International Journal of Toxicology
2019, Vol. 38(Supplement 2) 12S-32S

DOI: 10.1177/1091581819856582
journals.sagepub.com/home/ijt
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Safety Assessment of Alkyl Phosphates as Used in Cosmetics

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Abstract

The Expert Panel assessed the safety of 28 alkyl phosphates and concluded that these ingredients are safe in the current practices of use and concentration when formulated to be nonirritating. The ingredients in the alkyl phosphate family share a common phosphate core structure, and vary by the identity of the alkyl chains attached therein. Most of the alkyl phosphates function as surfactants in cosmetic ingredients; however, the triesters function as plasticizers rather than surfactants. The Panel reviewed the available animal and clinical data to determine the safety of these ingredients.

Keywords

alkyl phosphates, safety, cosmetics

Introduction

This report is a safety assessment of the following 28 alkyl phosphates as used in cosmetic formulations:

Potassium cetyl phosphate
Potassium C9-15 alkyl phosphate
Potassium C11-15 alkyl phosphate
Potassium C12-13 alkyl phosphate
Potassium C12-14 alkyl phosphate
Potassium lauryl phosphate
C8-10 alkyl ethyl phosphate
C9-15 alkyl phosphate
C20-22 alkyl phosphate
Castor oil phosphate
Cetearyl phosphate
Cetyl phosphate
Disodium lauryl phosphate
Disodium oleyl phosphate
Lauryl phosphate
Myristyl phosphate
Octyldecyl phosphate
Oleyl ethyl phosphate
Oleyl phosphate
Sodium lauryl phosphate
Stearyl phosphate
Dicetyl phosphate
Dimyristyl phosphate
Dioleyl phosphate
Tricetyl phosphate
Trilauryl phosphate
Trioleyl phosphate
Tristearyl phosphate

The ingredients in the alkyl phosphate family share a common phosphate core structure, and vary by the identity of the alkyl chains (ranging from 8-22 carbons in length) attached. Most of the alkyl phosphates are reported to function as surfactants in cosmetic ingredients; however, the triesters function as plasticizers rather than surfactants (Table 1).[1]

Much of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[2] The ECHA website provides summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited. In several instances, structural analogs were used as supporting substances to provide read-across. Specifically, phosphoric acid, C16-18 alkyl esters, and potassium salts are used as read-across for potassium cetyl phosphate. Although not identical, the distribution of chain-lengths for these 2 chemicals will have a

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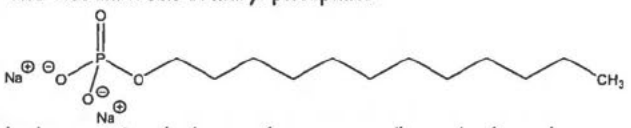
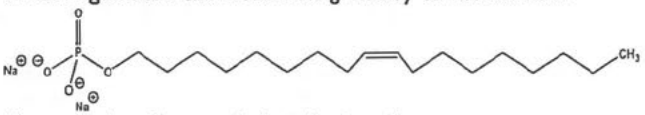
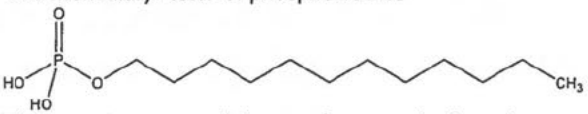
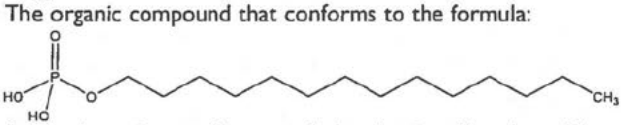
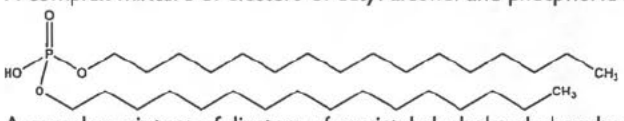
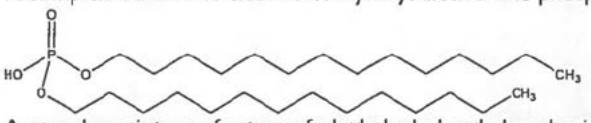
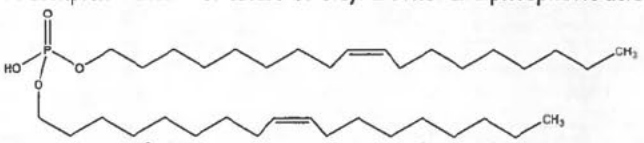
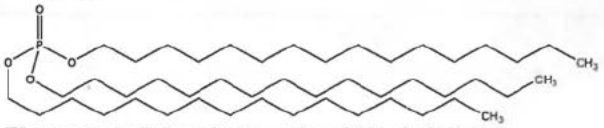
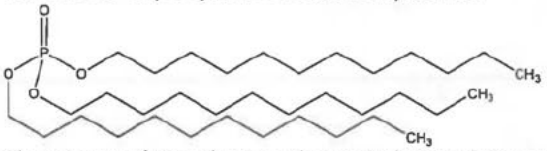
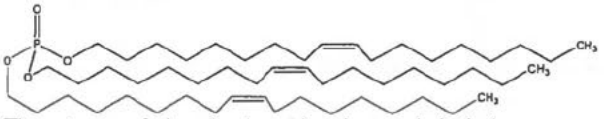
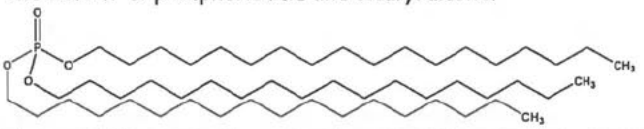
Table 1. Definitions and Functions of the Ingredients in this Safety Assessment.

Ingredient (CAS No.)	Definition[1]	Function(s)[1]
Potassium cetyl phosphate 90506-45-9 (generic); 17026-85-6; 19035-79-1; 84861-79-0	The potassium salt of a complex mixture of esters of phosphoric acid and cetyl alcohol; R, R', and R" of Figure 1 may be cetyl, hydrogen, or electron pairs with potassium cations	Surfactant—emulsifying agent
Potassium C9-15 alkyl phosphate 190454-07-0	The potassium salt of a complex mixture of esters of synthetic C9-15 alcohols with phosphoric acid; R, R', and R" of Figure 1 may be nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hydrogen, or electron pairs with potassium cations	Surfactant—cleansing agent
Potassium C11-15 alkyl phosphate	The potassium salt of the phosphoric ester of C11-15 alcohol; R, R', and R" of Figure 1 may be undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, hydrogen, or electron pairs with potassium cations	Surfactant—cleansing agent; surfactant—emulsifying agent
Potassium C12-13 alkyl phosphate	the potassium salt of a complex mixture of esters of phosphoric acid and C12-13 alcohols; R, R', and R" of Figure 1 may be dodecyl, tridecyl, hydrogen, or electron pairs with potassium cations	surfactant—cleansing agent
Potassium C12-14 alkyl phosphate	the potassium salt of a complex mixture of esters of phosphoric acid and a synthetic fatty alcohol containing 12 to 14 carbons in the alkyl chain; R, R', and R" of Figure 1 may be dodecyl, tridecyl, tetradecyl, hydrogen, or electron pairs with potassium cations.	Surfactant—cleansing agent
Potassium lauryl phosphate 39322-78-6	The potassium salt of lauryl phosphate; R, R', and R" of Figure 1 may be lauryl, hydrogen, or electron pairs with potassium cations	Surfactant—cleansing agent
C8-10 alkyl ethyl phosphate 68412-60-2	A mixture of phosphate esters of C8-10 alcohols and ethyl alcohol; R, R', and R" of Figure 1 may be ethyl, octyl, nonyl, decyl, hydrogen, or electron pairs with potassium cations	Viscosity increasing agent—nonaqueous
C9-15 alkyl phosphate 190454-07-0	A complex mixture of esters of synthetic C9-15 alcohols with phosphoric acid; R, R', and R" of Figure 1 may be nonyl, decyl, undecyl, dodecyl, tridecyl, tetradecyl, pentadecyl, or hydrogen	Surfactant—cleansing agent; surfactant—emulsifying agent
C20-22 alkyl phosphate 84962-18-5	A complex mixture of esters of phosphoric acid and C20-22 alcohols; R, R', and R" of Figure 1 may be eicosyl, heneicosyl, docosyl, or hydrogen	Surfactant – emulsifying agent
Castor oil phosphate	A complex mixture of esters of *Ricinus communis* (castor) seed oil and phosphoric acid; R, R', and R" of Figure 1 may be the fatty alcohol residues of castor oil, or hydrogen	Anticaking agent; emulsion stabilizer
Cetearyl phosphate 90506-73-3	A complex mixture of esters of cetearyl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be cetyl, stearyl, or hydrogen	Akin conditioning agent – miscellaneous
Cetyl phosphate 3539-43-3	a complex mixture of esters of phosphoric acid and cetyl alcohol; R, R', and R" of Figure 1 may be cetyl or hydrogen	surfactant – emulsifying agent
Disodium lauryl phosphate 7423-32-7	The disodium salt of lauryl phosphate 	Surfactant – emulsifying agent
Disodium oleyl phosphate	Is the organic salt that conforms generally to the formula: 	Surfactant – cleansing agent; surfactant – emulsifying agent
Lauryl phosphate 12751-23-4; 2627-35-2	The monolauryl ester of phosphoric acid 	Surfactant – emulsifying agent
Myristyl phosphate 10054-29-2	The organic compound that conforms to the formula: 	Oral care agent; surfactant – cleansing agent; surfactant – foam booster
Octyldecyl phosphate 97553-81-6	A complex mixture of esters of phosphoric acid and octyldecanol; R, R', and R" of Figure 1 may be the 2-octyldecyl or hydrogen	Surfactant – emulsifying agent
Oleyl ethyl phosphate 10483-96-2	A complex mixture of phosphate esters of oleyl and ethyl alcohols; R, R', and R" of Figure 1 may be ethyl, oleyl, or hydrogen	Surfactant – emulsifying agent

(continued)

Table 1. (continued)

Ingredient (CAS No.)	Definition[1]	Function(s)[1]
Oleyl phosphate 37310-83-1	A mixture of mono- and diesters of oleyl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be oleyl or hydrogen	Surfactant – emulsifying agent
Sodium lauryl phosphate 50957-96-5[36]	The sodium salt of a complex mixture of esters of lauryl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be lauryl, hydrogen, or electron pairs with sodium cations	Surfactant – cleansing agent; surfactant – emulsifying agent
Stearyl phosphate 2958-09-0	A mixture of mono- and diesters of stearyl alcohol and phosphoric acid; R, R', and R" of Figure 1 may be stearyl or hydrogen	Surfactant – emulsifying agent
Dicetyl phosphate 2197-63-9	A complex mixture of diesters of cetyl alcohol and phosphoric acid 	Surfactant – emulsifying agent
Dimyristyl phosphate 6640-03-5	A complex mixture of diesters of myristyl alcohol and phosphoric acid 	Surfactant – cleansing agent; surfactant – emulsifying agent
Dioleyl phosphate 14450-07-8	A complex mixture of esters of oleyl alcohol and phosphoric acid 	Emulsion stabilizer; hair conditioning agent; surfactant – emulsifying agent; surfactant – stabilizing agent; pH adjuster
Tricetyl phosphate 56827-95-3 68814-13-1	The triester of phosphoric acid and cetyl alcohol. It conforms to the formula: 	Plasticizer
Trilauryl phosphate 682-49-5	The triester of phosphoric acid and lauryl alcohol 	Plasticizer; skin conditioning agent – occlusive
Trioleyl phosphate 3305-68-8	The triester of phosphoric acid and oleyl alcohol that conforms generally to the formula: 	Plasticizer; skin conditioning agent – occlusive
Tristearyl phosphate 4889-45-6	The triester of phosphoric acid and stearyl alcohol 	Plasticizer

great deal of overlap, for example, both will contain 16-carbon chain lengths. 1-Octadecanol, phosphate, and potassium salt also are relevant to the safety of potassium cetyl phosphate because potassium cetyl phosphate is a distribution of chain-lengths (a mixture) attached to phosphate, with a mean peak at 16-carbons in length, and *1 octadecanol, phosphate, potassium salt* is a distribution of chain-lengths attached to phosphate, with a mean peak at 18-carbons in length. Both include some longer and some shorter fatty acid residues (eg, 14- and 18-carbon chains and 16- and 20-carbon chains, respectively). Accordingly, some read-across may be accessible between these 2 ingredients, as their mean chain-lengths only differ by 2 carbons and there are at least some literally identical chain-lengths shared by the 2 ingredients (in light of the complete length-distribution of each ingredient). Additionally, phosphoric acid and 2-ethylhexyl ester were justified as read-across for potassium lauryl phosphate because both are members of the phosphoric acid, alkyl ester family, and the characteristic and functional active center of both substances is the ester binding between the alcoholic compound and

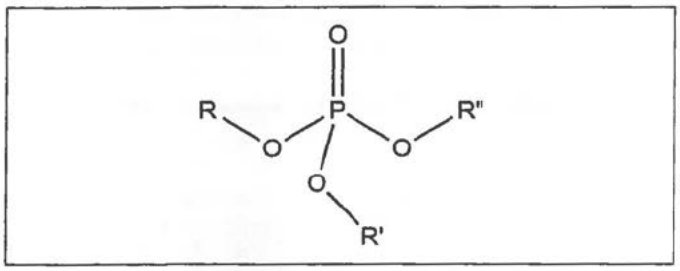


Figure 1. Alkyl phosphates, wherein R, R', and R" may be alkyl groupings (eg, cetyl), hydrogen, or shared electron pairs with potassium or sodium cations.

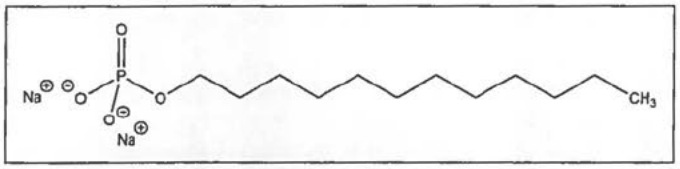


Figure 2. Disodium lauryl phosphate, for example, has sodium cations for R and R', and a lauryl chain for R".

phosphate. When providing information on a structural analog, the name of that analog is italicized to indicate read-across is being employed. However, the names of the ingredients in this report are written in accordance with the International Nomenclature naming conventions, that is, capitalized without italics or abbreviations.

Chemistry

Definition and Structure

Alkyl phosphates are the organic esters of ortho-phosphoric acid. These ingredients are mixtures of esters and salts wherein a phosphate may have 1 to 3 alkylations and 1 to 2 potassium or sodium cations (Figures 1 and 2; Table 1).

These ingredients share some similarities, in structures and properties, with the natural phosphatides, lecithin, and cephalin.[3] But these ingredients differ by the lack of core glyceryl structures and the resultant lack of susceptibility to enzymatic degradation. With solubility across polar and nonpolar solvents, it is not surprising that these ingredients are commonly used as surfactants, wetting agents, and emulsifiers in cosmetic applications.

Chemical and Physical Properties

The alkyl phosphates can be liquids or solids (Table 2). They have solubility in both polar and nonpolar solvents.

Methods of Manufacture

Alkyl phosphates can be prepared by reactions of fatty alcohols with polyphosphoric acid to yield the corresponding alkyl phosphates.[4] Dialkyl phosphates can be prepared by a stepwise procedure via the monoalkyl phosphate from pyrophosphoric acid using tetramethylammonium hydroxide as a base.[5] They also can be prepared by the reaction of 2 equivalents of alcohol with phosphorus oxychloride followed by hydrolysis of the intermediate phosphoroxychloride. Dialkyl phosphates also have been synthesized by the reaction of the appropriate alcohol with phosphorus trichloride followed by treatment with pyridine and carbon tetrachloride, which provides the corresponding trichloromethyl ester. Reaction of the triethylamine salt of acetic acid, followed by hydrolysis of the mixed anhydride that formed, yields the dialkyl phosphate.

C20-22 alkyl phosphate is obtained from the reaction of alcohols, C20-22 with phosphoric anhydride.[6]

Constituents/Impurities

C20-22 alkyl phosphate contains <1% phosphoric acid.[6] No other published constituent data were found, and no unpublished data were submitted.

Use

Cosmetic

Most of the alkyl phosphates are reported to function as surfactants in cosmetic ingredients; however, the triesters (ie, R, R', and R" are all alkyl; eg, tricetyl phosphate) function as plasticizers rather than surfactants (Table 1).[1] Surfactants, or surface-active agents, have the ability to lower the surface tension of water or to reduce the interfacial tension between 2 immiscible substances. Plasticizers are materials that soften synthetic polymers.

The Food and Drug Administration (FDA) collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). Voluntary Cosmetic Registration Program data obtained from the FDA in 2014,[7] and data received in 2013 to 2014 in response to surveys of the maximum reported use concentration by category that were conducted by the Personal Care Products Council (Council),[8,9] indicate that 13 of the 28 ingredients included in this safety assessment are currently used in cosmetic formulations.

According to the VCRP data, potassium cetyl phosphate is reported to be used in 375 formulations, the majority of which are leave-on formulations, dicetyl phosphate is reported to be used in 109 formulations, and cetyl phosphate in 94 formulations.[7] All other in-use ingredients are reported to be used in less than 15 formulations. The results of the concentration of use surveys conducted by the Council indicate potassium cetyl phosphate also has the highest concentration of use in a leave-on formulation; it is used at up to 8.3% in mascara products.[8] The highest concentration of use reported for products resulting in leave-on dermal exposure is 4.2% trioleyl phosphate in "other" make-up preparations.[9] Lauryl phosphate is used at 8.7% in a skin cleaning product, which is most likely a rinse-off formulation.[8] All available frequency and concentration of use data, for those ingredients currently in use, are reported

Table 2. Chemical and Physical Properties.

Property	Description	Reference
Potassium cetyl phosphate		
Physical characteristics	White to off-white powder, with no or a weakly fatty odor	3
Molecular weight	359.5	37
Solubility	Readily soluble in tepid water; soluble in the heated oil phase	3
Acid value	270-295	3
pH	6.5-8 (1% in water)	3
Potassium lauryl phosphate		
Physical characteristics	Solid white paste	19
Molecular weight	304.4	38
Solubility	Slightly soluble in water	19
Density	1.07 g/cm^3 (22°C)	19
Log P_{ow}	2.74	19
C20-22 alkyl phosphate		
Molecular weight	$\geq$378.53	6
Melting point	70-75°C	6
Solubility	$\leq 1 \times 10^{-3}$ g/L (20°C)	6
Specific gravity	0.6	6
Density	870 kg/m^3 (25°C)	20
Particle size distribution	ca. 2.8 mm $\leq$1.44 mm-12.2% 1.4 mm-$\leq$ 2 mm-33.8% 2 mm-$\leq$ 2.8 mm-32.1% 2.8 mm-$\leq$ 4 mm-21.8%	20
Cetyl phosphate		
Molecular weight	322	38
Boiling point	439.8°C	38
log P (estimated)	6.38 $\pm$ 0.21	38
Lauryl phosphate		
Physical characteristics	solid	39
Melting point	47°C	39
Solubility	Not soluble in water In paraffin, soy oil, or isopropyl palmitate: not soluble at room temperature; clear solution at 80°C	39
Octyldecyl phosphate		
Physical characteristics	Liquid	39
Melting point	<0°C	39
Solubility	Not soluble in water; clear solution in paraffin, soy oil, or isopropyl palmitate at room temperature and at 80°C	39
Oleyl phosphate		
Physical characteristics	Dark brown, high viscous liquid with a slightly castor oil-like odor Waxy solid	21 39
Molecular weight	348.5	38
Melting range	−77 to 53°C 45°C	21 39
Boiling point	477.9°	38
Solubility	Poorly water soluble In paraffin, soy oil, or isopropyl palmitate: not soluble at room temperature; clear solution at 80°C	21 39
Log K_{ow}	>1	21
Density	1.01 g/cm^3 (at 20°C)	21
Stearyl phosphate		
Physical characteristics	Solid	39
Molecular weight	350	38
Melting point	62°C	39
Boiling point	465.6°C	38
Solubility	Not soluble in water In paraffin, soy oil, or isopropyl palmitate: not soluble at room temperature; clear solution at 80°C	39
Log P (estimated)	7.44 $\pm$ 0.21	38
Dicetyl phosphate		
Physical characteristics	Solid white flakes	22
Molecular weight	546.8	38

(continued)

Table 2. (continued)

Property	Description	Reference
Boiling point	600.4°C	38
Log P (estimated)	14.95 ± 0.58	38
Dimyristyl phosphate		
Molecular weight	490.7	38
Boiling point	555.5°C	38
Log P (estimated)	12.83 ± 0.58	38
Dioleyl phosphate		
Molecular weight	626.9	38
Boiling point	680.1°C	38
Log P (estimated)	14.212	38
Tricetyl phosphate		
Molecular weight	771.3	38
Boiling point	616.5°C	38
Log P (estimated)	22.172	38
Trilauryl phosphate		
Molecular weight	603	38
Boiling point	522.2°C	38
Log P (estimated)	17.02	38
Trioleyl phosphate		
Molecular weight	849.4	38
Boiling point	805.2°C	38
Log P (estimated)	25.027	38
Tristearyl phosphate		
Molecular weight	855.4	38
Boiling point	660°C	38
Log P (estimated)	225.229	38

in Table 3. The ingredients not reported to be used, according to VCRP data and the Council survey, are listed in Table 4.

A few of the ingredients are used in products that could be incidentally ingested (eg, up to 1% trioleyl phosphate in lipsticks) or used near the eye or mucous membranes (eg, up to 8.3% potassium cetyl phosphate in mascara formulations). One ingredient, C20-22 alkyl phosphate, is reported to be used at 1.1% in a baby product. Additionally, according to the VCRP, dicetyl phosphate is used in a hair spray, which is a product that can be incidentally inhaled; however, the Council survey did not report a concentration of use for this product type. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 μm.[10,11] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[12,13]

All of the alkyl phosphates named in this safety assessment are listed in the European Union inventory of cosmetic ingredients.[14]

Noncosmetic

Potassium lauryl phosphate can be used as an optional finish component in poly(phenyleneterephthalamide) resins, which are indirect food additives intended for repeated contact with food; the total weight of potassium lauryl phosphate is not to exceed 1% of the base polymer [21CFR177.1632]. Tristearyl phosphate is approved as an indirect food additive as a substance permitted to be used in the formulation of defoaming agents used in the manufacture of paper and paperboard [21CFR176.210].

The use of dicetyl phosphate in niosomes (nonionic surfactant-based vesicles)[15-17] and solid lipid nanoparticles[18] has been investigated. Niosomes are microscopic vesicles composed of nonionic surface-active agent bilayers, and the intended use of these vesicles is as a drug delivery system.[16,17] Solid lipid nanoparticles are another possible dermal delivery system.[18]

Toxicokinetics

Oral

Potassium lauryl phosphate. Five male and 5 female F344 rats were given a single dose of 200 mg/kg bw phosphoric acid, 2-ethylhexyl ester in corn oil by gavage.[19] (As stated previously, information on phosphoric acid, 2-ethylhexyl ester is being provided as read-across for potassium lauryl phosphate. Specifically, with reference to the occurrence of esterases which take part in the mammalian phase I metabolism, it can be assumed that both phosphoric acid esters are hydrolyzed independent from the constitution of the alcoholic part. Since the ester binding is the specific target of endogenous esterases, it is justified to perform a read across between both ester-type

Table 3. Frequency and Concentration of Use According to Duration and Type of Exposure.

	# of Use[7]	Max. Conc. of Use (%)[8,9]	# of Uses[7]	Max. Conc. of Use (%)[8,9]	# of Uses[7]	Max. Conc. of Use (%)[8,9]
	Potassium cetyl phosphate		Potassium C9-15 alkyl phosphate		Potassium C12-13 alkyl phosphate	
Totals[a]	375	0.05-8.3	NR	0.001	2	**6.5**
Duration of use						
Leave-on	341	0.05-8.3	NR	NR	2	NR
Rinse off	30	0.5-1	NR	0.001	NR	6.5
Diluted for (bath) use	4	NR	NR	NR	NR	6.5
Exposure type						
Eye area	66	0.6-8.3	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	1; 129[b]; 96[c]	0.3[b]	NR	NR	NR	NR
Incidental inhalation-powder	1; 96[c]; 5[d]	0.14-3[d]	NR	NR	NR	NR
Dermal contact	329	0.05-3	NR	NR	2	6.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—non-coloring	NR	NR	NR	0.001	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR
Nail	1	NR	NR	NR	NR	NR
Mucous membrane	7	0.55	NR	NR	NR	6.5
Baby products	5	NR	NR	NR	NR	NR
	Potassium lauryl phosphate		C9-15 alkyl phosphate		C20-22 alkyl phosphate	
Totals[a]	4	NR	13	0.0011-0.12	**14**	**0.55-1.7**
Duration of use						
Leave-on	3	NR	8	0.0011-0.12	13	0.55-1.7
Rinse off	1	NR	5	0.0044-0.12	1	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	NR	NR	NR	NR	2	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	3[c]	NR	4[b]; 1[c]	NR	7[b]; 3[c]	NR
Incidental inhalation-powder	3[c]	NR	1[c]	0.12[d]	3[c]	0.55-1.7[d]
Dermal contact	4	NR	13	0.0011-0.12	14	0.55-1.7
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—non-coloring	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	1	0.0044	NR	NR
Baby products	NR	NR	NR	NR	NR	1.1
	Castor oil phosphate		Cetyl phosphate		Lauryl phosphate	
Totals[a]	2	NR	94	0.14-2	**2**	**0.25-8.7**
Duration of use						
Leave-on	2	NR	85	0.14-2	NR	3.8
Rinse off	NR	NR	9	0.5-1	2	0.25-8.7
Diluted for (bath) use	NR	NR	NR	NR	NR	NR
Exposure type						
Eye area	1	NR	7	0.14-2	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	2[b]	NR	1; 26[b]; 47[c]	NR	NR	NR
Incidental inhalation-powder	NR	NR	47[c]	0.25-2[c]	NR	3.8[d]
Dermal contact	2	NR	93	0.25-2	2	0.25-8.7
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—non-coloring	NR	NR	NR	NR	NR	NR

(continued)

Table 3. (continued)

	Castor oil phosphate		Cetyl phosphate		Lauryl phosphate	
Totals[a]	2	NR	94	0.14-2	**2**	**0.25-8.7**
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
	Stearyl phosphate		Dicetyl phosphate		Dioleyl phosphate	
Totals[a]	1	NR	109	0.038-4	1	0.4-1.5
Duration of use						
Leave-on	1	NR	60	0.2-4	NR	NR
Rinse off	NR	NR	49	0.038-1	1	0.4-1.5
Diluted for (bath) use	NR	NR	NR	NS	NR	NR
Exposure type						
Eye area	1	NR	8	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR
Incidental inhalation-spray	NR	NR	1; 13[b]; 14[d]	0.2-0.8[b]	NR	NR
Incidental inhalation-powder	NR	NR	14[d]	NR	NR	NR
Dermal contact	1	NR	31	0.26-4	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—non-coloring	NR	NR	29	0.038-1	NR	0.4
Hair-coloring	NR	NR	41	0.13-0.9	1	1.5
Nail	NR	NR	NR	NR	NR	NR
Mucous membrane	NR	NR	NR	NR	NR	NR
Baby products	NR	NR	NR	NR	NR	NR

	Trioleyl phosphate	
Totals[a]	3	0.02-4.2
Duration of use		
Leave-on	3	0.02-4.2
Rinse off	NR	NR
Diluted for (bath) use	NR	NR
Exposure type		
Eye area	NR	NR
Incidental ingestion	3	0.02-1
Incidental inhalation-spray	NR	NR
Incidental inhalation-powder	NR	NR
Dermal contact	NR	4.2
Deodorant (underarm)	NR	NR
Hair—non-coloring	NR	NR
Hair-coloring	NR	NR
Nail	NR	NR
Mucous membrane	3	0.02-1
Baby products	NR	NR

Abbreviations: NR, none reported; NS, survey results not yet received.

[a]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

[b]Includes products that can be sprays, but it is not known whether the reported uses are sprays

[c]Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

[d]Includes products that can be powders, but it is not known whether the reported uses are powders

substances in order to estimate potential metabolism. Urine and feces were collected every 12 hours for 72 hours after dosing. Analysis of the samples via ^{31}P-nuclear magnetic resonance spectroscopy indicated the ester was completely hydrolyzed to phosphate and 2-ethylhexanol; only a phosphate peak was found in the urine samples. The conclusion of this summary report stated phosphoric acid, 2-ethylhexyl ester was efficiently absorbed, metabolized, and excreted quantitatively by the body, and there was no indication of accumulation; however, no details were provided.

Table 4. Ingredients Not Reported to be Used.

Potassium C11-15 alkyl phosphate	Oleyl ethyl phosphate
Potassium C12-14 alkyl phosphate	Oleyl phosphate
C8-10 alkyl ethyl phosphate	Sodium lauryl phosphate
Cetearyl phosphate	Dimyristyl phosphate
Disodium lauryl phosphate	Tricetyl phosphate
Disodium oleyl phosphate	Trilauryl phosphate
Myristyl phosphate	Tristearyl phosphate
Octyldecyl phosphate	

Toxicological Studies

Single Dose (Acute) Toxicity

Dermal, oral, and inhalation single-dose toxicity testing has been performed with some alkyl phosphates (Table 5). These ingredients are relatively nontoxic. The dermal LD_{50} in rats was >2 g/kg bw for C20-22 alkyl phosphate,[20] oleyl phosphate,[21] and for 45.45% and 80% dicetyl phosphate.[22,23] In rats, the oral LD_{50} was >2 g/kg for 1 octadecanol, phosphate, potassium salt,[22] potassium C9-15 alkyl phosphate,[22] C20-22 alkyl phosphate,[20] oleyl phosphate,[21] and dimyristyl phosphate;[24] the oral LD_{50} of 25% potassium lauryl phosphate was 10.49 g/kg;[19] and for 10% cetyl phosphate it was > 4.7 g/kg.[22] In both the mouse[25] and rat,[26] the oral LD_{50} of a 25% suspension of dicetyl phosphate was > 5 g/kg. In a 4-hour exposure inhalation study, the LC_{50} of 1% aq. phosphoric acid, C16-18 alkyl esters, potassium salts was > 200 µl/L.[22]

Repeated Dose Toxicity

Repeated dose oral toxicity studies were performed in rats for several alkyl phosphates (Table 6). In 14-day studies, potassium lauryl phosphate had a no-observable adverse effect level (NOAEL) of 600 mg/kg bw/d for both males and females, and oral administration of up to 1000 mg/kg bw/d sodium lauryl phosphate for 14 days did not result in any adverse effects;[19] no remarkable effects were observed with up to 1000 mg/kg bw/d C20-22 alkyl phosphate by gavage.[20] The NOELs of myristyl phosphate in a 28-day dietary study were 1564 mg/kg bw/d for males and 227 mg/kg bw/d for females, and the NOAEL was 1564 mg/kg bw/d for females.[22] Oleyl phosphate had a NOAEL of 1000 mg/kg bw/d for male and female rats in a 28-day gavage study.[21] In a 91-day gavage study, potassium C9-15 alkyl phosphate had a benchmark dose lower confidence limit of 240.3 mg/kg bw/d in males and females.[22]

Reproductive and Developmental Toxicity

Potassium C9-15 alkyl phosphate was not embryotoxic, fetotoxic, or teratogenic in rats dosed by gavage on days 6 to 15 of gestation; the NOELs for developmental toxicity, embryotoxicity, fetotoxicity, and teratogenicity were 361 mg/kg bw/d (active ingredient [a.i.]), and the NOEL and NOAEL for maternal toxicity were 36.1 and 361 mg/kg bw/d (a.i.), respectively (Table 7).[22] For C20-22 alkyl phosphate, the NOELs for reproduction (mating and fertility) and neonatal toxicity, and the NOAEL for parental toxicity, were 1000 mg/kg bw/d in rats.[20] Oleyl phosphate also was not a reproductive toxicant in rats; in a gavage study, the NOAELs were 1000 mg/kg bw/d for maternal toxicity, reproductive performance in male and female rats, and development in F_1 offspring.[21] In a reproductive study with sodium lauryl phosphate in rats, the NOAEL for parental male and female animals and the NOEL for the F_1 generation were 1000 mg/kg bw/d.[19]

Genotoxicity

In vitro genotoxicity assays have been performed on several of the alkyl phosphates and the results of all these assays were negative (Table 8). 1-Octadecanol, phosphate, and potassium salt were negative in an Ames test,[22] and cetyl phosphate was not genotoxic in a mammalian cell gene mutation assay.[22] Potassium lauryl phosphate,[19] C20 22 alkyl phosphate,[20] and oleyl phosphate[21] were not mutagenic in the Ames test, mammalian cell gene mutation assay, or chromosomal aberration assay.

Carcinogenicity

Published carcinogenicity data were not found, and no unpublished data were submitted.

Irritation and Sensitization

Some alkyl phosphates were not dermal irritants, whereas several were irritating but not sensitizing, in nonhuman studies (Table 9). C20-22 alkyl phosphate, applied neat, was not irritating to rat skin,[20] nor was it a sensitizer in a guinea pig maximization test (GPMT).[20] Undiluted phosphoric acid, C16-18 alkyl esters, potassium salts produced some signs of irritation in the abraded skin of rabbits.[22] Potassium lauryl phosphate was irritating to rabbit skin as a 77% paste in one study, and highly irritating to rabbit skin in another (concentration not specified); it was not a sensitizer in a GPMT.[19] Cetyl phosphate and lauryl phosphate were not sensitizers in GPMTs, but challenge concentrations of 10% and 40% cetyl phosphate and an epidermal induction concentration of 12.5% lauryl phosphate were irritating.[22] Undiluted oleyl phosphate was irritating to rat skin; concentrations up to 5% did not demonstrate a potential for sensitization in a local lymph node assay.[21] (Alternative studies with oleyl phosphate did not demonstrate a potential for skin irritation or corrosion.) Dicetyl phosphate was not irritating to rat skin as an 80% paste,[22] was not irritating to rabbit skin when prepared as a 46.5% paste in olive oil (w/w),[27] and was not a sensitizer in a GPMT.[28] Dimyristyl phosphate, applied under an occlusive patch for 4 hours, was not irritating to rabbit skin,[29] nor was it an irritant or sensitizer in a GPMT at a concentration of 75% in distilled water.[30]

The C20-22 alkyl phosphate, 5% in an emulsion, was not an irritant or a sensitizer in a human repeated insult patch test

Table 5. Single-Dose Toxicity Studies.

Test article	Animals/Group	Vehicle	Concentration/Dose/ Protocol	LD50/LC50 Results	Reference
DERMAL					
C20-22 alkyl phosphate	5 Sprague-Dawley rats/sex	Paraffin oil	2 g/kg bw (10 ml/kg bw) applied using a 24-hour semi-occlusive patch • negative controls were exposed to distilled water	>2 g/kg bw • no cutaneous reactions or signs of toxicity were observed	20
Oleyl phosphate	5 Wistar rats/sex	Applied neat	2 g/kg applied using a 24-hour semi-occlusive patch	>2 g/kg bw • slight to severe erythema, slight edema, and other signs of irritation (e.g., wounds, crusting, and desquamation) were observed until study termination at day 14 in males and up to day 11 in females	21
Dicetyl phosphate, 80% paste	10 Sprague-Dawley rats/sex	Distilled water	2 g/kg using 24-hour occlusive patch; 4.4 mL/kg were applied • the test area was 5 cm^2	>2 g/kg bw • no signs of toxicity were observed	22
Dicetyl phosphate, 45.45% paste	5 Sprague-Dawley rats/sex	Olive oil	2 g/kg applied for 24 hour under an adhesive bandage	> 2 g/kg • no erythema or edema were observed • no clinical signs of toxicity	23
ORAL					
1-Octadecanol, phosphate, potassium salt	4 Wistar rats	Water	2 g/kg by gavage	> 2 g/kg	22
Potassium C9-15 alkyl phosphate	5 Sprague-Dawley rats/sex	None	2 g/kg (0.723 g/kg bw a.i.) by gavage	> 2 g/kg (0.723 g/kg bw a.i.) • no animals died during the study • piloerection, hunched posture, and other signs of toxicity were observed during the first three days	22
Potassium lauryl phosphate, 25%	10 female rats	Water	6.3-15.0 g/kg bw by gavage	10.49 g/kg	19
C20-22 alkyl phosphate	5 Sprague-Dawley rats/sex	Paraffin oil	2 g/kg by gavage	> 2 g/kg	20
Cetyl phosphate, 10%	10 Sprague-Dawley rats/sex	Distilled water	4.7 g/kg by gavage	>4.7 g/kg bw • two females of the 4700 mg/kg bw group died during the study	22
Oleyl phosphate	3 female Wistar rats	Sunflower oil	2 g/kg bw, by gavage	> 2 g/kg	21
Dicetyl phosphate, 25% suspension	5 OF1 mice/sex	Olive oil	5 g/kg, by gavage	> 5 g/kg no signs of toxicity; no mortality	25
Dicetyl phosphate, 25% suspension	5 Sprague-Dawley rats/sex	Olive oil	5 g/kg, by gavage	> 5 g/kg no signs of toxicity; no mortality	26
Dimyristyl phosphate	5 Sprague-Dawley rats/sex	Distilled water	2 g/kg, by gavage	> 2 g/kg no signs of toxicity; no mortality	24
INHALATION					
1% aq. *phosphoric acid, C16-18 alkyl esters, potassium salts*	10 Wistar rats/sex	In emulsion	200 µl/L nose-only exposure for 4 hour; the nebulizing nozzle produced an aerosol with particle sizes of 2-5 µm	>200 µl/L • one animal died within 24 h of dosing	22

Abbreviation: a.i., active ingredient.

Table 6. Repeated Dose Toxicity Studies.

Test article	Animals/Group	Study duration	Vehicle	Dose/Concentration	Results	Reference
ORAL						
Potassium lauryl phosphate	3 Wistar rats/sex	14 days	water	0, 60, 600, or 1000 mg/kg bw/d; by gavage	NOAEL = 600 mg/kg bw/d (males and females) • all animals survived until study termination • piloerection was observed in a few females of the high-dose group • slight decrease in absolute prostate weights and a slight increase in absolute and relative (to brain and to body) epididymis weights was observed in high dose males • slight-to-moderate increase in neutrophils, with a concurrent slight decrease in lymphocytes, and a slight, dose-dependent, increase in serum alkaline phosphatase levels, was reported in male and female high-dose animals	19
C20-22 alkyl phosphate	3 Sprague-Dawley rats/sex	14 days	Olive oil	0, 100, 300, or 1000 mg/kg bw/d, by gavage	• all animals survived until study termination • no macroscopic observations • slight decrease in feed consumption during week 2 in the mid- and high-dose females compared to controls	20
Sodium lauryl phosphate	rats (no./group not provided)	14 days	not specified	125, 250, 500, or 1000 mg/kg bw/d (no other details provided)	- no adverse effects were reported at any dose (no other details were provided)	19
Myristyl phosphate	5 Sprague-Dawley rats/sex	28 days	in feed	0, 227, 505, or 1564 mg/kg bw/d, in feed	NOEL = 1564 mg/kg bw/d (males); 227 mg/kg bw/d (females) NOAEL = 1564 mg/kg bw/d (females) • all animals survived until study termination; no clinical signs of toxicity • an increased incidence in focal corticomedullary mineralization was observed in mid- and high-dose female rats, but not in controls, and could be treatment-related • no other dose-related or toxicologically-significant changes were observed	22
Oleyl phosphate	5 Wistar rats/sex	28 days	Sunflower oil	0, 100, 300, or 1000 mg/kg bw/d	NOAEL = 1000 mg/kg bw/d (males and females) • no signs of toxicity were observed, and no animals died during the observation period • no effects on clinical chemistry or hematology parameters; no test-article-related gross or microscopic lesions were observed, and organ weights were similar in test and control animals	21
Potassium C9-15 alkyl phosphate (34.35% a.i.)	10 Sprague-Dawley rats/sex 5/sex in the control and high-dose recovery groups	91 days dosing; 14-day recovery period	Purified water	0, 8, 40, 200, and 1000 mg/kg bw/d; by gavage	BMDL10 = 240.3 mg/kg bw/d (males and females) BMD = 374.61 mg/kg bw/d • no animals died prior to study termination; some clinical signs, including salivation and respiratory sounds were noted in some animals during the testing period, but not in recovery animals • mild-to-marked hyperplasia of squamous epithelium in the forestomach of high-dose test, but not recovery, animals • mild hypertrophy in some 200 mg/kg bw animals, and mild-to-moderate hypertrophy of the cortical glomerular zone of the adrenal gland in most of the high-dose test animals; mild changes observed in recovery animals	22

Abbreviations: a.i., active ingredient; BMD, benchmark dose; BMDL, benchmark dose lower confidence limit; NOAEL, no-observable adverse effect level; NOEL, no-observed effect level.

Table 7. Reproductive and Developmental Toxicity Studies.

Test article	Animals/Group	Vehicle	Dose/Concentration	Procedure	Results	Reference
ORAL						
Potassium C9-15 alkyl phosphate (36.1% potassium salt)	25 gravid female Sprague-Dawley rats	deionized water	0, 36.1, 180.5, or 361 mg/kg bw/d (a.i.)	Animals were dosed by gavage on days 6-15 of gestation • the dams were killed on day 20 of gestation	Not embryotoxic, fetotoxic, or teratogenic • NOELs for developmental toxicity, embryotoxicity, fetotoxicity, and teratogenicity were 361 mg/kg bw/day (a.i.) • NOEL and NOAEL for maternal toxicity were 36.1 and 361 mg/ kg bw/day (a.i.), respectively • all animals survived until study termination • most common clinical sign reported was rales	22
C20-22 alkyl phosphate	10 Sprague-Dawley rats/sex	Olive oil	0, 100, 300, or 1000 mg/kg bw/d	Dosed by gavage • males were dosed from 2 wks prior to mating until the end of mating; females from 2 wks prior to mating until day 5 post-partum • observations and examinations included gross observations, body weights and feed consumption, clinical chemistry, hematology, neurobehavior, gross pathology, estrous cyclicity, parental and neonatal gross necropsy, and parental histopathology and organ weights	Not a reproductive toxicant • NOELs for reproduction (mating and fertility) and neonatal toxicity were 1000 mg/kg bw/d • NOAEL for parental toxicity was 1000 mg/kg bw/d • no notable effects were reported in any of the parameters examined • no treatment-related mortality was observed	20
Oleyl phosphate	12 Wistar rats/sex	Sunflower oil	0, 100, 300, or 1000 mg/kg bw/d	dosed once daily by gavage • males were dosed for 14 days prior to mating until necropsy (41 days total dosing period) • females were dosed 14 days prior to mating, through the gestation period, and up to lactation day 3, 4 or 5 (41 – 46 days total)	not a reproductive toxicant • NOAELs for maternal toxicity and reproductive performance in males and females, and for development in F_1 offspring, were 1000 mg/kg bw/d • no toxic effects • no negative effect on reproductive parameters - no effects in neonate development were noted	21
Sodium lauryl phosphate	Main group: 12 Sprague-Dawley rats/sex recovery group: 5 rats/ sex	Olive oil	main group: 0, 250, 500, or 1000 mg/ kg bw/d 14-day recovery group: 0 or 1000 mg/kg bw/day	dosed by gavage • the males of the main group and the males and females of the recovery groups were dosed 14 days prior to, 14 days during, and 14 days after mating • the females of the main group were dosed from 14 days prior to mating through day 4 of lactation	no reproductive or developmental effects were observed • NOEL for the F_1 generation was 1000 mg/kg bw/d • NOAEL for parental male and female animals was 1000 mg/kg bw/day • the test substance had an irritant effect on the stomachs of animals of all dose groups, causing local effects on the forestomach mucosa; no other dose-related toxic effects were observed	19

Abbreviations: a.i., active ingredient; NOAEL, no-observable adverse effect level; NOEL, no-observed effect level

Table 8. Genotoxicity Studies.

Test article	Concentration/Dose/Vehicle	Procedure	Test system	Results	Reference
In vitro					
1-Octadecanol, phosphate, potassium salt	0.051-5.009 mg/plate vehicle: sterile water	Ames test, with and without metabolic activation; negative and positive controls were used	Salmonella typhimurium TA97a; TA98; TA100; TA102; TA1535	Negative; controls gave valid results	22
Potassium lauryl phosphate	S. typhimurium: ≤2500 µg/plate without and ≤5000 µg/plate with metabolic activation Escherichia coli: ≤5000 µg/plate with and without metabolic activation vehicle: deionized water	Ames test, with and without metabolic activation; negative and positive controls were used	S. typhimurium TA1535, TA1537, TA98, and TA100 E. coli WP2 uvrA	Negative	19
Potassium lauryl phosphate	≤2000 µg/mL without and ≤1500 µg/mL with metabolic activation vehicle: cell culture medium	Mammalian cell gene mutation assay, with and without metabolic activation; negative and positive controls were used (2 runs)	Chinese hamster lung fibroblast V79 cells	Negative	19
Potassium lauryl phosphate	≤1000 µg/mL without and ≤1800 µg/mL with metabolic activation vehicle: cell culture medium	Chromosomal aberration assay, with and without metabolic activation; negative and positive controls were used (2 runs)	Chinese hamster lung fibroblast V79 cells	Negative	19
C20-22 alkyl phosphate	50-5000 µg/plate vehicle: acetone	Ames test, with and without metabolic activation; negative and positive controls were used	S. typhimurium TA1535, TA1537, TA98, and TA100 E. coli WP2 uvrA	Negative; controls gave valid results	20
C20-22 alkyl phosphate	0.0313-0.5 µg/mL vehicle: ethanol	Mammalian cell gene mutation assay, with and without metabolic activation; negative and positive controls were used	Mouse lymphoma L5178Y TK +/- cells	Negative; controls gave valid results	20
C20-22 alkyl phosphate	0.0625-1 µg/mL vehicle: ethanol	Chromosomal aberration assay, with and without metabolic activation; negative and positive controls were used	Human male peripheral blood lymphocytes	Negative; controls gave valid results	20
Cetyl phosphate	0.0316-1750 µg/mL, without activation 0.010-2500 µg/mL, with activation (cell culture medium)	Mammalian cell gene mutation assay; with and without metabolic activation	Chinese hamster lung fibroblasts (V79)	Negative	22
Oleyl phosphate	S. typhimurium: ≤50 µg/plate without and ≤5000 µg/plate with metabolic activation Escherichia coli: ≤5000 µg/plate with and without metabolic activation vehicle: not identified	Ames test, with and without metabolic activation; negative and positive controls were used	S. typhimurium TA1535, TA1537, TA98, and TA100 E. coli WP2 uvrA	Negative	21
Oleyl phosphate	≤75 µg/mL without and ≤130 µg/mL with metabolic activation vehicle: DMSO	Mammalian cell gene mutation assay, with and without metabolic activation; negative and positive controls were used	Chinese hamster ovary cells	Negative	21
Oleyl phosphate	≤45 µg/mL without and ≤110 µg/mL with metabolic activation vehicle: DMSO	Chromosomal aberration assay, with and without metabolic activation; negative and positive controls were used	Chinese hamster lung fibroblast V79 cells	Negative	21

Abbreviation: DMSO, dimethyl sulfoxide.

Table 9. Irritation and Sensitization Studies.

Test article	Concentration/Dose	Test pop.	Procedure	Results	Reference
Alternative studies					
Oleyl phosphate	Not specified	EpiSkin model	Performed according to OECD Guideline 439 and EU method B.46 applied to reconstituted human epidermis for 15 minutes, and the effect on cell viability was compared to that of the negative control (water)	Did not demonstrate skin irritation potential -cell viability results were above 50% when compared to the viability values obtained from the negative control	21
Oleyl phosphate	Not specified	In vitro membrane barrier	Corrositex model; the test was performed according to OECD Guideline 435 and INVITTOX protocol no. 116 • citric acid, 10% aq., was used as a negative control and sodium hydroxide as a positive control	No potential for skin corrosion	21
Non-human					
Phosphoric acid, C16-18 alkyl esters, potassium salts	neat; 0.5 mL	6 NZW rabbits	24-hour occlusive patch applied to a 2.5 cm^2 area of both clipped intact and abraded skin; the test sites were scored at 24 and 72 hours using the Draize scale	24 hours: 4/6 animals had an erythema score of ¼ at the abraded site; no edema 72 h; no erythema or edema	22
Potassium lauryl phosphate	77% paste in water; 0.5 mL; 500 mg	3 NZW rabbits	4-hour semi-occlusive patch applied to a 2.5 cm^2 area of shaved skin	Irritating 72 hour after patch removal: mean irritation score of 2.89/4 for erythema and 1.33/4 for edema • effects were fully reversible by day 21	19
Potassium lauryl phosphate	Paste in 0.9% sodium chloride solution (concentration not specified); 500 mg	6 albino Russian rabbits	24-hour occlusive patches applied to a 2.5 cm^2 area of clipped skin.	Highly irritating primary dermal irritation index was 6.67 at 72 hour	19
Potassium lauryl phosphate	Intradermal induction: 1% epidermal induction: 75% challenge: 10%	Female Dunkin-Hartley guinea pigs; 10 test and 5 control	GPMT • intradermal induction on day 1; epidermal induction (occlusive patch) on day 8; epidermal challenge (occlusive patch) on day 22 • vehicles used during epicutaneous induction were FCA with physiological saline and purified water; purified water served as the vehicle with the dermal patches	Not a sensitizer	19
C20-22 alkyl phosphate	Applied neat, 0.5 g/animal	3 female albino rabbits	Dermal irritation/corrosion study (OECD Guideline 404) • 4-hour occlusive patch applied to shaved skin	Not an irritant • no erythema or edema at any time; primary skin irritation score of 0 at each observation	20
C20-22 alkyl phosphate	intradermal induction: 3.125% in olive oil topical induction: 100% challenge: 50% in liquid paraffin and undiluted	11 female Dunkin-Hartley guinea pigs	GPMT • intradermal induction: 3 series of 2 x 0.1 mL of 50% FCA, test article, or 50/50 solution of test article + FCA • topical induction, day 8: 48 h occlusive patch, 0.5 ml • challenge, day 21: 24 h occlusive patch, 0.5 ml • included a vehicle control group	Not a sensitizer • one animal had slight erythema 24 and 48 h after challenge with undiluted test article	20

(continued)

Table 9. (continued)

Test article	Concentration/Dose	Test pop.	Procedure	Results	Reference
Cetyl phosphate	Intradermal induction: 0.5% in water epidermal induction: 40% challenge 1: 20% and 40% challenge 2: 1% and 10% vehicle: distilled water	Female Dunkin-Hartley guinea pigs; 20 test and 10 control	GPMT • intradermal induction on day 1; epidermal induction (48-hour occlusive patch) 24 hours after intradermal induction; epidermal challenge 1 (48-hour occlusive patch) 2 weeks after induction; challenge 2 (24-hour occlusive patch) 1 week after challenge 1	Not a sensitizer • 20% challenge: slight erythema in 8/20 test and 4/10 negative control animals after 24 hour 40% challenge: slight erythema in 13/20 test and 7/10 negative control animals after 24 hours • with the exception of the 20% negative controls, reactions persisted in all of these groups at 72	22
Lauryl phosphate	intradermal induction: 0.25% epidermal induction: 12.5% challenge: 0.25% and 0.5%	female Dunkin-Hartley guinea pigs; 20 test and 10 control	GPMT • intradermal induction on day 1; epidermal induction (48-h occlusive patch) 24 h after intradermal induction; epidermal challenge (24-h occlusive patches) 2 wks after induction	not a sensitizer • 12.5% induction dose was irritating, but no reactions were observed at challenge	22
Oleyl phosphate	undiluted; 2000 mg/kg	5 Wistar rats/sex	24-h semi-occlusive patch (previously cited in the single-dose toxicity table)	irritating slight to severe erythema, slight edema, and other signs of irritation (e.g., wounds, crusting, and desquamation) were observed until study termination at day 14 in males and up to day 11 in females (as reported in the single-dose toxicity table)	21
Oleyl phosphate	10%, 25%, 50%, and 75% in DMF	Female CBA/Ca mice, 1or 2/grp	Preliminary irritation study for LLNA (details not provided)	Significant irritation	21
Oleyl phosphate	0, 0.5%, 1%, 2.5%, and 5.0% (w/v) in DMF	5 female CBA/Ca mice	LLNA; performed according to OECD Guideline 429, EU method B.42, and EPA OPPTS 870.2600 positive controls were used	No potential for sensitization; ≤5% oleyl phosphate did not increase lymphoproliferation compared to the negative controls • not irritating	21
Dicetyl phosphate	0.5 g test article, prepared as a paste in 0.575 g olive oil (calculated as 46.5% w/w)	6 male NZW rabbits	4-hour semi-occlusive patch to intact skin; 1.2 mL of preparation test sites were scored 1, 24, 48, and 72 hours after patch removal	Non-irritating; slight desquamation of the epidermis at the application site • mean erythema score – 0.56 • mean edema score – 0.0	27
Dicetyl phosphate	80% paste in distilled water; 2000 mg/kg	10 Sprague-Dawley rats/sex	24-h occlusive patch (previously cited in the single-dose toxicity table)	not irritating (as reported in the single-dose toxicity table)	22
Dicetyl phosphate	intradermal induction: 5% in liquid paraffin epidermal induction: 50% paste with liquid paraffin epidermal challenge: 50% paste with liquid paraffin	10 Dunkin-Hartley guinea pigs/sex/group	GPMT • intradermal induction: 3 series of 2 × 0.1 mL of FCA, test article, or 50/50 solution of test article + FCA • 0.5 mL 10% SLS was painted on skin on day 8 • epidermal induction, day 9: 48 hours occlusive patch, 0.5 mL • challenge, 11 days after induction: 24 hours occlusive patch, 0.5 mL • included a test-article control group (ie, vehicle at induction and test article at challenge) and a positive control group (ie, 0.05% DNCB)	Not a sensitizer; no cutaneous intolerance • 2 test-article related mortality • weak to moderate irritation was reported in a preliminary study with injection of 1, 2.5, and 5% test article (4 animals)	28

(continued)

Table 9. (continued)

Test article	Concentration/Dose	Test pop.	Procedure	Results	Reference
Dimyristyl phosphate	0.5 g, moistened with water	3 male NZW rabbits	4-hour semi-occlusive patch	Not irritating; no erythema or edema	29
Dimyristyl phosphate	12.5%-75% in distilled water; 0.2 ml	3 female guinea pigs	0.1 mL injections of 25% FCA, 50% FCA, or distilled water were administered after a 1-week nontreatment period, 24 hour occlusive patches were applied; the sites were scored at 48 and 72 hour	No reactions were observed at any dose	30
Dimyristyl phosphate	75% in distilled water	Female guinea pigs; 10 test animals, 5 controls	Guinea pig maximization test • Intradermal induction: 50% aq. FCA, 12.5% aq. dimyristyl phosphate, or solution of 12.5% dimyristyl phosphate + 50% aq. FCA • 0.5 mL 10% SLS was painted on skin 24 hours prior to epidermal induction, which consisted of a 48 hour occlusive patch, 0.5 mL, with 75% test article • challenge, 11 days after induction: 24-hour occlusive patch, 0.5 mL	not an irritant or sensitizer	30
Human					
C20-22 alkyl phosphate	5% in an emulsion (emulsion not defined)	49 patients	HRIPT induction: three 48- or 72-hour occlusive patches (Finn chambers) with 20 μL of test material were applied per wk for 3 weeks; test sites were scored 30 minutes after patch removal challenge: after a 2-week nontreatment period, a 48-hour patch was applied to a previously untreated site; the test site was scored 24 and 48 hours after patch removal	Not an irritant or a sensitizer • the mean irritation index was 0.08 during induction and 0.06 at challenge • the GII was 0.08	20
Hair cream containing 1.0% dicetyl Phosphate	Undiluted; 0.2 g	108 patients	HRIPT induction: nine 2 cm^2 patches were each applied for 24 hours during induction (ie, 3x/week for 3 weeks), and the test sites were scored at 48- or 72 hours challenge: after a 10-15 days nontreatment period, 24-hour patches were applied to a previously untreated site; the test sites were scored 48 and 72 hours after application	Not a sensitizer • no adverse event were reported	31

Abbreviations: DMF, dimethylformamide; DNCB, dinitrochlorobenzene; FCA, Freund's complete adjuvant; GII, global irritation index; GPMT, guinea pig maximization test; HRIPT, human repeated insult patch test; LLNA, local lymph node assay; NZW, New Zealand White; SLS, sodium lauryl sulfate.

(HRIPT) completed in 49 patients.[20] In an HRIPT completed in 108 patients, a hair cream containing 1.0% dicetyl phosphate was not a sensitizer.[31]

Case Report

Trioleyl phosphate. A female patient with severe contact dermatitis on the eyelids was patch-tested with ingredients from the cosmetic formulation suspected of causing the reaction; the product was a lipstick that was mistaken for an eyeshadow.[22] The patient had positive reactions to 3 ingredients, one of which was trioleyl phosphate. The patch testing was repeated using patch test chambers secured to the back. Positive reactions were observed with 0.5% and 1% trioleyl phosphate in petrolatum on days 4 and 7, but not on day 2. The patient did not react to 1% to 10% cetyl phosphate in petrolatum. Negative results were reported in 20 control patients patch tested with 1% trioleyl phosphate in petrolatum.

Ocular Irritation

Some of the alkyl phosphates are reported to be ocular irritants (Table 10). A 10% solution of potassium lauryl phosphate, tested as a 50% dilution in the hen's egg test utilizing the chorioallantoic membrane (HET-CAM), demonstrated moderate ocular irritation potential,[32] and undiluted oleyl phosphate demonstrated the potential to be corrosive and a severe ocular irritant in an in vitro eye corrosive and severe irritant study.[21] In rabbit eyes, potassium lauryl phosphate was an irritant,[19] C20-22 alkyl phosphate was a moderate irritant,[20] and dicetyl phosphate was slightly irritating.[33] However, a 3% potassium cetyl phosphate solution, tested as a 50% dilution in the HET-CAM, demonstrated practically no ocular irritation potential,[34] and *phosphoric acid, C16-18 alkyl esters, potassium salts*[22] and dimyristyl phosphate[35] were classified as nonirritating to rabbit eyes.

Summary

This report addresses the safety of 28 alkyl phosphates as used in cosmetics. The ingredients in the alkyl phosphate family share a common phosphate core structure, and vary by the identity of the alkyl chains attached therein. In some instances, structural analogs were used as supporting substances to provide read-across. Specifically, phosphoric acid, C16-18 alkyl esters, potassium salts and 1-octadecanol, phosphate, potassium salt provided read-across for potassium cetyl phosphate, and phosphoric acid, 2-ethylhexyl ester provided read-across for potassium lauryl phosphate.

Most of the alkyl phosphates function as surfactants in cosmetic ingredients; however, the triesters function as plasticizers rather than surfactants. Voluntary Cosmetic Registration Program data obtained from the FDA in 2014, and data received in response to a survey of the maximum reported use concentration by category conducted by Council in 2013 to 2014, indicate that 13 of the 28 ingredients included in this safety assessment are used in cosmetic formulations. Potassium cetyl phosphate is reported to be used in 375 formulations, dicetyl phosphate in 109 formulations, and cetyl phosphate in 94 formulations. All other in-use ingredients are reported to be used in less than 15 formulations. Potassium cetyl phosphate has the highest concentration of use in a leave-on formulation, that is, up to 8.3% in mascara products. The highest concentration of use reported for products resulting in leave-on dermal exposure is 4.2% trioleyl phosphate in "other" make-up preparations.

A single oral dose of phosphoric acid, 2-ethylhexyl ester to F344 rats was completely hydrolyzed to phosphate and 2-ethylhexanol. The ester was reported to be efficiently absorbed, metabolized, and excreted quantitatively by the body and there was no indication of accumulation.

The alkyl phosphate ingredients are relatively nontoxic in single-dose studies. The dermal LD_{50} in rats was >2 g/kg bw for C20-22 alkyl phosphate, oleyl phosphate, and 45.45% and 80% dicetyl phosphate. The oral LD_{50} in rats was >2 g/kg for 1-octadecanol, phosphate, potassium salt, potassium C9-15 alkyl phosphate, C20-22 alkyl phosphate, oleyl phosphate, and dimyristyl phosphate. The oral LD_{50} of 25% potassium lauryl phosphate was 10.49 g/kg, and for 10% cetyl phosphate it was >4.7 g/kg. In both the mouse and rat, the oral LD_{50} of a 25% suspension of dicetyl phosphate was >5 g/kg. In a 4-hour inhalation study, the LC_{50} of 1% aq phosphoric acid, C16-18 alkyl esters, potassium salts was >200 µl/L.

In 14-day studies, potassium lauryl phosphate had a NOAEL of 600 mg/kg bw/d for both males and females, and oral administration of up to 1000 mg/kg bw/d sodium lauryl phosphate for 14 days did not result in any adverse effects; no remarkable effects were observed with up to 1000 mg/kg bw/d C20-22 alkyl phosphate by gavage. The NOELs of myristyl phosphate in a 28-day dietary study were 1564 mg/kg bw/d for males and 227 mg/kg bw/d for females; because an increased incidence in focal corticomedullary mineralization was observed in females fed 505 and 1564 mg/kg bw/d, the NOAEL was 1564 mg/kg bw/d for females. Oleyl phosphate had a NOAEL of 1000 mg/kg bw/d for male and female rats in a 28-day gavage study. In a 91-day gavage study, potassium C9-15 alkyl phosphate had a benchmark dose lower confidence limit of 240.3 mg/kg bw/d in males and females.

Potassium C9-15 alkyl phosphate was not embryotoxic, fetotoxic, or teratogenic in rats dosed by gavage on days 6 to 15 of gestation; the NOELs for developmental toxicity, embryotoxicity, fetotoxicity, and teratogenicity were 361 mg/kg bw/d (a.i.), and the NOEL and NOAEL for maternal toxicity were 36.1 and 361 mg/ kg bw/d (a.i.), respectively. For C20-22 alkyl phosphate, the NOELs for reproduction (mating and fertility) and neonatal toxicity, and the NOAEL for parental toxicity, were 1000 mg/kg bw/d in rats. Oleyl phosphate also was not a reproductive toxicant in rats; in a gavage study, the NOAELs were 1000 mg/kg bw/d for maternal toxicity, reproductive performance in male and female rats, and development in F_1 offspring. In a reproductive study in rats with sodium lauryl phosphate, the NOAEL for parental male and female animals and the NOEL for the F_1 generation was 1000 mg/kg bw/d.

Table 10. Ocular Irritation Studies.

Test article	Concentration/Dose	Test system	Method	Results	Reference
Alternative studies					
Potassium cetyl phosphate	3% solution diluted by 50% with distilled water	CAM	HET-CAM 0.3 mL was applied to the four CAMs; the CAM was rinsed after 20 seconds observations were made after 30 seconds, 2 minutes, and 5 minutes	Practically no ocular irritation potential • average score of 1.75/32	34
Potassium lauryl phosphate	10% solution diluted by 50% with distilled water		HET-CAM • procedure same as above	Moderate ocular irritation potential • average score of 12/32	32
Oleyl phosphate	Applied neat	Isolated chicken eyes	In vitro eye corrosives and severe irritants study • performed according to OECD Guideline 438	demonstrated the potential to be corrosive and a severe ocular irritant • corneal opacity was 4/4, the corneal thickness score was between 0-2/2, and the fluorescein score was 3/3. The test material was applied for 10 seconds	21
Non-human studies					
Phosphoric acid, C16-18 alkyl esters, potassium salts	Applied neat, 0.1 mL	3 NZW rabbit	Instilled into the conjunctival sac of the left eye; the eyes were not rinsed; the contralateral eye served as the untreated control	Not irritating • 4 of the animals had slight conjunctival redness, with one having a maximum score of 1/4; all redness was reversed by 48 or 72 hours • one rabbit had a chemosis score of ¼ at 24 hours; this effect subsided by 48 h	22
Potassium lauryl phosphate	77% paste; 0.1 g	3 NZW rabbits	Instilled into the conjunctival sac of one eye; the eye was rinsed after 24 hours	Irritating • effects on the conjunctivae, iris, and cornea in all animals at 24 hours, and signs of irritation were present in 2/3 animals after 7 days	19
Potassium lauryl phosphate	Neat; 0.05 g	3 Albino Russian rabbits	As above	Irritating • slight corneal opacity and signs of irritation were also observed for the conjunctivae and iris in all animals up to 24 hours after rinsing; severity of the effects had decreased by 72 hours after rinsing	19
C20-22 alkyl phosphate	Neat, 0.1 g	3 female NZW rabbits	Instilled into the conjunctival sac of the right eye; the eyes were not rinsed; the contralateral eye served as the untreated control	Moderately irritating • the max. overall irritation score was 21.3 on day 1 • slight to moderate conjunctival reactions observed 1 hour after instillation were totally reversible by day 7 and 8 • slight to moderate corneal reaction noted in 2 animals at 24 hour was totally reversible by days 4-6	20
Dicetyl phosphate	20% suspension in distilled water, 0.035 g	6 male NZW rabbits	as above	Slightly irritating • global average (24 hours +48 hours + 72 hours readings: conjunctiva, chemosis – 0.55, enathema – 0.0; iris, congestion – 0.83; corneal opacity – 0	33
Dimyristyl phosphate	Neat, 0.1 g	3 male NZW rabbits	As above	Nonirritating • conjunctival irritation was observed in all animals at 1 hour; reversible in 2 animals with 48 hours • congestion of the iris in one animal at 1 hour; reversible in <24 hours • corneal opacity in 1 animal at 24 hour, clear by 48 hour • all eyes were clear by day 5	35

Abbreviations: HET-CAM, hen's egg test utilizing the chorioallantoic membrane; NZW, New Zealand White.

1-Octadecanol, phosphate, and potassium salt were negative in an Ames test, and cetyl phosphate was not genotoxic in a mammalian cell gene mutation assay. Potassium lauryl phosphate, C20-22 alkyl phosphate, and oleyl phosphate were not mutagenic in the Ames test, mammalian cell gene mutation assay, or chromosomal aberration assay.

Some alkyl phosphates were not irritating to the skin, whereas several were irritating, but not sensitizing, in nonhuman studies. C20-22 alkyl phosphate, applied neat, was not irritating to rat skin, nor was it a sensitizer in a GPMT. Undiluted phosphoric acid, C16-18 alkyl esters, potassium salts produced some signs of irritation in the abraded skin of rabbits. Potassium lauryl phosphate was irritating to rabbit skin as a 77% paste in one study, and highly irritating to rabbit skin in another (concentration not specified); it was not a sensitizer in a GPMT. Cetyl phosphate and lauryl phosphate were not sensitizers in GPMTs, but challenge concentrations of 10% and 40% cetyl phosphate and an epidermal induction concentration of 12.5% lauryl phosphate were irritating. Undiluted oleyl phosphate was irritating to rat skin; concentrations up to 5% did not demonstrate a potential for sensitization in a local lymph node assay. (Alternative studies with oleyl phosphate did not demonstrate a potential for skin irritation or corrosion.) Dicetyl phosphate was not irritating to rat skin as an 80% paste, was not irritating to rabbit skin when prepared as a 46.5% paste in olive oil (w/w), and was not a sensitizer in a GPMT. Dimyristyl phosphate, applied under an occlusive patch for 4 hours, was neither irritating to rabbit skin, nor was it an irritant or sensitizer in a GPMT at a concentration of 75% in distilled water.

C20-22 alkyl phosphate, 5% in an emulsion, was not an irritant or a sensitizer in an HRIPT completed in 49 patients. In an HRIPT completed in 108 patients, a hair cream containing 1.0% dicetyl phosphate was not a sensitizer.

Some of the alkyl phosphates are reported to be ocular irritants. A 10% solution of potassium lauryl phosphate, tested as a 50% dilution in the HET-CAM, demonstrated moderate ocular irritation potential, and oleyl phosphate demonstrated the potential to be corrosive and a severe ocular irritant in an in vitro eye corrosive and severe irritant study. In rabbit eyes, potassium lauryl phosphate was an irritant, C20-22 alkyl phosphate was a moderate irritant and dicetyl phosphate was slightly irritating. However, a 3% potassium cetyl phosphate solution, tested as a 50% dilution in a HET-CAM, demonstrated practically no ocular irritation potential, and phosphoric acid, C16-18 alkyl esters, potassium salts and dimyristyl phosphate[35] were classified as non-irritating to rabbit eyes.

Discussion

The Panel reviewed the safety of 28 ingredients in the alkyl phosphate family; these ingredients share a common phosphate core structure, varying by the identity of the alkyl chains attached. The Panel acknowledged that much of the data were obtained from ECHA summaries, and in several instances, structural analogs were used as supporting substances to provide read-across. The Panel found this read-across appropriate to support the safety of the alkyl phosphates named in this report because the analogs contained chain length distributions that had a great deal of overlap with the alkyl phosphate ingredients.

The Panel noted there were little to no safety test data on the triester phosphates included in this safety assessment. However, based on the molecular weights of the triesters ($\geq$603), and the calculated log P values ($\geq$17.02), the Panel does not expect these ingredients to penetrate through the skin. Therefore, the Panel determined that it was appropriate to include the triesters among the ingredients in this safety assessment and to conclude on their safety.

Although there were no impurities data, based on the method of manufacture and the absence of adverse effects in repeat oral toxicity studies, the Panel was not concerned with the absence of these data.

Finally, the Panel was concerned that the potential exists for ocular and/or dermal irritation with the use of products formulated using alkyl phosphates, and the Panel specified that products containing alkyl phosphates must be formulated to be non-irritating. Specifically, the Panel recognized the potential for ocular irritation when potassium cetyl phosphate is used at up to 8.3% in mascara products. Additionally, some of the alkyl phosphates were irritating to the skin of animals; however, these studies were conducted with concentrations that were much greater than the concentrations reported to be used in cosmetics.

Conclusion

The CIR Expert Panel concluded the following 28 alkyl phosphates are safe in the present practices of use and concentration in cosmetics when formulated to be non-irritating:

Potassium cetyl phosphate
Potassium C9-15 alkyl phosphate
Potassium C11-15 alkyl phosphate*
Potassium C12-13 alkyl phosphate
Potassium C12-14 alkyl phosphate*
Potassium lauryl phosphate
C8-10 alkyl ethyl phosphate*
C9-15 alkyl phosphate
C20-22 alkyl phosphate
Castor oil phosphate
Cetearyl phosphate*
Cetyl phosphate
Disodium lauryl phosphate*
Disodium oleyl phosphate*
Lauryl phosphate
Myristyl phosphate*
Octyldecyl phosphate*
Oleyl ethyl phosphate*
Oleyl phosphate*
Sodium lauryl phosphate*
Stearyl phosphate
Dicetyl phosphate

Dimyristyl phosphate*
Dioleyl phosphate
Tricetyl phosphate*
Trilauryl phosphate*
Trioleyl phosphate
Tristearyl phosphate*

*Not reported to be in current use. Were ingredients in this group not in current use to be used in the future, the expectation is that they would be used in product categories and at concentrations comparable to others in this group.

Author's Note

Unpublished sources cited in this report are available from the Executive Director, Cosmetic Ingredient Review, 1620L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contribution

Fiume M. contributed to conception and design, acquisition, analysis, and interpretation, drafted manuscript, and critically revised manuscript; Bergfeld W. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Belsito D. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Hill R. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Klaassen C. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Liebler D. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Marks J. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Shank R. contributed to conception and design, and critically revised manuscript; Slaga T. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Snyder P. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Gill L. contributed to conception and design, analysis and interpretation, and critically revised manuscript; Heldreth B. contributed to analysis and interpretation and critically revised manuscript. All authors gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The articles in this supplement were sponsored by the Cosmetic Ingredient Review. The Cosmetic Ingredient Review is financially supported by the Personal Care Products Council.

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