical abstracts service.
[a] Although the amino acids are typically zwitterionic in situ, the acid and base groups are drawn uncharged for simplicity (except in the case of salts).

Table 3. Physical and Chemical Properties.

Property	Value	Reference
Alanine		
Physical form	Crystals	19
Molecular weight, g/mol	89.09	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	76.7	20
Density/specific gravity	1.401	19
Vapor pressure, mm Hg @ 25°C	0.0661	20
Boiling point, °C @ 760 mm Hg	212.9	20
Water solubility, g/L @ 25°C	166.5	19
Other solubility	Insol in ether	19
log P @ 25°C	−0.574	20
Disassociation constants (pK_a, pK_b)	pK_1 2.34; pK_2 9.69	19
Arginine		
Physical form	Crystals	19
Molecular weight, g/mol	174.20	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	118.7	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.46	20
Vapor pressure, mm Hg @ 25°C	2.08E−6	20
Boiling point, °C @ 760 mm Hg	367.6	20
Water solubility	Freely sol in water	19
Other solubility	Sparingly sol in alc. Insol in ether	19
log P @ 25°C	−1.652	20
Disassociation constants (pK_a, pK_b)	pK_1 2.17; pK_2 9.04; pK_3 12.48	19
Arginine HCl		
Physical form	Prisms	19
Molecular weight, g/mol	210.66	19
Water solubility	Freely sol in water	19
Other solubility	Slightly sol in hot alc	19
Asparagine		
Physical form	Crystals	19
Color	White	19
Molecular weight, g/mol	132.12	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	94.0	20
Density/specific gravity	1.543	19
Vapor pressure, mm Hg @ 25°C	6.74E−9	20
Melting point, °C	234-235	19
Boiling point, °C @ 760 mm Hg	438.0	20
Water solubility	Sol in water	19
Other solubility	Sol in acids and alkalies. Practically insol in methanol, ethanol, ether, benzene	19
log P @ 25°C	−1.880	20
Disassociation constants (pK_a, pK_b)	pK_1 2.02; pK_2 8.80	19
Aspartic acid		
Physical form	Crystals	19

(continued)

Table 3. (continued)

Property	Value	Reference
Molecular weight, g/mol	133.10	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	87.8	20
Density/specific gravity	1.661	19
Vapor pressure, mm Hg @ 25°C	2.89E−3	20
Melting point, °C	270-271	19
Boiling point, °C @ 760 mm Hg	264.1	20
Water solubility, g/L @ 20°C	4.5	19
Other solubility	Sol in dilute sol of mineral acids, alkalies. Practically insol in alc and ether	19
log P @ 25°C	−1.075	20
Disassociation constants (pK_a, pK_b)	pK_1 1.88; pK_2 3.65; pK_3 9.60	19
Cysteine		
Physical form	Crystals	19
Molecular weight, g/mol	121.16	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	90.7	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.334	20
Boiling point, °C @ 760 mm Hg	293.9	20
Water solubility	Freely sol in water	19
Other solubility	Freely sol in alc, acetic acid, ammonia. Insol in ether, acetone, ethyl acetate, benzene, carbon disulfide, carbon tet	19
log P @ 25°C	0.085	20
Disassociation constants (pK_a, pK_b)	pK_1 1.71; pK_2 8.33; pK_3 10.78	19
Cysteine HCl		
Physical form	Crystals or crystalline powder	19
Molecular weight, g/mol	157.62	19
Water solubility	Sol in water	19
Other solubility	Sol in alc and acetone	19
Cystine		
Physical form	Crystals	19
Molecular weight, g/mol	240.30	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	152.8	20
Density/specific gravity @ 20°C and 760 mm Hg	1.571	20
Vapor pressure, mm Hg@ 25°C	4.62E−10	20
Boiling point, °C @ 760 mm Hg	468.2	20
Water solubility, g/L @ 25°C	0.112	19
Other solubility	Insol in alc	19
log P @ 25°C	0.773	20
Disassociation constants (pK_a, pK_b) @ 35°C	pK_1 1; pK_2 2.1; pK_3 8.02; pK_4 8.71	19
Glutamic acid		
Physical form	Crystals	19
Molecular weight, g/mol	147.13	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	104.3	20
Density/specific gravity	1.538	19
Vapor pressure, mm Hg @ 25°C	2.55E−5	20
Melting point, °C	160	19
Boiling point, °C @ 760 mm Hg	333.8	20
Water solubility, g/L @ 25°C	8.64	19
Other solubility	Insol in methanol, ethanol, ether, acetone, glacial acetic acid, and neutral solvents	19
log P @ 25°C	−0.969	20
Disassociation constants (pK_a, pK_b)	pK_1 2.19; pK_2 4.25; pK_3 9.67	19
Glutamine		
Physical form	Crystals	19
Molecular weight, g/mol	146.14	19
Molecular volume, cm^3/mol 20°C and 760 mm Hg	110.5	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.321	20
Vapor pressure, mm Hg @ 25°C	3.50E−9	20

(continued)

Table 3. (continued)

Property	Value	Reference
Boiling point, °C @ 760 mm Hg	445.6	20
Water solubility, g/L @ 30°C	48.1	19
Other solubility	Practically insol in methanol, ethanol, ether, benzene, acetone, ethyl acetate, chloroform	19
log P @ 25°C	−1.576	20
Disassociation constants (pK_a, pK_b)	pK_1 2.17; pK_2 9.13	19
Glycine		
Physical form	Crystals	19
Molecular weight, g/mol	75.07	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	59.8	20
Density/specific gravity	1.595	19
Vapor pressure, mm Hg @ 25°C	0.0123	20
Boiling point, °C @ 760 mm Hg	240.9	20
Water solubility, g/L @ 25°C	250	19
Other solubility	Practically insol in ether	19
log P @ 25°C	−0.928	20
Disassociation constants (pK_a, pK_b)	pK_1 2.34; pK_2 9.60	19
Histidine		
Physical form	Crystals	19
Molecular weight, g/mol	155.15	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	108.9	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.423	20
Vapor pressure, mm Hg @ 25°C	3.25E−9	20
Boiling point, °C @ 760 mm Hg	458.9	20
Water solubility, g/L @ 25°C	41.9	19
Other solubility	Insol in neutral solvents	19
log P @ 25°C	−1.418	20
Disassociation constants (pK_a, pK_b)	pK_1 1.82; pK_2 6.00; pK_3 9.17	19
Histidine HCl		
Physical form	Crystals	19
Molecular weight, g/mol	191.62	19
Water solubility	Fairly sol	19
Other solubility	Insol in alc, ether	19
Isoleucine		
Physical form	Crystals	19
Molecular weight, g/mol	131.17	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	126.6	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.035	19
Vapor pressure, mm Hg @ 25°C	0.0309	20
Boiling point, °C @ 760 mm Hg	225.8	20
Water solubility, g/L @ 23.7°C	33.85	19
Other solubility	Sparingly sol in hot alc and hot acetic acid. Insol in ether	19
log P @ 25°C	0.799	20
Disassociation constants (pK_a, pK_b)	pK_1 2.36; pK_2 9.68	19
Leucine		
Physical form	Crystals	19
Color	White	19
Molecular weight, g/mol	131.17	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	126.6	20
Density/specific gravity,	1.293	19
Vapor pressure, mm Hg @ 25°C	0.0309	20
Boiling point, °C @ 760 mm Hg	225.8	20
Water solubility, g/L @ 25°C	24.26	19
Other solubility	Insol in ether	19
log P @ 25°C	0.799	20
Disassociation constants (pK_a, pK_b) @ 25°C	pK_1 2.55; pK_2 9.79	20
Lysine		
Physical form	Crystals	19

(continued)

Table 3. (continued)

Property	Value	Reference
Molecular weight, g/mol	146.19	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	129.9	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.125	20
Vapor pressure, mm Hg @ 25°C	1.23E−4	20
Boiling point, °C @ 760 mm Hg	311.5	20
Water solubility	Freely sol	19
Other solubility	Insol in neutral solvents	19
log P @ 25°C	−0.734	20
Disassociation constants (pK_a, pK_b)	pK_1 2.18; pK_2 8.95; pK_3 10.53	19
Lysine HCl		
Physical form	Crystals	19
Molecular weight, g/mol	182.65	19
Melting point, °C	263-264	19
Methionine (L-)		
Physical form	Crystals	19
Molecular weight, g/mol	149.21	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	123.7	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.206	20
Vapor pressure, mm Hg @ 25°C	1.70E−4	20
Melting point, °C	280-282	19
Boiling point, °C @ 760 mm Hg	306.9	20
Water solubility	Sol	19
Other solubility	Insol in ether, benzene, acetone	19
log P @ 25°C	0.217	20
Disassociation constants (pK_a, pK_b) @ 25°C	pK_1 2.23; pK_2 9.40	20
Methionine (DL-)		
Physical form	Crystals	19
Molecular weight, g/mol	149.21	20
Molecular volume, cm^3/mol 20°C and 760 mm Hg	123.7	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.206	20
Vapor pressure, mm Hg @ 25°C	1.70E−4	20
Boiling point, °C @ 760 mm Hg	306.9	20
Water solubility, g/L @ 25°C	33.8	19
Other solubility	Sol in dil acids, alkalies, Slightly sol in alc. Insol in ether	19
log P @ 25°C	0.217	20
Disassociation constants (pK_a, pK_b)	pK_1 2.28; pK_2 9.21	19
Phenylalanine		
Physical form	Crystals	19
Molecular weight, g/mol	165.19	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	137.4	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.201	20
Vapor pressure, mm Hg	3.13E−4	20
Boiling point, °C @ 760 mm Hg	307.5	20
Water solubility, g/L @ 25°C	29.6	19
Other solubility	Slightly sol in methanol, ethanol	19
log P @ 25°C	0.235	20
Disassociation constants (pK_a, pK_b)	pK_1 1.83; pK_2 9.13	19
Proline		
Physical form	Crystals	19
Molecular weight, g/mol	115.13	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	96.9	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.186	20
Vapor pressure, mm Hg @ 25°C	6.15E−3	20
Boiling point, °C @ 760 mm Hg	252.2	20
Water solubility, g/L @ 25°C	1623	19
Other solubility	Insol in ether, butanol, isopropanol	19
log P @ 25°C	−0.060	20

(continued)

Table 3. (continued)

Property	Value	Reference
Disassociation constants (pK_a, pK_b)	pK_1 1.99; pK_2 10.60	19
Serine		
Physical form	Crystals	19
Molecular weight, g/mol	105.09	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	74.2	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.415	20
Vapor pressure, mm Hg @ 25°C	7.17E−8	20
Boiling point, °C @ 760 mm Hg	394.8	20
Water solubility	Sol	19
Other solubility	Insol in neutral solvents	19
log P @ 25°C	−1.49	20
Disassociation constants (pK_a, pK_b)	pK_1 2.16; pK_2 9.10	20
Threonine		
Physical form	Crystals	19
Molecular weight, g/mol	119.12	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	91.1	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg °C	1.307	20
Vapor pressure, mm Hg	3.77E−6	20
Boiling point, °C @ 760 mm Hg	345.8	20
Water solubility	Freely sol	19
Other solubility	Insol in neutral solvents	19
log P @ 25°C	−1.136	20
Disassociation constants (pK_a, pK_b	pK_1 2.63; pK_2 10.43	19
Tryptophan		
Physical form	Crystals	19
Molecular weight, g/mol	204.23	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	149.8	20
Density/specific gravity, g/cm^3 @ 20°C and 760 mm Hg	1.362	20
Vapor pressure, mm Hg @ 25°C	8.30E−9	20
Boiling point, °C @ 760 mm Hg	447.9	20
Water solubility, g/L @ 25°C	11.36	19
Other solubility	Sol in hot alc and alkali hydroxides. Insol in chloroform	19
log P @ 25°C	0.704	20
Disassociation constants (pK_a, pK_b) @°C	pK_1 2.38; pK_2 9.39	19
Tyrosine		
Physical form	Crystals	19
Molecular weight, g/mol	181.19	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	1.358	20
Density/specific gravity	1.456	19
Vapor pressure, mm Hg @ 25°C	1.27E−6	20
Boiling point, °C @ 760 mm Hg	385.2	20
Water solubility, g/L @ 25°C	0.045	19
Other solubility	Sol in alkaline soln. Insol in neutral solvents	19
log P @ 25°C	−0.418	20
Disassociation constants (pK_a, pK_b)	pK_1 2.20; pK_2 9.11; $pK_3$10.07	19
Valine		
Physical form	Crystals	19
Molecular weight, g/mol	117.15	19
Molecular volume, cm^3/mol @ 20°C and 760 mm Hg	110.1	20
Density/specific gravity	1.230	19
Vapor pressure, mm Hg @ 25°C	0.0633	20
Melting point, °C	315	19
Boiling Point, °C @ 760 mm Hg	213.6	20
Water solubility, g/L @ 25°C	57.4	19
Other solubility	Insol in neutral solvents	19
log P @ 25°C	0.289	20
Disassociation constants (pK_a, pK_b)	pK_1 2.32; pK_2 9.62	19

Abbreviation: alc, alcohol; dil, dilute; soln, solution.

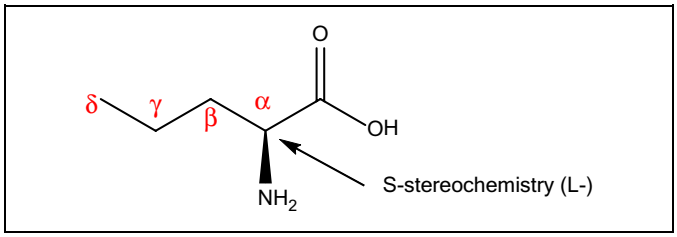


Figure 1. General structure for α-amino acids (see Discussion section).

hair dyes and nonspray deodorants. No use concentrations were reported for asparagine, sodium aspartate, dipotassium aspartate, calcium aspartate, sodium glycinate, and magnesium glycinate. In some cases, reports of uses were received in the VCRP, but no concentration of use data were available. For example, asparagine is reported to be used in 9 formulations, but no use concentration data were available. In other cases, no reported uses were received in the VCRP, but a use concentration was provided in the industry survey. For example, calcium glycinate was not reported in the VCRP to be in use, but the industry survey indicated that it is used in leave-on formulations at up to 3%. It should be presumed that calcium glycinate is used in at least one cosmetic formulation.

Products containing amino acids are reported to be used on baby skin, may be applied to the eye area or mucous membranes, or could be incidentally ingested. Additionally, amino acids are used in cosmetic sprays, including hair and other propellant and pump spray products, and could possibly be inhaled. The maximum concentration of amino acids reported to be used in a spray product is 0.3% glycine in a face spray. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm, with propellant sprays yielding a greater fraction of droplets/particles <10 μm compared with pump sprays.[11,12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, able to enter the lungs) to any appreciable amount.[13,14]

Noncosmetic

The "L-" amino acids are considered GRAS direct food additives by the FDA and may be in the free, hydrated, or anhydrous forms or as the hydrochloride, sodium, or potassium salts (21 CFR §172.320). "DL-" and "L-" amino acids are described as food additives by the USP Food Chemicals Codex.[7]

In addition to food additives and supplements, amino acids also may be used in the production of pesticides as source materials of chemical synthesis.[15,16]

Toxicological Studies

The amino acids in this assessment are found in foods, and the daily exposure from food use would result in a much larger systemic dose than that resulting from use in cosmetic products. Numerous studies and reviews have been published in the literature about the safety of dietary exposure to amino acids, including a review by the Joint *Food and Agriculture Organization* of the United Nations/World Health Organization Expert Committee on Food Additives that summarized studies on oral acute and chronic exposure/carcinogenicity studies and genotoxicity and found no safety concerns for these substances at the amounts they are used in flavoring agents.[17] Also, as noted earlier, the "L-" amino acids are considered GRAS in direct food additives by the FDA, and both "DL-" and "L-" amino acids are described as food additives in the USP Food Chemicals Codex. Consequently, the systemic toxicity potential is not addressed further in this report. The safety focus of use of these amino acids as cosmetic ingredients is on the potential for irritation and sensitization.

Enzyme Regulation

In an in vitro study using human keratinocytes, continuous application of arginine (L-) for 24 or 48 hours at concentrations of 10 to 50 mmol/L was found to increase endogenous intrakeratinocytic urea synthesis through increased activity of keratinocytic arginase.[18]

Irritation and Sensitization

Irritation

Dermal. Non-human irritation studies are presented in Table 5. These data show tested ingredients to be nonirritating.

Ocular. Non-human and human ocular irritation studies are presented in Table 6. The findings range from nonirritating to moderately irritating.

Sensitization

Non-human and human sensitization studies are presented in Table 7. No irritation was reported during induction, and no sensitization was reported at challenge.

Phototoxicity

Phototoxicity studies are presented in Table 8. No phototoxicity was reported.

Summary

Amino acids are critical to life and metabolic function. Because amino acids are present in all living organisms, they are not considered to pose any significant safety concern following oral exposure except to individuals with certain genetic disorders, and their general biology is well characterized.

The amino acids and their salts are used primarily as hair-conditioning agents and skin-conditioning agents in cosmetic formulations. Arginine has the most reported uses in cosmetic and personal care products, with a total of 440. The maximum

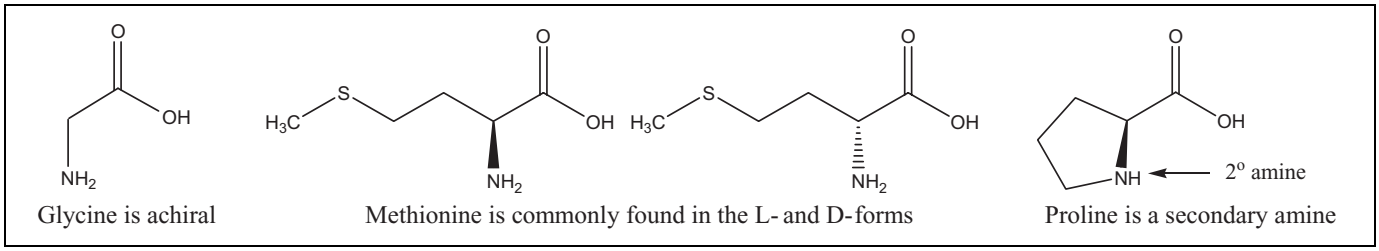


Figure 2. Exceptions in natural amino acid chirality and amine substitution—glycine, methionine, and proline.

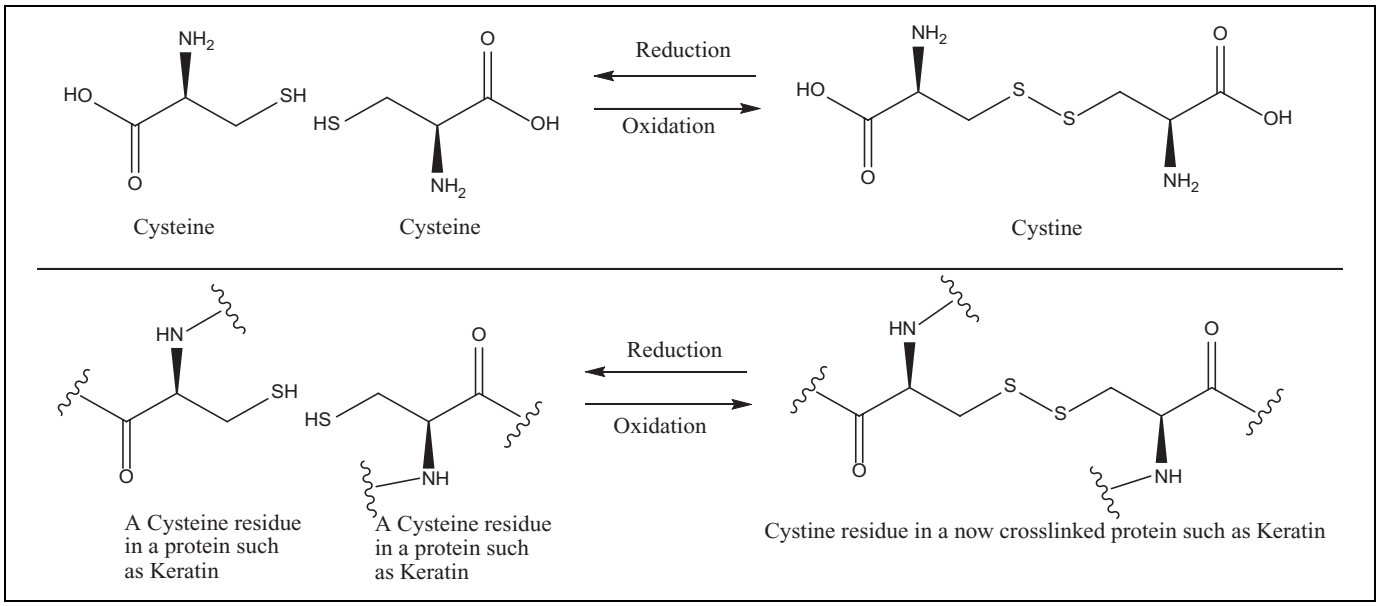


Figure 3. Cysteine/cystine redox chemistry.

use concentration range for arginine is $2.0 \times 10^{-5}\%$ to 18%. Glycine has the second greatest number of overall uses reported, with a total of 323, and has a maximum use concentration range of $5.0 \times 10^{-4}\%$ to 4%. The maximum concentration of amino acids reported to be used in a spray product is 0.3% glycine in a face spray.

The "L-" amino acids are considered GRAS in direct food additives by the FDA. In addition to food additives and supplements, amino acids may be used in the production of pesticides as source materials of chemical synthesis.

An in vitro study using human keratinocytes found that continuous application of arginine (L-) increased endogenous intrakeratinocytic urea synthesis through increased activity of keratinocytic arginase.

Cysteine HCl and methionine were used as negative controls in in vitro assays to predict potential skin irritants.

In separate efficacy studies, arginine, cysteine, and glycine did not produce any adverse effects in rats, guinea pigs, or mouse skin models. Glutamic acid was used as a negative control in an in vitro study to identify skin sensitizers.

Human repeat insult patch test studies of many products containing amino acid ingredients concluded that products containing these ingredients were not dermal irritants or sensitizers.

In several validation studies for in vitro phototoxicity assays, histidine was used as a negative control. Magnesium aspartate up to 0.5% and 1% tyrosine were not phototoxic in assays using yeast.

Discussion

The Cosmetic Ingredient Review Expert Panel (Panel) acknowledged that the safety of α-amino acids as direct food additives has been well established based on extensive research through acute and chronic dietary exposures. The Panel determined that this body of research, coupled with the available irritation and sensitization data and use concentrations that are at levels much lower than those consumed daily in the diet, were a sufficient basis for determining the safety of α-amino acids in cosmetic products.

The Panel discussed the issue of incidental inhalation exposure from hair sprays, face and neck sprays, and suntan sprays. No inhalation data were available. These ingredients reportedly are used at concentrations up to 0.3% in cosmetic products that may be aerosolized. The Panel noted that 95% to 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the

Table 4. Frequency and Concentration of Use According to Duration and Type of Exposure.[9,10]

	Alanine[a]		Arginine		Arginine HCl	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	294	3.0×10^{-7} to 0.1	505	0.00002-18	52	0.004-0.1
Duration of use						
Leave-on	252	3.0×10^{-7} to 0.1	411	0.00002-2	33	0.004-0.02
Rinse-off	42	5.0×10^{-7} to 0.06	89	0.00004-18	19	0.004-0.1
Diluted for (bath) use	NR	NR	5	NR	NR	NR
Exposure type						
Eye area	20	0.0004-0.05	58	0.00002-2	4	NR
Incidental ingestion	NR	0.00003	1	0.00003-0.001	NR	NR
Incidental inhalation—spray	NR	3.0×10^{-7}; 0.0007 aerosols; 0.001-0.01 pump sprays	NR	0.2; 0.0001-0.1 aerosols; 0.0003-0.1 pumps	6	NR
Incidental inhalation—powder	NR	NR	1	NR	NR	NR
Dermal contact	263	3.0×10^{-7} to 0.1	415	0.00002-18	26	0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	30	5.0×10^{-7} to 0.05	71	0.00004-3	26	0.004-0.1
Hair—coloring	NR	0.05	1	0.004-0.8	NR	NR
Nail	NR	NR	1	0.5	NR	0.004
Mucous membrane	2	0.00003	14	0.00003-0.001	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

	Asparagine		Aspartic acid[c]		Calcium glycinate	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	9	NR	165	0.000005-1	NR	3
Duration of use						
Leave-on	4	NR	117	0.000005-0.6	NR	3
Rinse off	5	NR	48	0.0001-1	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	10	0.2	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	NR	0.003-0.2 aerosols	NR	NR
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	3	NR	120	0.000005-0.2	NR	3
Deodorant (underarm)	NR	NR	NR	NR	NR	3 (not spray)
Hair—noncoloring	6	NR	45	0.0001-1	NR	NR
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

	Cysteine[d]		Cysteine HCl[e]		Cystine	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	25	0.0001-5	5	0.0001-6	11	0.001-3
Duration of use						
Leave-on	18	0.0001-0.05	1	0.0001	5	0.001
Rinse-off	7	0.0001-5	4	0.0001-6	6	0.001-3
Diluted for (bath) use	NR	NR	NR	NR	NR	NR

(continued)

Table 4. (continued)

	Cysteine[d]		Cysteine HCl[e]		Cystine	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Exposure type						
Eye area	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation—spray	2	0.001	NR	NR	NR	NR
Incidental inhalation—powder	NR	0.05	NR	NR	NR	NR
Dermal contact	10	0.0009-0.05	1	NR	3	0.001
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	11	0.0001-5	3	0.0001-6	8	0.001-3
Hair—coloring	NR	NR	1	NR	NR	NR
Nail	4	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

	Glutamic acid[f]		Glutamine[g]		Glycine	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals	308	0.000004-2	16	0.002-0.005	364	0.0005-4
Duration of use						
Leave-on	217	0.000004-0.4	15	0.002	252	0.0007-4
Rinse off	91	0.00003-2	1	0.005	112	0.0005-4
Diluted for (bath) use	NR	0.1	NR	NR	NR	0.2-0.4
Exposure type						
Eye area	21	0.000004-0.08	1	NR	21	0.001-0.3
Incidental ingestion	NR	0.00003	NR	NR	1	0.01
Incidental inhalation—spray	NR	NR	NR	NR	8	0.3; 0.0007 aerosols; 0.01-0.1 pump sprays
Incidental inhalation—aerosol	NR	NR	NR	NR	1	NR
Dermal contact	208	0.000004-0.2	15	0.002-0.005	271	0.001-4
Deodorant (underarm)	NR	NR	NR	NR	4	0.5-4 (not spray)
Hair—noncoloring	89	0.00003-2	1	NR	83	0.0005-2
Hair—coloring	5	0.01	NR	NR	8	0.004-4
Nail	NR	NR	NR	NR	NR	0.5-1
Mucous membrane	1	0.00003-0.1	NR	NR	5	0.01-1
Baby products	NR	NR	NR	NR	1	NR

	Histidine		Histidine HCl[h]		Isoleucine[i]	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	66	0.00009-0.05	11	0.00003-0.07	30	0.0003-0.002
Duration of use						
Leave-on	51	0.00009-0.05	11	0.00003-0.07	25	0.0003-0.002
Rinse-off	15	0.0004-0.0008	NR	NR	5	0.001-0.002
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	4	NR	1	0.01	1	NR
Incidental ingestion	NR	0.001	NR	0.00003	NR	0.001
Incidental inhalation—spray	NR	0.00009 aerosols; 0.0003 pump sprays	NR	NR	NR	0.0003 aerosols

(continued)

Table 4. (continued)

	Histidine		Histidine HCl[h]		Isoleucine[i]	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Incidental inhalation—powder	NR	NR	1	NR	NR	NR
Dermal contact	41	0.0003-0.05	11	0.01-0.07	26	0.001
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	25	0.00009-0.0008	NR	NR	4	0.0003-0.002
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	0.001	NR	0.00003	NR	0.001
Baby products	NR	NR	NR	NR	NR	NR

	Leucine[j]		Lysine[k]		Lysine HCl[l]	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	33	0.0009-0.001	151	1.0×10^{-7} to 0.7	47	0.00003-0.6
Duration of use						
Leave-on	28	0.0009-0.001	139	0.00002-0.7	36	0.00003-0.6
Rinse-off	5	NR	12	1.0×10^{-7} to 0.04	11	0.0008-0.1
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	10	0.00002-0.04	3	0.001
Incidental ingestion	NR	0.001	1	NR	1	0.00003-0.001
Incidental inhalation—spray	NR	NR	NR	NR	1	NR
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	28	0.0009	140	1.0×10^{-7} to 0.7	18	0.0002-0.6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	5	NR	10	0.00004	28	0.0008-0.2
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	0.001	1	NR	1	0.00003-0.001
Baby products	NR	NR	NR	NR	NR	NR

	Magnesium aspartate		Methionine[m]		Phenylalanine	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	107	0.00005-0.1	30	0.0001-0.07	39	0.00009-0.03
Duration of use						
Leave-on	87	0.0003-0.1	24	0.0001-0.005	30	0.00009-0.03
Rinse-off	19	0.00005-0.06	6	0.0001-0.07	9	0.0004-0.0008
Diluted for (bath) use	1	NR	NR	NR	NR	NR
Exposure type						
Eye area	19	0.005-0.05	NR	NR	2	0.005
Incidental ingestion	NR	0.001	NR	NR	NR	NR
Incidental inhalation—spray	NR	NR	NR	NR	NR	0.00009 aerosols
Incidental inhalation—powder	NR	0.0003	NR	NR	1	NR
Dermal contact	106	0.0003-0.1	23	0.001-0.005	29	0.0004-0.03
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	1	0.00005-0.005	7	0.0001-0.07	9	0.00009-0.001
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	0.001	NR	NR	NR	NR
Mucous membrane	2	0.0005-0.003	NR	NR	NR	NR
Baby products	NR	0.0003-0.005	NR	NR	NR	NR

(continued)

Table 4. (continued)

	Potassium aspartate		Proline[n]		Serine[o]	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	14	0.0003-0.008	279	0.00001-2	334	0.00003-2
Duration of use						
Leave-on	9	0.0003-0.008	223	0.0001-2	299	0.00003-2
Rinse-off	5	0.005	56	0.00001-1	35	0.0002-1
Diluted for (Bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	14	0.0001-0.2	38	0.002-0.3
Incidental Ingestion	NR	0.001	1	NR	NR	0.00003-0.05
Incidental inhalation—spray	NR	NR	4	0.0003 aerosols	NR	0.08; 0.0005 aerosols
Incidental inhalation—powder	NR	0.0003	NR	NR	9	NR
Dermal contact	13	0.0003-0.008	232	0.0001-1	309	0.002-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	1	0.005	15	0.00001-0.03	14	0.0002-1
Hair—coloring	NR	NR	29	NR	NR	NR
Nail	NR	NR	2	2	2	0.004
Mucous membrane	NR	0.001	2	NR	2	0.00003-0.05
Baby products	NR	0.0003-0.005	NR	NR	1	NR

	Sodium glutamate		Sodium glycinate		Threonine[p]	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	19	0.01-2	16	NR	170	0.00002-0.05
Duration of use						
Leave-on	18	0.01-2	NR	NR	126	0.00003-0.02
Rinse-off	1	0.01	16	NR	44	0.00002-0.05
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	1	0.5-2	NR	NR	10	0.0002-0.003
Incidental ingestion	NR	0.2	NR	NR	NR	0.00003-0.001
Incidental inhalation—spray	NR	NR	NR	NR	NR	0.0003 aerosols
Incidental inhalation—powder	NR	NR	NR	NR	NR	NR
Dermal contact	19	0.01-2	NR	NR	130	0.0001-0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	NR	1	NR	NR	10	0.00002-0.002
Hair—coloring	NR	0.01	16	NR	29	0.05
Nail	NR	NR	NR	NR	1	0.004
Mucous membrane	1	0.2	NR	NR	1	0.00003-0.001
Baby products	NR	NR	NR	NR	NR	NR

	Tryptophan		Tyrosine		Valine	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Totals[b]	15	0.0001	56	0.0005-1	32	0.0004-1
Duration of use						
Leave-on	13	NR	49	0.0009-1	26	0.0004-0.5
Rinse-off	2	0.0001	7	0.0005-0.001	6	0.002-1
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	2	NR	3	0.004-1	1	NR
Incidental ingestion	NR	NR	NR	NR	NR	0.001

(continued)

Table 4. (continued)

	Tryptophan		Tyrosine		Valine	
	# of uses	Max conc of use, %	# of uses	Max conc of use, %	# of uses	Max conc of use, %
Incidental inhalation—spray	NR	NR	9	NR	NR	0.0004 aerosols
Incidental inhalation—powder	NR	NR	1	0.05	NR	NR
Dermal contact	13	NR	47	0.0009-1	28	0.0009-0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—noncoloring	2	0.0001	9	0.0005	4	0.0004-1
Hair—coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	0.001
Baby products	NR	NR	NR	NR	NR	NR

Abbreviations: conc, concentration; NR, no reported uses.
[a]The VCRP listed separate entries for alanine and L-alanine, which have been combined in this table. L-Alanine has a total of 19 uses, 9 in rinse-off products and 10 in leave-on products. In all, 13 uses lead to a dermal exposure, and 6 uses are to hair (noncoloring).
[b]Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types my not equal the sum of total uses.
[c]The VCRP listed separate entries for aspartic acid and L-aspartic acid, which have been combined in this table. L-Aspartic acid has a total of 3 uses, 2 in rinse-off products and 1 in leave-on products. In all, 1 use leads to a dermal exposure, and 2 uses are to hair (noncoloring).
[d]The VCRP listed separate entries for cysteine and L-cysteine, which have been combined in this table. L-Cysteine has a total of 3 uses, all in rinse-off products. In all, 1 use leads to a dermal exposure, and 2 uses are to hair (noncoloring).
[e]The VCRP listed only an entry for L-cysteine HCl. These data have been combined with the concentration of use data for cysteine HCl.
[f]The VCRP listed separate entries for glutamic acid, DL-glutamic acid, and L-glutamic acid, which have been combined in this table. DL-Glutamic acid has a total of 2 uses, all in leave-on products. Both uses are a dermal exposure. L-Glutamic acid has a total of 14 uses, 8 uses in leave-on products and 6 uses in rinse-off products. In all, 8 uses are a dermal exposure, and 6 uses are to hair (noncoloring).
[g]The VCRP listed only an entry for L-glutamine. These data have been combined with the concentration of use data for glutamine.
[h]The VCRP listed only an entry for L-histidine HCl. These data have been combined with the concentration of use data for histidine HCl.
[i]The VCRP listed only an entry for L-isoleucine. These data have been combined with the concentration of use data for isoleucine.
[j]The VCRP listed only an entry for L-leucine. These data have been combined with the concentration of use data for leucine.
[k]The VCRP listed separate entries for lysine, DL-lysine, and L-lysine, which have been combined in this table. DL-Lysine has 1 use in a leave-on product with dermal exposure. L-Lysine has a total of 16 uses, 13 uses in leave-on products and 3 uses in rinse-off products. In all, 1 use is in the eye area, 13 uses are a dermal exposure, and 3 uses are to hair (noncoloring).
[l]The VCRP listed only an entry for L-lysine HCl. These data have been combined with the concentration of use data for lysine HCl.
[m]The VCRP listed separate entries for methionine and L-methionine, which have been combined in this table. L-methionine has a total of 2 uses, both in leave-on products with a dermal exposure.
[n]The VCRP listed separate entries for proline and DL-proline, which have been combined in this table. DL-Proline has a total of 9 uses, 3 in leave-on products and 6 in rinse-off products. In all, 1 use may lead to incidental ingestion, 1 use may be to the mucous membranes, 2 uses are dermal exposures, and 6 uses are to the hair (coloring).
[o]The VCRP listed separate entries for serine and L-serine, which have been combined in this table. L-Serine has a total of 40 uses, 32 in leave-on products and 8 in rinse-off products. In all, 2 uses are in the eye area, 1 use is in nail products, 34 uses are dermal exposures, and 5 uses are to hair (noncoloring).
[p]The VCRP listed separate entries for threonine and L-threonine, which have been combined in this table. L-Threonine has a total of 7 uses, 5 in leave-on products and 2 in rinse-off products. In all, 5 uses are dermal exposures and 2 are to the hair (noncoloring).

breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic toxic effects. The Panel considered other data available to characterize the potential for α-amino acids to cause systemic toxicity, irritation, sensitization, or other effects. They noted that numerous studies and reviews have been published in the literature regarding the safety of dietary exposure to amino acids, including studies on oral acute and chronic toxicity, carcinogenicity, and genotoxicity, which found no safety concerns for these substances in the amounts at which they are consumed in flavoring agents. Additionally, little or no irritation or sensitization was observed in multiple tests of dermal and ocular exposure. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

The Panel recognized that there are issues with sodium glutamate and phenylalanine in the diet for certain individuals. However, the Panel determined that the concentrations of these amino acids in cosmetic products are at levels that would not be significantly absorbed through topical application or incidental ingestion and, thus, would not cause systemic reactions in individuals.

Although the *International Cosmetic Dictionary and Handbook* does not distinguish among the α-amino acids used in cosmetics that are L-stereoisomers from those that are D-stereoisomers (or are mixtures of L- and D-stereoisomers), the Panel noted that the L-amino acids are GRAS direct food additives by the FDA (except methionine which is GRAS as a racemic mixture, and glycine which is GRAS and has no

Table 5. Dermal Non-Human Irritation Studies.

Ingredient	Concentration	Method	Results	Reference
L-Arginine	5% in distilled water	Draize test in 4 male New Zealand albino rabbits	Nonirritating	21
Aspartic acid	0.2% in an eye gel	EPISKIN reconstructed human epidermis model	Potentially a nonirritant	22
Cysteine HCl	500 mmol/L as a negative control	In vitro cell detachment and growth inhibition assays to predict potential skin irritants	Negative	23
Glycine	2% in a moisturizer	EPISKIN reconstructed human epidermis model	Potentially a nonirritant	24
Methionine	500 mmol/L as a negative control	In vitro cell detachment and growth inhibition assays to predict potential skin irritants	Negative	23
Serine	0.3% in an eye gel	EPISKIN reconstructed human epidermis model	Potentially a nonirritant	25

Table 6. Ocular Irritation Studies.

Ingredient	Concentration	Method	Results	Reference
Non-human				
L-Arginine	5% in distilled water	Draize test in 4 male New Zealand albino rabbits	Nonirritating	21
Arginine	1.4% in an eye gel	EpiOcular irritation study	Nonirritating	26
Aspartic acid	0.2% in an eye gel	Calf cornea method (BCOP)	Weakly irritating	27
Aspartic acid	0.2% in an eye gel	HET-CAM method	Moderately irritating	28
Cysteine	5% with 0.1% arginine in a permanent reducing lotion	Calf cornea method (BCOP)	Weakly irritating	29
Arginine	0.1% with 5% cysteine in a permanent reducing lotion	Calf cornea method (BCOP)	Weakly irritating	29
Glycine	2% in a moisturizer	HET-CAM method	Irritating	30
Glycine	2% in a moisturizer	Calf cornea method (BCOP)	Weakly irritating	31
Magnesium aspartate	0.1% in an eye cream	HET-CAM method	Moderately irritating	32
Magnesium aspartate	0.05% with 1% tyrosine in an eye cream	HET-CAM method	Slightly irritating	33
Tyrosine	1% with magnesium aspartate in an eye cream	HET-CAM method	Slightly irritating	33
Serine	0.3% in an eye gel	Calf cornea method (BCOP)	Weakly irritating	34
Human				
Magnesium aspartate	0.05% with 1% tyrosine in an eye cream	2-Week in-use ocular tolerance study in 19 patients	Good ocular comfort, safety, and tolerance	35
Tyrosine	1% with 0.05% magnesium aspartate in an eye cream	2-Week in-use ocular tolerance study in 19 patients	Good ocular comfort, safety, and tolerance	35
Magnesium aspartate	0.05% with 1% tyrosine in a product	Clinical eye sting study in 12 patients	Slight potential for stinging	36
Tyrosine	1% with 0.05% magnesium aspartate in a product	Clinical eye sting study in 12 patients	Slight potential for stinging	36
Glycine	7.5% in a pencil eye liner	14-Day controlled usage study in 28 patients	No eye irritation	37
Proline	0.1% in an eye cream	4-Week controlled clinical usage study in 29 patients applied to eye area	No eye irritation	38

Abbreviations: BCOP, bovine corneal opacity and permeability; HET-CAM, Hen's egg test—chorioallantoic membrane.

stereocenter). Amino acids with a mixture of the 2 stereoisomers (DL-) have approved uses as food additives according to the USP Food Chemicals Codex. The FDA VCRP has received reported uses of the DL-mixtures in addition to L-amino acids in cosmetics. However, no cosmetic uses were reported for α-amino acid ingredients that are specifically the D-stereoisomers. The Panel does not anticipate that there are significant toxicological differences in cosmetic applications between the 2 stereoisomers.

Conclusion

The Panel concluded that α-amino acids, listed below, are safe in the present practices of use and concentration in cosmetics.

Alanine
Arginine
Arginine HCl
Asparagine
Aspartic Acid
Calcium Aspartate*
Calcium Glycinate
Cysteine
Cysteine HCl
Cystine

Table 7. Dermal Sensitization Studies.

Ingredient	Concentration	Method	Results	Reference
Non-human				
Aginine	0.2-1.0 g in a wound dressing composed of a hyaluronic acid sponge, final concentration not specified	Efficacy study in Sprague-Dawley rats	No adverse effects	39
L-Arginine	5% in distilled water	Maximization test in 10 female Dunkin-Hartley albino guinea pigs	Negative	21
Cysteine	Up to 13%	Efficacy studies for the treatment of sesquiterpene lactone-induced acute contact dermatitis in albino guinea pigs	No adverse effects	40,41
Glutamic acid	Concentrations not specified, used as a negative control	Cell-based in vitro gene expression studies to identify skin sensitizers	Negative	42,43
Glycine	1 mmol/L in 50% ethanol in a topical-barrier recovery accelerator	A mouse skin model for chronic eczematous dermatitis	No adverse effects	44
Human				
Alanine	0.04% in a face and neck product with 0.15% arginine, 0.01% glutamic acid, 0.05% histidine, 0.01% lysine, and 0.13% serine	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	45
Arginine	0.15% in a face and neck product with 0.04% alanine, 0.01% glutamic acid, 0.05% histidine, 0.01% lysine, and 0.13% serine	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	45
Arginine	0.025% in a face and neck product with 0.025% glycine and 0.005% methionine	HRIPT with 102 patients; semiocclusive	No dermal irritation or sensitization	45
Arginine	0.27% in a suntan product with 0.07% histidine HCl, 0.03% phenylalanine, and 0.03% tyrosine	HRIPT with 104 patients; occlusive	No dermal irritation or sensitization	45
Arginine	1% in a face and neck product	HRIPT with 56 patients; semiocclusive	No dermal irritation or sensitization	45
Arginine	1.1% in a mascara	HRIPT with 105 patients; semiocclusive	No dermal sensitization	46
Arginine	1.4% in an eye gel	HRIPT with 115 patients; occlusive	No dermal irritation or sensitization	47
Arginine	1.4% in an eye gel	4-Week controlled clinical usage study in 34 patients	Very well tolerated	48
Arginine	1.4% in a facial scrub/cleansing masque	HRIPT in 108 patients; occlusive	No dermal irritation or sensitization	49
Arginine	1.4% in a facial scrub/cleansing masque	4-Week controlled clinical usage study in 48 patients	Very well tolerated	50
Arginine	1.35% in a face and neck product	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	51
Arginine	1.5% in a scalp treatment	HRIPT with 106 patients; semiocclusive	No dermal irritation or sensitization	52
Aspartic acid	0.2% in an eye gel	HRIPT with 107 patients; occlusive	No dermal irritation or sensitization	53
Aspartic acid	0.2% in a face lotion	HRIPT with 102 patients; occlusive	No dermal irritation or sensitization	54
Aspartic acid	0.92% in a leave-on hair masque	HRIPT with 102 patients; semiocclusive	No skin reactivity	55
Magnesium aspartate	0.1% in a face cream	HRIPT with 210 patients; semiocclusive	No dermal sensitization	56
Glutamic acid	0.01% in a face and neck product with 0.04% alanine and 0.15% arginine, 0.05% histidine, 0.01% lysine, and 0.13% serine	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	45

(continued)

Table 7. (continued)

Ingredient	Concentration	Method	Results	Reference
Glycine	1% in a shave cream (10% dilution tested)	HRIPT with 103 patients; semiocclusive	No dermal irritation or sensitization	57
Glycine	0.025% in a face and neck product with 0.025% arginine and 0.005% methionine	HRIPT with 102 patients; semiocclusive	No dermal irritation or sensitization	45
Glycine	1% in a cuticle cream	HRIPT with 107 patients	No dermal irritation or sensitization	58
Glycine	2% in a moisturizer	HRIPT with 104 patients; occlusive	No dermal irritation or sensitization	59
Glycine	2% in a moisturizer	HRIPT with 112 patients; occlusive	No dermal irritation or sensitization	60
Glycine	2.784% in an A/P roll-on	HRIPT in 108 patients; semiocclusive	No dermal irritation or sensitization	61
Histidine	0.05% in a face and neck product with 0.04% alanine, 0.15% arginine, 0.01% glutamic acid, 0.01% lysine, and 0.13% serine	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	45
Histidine HCl	0.07% in a suntan product with 0.27% arginine, 0.03% phenylalanine, and 0.03% tyrosine	HRIPT with 104 patients; occlusive	No dermal irritation or sensitization	45
Lysine	0.01% in a face and neck product with 0.04% alanine, 0.15% arginine, 0.01% glutamic acid, 0.05% histidine, and 0.13% serine	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	45
Lysine	0.65% in a face highlighter	HRIPT with 106 patients; semiocclusive	No dermal irritation or sensitization	62
Lysine	0.65% in a makeup preparation	HRIPT with 213 patients; semiocclusive	No dermal irritation or sensitization	63
Methionine	0.005% in a face and neck product with 0.025% arginine, and 0.025% glycine	HRIPT with 102 patients; semiocclusive	No dermal irritation or sensitization	45
Phenylalanine	0.03% in a suntan product with 0.27% arginine, 0.07% histidine HCl, and 0.03% tyrosine	HRIPT with 104 patients; occlusive	No dermal irritation or sensitization	45
Proline	0.1% in an eye cream	HRIPT with 112 patients; occlusive	No dermal irritation or sensitization	64
Serine	0.13% in a face and neck product with 0.04% alanine, 0.15% arginine, 0.01% glutamic acid, 0.05% histidine, and 0.01% lysine	HRIPT with 104 patients; semiocclusive	No dermal irritation or sensitization	45
Serine	0.3% in an eye gel	HRIPT with 50 patients	No dermal irritation or sensitization	65
Serine	0.3% in an eye cream	HRIPT with 50 patients; occlusive	No dermal irritation or sensitization	66
Tyrosine	0.03% in a suntan product with 0.27% arginine, 0.07% histidine HCl, and 0.03% phenylalanine	HRIPT with 104 patients; occlusive	No dermal irritation or sensitization	45
D,L-Valine	0.5% in a hair care product	Single application epicutaneous patch test; occlusive	No adverse reactions	67

Abbreviation: HRIPT, human repeat insult patch test.

Dipotassium Aspartate*	Isoleucine	Methionine	Sodium Glutamate
Glutamic Acid	Leucine	Phenylalanine	Sodium Glycinate
Glutamine	Lysine	Potassium Aspartate	Threonine
Glycine	Lysine HCl	Proline	Tryptophan
Histidine	Magnesium Aspartate	Serine	Tyrosine
Histidine HCl	Magnesium Glycinate*	Sodium Aspartate*	Valine

Table 8. Phototoxicity Studies.

Ingredient	Concentration	Method	Results	Reference
L-Histidine	Up to 3.3% as a negative control	SkinEthic reconstructed human epidermis validation assay	Not phototoxic	68
L-Histidine	Up to 10% as a negative control	Skin^2 ZK 1350 human dermal model validation assay	Not phototoxic	69
Magnesium aspartate	0.1% in an eye cream	Assessment on *Saccharomyces cerevisiae*	Not phototoxic	70
Magnesium aspartate	0.5% with 1% tyrosine in an eye cream	Assessment on *Saccharomyces cerevisiae*	Not phototoxic	71
Tyrosine	1% with 0.5% magnesium aspartate in an eye cream	Assessment on *Saccharomyces cerevisiae*	Not phototoxic	71

If the ingredients in this group not reported in current use (as indicated by *) are to be used in cosmetics in the future, the expectation is that they would be used at concentrations comparable to others in this group.

Authors' Note

Unpublished sources cited in this report are available from the Director, Cosmetic Ingredient Review, 1101 17th St, Suite 412, Washington, DC 20036, USA.

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