Safety Assessment of α-Amino Acids as Used in Cosmetics

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ABSTRACT

The Cosmetic Ingredient Review Expert Panel (the 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.

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 also 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 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 Food and Drug Administration (FDA), thus oral toxicity was not a focus for these ingredients in this assessment.

Monosodium glutamate has been reported to be associated with a human condition known as "MSG symptom complex" in which such symptoms 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 of 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 with an amine group on the immediately adjacent (α) carbon.

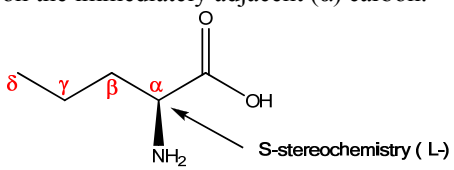


Figure 1. α-amino acids

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. Additionally, all of the natural amino acids contain primary amines (i.e. acids with an NH_2 group pendant from the α-carbon), except proline, which is a secondary amine.

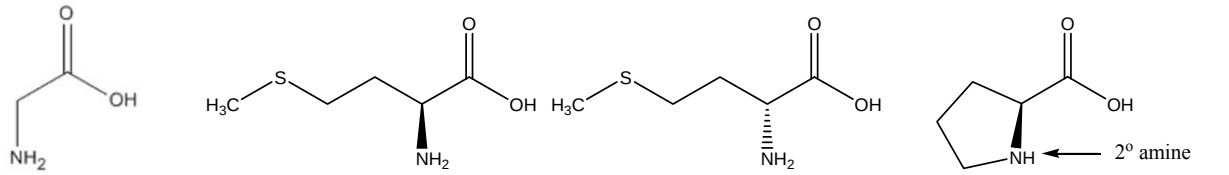


Figure 2. Exceptions in natural amino acid chirality and amine substitution

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

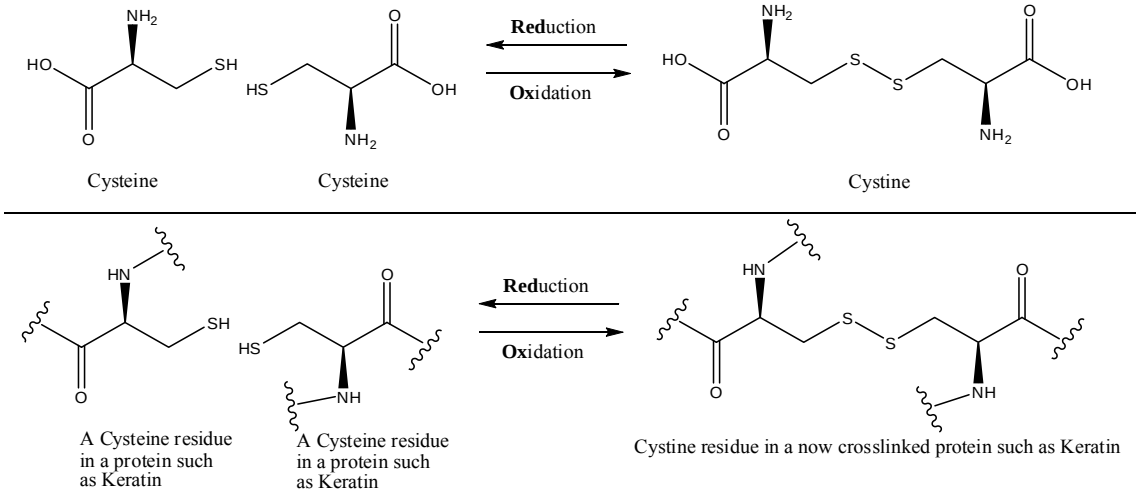


Figure 3. Cysteine/Cystine redox chemistry

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, removes 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, 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. According to information supplied to the Food and Drug Administration (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; 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 hair dyes and non-spray 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 (i.e., able to enter the lungs) to any appreciable amount.[13,14]

Non-Cosmetic

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 FAO/WHO Expert Committee on Food Additives (JECFA) 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-h at concentrations of 10-50 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.

Ocular

Non-human and human ocular irritation studies are presented in Table 6.

Sensitization

Non-human and human sensitization studies are presented in Table 7.

Phototoxicity

Phototoxicity studies are presented in Table 8.

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 use concentration range for arginine is 2.0×10^{-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 5.0×10^{-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 Generally Recognized As Safe (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.

HRIPT 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 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% – 99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the 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.

While the *International Cosmetic Dictionary and Handbook* does not distinguish among the α-amino acids used in cosmetics that are L-sterioisomers from those that are D-stereoisomers (or are mixtures of L- and D-stereoisomers), the Panel noted that the L-amino acids are Generally Recognized As Safe (GRAS) direct food additives by the FDA (except Methionine which is GRAS as a racemic mixture, and Glycine which is GRAS and has no 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 Voluntary Cosmetic Registration Program (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 CIR Expert 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
Dipotassium Aspartate*
Glutamic Acid
Glutamine
Glycine
Histidine
Histidine HCl
Isoleucine
Leucine
Lysine
Lysine HCl
Magnesium Aspartate
Magnesium Glycinate*
Methionine
Phenylalanine
Potassium Aspartate
Proline
Serine
Sodium Aspartate*
Sodium Glutamate
Sodium Glycinate
Threonine
Tryptophan
Tyrosine
Valine

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

TABLES AND FIGURES

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	

Table 2. Definitions, functions, and idealized structures of alpha-amino acid ingredients in this safety assessment. 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).

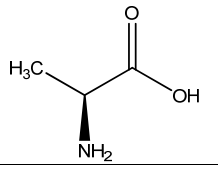
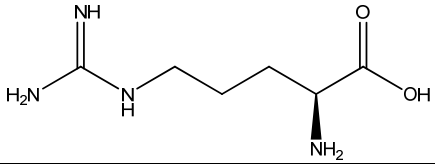
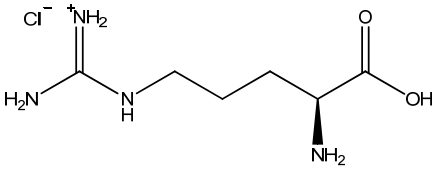
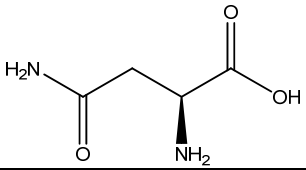
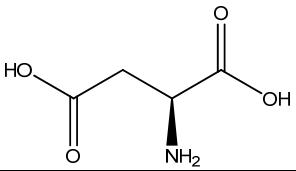
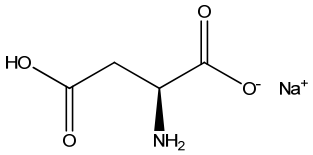
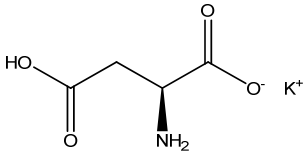
Ingredient CAS No.	Definition	Formula/structure
Alanine 56-41-7	Alanine is the amino acid that conforms to the formula. *Alanine is the α-methyl substituted amino acid of proteins.*	
Arginine 74-79-3	Arginine is the amino acid that conforms to the formula. *Arginine is the α-guanidinylpropyl substituted 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.*	

Table 2. Definitions, functions, and idealized structures of alpha-amino acid ingredients in this safety assessment. 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).

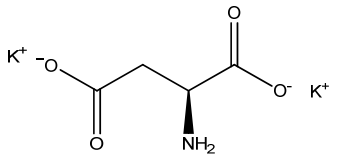
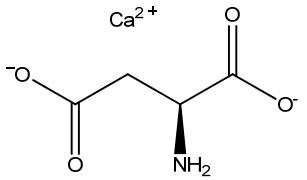
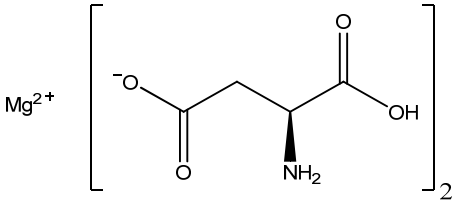
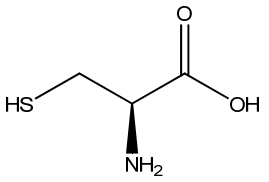
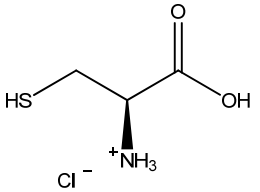
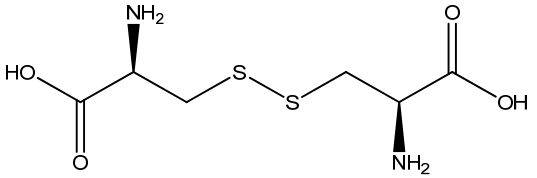
Ingredient CAS No.	Definition	Formula/structure
Dipotassium Aspartate 14007-45-5	Dipotassium Aspartate is the dipotassium salt of Aspartic Acid.	
Calcium Aspartate 21059-46-1	Calcium Aspartate is the calcium salt of Aspartic Acid (q.v.) that conforms to the formula.	
Magnesium Aspartate 2068-80-6 18962-61-3	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.*	

Table 2. Definitions, functions, and idealized structures of alpha-amino acid ingredients in this safety assessment. 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).

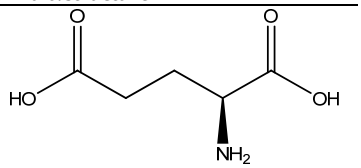
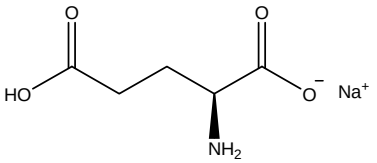
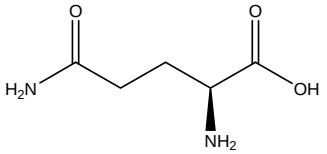
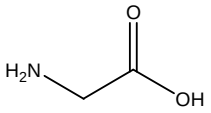
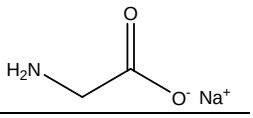
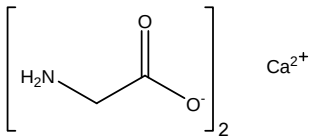
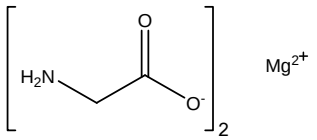
Ingredient CAS No.	Definition	Formula/structure
		
Sodium Glutamate 16177-21-2 142-47-2 6106-04-3 (hydrate)	Sodium Glutamate is the monosodium salt of the L-form of glutamic acid. It conforms to the formula. *Sodium Glutamate (MSG) is the monosodium salt of Glutamic Acid.*	
Glutamine 56-85-9	Glutamine is the organic compound that conforms to the formula. *Glutamine is the α-propanamidyl substituted amino acid of proteins.*	
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.*	

Table 2. Definitions, functions, and idealized structures of alpha-amino acid ingredients in this safety assessment. 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).

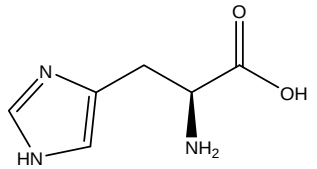
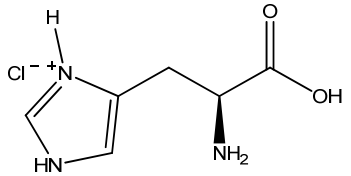
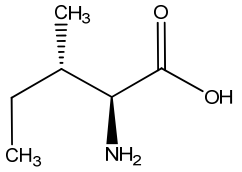
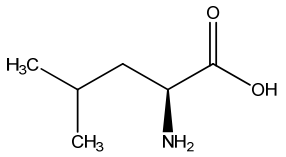
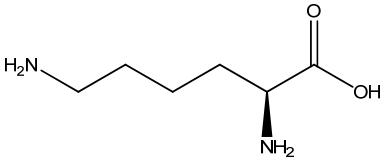
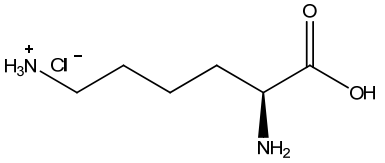
Ingredient CAS No.	Definition	Formula/structure
		
Histidine HCl 645-35-2 5934-29-2 (hydrate)	Histidine HCl is the amine salt that conforms to the formula. *Histidine HCl is the hydrochloride salt of Histidine.*	
Isoleucine 73-32-5	Isoleucine is the amino acid that conforms to the formula. *Isoleucine 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.*	
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.*	

Table 2. Definitions, functions, and idealized structures of alpha-amino acid ingredients in this safety assessment. 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).

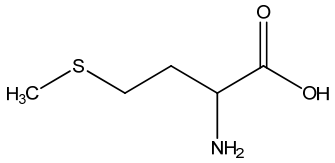
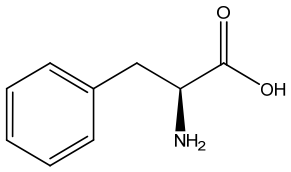
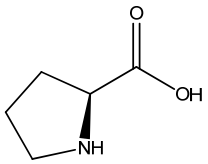
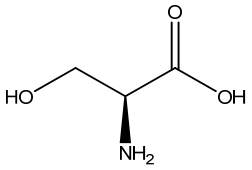
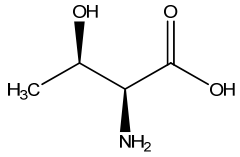
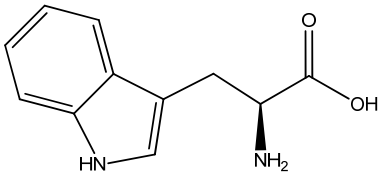
Ingredient CAS No.	Definition	Formula/structure
		
Phenylalanine 63-91-2 62056-68-2	Phenylalanine is the amino acid that conforms to the formula. *Phenylalanine is the α-benzyl substituted amino acid of proteins.*	
Proline 147-85-3	Proline is the amino acid that conforms to the formula. *Proline is the 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.*	

Table 2. Definitions, functions, and idealized structures of alpha-amino acid ingredients in this safety assessment. 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).

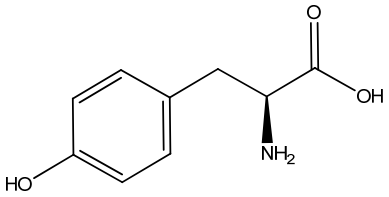
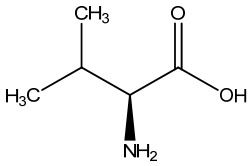
Ingredient CAS No.	Definition	Formula/structure
		
Valine 72-18-4	Valine is the amino acid that conforms to the formula. *Valine is the α-isopropyl substituted amino acid of proteins.*	

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 & 760 mmHg	76.7	[20]
Density/Specific Gravity	1.401	[19]
Vapor pressure mmHg @ 25 °C	0.0661	[20]
Boiling Point °C @760 mmHg	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 (pKa, pKb)	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 & 760 mmHg	118.7	[20]
Density/Specific Gravity g/cm^3 @ 20 °C & 760 mmHg	1.46	[20]
Vapor pressure mmHg@ 25 °C	2.08E-6	[20]
Boiling Point °C @760 mmHg	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 (pKa, pKb)	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]

Table 3. Physical and chemical properties.

Asparagine		
Physical Form	Crystals	[19]
Color	White	[19]
Molecular Weight g/mol	132.12	[19]
Molecular Volume cm^3/mol @ 20 °C & 760 mmHg	94.0	[20]
Density/Specific Gravity	1.543	[19]
Vapor pressure mmHg @ 25 °C	6.74E-9	[20]
Melting Point °C	234-235	[19]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	pK_1 2.02; pK_2 8.80	[19]
Aspartic Acid		
Physical Form	Crystals	[19]
Molecular Weight g/mol	133.10	[19]
Molecular Volume cm^3/mol @ 20 °C & 760 mmHg	87.8	[20]
Density/Specific Gravity	1.661	[19]
Vapor pressure mmHg@ 25 °C	2.89E-3	[20]
Melting Point °C	270-271	[19]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	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 & 760 mmHg	90.7	[20]
Density/Specific Gravity g/cm^3 @ 20 °C & 760 mmHg	1.334	[20]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	pK_1 1.71; pK_2 8.33; pK_3 10.78	[19]

Table 3. Physical and chemical properties.

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 & 760 mmHg	152.8	[20]
Density/Specific Gravity @ 20 °C & 760 mmHg	1.571	[20]
Vapor pressure mmHg@ 25 °C	4.62E-10	[20]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb) @ 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 & 760 mmHg	104.3	[20]
Density/Specific Gravity	1.538	[19]
Vapor pressure mmHg@ 25 °C	2.55E-5	[20]
Melting Point °C	160	[19]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	pK_1 2.19; pK_2 4.25; pK_3 9.67	[19]

Table 3. Physical and chemical properties.

Glutamine		
Physical Form	Crystals	[19]
Molecular Weight g/mol	146.14	[19]
Molecular Volume cm^3/mol 20 °C & 760 mmHg	110.5	[20]
Density/Specific Gravity g/cm^3 @ 20 °C & 760 mmHg	1.321	[20]
Vapor pressure mmHg@ 25 °C	3.50E-9	[20]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	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 & 760 mmHg	59.8	[20]
Density/Specific Gravity	1.595	[19]
Vapor pressure mmHg@ 25 °C	0.0123	[20]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	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 & 760 mmHg	108.9	[20]
Density/Specific Gravity g/cm^3 @ 20 °C & 760 mmHg	1.423	[20]
Vapor pressure mmHg@ 25 °C	3.25E-9	[20]
Boiling Point °C @ 760 mmHg	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 (pKa, pKb)	pK_1 1.82; pK_2 6.00; pK_3 9.17	[19]

Table 3. Physical and chemical properties.

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 ºC & 760 mmHg	126.6	[20]
Density/Specific Gravity g/cm^3@ 20 ºC & 760 mmHg	1.035	[19]
Vapor pressure mmHg@ 25 ºC	0.0309	[20]
Boiling Point ºC @ 760 mmHg	225.8	[20]
Water Solubility g/L @ 23.7 ºC	33.85	[19]
Other Solubility	Sparingly sol in hot alc and hot acetic acid. Insol in ether.	[19]
log P @ 25 ºC	0.799	[20]
Disassociation constants (pKa, pKb)	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 ºC & 760 mmHg	126.6	[20]
Density/Specific Gravity	1.293	[19]
Vapor pressure mmHg@ 25 ºC	0.0309	[20]
Boiling Point ºC @ 760 mmHg	225.8	[20]
Water Solubility g/L @ 25 ºC	24.26	[19]
Other Solubility	Insol in ether	[19]
log P @ 25 ºC	0.799	[20]
Disassociation constants (pKa, pKb) @ 25 ºC	pK_1 2.55; pK_2 9.79	[20]

Table 3. Physical and chemical properties.

Lysine		

Physical Form	Crystals	[19]
Molecular Weight g/mol	146.19	[19]
Molecular Volume cm^3/mol @20 ºC & 760 mmHg	129.9	[20]
Density/Specific Gravity g/cm^3@ 20 ºC & 760 mmHg	1.125	[20]
Vapor pressure mmHg@ 25 ºC	1.23E-4	[20]
Boiling Point ºC @ 760 mmHg	311.5	[20]
Water Solubility	Freely sol	[19]
Other Solubility	Insol in neutral solvents.	[19]
log P @ 25 ºC	-0.734	[20]
Disassociation constants (pKa, pKb)	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 ºC	263-264	[19]
Methionine (L-)		
Physical Form	Crystals	[19]
Molecular Weight g/mol	149.21	[19]
Molecular Volume cm^3/mol @ 20 ºC & 760 mmHg	123.7	[20]
Density/Specific Gravity g/cm^3 @ 20 ºC & 760 mmHg	1.206	[20]
Vapor pressure mmHg@ 25 ºC	1.70E-4	[20]
Melting Point ºC	280-282	[19]
Boiling Point ºC @ 760 mmHg	306.9	[20]
Water Solubility	Sol	[19]
Other Solubility	Insol in ether, benzene, acetone	[19]
log P @ 25 ºC	0.217	[20]
Disassociation constants (pKa, pKb) @ 25 ºC	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 ºC & 760 mmHg	123.7	[20]
Density/Specific Gravity g/cm^3 @ 20 ºC & 760 mmHg	1.206	[20]
Vapor pressure mmHg@ 25ºC	1.70E-4	[20]
Boiling Point ºC @760 mmHg	306.9	[20]
Water Solubility g/L @ 25 ºC	33.8	[19]
Other Solubility	Sol in dil acids, alkalies, Slightly sol in alc. Insol in ether.	[19]
log P @ 25 ºC	0.217	[20]
Disassociation constants (pKa, pKb)	pK_1 2.28; pK_2 9.21	[19]

Table 3. Physical and chemical properties.

Phenylalanine		
Physical Form	Crystals	[19]
Molecular Weight g/mol	165.19	[19]
Molecular Volume cm^3/mol @20 ºC & 760 mmHg	137.4	[20]
Density/Specific Gravity g/cm^3 @ 20 ºC & 760 mmHg	1.201	[20]
Vapor pressure mmHg	3.13E-4	[20]
Boiling Point ºC @ 760 mmHg	307.5	[20]
Water Solubility g/L @ 25 ºC	29.6	[19]
Other Solubility	Slightly sol in methanol, ethanol	[19]
log P @ 25 ºC	0.235	[20]
Disassociation constants (pKa, pKb)	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 ºC & 760 mmHg	96.9	[20]
Density/Specific Gravity g/cm^3@ 20 ºC & 760 mmHg	1.186	[20]
Vapor pressure mmHg@ 25 ºC	6.15E-3	[20]
Boiling Point ºC @ 760 mmHg	252.2	[20]
Water Solubility g/L @ 25 ºC	1623	[19]
Other Solubility	Insol in ether, butanol, isopropanol.	[19]
log P @ 25 ºC	-0.060	[20]
Disassociation constants (pKa, pKb)	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 ºC & 760 mmHg	74.2	[20]
Density/Specific Gravity g/cm^3 @ 20 ºC & 760 mmHg	1.415	[20]
Vapor pressure mmHg@ 25ºC	7.17E-8	[20]
Boiling Point ºC @760 mmHg	394.8	[20]
Water Solubility	Sol	[19]
Other Solubility	Insol in neutral solvents.	[19]
log P @ 25 ºC	-1.49	[20]
Disassociation constants (pKa, pKb)	pK_1 2.16; pK_2 9.10	[20]

Table 3. Physical and chemical properties.

Threonine		
Physical Form	Crystals	[19]
Molecular Weight g/mol	119.12	[19]
Molecular Volume cm^3/mol @ 20 ºC & 760 mmHg	91.1	[20]
Density/Specific Gravity g/cm^3 @ 20 ºC & 760 mmHg ºC	1.307	[20]
Vapor pressure mmHg	3.77E-6	[20]
Boiling Point ºC @ 760 mmHg	345..8	[20]
Water Solubility	Freely sol	[19]
Other Solubility	Insol in neutral solvents.	[19]
log P @ 25 ºC	-1.136	[20]
Disassociation constants (pKa, pKb	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 ºC & 760 mmHg	149.8	[20]
Density/Specific Gravity g/cm^3 @ 20 ºC & 760 mmHg	1.362	[20]
Vapor pressure mmHg@ 25 ºC	8.30E-9	[20]
Boiling Point ºC @ 760 mmHg	447.9	[20]
Water Solubility g/L @ 25 ºC	11.36	[19]
Other Solubility	Sol in hot alc and alkali hydroxides. Insol in chloroform.	[19]
log P @ 25 ºC	0.704	[20]
Disassociation constants (pKa, pKb) @ºC	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 ºC & 760 mmHg	1.358	[20]
Density/Specific Gravity	1.456	[19]
Vapor pressure mmHg@ 25 ºC	1.27E-6	[20]
Boiling Point ºC @ 760 mmHg	385.2	[20]
Water Solubility g/L @ 25 ºC	0.045	[19]
Other Solubility	Sol in alkaline soln. Insol in neutral solvents.	[19]
log P @ 25 ºC	-0.418	[20]
Disassociation constants (pKa, pKb)	pK_1 2.20; pK_2 9.11; $pK_3$10.07	[19]

Table 3. Physical and chemical properties.

Valine		
Physical Form	Crystals	[19]
Molecular Weight g/mol	117.15	[19]
Molecular Volume cm^3/mol @ 20 ºC & 760 mmHg	110.1	[20]
Density/Specific Gravity	1.230	[19]
Vapor pressure mmHg@ 25 ºC	0.0633	[20]
Melting Point ºC	315	[19]
Boiling Point ºC @ 760 mmHg	213.6	[20]
Water Solubility g/L @ 25 ºC	57.4	[19]
Other Solubility	Insol in neutral solvents.	[19]
log P @ 25 ºC	0.289	[20]
Disassociation constants (pKa, pKb)	pK_1 2.32; pK_2 9.62	[19]

Table 4. Frequency and concentration of use according to duration and type of exposure[9,10]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Alanine[a]		**Arginine**		**Arginine HCl**	
Totals*	**294**	**$3.0x10^{-7}$-0.1**	**505**	**0.00002-18**	**52**	**0.004-0.1**
Duration of Use						
Leave-On	252	$3.0x10^{-7}$-0.1	411	0.00002-2	33	0.004-0.02
Rinse-Off	42	$5.0x10^{-7}$-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	$3.0x10^{-7}$; 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	$3.0x10^{-7}$-0.1	415	0.00002-18	26	0.02
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	30	$5.0x10^{-7}$-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[b]**		**Calcium Glycinate**	
Totals*	**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 - Non-Coloring	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[c]		**Cysteine HCl[d]**		**Cystine**	
Totals*	**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*
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 - Non-Coloring	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

Table 4. Frequency and concentration of use according to duration and type of exposure[9,10]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Glutamic Acid[e]		**Glutamine[f]**		**Glycine**	
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 - Non-Coloring	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[g]**		**Isoleucine[h]**	
Totals*	**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
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 - Non-Coloring	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[i]		**Lysine[j]**		**Lysine HCl[k]**	
Totals*	**33**	**0.0009-0.001**	**151**	**$1.0x10^{-7}$-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*	*$1.0x10^{-7}$-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	$1.0x10^{-7}$-0.7	18	0.0002-0.6
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	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

Table 4. Frequency and concentration of use according to duration and type of exposure[9,10]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Magnesium Aspartate		**Methionine[l]**		**Phenylalanine**	
Totals*	**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 - Non-Coloring	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

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Potassium Aspartate		**Proline[m]**		**Serine[n]**	
Totals*	**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 - Non-Coloring	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

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Sodium Glutamate		**Sodium Glycinate**		**Threonine[o]**	
Totals*	**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 - Non-Coloring	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

Table 4. Frequency and concentration of use according to duration and type of exposure[9,10]

	# of Uses	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*	*# of Uses*	*Max Conc of Use (%)*
	Tryptophan		**Tyrosine**		**Valine**	
Totals*	**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
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 - Non-Coloring	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

* 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.

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. 13 uses lead to a dermal exposure, and 6 uses are to hair (non-coloring).

[b] 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. 1 use leads to a dermal exposure, and 2 uses are to hair (non-coloring).

[c] 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. 1 use leads to a dermal exposure, and 2 uses are to hair (non-coloring).

[d] The VCRP only listed an entry for L-Cysteine HCl. This data has been combined with the concentration of use data for Cysteine HCl.

[e] 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. 8 uses are a dermal exposure, and 6 uses are to hair (non-coloring).

[f] The VCRP only listed an entry for L-Glutamine. This data has been combined with the concentration of use data for Glutamine.

[g] The VCRP only listed an entry for L-Histidine HCl. This data has been combined with the concentration of use data for Histidine HCl.

[h] The VCRP only listed an entry for L-Isoleucine. This data has been combined with the concentration of use data for Isoleucine.

[i] The VCRP only listed an entry for L-Leucine. This data has been combined with the concentration of use data for Leucine.

[j] 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. 1 use is in the eye area, 13 uses are a dermal exposure, and 3 uses are to hair (non-coloring).

[k] The VCRP only listed an entry for L-Lysine HCl. This data has been combined with the concentration of use data for Lysine HCl.

[l] 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.

[m] 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. 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).

[n] 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 8in rinse-off products. 2 uses are in the eye area, 1 use is in nail products, 34 uses are dermal exposures, and 5 uses are to hair (non-coloring).

[o] 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. 5 uses are dermal exposures and 2 are to the hair (non-coloring).

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	Non-irritating	[21]
Aspartic Acid	0.2% in an eye gel	EPISKIN reconstructed human epidermis model	Potentially a non-irritant	[22]
Cysteine HCl	500 mM 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 non-irritant	[24]
Methionine	500 mM 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 non-irritant	[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	Non-irritating	[21]
Arginine	1.4% in an eye gel	EpiOcular irritation study	Non-irritating	[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 subjects	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 subjects	Good ocular comfort, safety, and tolerance	[35]
Magnesium Aspartate	0.05% with 1% Tyrosine in a product	Clinical eye sting study in 12 subjects	Slight potential for stinging	[36]
Tyrosine	1% with 0.05% Magnesium Aspartate in a product	Clinical eye sting study in 12 subjects	Slight potential for stinging	[36]
Glycine	7.5% in a pencil eye liner	14-day controlled usage study in 28 subjects	No eye irritation	[37]
Proline	0.1% in an eye cream	4-week controlled clinical usage study in 29 subjects applied to eye area	No eye irritation	[38]

Table 7. Dermal sensitization studies.

Ingredient	Concentration	Method	Results	Reference
Non-Human				
Arginine	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 subjects; semi-occlusive	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 subjects; semi-occlusive	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 subjects; semi-occlusive	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 subjects; occlusive	No dermal irritation or sensitization	[45]
Arginine	1% in a face and neck product	HRIPT with 56 subjects; semi-occlusive	No dermal irritation or sensitization	[45]
Arginine	1.1% in a mascara	HRIPT with 105 subjects; semi-occlusive	No dermal sensitization	[46]
Arginine	1.4% in an eye gel	HRIPT with 115 subjects; occlusive	No dermal irritation or sensitization	[47]
Arginine	1.4% in an eye gel	4-week controlled clinical usage study in 34 subjects	Very well tolerated	[48]
Arginine	1.4% in a facial scrub/cleansing masque	HRIPT in 108 subjects; occlusive	No dermal irritation or sensitization	[49]
Arginine	1.4% in a facial scrub/cleansing masque	4-week controlled clinical usage study in 48 subjects	Very well tolerated	[50]
Arginine	1.35% in a face and neck product	HRIPT with 104 subjects; semi-occlusive	No dermal irritation or sensitization	[51]
Arginine	1.5% in a scalp treatment	HRIPT with 106 subjects; semi-occlusive	No dermal irritation or sensitization	[52]
Aspartic Acid	0.2% in an eye gel	HRIPT with 107 subjects; occlusive	No dermal irritation or sensitization	[53]
Aspartic Acid	0.2% in a face lotion	HRIPT with 102 subjects; occlusive	No dermal irritation or sensitization	[54]
Aspartic Acid	0.92% in a leave-on hair masque	HRIPT with 102 subjects; semi-occlusive	No skin reactivity	[55]
Magnesium Aspartate	0.1% in a face cream	HRIPT with 210 subjects; semi-occlusive	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 subjects; semi-occlusive	No dermal irritation or sensitization	[45]
Glycine	1% in a shave cream (10% dilution tested)	HRIPT with 103 subjects; semi-occlusive	No dermal irritation or sensitization	[57]

Table 7. Dermal sensitization studies.

Ingredient	Concentration	Method	Results	Reference
Glycine	0.025% in a face and neck product with 0.025% Arginine and 0.005% Methionine	HRIPT with 102 subjects; semi-occlusive	No dermal irritation or sensitization	[45]
Glycine	1% in a cuticle cream	HRIPT with 107 subjects	No dermal irritation or sensitization	[58]
Glycine	2% in a moisturizer	HRIPT with 104 subjects; occlusive	No dermal irritation or sensitization	[59]
Glycine	2% in a moisturizer	HRIPT with 112 subjects; occlusive	No dermal irritation or sensitization	[60]
Glycine	2.784% in an A/P roll-on	HRIPT in 108 subjects; semi-occlusive	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 subjects; semi-occlusive	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 subjects; 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 subjects; semi-occlusive	No dermal irritation or sensitization	[45]
Lysine	0.65% in a face highlighter	HRIPT with 106 subjects; semi-occlusive	No dermal irritation or sensitization	[62]
Lysine	0.65% in a makeup preparation	HRIPT with 213 subjects; semi-occlusive	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 subjects; semi-occlusive	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 subjects; occlusive	No dermal irritation or sensitization	[45]
Proline	0.1% in an eye cream	HRIPT with 112 subjects; 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 subjects; semi-occlusive	No dermal irritation or sensitization	[45]
Serine	0.3% in an eye gel	HRIPT with 50 subjects	No dermal irritation or sensitization	[65]
Serine	0.3% in an eye cream	HRIPT with 50 subjects; 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 subjects; 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]

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]

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