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Safety Assessment of Saccharide Esters as Used in Cosmetics

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Abstract

This is a safety assessment of 40 saccharide ester ingredients as used in cosmetics. The saccharide esters are reported to function in cosmetics as emollients, skin-conditioning agents, fragrance ingredients, and emulsion stabilizers. The Expert Panel for Cosmetic Ingredient Safety (Panel) reviewed the relevant data for these ingredients. The Panel concluded that the saccharide esters are safe in cosmetics in the present practices of use and concentrations described in this safety assessment.

Keywords

cosmetic, safety, saccharide esters

Introduction

This safety assessment includes the 40 saccharide esters listed below. Maltitol Laurate has been reviewed previously by the Expert Panel for Cosmetic Ingredient Safety (Panel); in 2008, the Panel concluded that this ingredient is safe as used in cosmetics.[1] Neither safety test were data available for Maltitol Laurate nor was it used in cosmetics, at the time it was previously reviewed; however, available Maltitol and Lauric Acid safety test data were used by the Panel to infer safety for Maltitol Laurate.

The saccharide esters below are listed in alphabetical order; they are also shown in Table 1, ordered by subgroups according to chain length.

Glucose Pentaacetate	Sucrose Palmitate/Stearate or Sucrose Stearate-Palmitate Ester
Maltitol Laurate	Sucrose Pentaerucate
Raffinose Isostearate	Sucrose Pentahydroxystearate
Raffinose Myristate	Sucrose Polybehenate
Raffinose Oleate	Sucrose Polycottonseedate
Sucrose Acetate Isobutyrate	Sucrose Polylaurate
Sucrose Acetate/Stearate	Sucrose Polylinoleate
Sucrose Benzoate	Sucrose Polyoleate
Sucrose Cocoate	Sucrose Polysoyate
Sucrose Dilaurate	Sucrose Polystearate
Sucrose Dipalmitate	Sucrose Stearate
Sucrose Distearate	Sucrose Tetrahydroxystearate
Sucrose Hexaerucate	Sucrose Tetraisostearate
Sucrose Hexaoleate/ Hexapalmitate/ Hexastearate	Sucrose Tetrastearate Triacetate
Sucrose Hexapalmitate	Sucrose Tribehenate
Sucrose Laurate	Sucrose Trilaurate
Sucrose Myristate	Sucrose Tristearate
Sucrose Octaacetate	Trehalose Isostearate Esters
Sucrose Oleate	Trehalose Undecylenoate
Sucrose Palmitate	Xylityl Sesquicaprylate

Sucrose Palmitate/Stearate, Sucrose Dipalmitate, and Sucrose Stearate-Palmitate Ester are not found in the *International Cosmetic Ingredient Dictionary and Handbook* (INCI; *Dictionary*),[2] but they are included in the US Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) as ingredients used in cosmetic products.[3] Thus, they are included in this safety assessment. The VCRP provides

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data on Sucrose Palmitate/Stearate and Sucrose Stearate-Palmitate Ester as separate ingredients, however structurally they are considered to have the same definition; thus, they are presented in the Definitions and Functions table (Table 2) as 1 entry under both names.

The saccharide esters have various reported functions in cosmetics, including use as emollients, skin-conditioning agents, fragrance ingredients, emulsion stabilizers, and plasticizers.[2] Xylityl Sesquicaprylate is used as an antimicrobial agent, humectant, skin-conditioning agent, and surfactant. Trehalose Undecylenoate is used as a hair-conditioning agent and surfactant. Functions reported for each ingredient are listed in Table 2.

The saccharide ester ingredients in this report are structurally related carboxylic acid esters of simple saccharides. Most of these carboxylic acids are fatty acids or mixtures of fatty acids from plant sources. All of the saccharide moieties of these ingredients, except Raffinose and Xylitol, have been evaluated by the Panel (2014) and found to be safe as used in cosmetics; the conclusions for these saccharide moieties are presented in Table 3.[1,4-15] A safety assessment of Decyl Glucoside and other alkyl glucosides (differing from the glucose ester ingredients of this report only in the number of glucose equivalents) was completed (2013) with the conclusion of safe as used in cosmetics when formulated to be nonirritating.[16] Several of the constituent acids that are used to synthesize some of the saccharide esters in this report have been reviewed previously by the Panel and found to be safe as used in cosmetics; summaries of those safety conclusions are also presented in Table 3.[1,4,15]

Sucrose Acetate Isobutyrate is generally recognized as safe (GRAS) for use as a direct food additive in the United States.[17] Given its GRAS status, the focus of this assessment for Sucrose Acetate Isobutyrate will be on assessing the potential for local effects, primarily dermal irritation and sensitization.

This safety assessment includes relevant published and unpublished data that are available for each end point that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the end points that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review website (https://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites; https://www.cir-safety.org/supplementaldoc/cir-report-format-outline). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Study reports and unpublished data included in this safety assessment were found on the European Chemicals Agency (ECHA) website,[18] on the Australian Government Department of Health's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) website,[19,20] and in a report published by the World Health Organization (WHO).[21] The ECHA and NICNAS websites provide data summaries from industry. The WHO report is cited when industry data submitted to the WHO are included in this safety assessment.

Chemistry

Definition and Structure

The ingredients in this report are all carboxylic esters of small saccharides. These synthetic ingredients are the end products of the esterification of simple saccharides with a carboxylic acid, such as acetic acid or a fatty acid. The sugar entity that comprises the saccharide esters is glucose (monosaccharide), sucrose (disaccharide composed of glucose and fructose), the sugar alcohol maltitol derived from maltose (a disaccharide composed of 2 glucose molecules, α-1,4 bond), trehalose (disaccharide composed of 2 glucose molecules, α-1,1 bond), raffinose (trisaccharide composed of galactose, glucose, and fructose), or xylityl derived from the sugar alcohol xylitol, which is derived from xylose (monosaccharide). While the names and definitions of some of these ingredients imply single, discrete chemical entities, it is more likely that all are mixtures of saccharide esters varying in chain length, degree of esterification, and/or regiospecificity of substitution. For example, Maltitol Laurate contains a monoester of maltitol and lauric acid but, without further specification, it is unknown whether it also contains (1) other chain-length fatty acid residues (eg, myristate); (2) di-, tri-, or tetraesters; or (3) esterification at a different active site (free hydroxyl group; Figure 1).

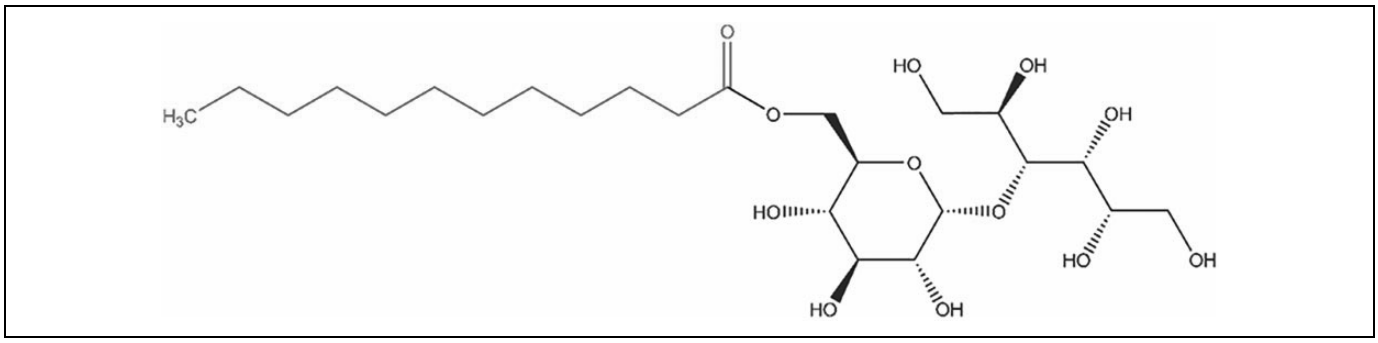

Figure 1. Maltitol Laurate, a saccharide ester.

The wide variation in hydrophilic-lipophilic balance (HLB), which is characteristic of small-saccharide (sugar) esters, allows these chemicals to function as oil-in-water (high HLB values) and water-in-oil emulsifiers (low HLB values).[22] The less-highly substituted esters (eg, mono-, di-, and tri-) are used for water-in-oil or oil-in-water emulsions, depending on the degree of esterification. More highly substituted sucrose esters have lower HLB values (increased lipophilicity); less highly substituted esters have higher HLB values (increased hydrophilicity). Secondary to the extent of substitution is the influence of the fatty acid chain length; the shorter the chain, the higher the HLB value.

The ingredients included in this safety assessment are defined (in order by subgroups according to chain length) in Table 2, and structures and functions in cosmetics, as presented in the *Dictionary*, are also provided.

Chemical and Physical Properties

Sucrose fatty acid esters (eg, Sucrose Laurate) may be stiff gels, soft solids, or white/slightly gray powders (Table 4).[23] Generally, they are sparingly soluble in water, depending on the percentage of mono esters, and soluble in ethanol. For instance, Sucrose Trilaurate has an estimated water solubility of 1.35×10^{-12} mg/L, while Sucrose Laurate (ie, 2 fewer fatty acyl chains) has an estimated water solubility of 42.37 mg/L.[24]

Method of Manufacture

Sucrose fatty acid esters (eg, Sucrose Laurate) that are used in food may be prepared from sucrose, transesterified with the methyl or ethyl esters of edible fatty acids.[23] Sucrose may also be transesterified with edible, naturally occurring vegetable oils (fatty esters of glycerol). In either type of preparation food-grade solvents, such as ethyl acetate, methyl ethyl ketone, dimethyl sulfoxide, or isobutanol may be used.

Impurities

Lead impurities are acceptable at not more than (NMT) $\leq$1 mg/kg (1 ppm) in Sucrose Acetate Isobutyrate used in food (based on atomic absorption spectrophotometric method), with a Sucrose Acetate Isobutyrate purity of not less than $\geq$98.8% and $\leq$101.9%, according to the *Food Chemicals Codex*.[23] The saponification value of Sucrose Acetate Isobutyrate used in food is acceptable at $\geq$ 524 and $\leq$540 (acid value acceptable at $\leq$0.2). The following acceptance criteria apply to sucrose fatty acid esters (purity $\geq$ 80.0% of combined mono-, di-, and triesters of sucrose) in food: $\leq$ 2 mg/kg (2 ppm) lead (based on atomic absorption spectrophotometric method); $\leq$2 mg/kg (2 ppm) dimethyl sulfoxide (based on gas chromatography/flame photometric detection method); $\leq$350 mg/kg (350 ppm) ethyl acetate, $\leq$10 mg/kg (10 ppm) isobutanol, $\leq$10 mg/kg (10 ppm) methanol, and $\leq$10 mg/kg (10 ppm) methyl ethyl ketone (based on gas chromatography/flame ionization method); $\leq$6 acid value; $\leq$ 5.0% free sucrose (based on high-performance liquid chromatography/refractive index method); and $\leq$2.0% sulfated ash residue on ignition.

Sucrose Polycottonseedate. Sucrose Polycottonseedate contains mixtures of cottonseed acid esters.[2] Cottonseed Acid is derived from Cottonseed Oil; impurities that may be found in cottonseed oils, and are known to be toxic, include gossypol, aflatoxin, cyclopropenoid fatty acids, heavy metals, polychlorinated biphenyls, and pesticide residues.[25] In a Panel safety assessment published in 2001,[25] the Panel concluded that Hydrogenated Cottonseed Oil, Cottonseed (Gossypium) Oil, Cottonseed Acid, Cottonseed Glyceride, and Hydrogenated Cottonseed Glyceride are safe as used in cosmetic products, with the stipulation that established limits on gossypol ($<$ 450 ppm), heavy metals (lead $\leq$ 0.1 mg/kg; arsenic $\leq$ 3 ppm; mercury $\leq$ 1 ppm), and pesticide concentrations ($\leq$ 3 ppm with NMT 1 ppm for any specific residue) are not exceeded.

Use

Cosmetic

The Panel evaluated the safety of the cosmetic ingredients included in this assessment based on the expected use of and potential exposure to the ingredients in cosmetics. The data received from the FDA are collected from manufacturers through the FDA VCRP and include the use of individual ingredients in cosmetics by cosmetic product category. The data received from the cosmetic industry are collected by the Personal Care Products Council (Council) in response to a survey of the maximum reported use concentrations by product category. The VCRP data obtained from the FDA in 2016[3] indicated that the ingredients most frequently used are Sucrose Acetate Isobutyrate (274 reported uses), Sucrose Stearate (156 reported uses), and Sucrose Cocoate (139 reported uses; Table 5). The 2015 to 2016 concentration of use survey data[26] indicated that the highest maximum reported concentrations of use are as follows: 87.7% Sucrose Polycottonseedate (in lipstick); 31% Sucrose Acetate Isobutyrate (up to 31% in eye shadow and foundation; up to 27% in lipstick); 20.6% Sucrose Cocoate (in shaving soap); 15% Sucrose Tetrastearate Triacetate (up to 10% in lipstick; up to 15% in mascara); and 14.3% Sucrose Benzoate (in nail polish and enamel).

The frequency and concentration of use data are summarized, alphabetically by ingredient, in Table 5. Following the Council's industry survey, there were no concentrations of use reported for Sucrose Dipalmitate and Sucrose Palmitate/Stearate or Sucrose Stearate-Palmitate Ester. Although listed together in Tables 1 and 2, Sucrose Palmitate/Stearate and Sucrose Stearate-Palmitate Ester are listed separately in Table 5 because the data for each are reported separately by the VCRP.[3] Only 1 ingredient (Maltitol Laurate) has been reviewed previously by the Panel, but there were no frequency or concentration of use data for this ingredient presented in the 2008 report.[1]

According to 2016 VCRP data, there is 1 reported use of this ingredient in shampoos non-coloring.[3]

The 14 saccharide esters that are included in this safety assessment, but are not currently in use according to the VCRP and Council industry survey, are presented in Table 6.

In some cases, reported uses of saccharide esters were available in the VCRP data, but concentration of use data was not provided. For example, Maltitol Laurate is reported to be used in 1 cosmetic formulation, but no use concentration data were reported.[3] Conversely, there were instances in which no reported uses were indicated in the VCRP data, but a use concentration was provided for the ingredient in the industry survey. For example, Trehalose Undecylenoate was not reported in the VCRP data, but the industry survey indicated that it is used in leave-on formulations at up to 0.05% (in tonics, dressings, and other hair grooming aids) and in rinse-off formulations at up to 0.25%.[26] It should be presumed in these cases that there is at least one use in every category for which a concentration of use is reported.

Saccharide esters were reported to be used in perfumes, hair sprays, and deodorant sprays, and therefore, could possibly be inhaled. As examples, Sucrose Laurate was reportedly used in pump hair sprays at concentrations up to 1.2%; Sucrose Stearate was reportedly used in aerosol deodorant sprays at concentrations up to 0.23%.[26] 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 below 10 μm compared with pump sprays.[27-30] 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.[27,28] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[28] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays. Sucrose Tristearate was reported to be used in face powders at concentrations up to 2%[26] and could possibly be inhaled. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[31-33]

Saccharide esters were reported to be used in cosmetic formulations indicative of potential eye exposure (Sucrose Acetate Isobutyrate up to 31% in eye shadow), possible mucous membrane exposure (Sucrose Polycottonseedate up to 87.7% in lipstick), and possible ingestion (Sucrose Polycottonseedate up to 87.7% in lipstick).[3,26] These ingredients are also incorporated into various baby products (eg, Sucrose Stearate is reported to be used in 4 baby products, but no concentration of use was reported).[3]

None of the saccharide esters named in this report are restricted from use in any way under the rules governing cosmetic products in the European Union.[34]

Non-Cosmetic

The non-cosmetic uses of the saccharide esters (Table 7) consist largely of either direct or indirect food additives, as specified in the Code of Federal Regulations (CFR) Title 21. Sucrose fatty acid esters are listed as direct food additives (21CFR172.859). Sucrose Acetate Isobutyrate is GRAS for use as a direct food additive in the United States.[17] Sucrose Octaacetate has been present in over the counter (OTC) drugs as nail-biting and thumb-sucking deterrents. However, the FDA has stated that Sucrose Octaacetate cannot be GRAS and effective in this application because the available safety data are not adequate to assess the safety of the use of Sucrose Octaacetate for this purpose (21CFR310.536):

> Any OTC drug product that is labeled, represented, and promoted as a nail biting or thumb sucking deterrent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) for which an approved application or abbreviated application . . . is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act. Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as a nail biting or thumb sucking deterrent is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs . . . (21CFR310.536)

The following saccharide esters are listed as inactive ingredients in FDA-approved drug products: Sucrose Laurate at 30 mg in a gelatin-coated capsule for oral administration; Sucrose Palmitate at 10 mg in a powder for suspension intended for oral administration; Sucrose Stearate/Sucrose Distearate at 5% (w/w) in a topical emulsion cream; Sucrose Stearate at up to 44.5% in a sustained-action capsule or an extended-release tablet for oral administration.[35]

Toxicokinetic Studies

Dermal Penetration

Human

Sucrose Laurate. Tape-stripping studies were conducted on the transport of elastic vesicles into human skin to understand the effects of occlusion and the duration and volume of application.[36] Vesicles have been used to increase the transport rate of drugs through the skin, although in tests reported here drugs were not used in the vesicle formulations. Elastic liquid-state vesicles (100-120 nm and composed of molar ratio 50:50:5; Sucrose Laurate: micelle-forming surfactant PEG-8-L: sulfosuccinate stabilizer) containing Sucrose Laurate (30% mono-, 40% di-, and 30% triesters) were evaluated in human subjects

($n \geq 3$). In all of the tests, a 0.05 M citrate buffer solution (pH 5.0) was used as a control applied to the skin; no vesicles without Sucrose Laurate were used as a control. Electron micrographs corresponding to tape strip 1 (skin surface) and either 9 or 15 (deeper layers of stratum corneum) were reported for all the test conditions. In the duration test, the vesicles were applied nonocclusively (20 µL to a 1 cm^2 skin surface area), and tape-stripping was performed 1 and 4 hours after the solution had dried (evaporation of vesicle solutions was necessary to establish an osmotic gradient thought to facilitate transport into the skin). After the 1 and 4-hour treatments, vesicles were observed up to the 9th and 15th strips, respectively, with extensive vesicle fusion (multiple vesicles forming conglomerates at the skin surface and in stratum corneum) in the 4-hour treatment. In the volume test, 20 µL and 100 µL of vesicle formulation were applied non occlusively, and tape-stripping was performed 1 hour after the solution had dried. The skin surface showed no difference, based on comparison of skin structure as seen in electron micrographs, between the 20 µL and 100 µL volumes; however, in the stratum corneum, the 100 µL volume, as compared to 20 µL, increased the amount of intact vesicles (maintaining individual vesicle formation as depicted in electron micrographs) and fused vesicle material in the 9th strip. The presence of intact and fused vesicles was also noted in the electron micrographs of the first tape strips with the 20 µL and 100 µL treatments; little vesicle material was observed in the 15th tape strips at either volume tested.

The effect of occlusion was evaluated in a test performed by applying 100 µL of vesicle formulation, both occlusively and for comparison, nonocclusively, for 1 hour, after which the skin surface was wiped off and tape-stripping performed. Results from the occlusion test were: the skin surface contained vesicles (intact and fused, similar to controls) for occluded and nonoccluded samples and lipid plaques (the authors postulated that lipid plaques were the dispersal of vesicle fragments or components into the stratum corneum) in the occluded samples; unlike in nonoccluded samples, the occluded samples showed that the stratum corneum had few intact vesicles in the 9th strip, and lipid plaques were found in the 9th and 15th strips; lipid plaques may have enhanced skin permeability by disrupting intercellular skin structure organization; very few intact vesicles were present in the deeper layers of the stratum corneum during occlusion. Fast penetration of vesicles into the stratum corneum for nonocclusive treatment was noted. The researchers indicated that nonocclusive conditions facilitated the elastic vesicle incorporation into the skin by establishing a transepidermal osmotic gradient.

Penetration Enhancement

A synopsis of penetration enhancement experiments is provided below; details are provided in Table 8.

In vitro. Penetration enhancement tests in vitro showed Sucrose Laurate (1.5%) evaluated in the pH range of 6 to 8 in mouse skin to be a potent percutaneous absorption enhancer for the drug lidocaine,[37] and in rat skin Sucrose Laurate (30% aqueous solution) was found to be a penetration enhancer for the drug cyclosporine.[38] Experiments in micropig skin, evaluating polyphenols in oil-in-water microemulsions (25:19:5:60, Sucrose Laurate: ethanol: isopropyl myristate: water), showed rapid distribution from the microemulsion vehicle to the epidermis, but slower dispersion from epidermis to dermis; hydrophilic polyphenols were distributed slightly more to the epidermis, and hydrophobic (small molecular weight) polyphenols distributed mainly to the dermis.[39] Sucrose Laurate and Sucrose Myristate (variable between 0.1 and 3 mg/mL) showed a concentration-dependent enhancement of paracellular permeability of a fluorescein isothiocyanate-labeled dextran marker in human nasal epithelial cells.[40] In a nanoemulsion, Sucrose Stearate (1%) was a permeation enhancer for progesterone in an in vitro porcine skin test.[41]

Animal. Animal tests revealed that Sucrose Laurate (5% in a hydrogel) increased skin hydration and penetration of the drug ibuprofen in a mouse tape-stripping experiment[42]; in rabbits, Sucrose Laurate (5% and 15% in a hydrophilic gel) increased epidermal skin-fold thickness and was a percutaneous absorption enhancer of the drug estradiol.[43] In an experiment in which rats were exposed to the drug sumatriptan succinate and 0.5% Sucrose Laurate by intranasal administration, results showed that Sucrose Laurate enhanced the effect of intranasal absorption of sumatriptan succinate.[44] Sucrose Cocoate (0.5%), when exposed via nasal administration using a pipette or by ocular installation, was found to increase the absorption of drugs (insulin and calcitonin) 9-fold (nasal) and 4-fold (ocular) in rats.[45]

Human. Sucrose Palmitate (2%) and Sucrose Stearate (0.5%) in a tape-stripping (12×) experiment in human subjects increased skin absorption of the drug aceclofenac, which was then detected at all depths of the stratum corneum.[46] Sucrose Oleate and Sucrose Laurate, both tested at 2% and 10% in human subjects, increased skin penetration of the drug 4-hydroxybenzonitrile.[47]

Absorption, Distribution, Metabolism, Excretion

A brief summary of absorption, distribution, metabolism, and excretion studies is provided below; details are provided in Table 9.

In vitro. Experiments showed that a mixture of 1 µmol/mL Sucrose Palmitate and Sucrose Stearate ([^{14}C] radiolabels on either the sucrose or ester portion) was not transported from mucosal to serosal solution in everted intestinal sacs of rats; hydrolysis by mucosal homogenates from the rats was 10% to 30%, compared with little hydrolysis in whole blood.[48] Results from another rat test indicated that up to 250 µg/mL [^{14}C]Sucrose Acetate Isobutyrate (label on sucrose) was 75% hydrolyzed by intestinal homogenates in 6 hours; less hydrolysis occurred in the stomach and liver.[49] A study, in which human fecal homogenates were incubated with 1 mg/mL and

0.1 mg/mL [^{14}C]Sucrose Acetate Isobutyrate (label on sucrose), resulted in 40% and 60% hydrolysis, respectively, in 16 hours.[49]

Animal. In oral studies in rats, Glucose Pentaacetate (20% aqueous solution, no radioactive label used) was rapidly absorbed (> 90% in 4 hours),[50] and excretion occurred mostly in the feces after administration of a [^{14}C]Sucrose Palmitate and Sucrose Stearate mixture (details on radiolabeling are specified in Table 9)[48]; a mixture of sucrose esters (250 mg/kg, radiolabels on either sucrose or ester portion, see Table 9 for details), including Sucrose Hexastearate, was hydrolyzed prior to intestinal absorption (less esterified compounds were better absorbed) and largely excreted in feces (>96%-99% of radioactivity) at 120 hours postdosing[51]; and 200 mg/kg of Sucrose Octaisobutyrate (a component of Sucrose Acetate Isobutyrate, ^{14}C label on sucrose) was excreted in feces (78%-93% of dosed radioactivity), excreted as a volatile product (3%-15% of dosed radioactivity), and eliminated in urine (1% to 2% of dosed radioactivity).[52] In dogs and monkeys orally administered 200 mg/kg of Sucrose Octaisobutyrate ([^{14}C] label on sucrose), no dosed radioactivity was detected in whole blood or plasma and excretion in feces was 77% to 94% of dosed radioactivity and 62% to 85% of dosed radioactivity, respectively.[52] In dogs, Sucrose Octaisobutyrate was slowly absorbed, with less extensive hydrolysis in the gut, as compared to rats; in monkeys it was not absorbed or hydrolyzed in the gut.[52]

Human. In single-dose (0.1 g or 1.0 g Sucrose Acetate Isobutyrate) and multidose (1 g/d Sucrose Acetate Isobutyrate for 7 d) oral exposure studies, results indicated that < 0.4% were excreted in urine as the parent compound or metabolite with a disaccharide moiety.[49] In a fecal excretion study, 0.1 g/d Sucrose Acetate Isobutyrate was administered to 1 subject for 7 days and no unchanged Sucrose Acetate Isobutyrate or metabolites were detected in fecal samples. The absorption of partially esterified sucrose molecules from the intestinal tract was insignificant. In a different test, human subjects were administered a single, oral dosage of 1.0 to 1.2 mg/kg Sucrose Acetate Isobutyrate (radiolabel on sucrose) and exhaled 41% to 66% of dosed radioactivity in the breath within 30 days postadministration; 15% to 21% of dosed radioactivity was eliminated in urine and 10% of dosed radioactivity was excreted in feces.[53]

Toxicological Studies

Acute Toxicity Studies

Provided below is a synopsis of the acute (single exposure) toxicity studies that are presented in detail in Table 10.

The LD_{50} was reported to be > 20 g/kg in a study in which a single dosage of Sucrose Acetate Isobutyrate was dermally applied to rats.[18] For rats and monkeys orally administered single dosages of Sucrose Acetate Isobutyrate, the LD_{50} was reported to be > 5 g/kg and > 20 g/kg, respectively.[18] In dogs orally administered a single dosage of 2 g/kg Sucrose Acetate Isobutyrate, an increase in plasma bromosulfophthalein (BSP) levels was reported.[21] Constituent esters of Sucrose Acetate Isobutyrate, namely Sucrose Hexaacetate Diisobutyrate and Sucrose Octaisobutyrate, were both shown to increase BSP levels in dogs when single dosages up to 1 g/kg were orally administered; however body weight and gross clinical observations were unaffected by the treatment. Overall, single, high dosages of Sucrose Acetate Isobutyrate, administered through dermal and oral exposure, were well-tolerated in animals.

Short-Term Toxicity Studies

Below is a synopsis of the short-term toxicity studies that are presented in detail in Table 11.

Animal. Sucrose Acetate Isobutyrate was well-tolerated in orally exposed animals. In rats, a no-observed-adverse-effect concentration (NOAEC) was reported for doses up to 10% daily in the diet for 6 weeks (decrease in mean heart weight for treated males was noted)[54]; monkeys dosed up to 10 g/kg/d in the diet (for 15 days) showed no change in body weight, food consumption, or clinical parameters[21]; mice dosed up to 5 g/kg/d in the diet (for 4 weeks) were unaffected by the treatment[55]; in a 2-week study in dogs dosed up to 0.5% daily in the diet, BSP retention was reported at 0.3% and 0.5%.[21] Sucrose Polysoyate was orally administered to rats and dogs. In rats dosed for 28 days, a no-observed-effect concentration (NOEC) of 15% was reported; softer feces, lower growth rates (dose-related), and a dose-dependent heart weight decrease were observed.[19,20] Two studies in dogs reported an NOAEC and (NOEC) of 15% daily in the diet for 28 days; results showed a higher food consumption in treated animals compared to controls, yet hematology, urine, and organs were unaffected by treatment.[19,20]

Human. In 3 different studies conducted in human subjects orally administered up to 0.02 g/kg/d Sucrose Acetate Isobutyrate for 14 days, results showed no blood chemistry or hematological abnormalities.[21]

Subchronic Toxicity Studies

Below is a synopsis of the subchronic toxicity studies that are presented in detail in Table 11.

An NOAEL of 10% daily in the diet was reported in a 12-week study in rats orally administered Sucrose Acetate Isobutyrate; a decrease in mean heart weights in all treated males was observed.[54] In 13-week studies in rats dosed with up to 9% Sucrose Acetate Isobutyrate daily in the diet, slight diarrhea was reported, but no toxic effects were observed.[18,21] Dogs orally administered up to 5% Sucrose Acetate Isobutyrate daily in the diet for 91 days showed a moderate elevation in serum alkaline phosphatase (SAP) liver enzyme, heavier liver weights compared to controls, and a functional effect on the liver (reversible when Sucrose Acetate Isobutyrate was removed from the diet).[18] In rats orally administered Sucrose Polysoyate for approximately 90 days, an NOEC of 15% daily in the diet was reported; softer feces and lower growth rates were noted,

an increase in food consumption was seen with increasing doses, however no toxicity was observed.[19,20]

Chronic Toxicity

Provided below is a summary of the chronic toxicity studies that are presented in detail in Table 11.

Sucrose Acetate Isobutyrate was evaluated in monkeys in a 1-year study in which an NOAEL of 2.4 g/kg/d (the highest dosage rate tested) was reported.[56] Although statistically significant changes in hematological parameters were reported at the higher dosage rates (1.45-2.4 g/kg/d), overall the treatment was well-tolerated. Reported from a 1-year rat study testing Sucrose Acetate Isobutyrate was an NOAEL of 2 g/kg/d (highest dosage rate tested).[55] Body weight gain decreases were observed in males and females (2 g/kg/d); 1 female death (0.5 g/kg/d) was noted, 1 female was killed in a moribund condition (2 g/kg/d), and 1 control and 2 treated rats died during blood collection. Small, but statistically significant hematology differences between control and treated groups occurred at varying dosage rates and time points in the study; however all resolved by 54 weeks. The same researchers conducted 2-year toxicity studies (including evaluations for carcinogenicity; see Carcinogenicity section in-text) in rats and mice. Survival rates for rats were 46% to 78% and for mice were 66% to 80%. The NOAELs reported for rats and mice were 2 g/kg bw/d (highest dosage rate tested) and 2.5 g/kg/d, respectively. In mice, the NOAEL did not include the highest dosage rate tested (5 g/kg/d) because at that dosage rate, there was a treatment-related decrease in mean absolute and relative kidney weights observed at necropsy in males, compared to controls. Another 2-year toxicity study (carcinogenicity evaluations were performed; see Carcinogenicity section in-text) was conducted in rats (concentration up to 9.38% in diet).[21] A dose-related increase in absolute and relative kidney weights was noted; however the organ weight findings were deemed inconclusive because of discrepancies in male body weights, as compared to controls, and low survival numbers. Within 10 weeks of the study, 4 males dosed with 9.38% died (massive hemorrhages in multiple organs were reported), but the deaths were not attributed to treatment (no further details specified).

Developmental and Reproductive Toxicity Studies

Provided below is a summary of the developmental and reproductive toxicity (DART) studies that are presented in detail in Table 12.

Four oral-exposure DART studies are reported for Sucrose Acetate Isobutyrate in rats and rabbits. In a 3-generation dietary study in which male rats were dosed daily for 10 weeks and female rats for 2 weeks prior to mating, teratogenic and developmental toxic effects were not observed and an NOAEL of 2 g/kg/d, the highest dosage rate tested, was reported.[57] In another dietary study, rats fed 9.38% in the diet for 5 weeks (rats bred 3× during weeks 9-36) showed fewer pregnancies and fewer pup births with survival to weaning. However, this was attributed to the potentially reduced nutritive value of the diet.[21] In a study in which rabbits were dosed on days 7 to 19 of gestation by gavage, an NOAEL of 1.2 g/kg/d was reported; 2 of 16 rabbits dosed at this level died on day 17 of gestation, but teratogenic or developmental toxic effects were not observed.[42]

Genotoxicity Studies

Below is a synopsis of the genotoxicity studies that are presented in detail in Table 13.

In Vitro

Maltitol Laurate and Sucrose Acetate Isobutyrate were evaluated in vitro. Maltitol Laurate (40%) was negative in an Ames test performed using *Salmonella typhimurium*.[58] An Ames test conducted in *S typhimurium* cells showed that Sucrose Acetate Isobutyrate was negative for genotoxicity as a mutagen, clastogen, and DNA-damaging agent at concentrations up to 10000 μg/plate (nontoxic; no increase in number of revertants).[59] A mutation assay in Chinese Hamster Ovarian/Hypoxanthine-Guanine Phosphoribosyl Transferase (CHO/HGPRT) cells showed no increase in mutation frequency up to 1000 μg/mL Sucrose Acetate Isobutyrate. A chromosomal aberration assay in CHO cells showed no increase in aberrations up to 2000 μg/mL Sucrose Acetate Isobutyrate. An unscheduled DNA synthesis assay in rat hepatocytes was nontoxic for test substance Sucrose Acetate Isobutyrate at concentrations up to 10000 μg/mL.

In Vivo

A study in which male rats were administered a single dosage (2000 mg/kg) of Sucrose Acetate Isobutyrate by gavage and subsequently mated with untreated females several times during the 7 weeks postdosing yielded negative results for dominant lethal mutations.[18]

Carcinogenicity Studies

Animal

Sucrose Acetate Isobutyrate. In a 2-year chronic study (Table 11) that also evaluated carcinogenicity, F344 rats (n = 50/sex/dosage rate) were fed a diet containing Sucrose Acetate Isobutyrate.[55] The nominal dosage rates were 0 (control group 1), 0 (control group 2), 0.5, 1.0, and 2.0 g/kg/d. The highest tested concentration of Sucrose Acetate Isobutyrate in the diet (less than 5%) was not expected to cause nutritional deficiencies in this long-term study. Sucrose Acetate Isobutyrate was not carcinogenic; no treatment-related tumors were found, only tumors typical of those that occur spontaneously in the F344 rat were noted.

A 2-year chronic dietary study (Table 11), also evaluating carcinogenicity, was conducted in $B6C3F_1$ mice (n = 50/sex/dosage rate).[55] A 4-week range finding study (Table 11) was

conducted at 0, 0.625, 1.25, 2.5, and 5.0 g/kg/d Sucrose Acetate Isobutyrate (n = 10/sex/dosage rate). Results indicated that Sucrose Acetate Isobutyrate was well-tolerated. Dosage rates selected for the 2-year carcinogenicity study were 0, 0, 1.25, 2.5, and 5.0 g/kg/d Sucrose Acetate Isobutyrate (highest dietary concentration of Sucrose Acetate Isobutyrate at 4.4%). Sucrose Acetate Isobutyrate was not carcinogenic; tumors found were typical of those that occur spontaneously in the $B6C3F_1$ mouse and were not treatment-related.

Carcinogenicity in Sprague-Dawley rats was evaluated (n = 10/sex/dose level) at 0%, 0.38%, and 9.38% Sucrose Acetate Isobutyrate in the diet for 2 years in a chronic study (Table 11).[21] No Sucrose Acetate Isobutyrate treatment-related lesions were found upon histological examination, therefore the study results were negative for carcinogenicity.

Other Relevant Studies

Cytotoxicity Studies

Provided below is a synopsis of cytotoxicity studies presented in detail in Table 14.

In vitro. Tests on various cell cultures were conducted to evaluate the cytotoxicity of Sucrose Laurate and/or Sucrose Myristate. Human nasal epithelial cell death in the lactate dehydrogenase assay of Sucrose Laurate was < 25% at 0.1 mg/mL and of Sucrose Myristate was 50% to 75% at 0.1 to 0.3 mg/mL; the 3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay test indicated that cell viability was 100% with 0.1 mg/mL Sucrose Laurate and 100% with 0.03 mg/mL Sucrose Myristate.[40]

Dermal Irritation and Sensitization Studies

Irritation

Details of dermal irritation and sensitization studies found in Tables 15 and Table 16 are summarized below.

Animal. Skin irritation testing of Sucrose Laurate in animals resulted in the following: a hydrogel formulation (concentration of Sucrose Laurate unknown) containing 5% ibuprofen was nonirritating to mouse skin[42]; 5% and 15% hydrophilic gel formulations (also containing the drug estradiol) yielded increased epidermal thickness and some irritation potential when tested in rabbits[43]; a 2% solution was nonirritating when tested in guinea pigs.[38] Sucrose Acetate Isobutyrate (0.5 mL applied directly to shaved skin with an occlusive covering for 24 hours) was nonirritating to guinea pig skin.[18] The saccharide esters evaluated were generally nonirritating, with sporadic occurrences of slight irritation.

Human. Sucrose Stearate and Sucrose Palmitate (up to 2% in a nanoemulsion containing the drug aceclofenac), evaluated for irritation potential in a 24-hour occlusive patch test in human subjects, produced a decrease in stratum corneum hydration. However, no adverse skin reactions were visible and the treatment was tolerable to the skin.[46] Human patch tests evaluating Sucrose Pentahydroxystearate (100%) and Sucrose Tetraisostearate (100%) for irritation were negative (0% after 24 hours, no further details specified).[58] Sucrose Polycottonseedate (up to 1% in formulation) was slightly irritating in a 21-day occlusive patch test in human subjects.[20] Sucrose Polycottonseedate (up to 13% solution) and Sucrose Polybehenate (up to 3% solution) were nonirritating in a 5-day occlusive patch test in human subjects.[19,20] Moderate skin irritation observed in 4 of 30 humans subjects dermally exposed to cleansing cloths containing Sucrose Polycottonseedate (up to 17.19%) was thought to be caused by constituents in the formulation other than the saccharide ester.[20] Overall, the saccharide esters were characterized as nonirritating to human skin in the studies summarized in this safety assessment; for the intermittent irritation noted in a few of the tests (see Tables 15 and 16), it was reported to be slight to mild in a relatively small percentage of the total population of subjects evaluated.

Sensitization

Animal. Slight, transient irritation was noted in a study testing Sucrose Acetate Isobutyrate (20% solution in 9:1, acetone: corn oil) for 24 hours on hairless guinea pig skin.[60] A delayed sensitization experiment was also conducted in guinea pigs (induction and challenge phase concentrations were not specified) and no sensitization was reported. In a Guinea Pig Maximization Test evaluating Sucrose Acetate Isobutyrate (1% solution at induction; 10% solution at challenge), no sensitization was observed.[18] Sucrose Acetate Isobutyrate was nonsensitizing in animals.

Human. Sucrose Acetate Isobutyrate (20% solution) in a human repeat insult patch test (HRIPT) was nonirritating and nonsensitizing.[18] In an HRIPT, Sucrose Polybehenate (~3%) and Sucrose Polycottonseedate (~13%) were nonirritating and nonsensitizing[19,20] Sucrose Polycottonseedate (~16%-17% in facial cleansing cloths) was nonirritating and nonsensitizing in an HRIPT.[20] Sucrose Polycottonseedate (88% in a lipstick topcoat matrix) was nonsensitizing in human subjects and the only reaction reported was skin staining in 1 subject.[61] The saccharide esters evaluated were nonsensitizing in human subjects.

Ocular Irritation

Animal

Sucrose Laurate. A study in Japanese white female rabbits was conducted to evaluate the effects of Sucrose Laurate on rabbit eyes.[62] A Maximum Draize Rabbit Eye Score (MDES) test was performed by instilling 0.1 mL of 10% Sucrose Laurate solution, prepared from a 38% Sucrose Laurate solution, into the conjunctival sac of the left eye (right eye served as untreated control) of each of 3 rabbits. There was no eye washing post-application. Observations were made at 1, 3, 6, 24, 48, 72, and 96 hours post-treatment. The observed MDES score reported

for Sucrose Laurate was 21 (no further irritation results provided). The threshold score of around 20 was considered by the authors to be the value below which corneal damage was not observed.

Sucrose Acetate Isobutyrate. A study evaluating the irritation of Sucrose Acetate Isobutyrate in New Zealand White rabbit eyes was conducted.[18] The guidelines followed in this study were similar to OECD 405 (Acute Eye Irritation/Corrosion), using good laboratory practice. To all of the eyes of 3 rabbits, 0.1 mL of a 50% Sucrose Acetate Isobutyrate dilution in corn oil was instilled into the conjunctival sac (3 washed and 3 unwashed eyes, following application). To another unwashed eye, 0.1 mL of corn oil was instilled into the conjunctival sac for use as a control. Observations were noted for 72 hours postapplication. The control performed as expected. Moderate erythema of conjunctivae and nictitating membranes were noted in all unwashed eyes 1 hour postapplication; slight erythema of conjunctivae and nictitating membranes observed in 2 of 3 unwashed eyes 24 hours postapplication. At 48 hours postapplication, 2 of 3 unwashed eyes were normal and at 72 hours postapplication, all 3 unwashed eyes were normal. There was slight (in 2 of 3 eyes) to moderate (in 1 of 3 eyes) erythema of conjunctivae and nictitating membranes in washed eyes 1 hour postapplication. All washed eyes were normal at 24 hours postapplication (no corneal or adnexal staining seen when eyes were examined with fluorescein dye). Sucrose Acetate Isobutyrate was slightly irritating to rabbit eyes.

Summary

The 40 saccharide esters included in this safety assessment have a variety of reported functions in cosmetics, that is, surfactants, humectants, emulsion stabilizers, emollients, and skin-conditioning agents.

The VCRP data obtained from the FDA in 2016 indicated that Sucrose Acetate Isobutyrate has the highest reported number of uses (274) with the next highest reported for Sucrose Stearate (156) and Sucrose Cocoate (139). Concentration of use industry survey data obtained by the Council in 2015 to 2016 indicated that the highest maximum reported concentrations of use are for Sucrose Polycottonseedate (87.7% in lipstick), Sucrose Acetate Isobutyrate (31% in eye shadow and foundation; 27% in lipstick), Sucrose Cocoate (20.6% in shaving soap), Sucrose Tetrastearate Triacetate (15% in mascara and 10% in lipstick), and Sucrose Benzoate (14.3% in nail polish and enamel). There were no concentrations of use reported in a Council industry survey for Sucrose Dipalmitate and Sucrose Palmitate/Stearate or Sucrose Stearate-Palmitate Ester. There are 14 saccharide esters included in this safety assessment that are not reported to be in use according to the 2016 VCRP data and the 2015 to 2016 Council concentration of use industry survey.

Saccharide esters are used as penetration enhancers in pharmaceutical applications. They are also incorporated into foods as direct and indirect food additives (ie, flavoring substances and emulsion stabilizers). Sucrose Acetate Isobutyrate is a GRAS direct food additive. Sucrose Laurate, Sucrose Palmitate, Sucrose Stearate, and Sucrose Distearate are listed as inactive ingredients in FDA-approved drug products.

Human dermal penetration studies showed at 1 hour postdermal (nonocclusive) application of elastic vesicles (containing a molar ratio of 50:50:5; Sucrose Laurate: micelle-forming surfactant; PEG-8-L: stabilizer sulfosuccinate) that Sucrose Laurate was observed up to the ninth tape strip and after 4 hours up to the 15th strip, suggesting that Sucrose Laurate permeated the stratum corneum.

The in vitro penetration enhancement studies demonstrated that Sucrose Laurate was a percutaneous absorption enhancer for the drug lidocaine at pH 6, in mice. Micropig experiments (in vitro) showed that Sucrose Laurate enhanced skin incorporation of polyphenols with accumulation of hydrophilic polyphenols occurring more in the epidermis and accumulation of lower molecular weight hydrophobic polyphenols more in the dermis. Sucrose Laurate, in in vitro rat skin tests, exhibited effective skin penetration-enhancing properties for dermal hydrophilic drug (cyclosporine A) delivery. Sucrose Laurate and Sucrose Myristate (variable between 0.1 and 3 mg/mL) showed a concentration-dependent enhancement of paracellular permeability of a fluorescein isothiocyanate-labeled dextran marker in human nasal epithelial cells. Sucrose Stearate was shown to be an emulsifier and dermal drug (eg, fluconazole) penetration enhancer in pig skin (in vitro).

Penetration enhancement studies (in vivo) testing Sucrose Laurate in mice showed increased skin hydration and penetration of ibuprofen and facilitated the absorption of lipophilic hydrocarbon components of the hydrogel (vehicle containing Sucrose Laurate) in the stratum corneum. Sucrose Laurate was a good intranasal absorption enhancer for the drug sumatriptan in rats. Experiments conducted in rabbits in vivo showed that Sucrose Laurate increased dermally administered drug (estradiol) bioavailability by 15%; Sucrose Laurate was a percutaneous absorption enhancer in single dose drug (estradiol) applications, but less effective after multiple applications. Skin biopsies from the application sites of rabbits treated with 5% and 15% Sucrose Laurate exhibited substantially greater thickness. Sucrose Cocoate, when exposed via nasal administration using a pipette or by ocular installation, was found to increase the absorption of drugs (insulin and calcitonin) 9-fold (nasal) and 4-fold (ocular) in rats. In human subjects, Sucrose Palmitate (2%) and Sucrose Stearate (0.5%) were found to be absorption enhancers of the dermally applied drug aceclofenac, which was subsequently detected at all depths of the stratum corneum.

Toxicokinetic studies in vitro showed that a mixture of Sucrose Palmitate and Sucrose Stearate (1 μmol/mL, [^{14}C] labels on either sucrose or ester portion) was not transported from mucosal to serosal solution in everted intestinal sacs of rats; hydrolysis by mucosal homogenates from the rats was 10% to 30%, compared with little hydrolysis in whole blood. Results from another rat test indicated that up to 250 μg/mL [^{14}C]Sucrose Acetate Isobutyrate (label on sucrose) was 75% hydrolyzed by intestinal mucosa in 6 hours; less hydrolysis

occurred in the stomach and liver. A study in which human fecal homogenates were incubated with 1 mg/mL or 0.1 mg/mL [^{14}C]Sucrose Acetate Isobutyrate (label on sucrose) resulted in 40% and 60% hydrolysis, respectively, in 16 hours.

Toxicokinetic tests conducted in rats (oral exposure) revealed the following: Glucose Pentaacetate (20% aqueous solution, no radioactive label used) was rapidly absorbed (>90%) in 4 hours; a mixture of Sucrose Palmitate and Sucrose Stearate (up to 250 mg/kg) was excreted in feces (30%-67% of dosed radioactivity), exhaled (11% to 49% of dosed radioactivity), and not detected in urine or blood at 120 hours postdosing; a mixture of sucrose esters (250 mg/kg), including Sucrose Hexastearate, were hydrolyzed prior to intestinal absorption (less esterified compounds were better absorbed) and largely excreted in feces (> 95% of dosed radioactivity) at 120 hours postdosing; 200 mg/kg of Sucrose Octaisobutyrate (a component of Sucrose Acetate Isobutyrate) was excreted in feces (78%-93% of the dose of radioactivity), excreted as a volatile product (3%-15% of the dose of radioactivity), and eliminated in urine (1%-2% of the dose of radioactivity). In dogs and monkeys orally administered 200 mg/kg of Sucrose Octaisobutyrate, no radioactivity was detected in whole blood or plasma and excretion in feces was 77% to 94% of dose of radioactivity and 62% to 85% of the dose of radioactivity, respectively. In dogs, Sucrose Octaisobutyrate was slowly absorbed with less extensive hydrolysis in the gut, compared to rats; in monkeys it was not absorbed or hydrolyzed in the gut.

In single-dose (0.1 g or 1.0 g Sucrose Acetate Isobutyrate) and multidose (1 g/d Sucrose Acetate Isobutyrate for 7 days) oral-exposure toxicokinetic studies in human subjects, results indicated that <0.4% were excreted in urine as the parent compound or metabolite with a disaccharide moiety. In a fecal excretion study, 0.1 g/d Sucrose Acetate Isobutyrate was administered to 1 subject for 7 day and no unchanged Sucrose Acetate Isobutyrate or metabolites were detected in fecal samples. The absorption of partially esterified sucrose molecules from the intestinal tract was insignificant. In a different study in human subjects who were administered a single, oral dosage of 1.0 to 1.2 mg/kg Sucrose Acetate Isobutyrate exhaled 41% to 66% of the oral dose of radioactivity in the breath within 30 days postadministration; 15% to 21% of the dose of radioactivity was eliminated in urine and 10% was excreted in feces.

The acute toxicity studies in rats evaluated dermal and oral exposure to Sucrose Acetate Isobutyrate for which LD_{50} > 20 g/kg and LD_{50} > 5 g/kg were reported, respectively. In 1 study, rats and mice were orally dosed with 25.6 g/kg of Sucrose Acetate Isobutyrate. No mortality was observed for the mice and 1 of the 7 rats died. Sucrose Acetate Isobutyrate (5 g/kg) and Sucrose Octaisobutyrate (5 g/kg) were orally administered to monkeys in a study which found that liver metabolism parameters were unaffected by the treatment. However, in dogs that were orally administered 2 g/kg Sucrose Acetate Isobutyrate, measured plasma concentrations of BSP were found to be elevated. In another test in monkeys, the LD_{50} was reported to be > 20 g/kg for oral administration of Sucrose Acetate Isobutyrate.

In short-term studies, Sucrose Acetate Isobutyrate was well-tolerated in orally exposed animals. In rats, an NOAEC was reported for doses up to 10% daily in the diet for 6 weeks; monkeys dosed up to 10 g/kg/d in the diet (15 days) showed no change in body weight, food consumption, or clinical parameters; mice dosed up to 5 g/kg/d in the diet (4 weeks) were unaffected by the treatment; in a 2-week study in dogs dosed up to 0.5% daily in the diet, BSP retention was reported at 0.3% and 0.5%. In rats dosed with Sucrose Polysoyate in the diet for 28 days, an NOEC of 15% was reported; softer feces, lower growth rates (dose-related), and a dose-dependent heart weight decrease were observed. Two studies in dogs reported an NOAEC and an NOEC of 15% daily in the diet for 28 days for Sucrose Polysoyate; results showed a higher food consumption in treated animals compared to controls, yet hematology, urine, and organs were unaffected by treatment.

In a 12-week subchronic study in rats orally administered Sucrose Acetate Isobutyrate, an NOAEC of 10% daily in the diet was reported; a decrease in mean heart weights in all treated males was observed. In 13-week studies in rats dosed with up to 9% Sucrose Acetate Isobutyrate daily in the diet, slight diarrhea was reported, but no toxic effects were observed. Dogs orally administered up to 5% of Sucrose Acetate Isobutyrate daily in the diet for 91 days showed a moderate elevation in SAP liver enzyme, heavier liver weights compared to controls, and a functional effect on the liver (reversible when Sucrose Acetate Isobutyrate was removed from the diet). In rats orally administered Sucrose Polysoyate for approximately 90 days, an NOEC of 15% daily in the diet was reported; softer feces and lower growth rates were noted, an increase in food consumption was seen with increasing doses, however no toxicity was observed.

Chronic toxicity studies testing Sucrose Acetate Isobutyrate orally administered to animals reported an NOAEL of 2 g/kg/d for 1 year in rats and an NOAEL of 2.4 g/kg/d for 1 year in monkeys. In the rat study, body weight gain decreases were observed in males and females (2 g/kg/d); 1 female death (0.5 g/kg/d) was noted, 1 female was killed in a moribund condition (2 g/kg/d), and 1 control and 2 treated rats died during blood collection. In 2-year studies conducted in animals, the NOAELs reported for rats and mice were 2 g/kg/d (highest dosage rate tested) and 2.5 g/kg/d, respectively. In mice, the NOAEL did not include the highest dosage rate tested (5 g/kg/d) because at that dosage rate a treatment-related decrease in mean absolute and relative kidney weights was observed at necropsy in males compared to controls. Another 2-year study conducted in rats (dosing up to 9.38% in diet) showed a dose-related increase in absolute and relative kidney weights, however the organ weight findings were deemed inconclusive because of discrepancies in male body weights compared to controls and low survival numbers. Within 10 weeks of the study, 4 males dosed with 9.38% died (massive hemorrhages in multiple organs were reported), but the deaths were not attributed to treatment (no further details specified).

Developmental and reproductive toxicity studies reported an NOAEL of 2 g/kg/d Sucrose Acetate Isobutyrate in rats (dosed daily in the diet for 10 weeks, males, and for 2 weeks, females, prior to mating) and an NOAEL of 1.2 g/kg/d Sucrose Acetate Isobutyrate in rabbits (dosed on days 7-19 of gestation by gavage). Sucrose Acetate Isobutyrate was not found to impair reproduction or produce toxic teratogenic/developmental effects in rats and rabbits. Rats fed 9.38% Sucrose Acetate Isobutyrate for 5 weeks (rats bred 3× in weeks 9-36) resulted in decreased pregnancies and decreased number of pups surviving to weaning, but this may have been attributed to compromised nutritional value of the diet at high Sucrose Acetate Isobutyrate concentrations.

Maltitol Laurate (40%) was negative in an Ames test performed using *S typhimurium*. An Ames test conducted in *S typhimurium* cells showed that Sucrose Acetate Isobutyrate was negative for genotoxicity as a mutagen, clastogen, and DNA-damaging agent at concentrations up to 10000 μg/plate (nontoxic; no increase in number of revertants). A mutation assay in CHO/HGPRT cells showed no increase in mutation frequency up to 1000 μg/mL Sucrose Acetate Isobutyrate. A chromosomal aberration assay in CHO cells showed no increase in aberrations up to 2000 μg/mL Sucrose Acetate Isobutyrate. An unscheduled DNA synthesis assay in rat hepatocytes was nontoxic for test substance Sucrose Acetate Isobutyrate at concentrations up to 10000 μg/mL. An in vivo animal study in rats tested for dominant lethal mutations showed negative results up to 2000 mg/kg Sucrose Acetate Isobutyrate (male rats were dosed once by gavage 2 hours prior to mating with untreated females; males were mated several times with untreated females during the 7 weeks postdosing).

Carcinogenicity bioassays, of 2-year duration, were conducted in rats (up to 2 g/kg/d Sucrose Acetate Isobutyrate) and mice (up to 5 g/kg/d Sucrose Acetate Isobutyrate); study results were negative for carcinogenicity. Another test in rats dosed up to 9.38% Sucrose Acetate Isobutyrate in the diet for 2 years indicated no treatment-related lesions.

Cytotoxicity tests evaluating Sucrose Laurate and Sucrose Myristate on human nasal epithelial cells showed cell death in a lactate dehydrogenase assay was $< 25\%$ for Sucrose Laurate (0.1 mg/mL) and was 50% to 75% for Sucrose Myristate (0.1 to 0.3 mg/mL); the 3 (4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay test indicated that cell viability was 100% for Sucrose Laurate (0.1 mg/mL) and 100% for Sucrose Myristate (0.03 mg/mL).

Dermal exposure studies in test animals indicated that Sucrose Laurate (unknown concentration) in a hydrogel was nonirritating, and 5% to 15% had some irritation potential but was well-tolerated. A 20% Sucrose Acetate Isobutyrate solution caused slight, transient irritation. In humans, Sucrose Palmitate and Sucrose Stearate (up to 2% in oil/water nanoemulsions) substantially decreased hydration in the stratum corneum during an occlusive irritation profile test, however no adverse skin reactions were visually observed, and the treatment was tolerable to the skin. In human patch tests evaluating irritation, Sucrose Pentahydroxystearate (100%) and Sucrose Tetraisostearate (100%) were negative (0% after 24 hours, no further details); Sucrose Polycottonseedate at 0.5% to 1% was slightly irritating. Moderate skin irritation observed in 4 of 30 humans subjects dermally exposed to cleansing cloths containing Sucrose Polycottonseedate (up to $\sim$17%) was thought to be caused by constituents in the formulation and not the saccharide ester.

A 1% solution (at induction) of Sucrose Acetate Isobutyrate was nonsensitizing in a Guinea Pig Maximization Test. In humans, Sucrose Acetate Isobutyrate (20% in an HRIPT) was found to be nonirritating and nonsensitizing; in an HRIPT, Sucrose Polybehenate ($\sim$3%) and Sucrose Polycottonseedate ($\sim$13%) were nonirritating and nonsensitizing; an HRIPT evaluating Sucrose Polycottonseedate (up to $\sim$17%) was deemed to be nonirritating and nonsensitizing; Sucrose Polycottonseedate (88% in a lipstick topcoat matrix) in an HRIPT was found to be nonsensitizing and the only reaction reported was skin staining in 1 subject.

A 10% Sucrose Laurate solution and a 50% Sucrose Acetate Isobutyrate solution were slightly irritating to rabbit eyes.

Discussion

The Panel considered relevant systemic toxicity, reproductive and developmental toxicity, genotoxicity, carcinogenicity, and irritation and sensitization data to assess the safety of the saccharide esters. They noted an absence of systemic toxicity at high dosages of Sucrose Acetate Isobutyrate in acute dermal ($LD_{50} > 20$ g/kg) and oral ($LD_{50} > 5$ g/kg) exposure studies in rats, in a 2-week oral study in humans (0.02 g/kg/d Sucrose Acetate Isobutyrate), and in chronic, oral administration animal studies (2-year duration, NOAELs of 2-2.5 g/kg/d). Sucrose Acetate Isobutyrate was nontoxic in developmental and reproductive tests, showed an absence of genotoxic potential in an Ames test and genetic mutation experiments, and was noncarcinogenic in chronic studies. Sucrose Laurate (10%) and Sucrose Acetate Isobutyrate (50%) were slightly irritating to rabbit eyes; however the doses applied were considerably higher than the concentrations at which those ingredients are reported to be used in cosmetics. The saccharide esters are metabolized to products that are common, physiologic intermediates and nutrients, thus supporting a safe toxicity profile. The data presented in this safety assessment affirm the lack of toxicity of saccharide esters for use in cosmetics.

The Panel noted gaps in the data available to address some end points for some of the saccharide esters in this safety assessment. However, structural similarity and similarities in reported functions and concentrations of use in cosmetics of the ingredient groups enable the read-across of the data available for some of the ingredients to the ingredients with data gaps to support the safety of the entire group. For instance, the Panel applied read-across to the single-chain length subgroup of these ingredients to assess the potential for dermal irritation and sensitization of these ingredients based on the data available for Sucrose Polybehenate to address these end points. For the mixed-chain length subgroup, read-across was applied using

multiple-end point safety data for Sucrose Acetate Isobutyrate and dermal irritation and sensitization safety data for Sucrose Polycottonseedate. The Panel noted that Sucrose Acetate Isobutyrate has a lower molecular weight, and therefore, a greater potential for oral and dermal absorption and thus would have a greater potential to exert biological effects than most of the ingredients for which it was used as a read-across analog.

As part of the safety determination, the Panel referred to the GRAS status of Sucrose Acetate Isobutyrate, for use as a direct food additive, and the use of several saccharide esters as direct and indirect food additives.

In animal and human studies evaluating several saccharide esters, dermal irritation was reported to be none, in most cases, and slight to mild in sporadic occurrences. In 1 animal study, up to 15% Sucrose Laurate yielded some evidence of irritation potential, but was noted to be generally well-tolerated. In humans, Sucrose Polycottonseedate was slightly irritating (up to 1%) in 1 study, but in 2 other studies ($\sim$13% and $\sim$16%-17%) it was not irritating; tested at 88% (lipstick topcoat, n = 108 subjects) in an HRIPT, Sucrose Polycottonseedate was nonsensitizing, and the only reaction reported was one instance of skin staining during induction. Moderate irritation responses were reported in 1 human study (up to 17% Sucrose Polycottonseedate). However, the researchers conducting the study suspected the irritation was related to constituent ingredients in the formulation and not to Sucrose Polycottonseedate. Therefore, the Panel considered the potential for saccharide esters to cause dermal irritation to be low and not of concern. The sensitization data reported in this safety assessment indicated that saccharide esters are nonsensitizing.

The Panel recognized that saccharide esters can enhance the penetration of other ingredients through the skin. The Panel cautioned that care should be taken when formulating cosmetic products that may contain these ingredients in combination with any ingredients for which safety was based on data supporting a lack of dermal absorption, or for which dermal absorption was a concern.

The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical ingredients. They emphasized that the cosmetics industry should continue to use current good manufacturing practices to limit impurities. Aflatoxins have been detected in Cottonseed Oil. The Panel believes that aflatoxins will not be present at levels of toxicological concern in Cottonseed Oil or Cottonseed Oil derivatives (eg, Cottonseed Acid), used in the esterification reaction with sucrose to produce Sucrose Polycottonseedate. The Panel recognized the US Department of Agriculture designation of $\leq$ 15 ppb as corresponding to "negative" aflatoxin content.

The Panel discussed the issue of incidental inhalation exposure from perfumes, hair sprays, deodorant sprays, and face powders. There were no inhalation toxicity data available. Sucrose Laurate is reportedly used at concentrations up to 1.2% in cosmetic products that may be aerosolized and Sucrose Tristearate is used up to 2% in face powder that may become airborne. The Panel noted that droplets/particles produced in cosmetic aerosols and loose-powder cosmetic products would not be respirable to any appreciable amount. In principle, inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. However, 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 effects. 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.

Conclusion

The Panel concluded that the following 40 ingredients are safe in cosmetics in the present practices of use and concentration described in this safety assessment:

Glucose Pentaacetate*	Sucrose Hexaoleate/Hexapalmitate/ Hexastearate
Maltitol Laurate	Sucrose Hexapalmitate*
Raffinose Isostearate*	Sucrose Laurate
Raffinose Myristate*	Sucrose Myristate
Raffinose Oleate*	Sucrose Octaacetate*
Sucrose Acetate Isobutyrate	Sucrose Oleate*
Sucrose Acetate/Stearate	Sucrose Palmitate
Sucrose Benzoate	Sucrose Palmitate/Stearate or Sucrose Stearate-Palmitate Ester
Sucrose Cocoate	Sucrose Pentaerucate*
Sucrose Dilaurate	Sucrose Pentahydroxystearate*
Sucrose Dipalmitate	Sucrose Polybehenate
Sucrose Distearate	Sucrose Polycottonseedate
Sucrose Hexaerucate*	Sucrose Polylaurate
Sucrose Polylinoleate*	Sucrose Tribehenate*
Sucrose Polyoleate	Sucrose Trilaurate
Sucrose Polysoyate	Sucrose Tristearate
Sucrose Polystearate	Trehalose Isostearate Esters
Sucrose Stearate	Trehalose Undecylenoate
Sucrose Tetrahydroxystearate*	Xylityl Sesquicaprylate*
Sucrose Tetraisostearate	
Sucrose Tetrastearate Triacetate	

*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 Director, Cosmetic Ingredient Review, 1620 L Street, NW, Suite 1200, Washington, DC 20036, USA.

Author Contribution

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

Declaration of Conflicting Interests

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Table 1. Saccharide Esters Subgroups Ordered by Chain Length.

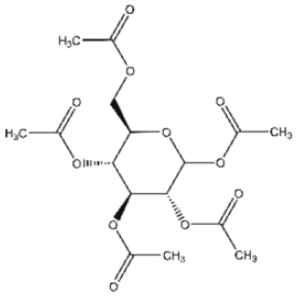
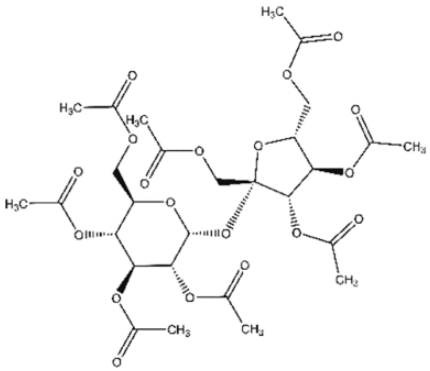
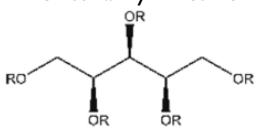
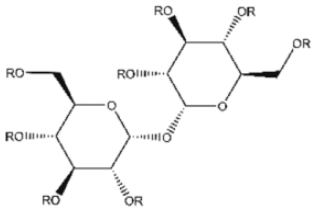
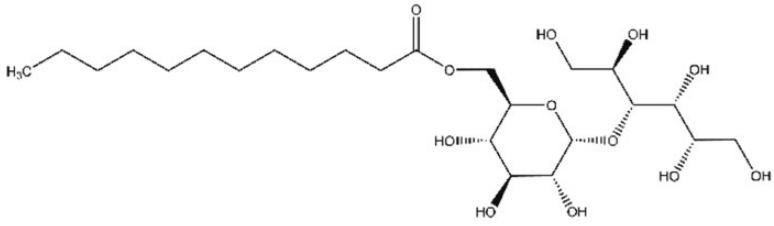
Alkyl Fatty Acid Esters-single chain length*	Alkyl Fatty Acid Esters-mixed chain length*	Non-Alkyl Esters
Glucose Pentaacetate (C2)	Sucrose Acetate Isobutyrate (C2, C4 branched)	Sucrose Benzoate
Sucrose Octaacetate (C2)	Sucrose Acetate/Stearate (C2, C18)	
Xylityl Sesquicaprylate (C8)	Sucrose Tetrastearate Triacetate (C18, C2)	
Trehalose Undecylenoate (C11:1)		
Maltitol Laurate (C12)	Sucrose Palmitate/Stearate or Sucrose Palmitate-Stearate Ester** (C16, C18)	
Sucrose Laurate (C12)	Sucrose Polysoyate (Soybean Oil fatty acid distribution: Oleic Acid, C18:1, 11.5%-60.0%; Linoleic Acid, C18:3, 2.9%-12.1%)[14]	
Sucrose Polylaurate (C12)	Sucrose Hexaoleate/Hexapalmitate/Hexastearate (C16, C18, C18:1)	
Sucrose Dilaurate 2(C12)	Sucrose Cocoate (Coconut Oil fatty acid distribution: Caproic Acid, C6, 0%-1%; Caprylic Acid, C8, 5%-9%; Capric Acid, C10, 6%-10%; Lauric Acid, C12, 44%-52%; Myristic Acid, C14, 13%-19%; Palmitic Acid, C16, 8%-11%; Palmitoleic Acid, C16:1, 0%-1%; Stearic Acid, C18, 1%-3%; Oleic Acid, C18:1, 5%-8%; Linoleic Acid, C18:2, trace-2.5%)[14]	
Sucrose Trilaurate 3(C12)	Sucrose Polycottonseedate (Cottonseed Oil fatty acid distribution: Myristic Acid, C14, 2%; Palmitic Acid, C16, 21%; Oleic Acid, C18:1, 30%; Linoleic Acid, C18:2, 45%; Stearic Acid, C18, trace; Arachidic Acid, C20, trace)[14]	
Sucrose Myristate (C14)		
Raffinose Myristate (C14)		
Sucrose Palmitate (C16)		
Sucrose Dipalmitate (C16)		
Raffinose Isostearate (C16 branched)		
Sucrose Hexapalmitate 6(C16)		
Sucrose Stearate (C18)		
Sucrose Polystearate (C18)		
Sucrose Oleate (C18:1)		
Sucrose Polyoleate (C18:1)		
Sucrose Polylinoleate (C18:2)		
Trehalose Isostearate Esters (C18 branched)		
Raffinose Oleate (C18)		
Sucrose Distearate 2(C18)		
Sucrose Tristearate 3(C18)		
Sucrose Tetraisostearate (C18 branched)		
Sucrose Tetrahydroxystearate 4(C18: OH)		
Sucrose Pentahydroxystearate 5(C18: OH)		
Sucrose Polybehenate (C22)		
Sucrose Tribehenate 3(C22)		
Sucrose Pentaerucate 5(C22:1)		
Sucrose Hexaerucate 6(C22:1)		

*Carbon chain length is indicated in parentheses; the number of double bonds or the double bonded hydroxyl group (in structures where these exist) within the chain is preceded by a colon.

**In the FDA VCRP data, both names are listed, but they refer to the same ingredient.

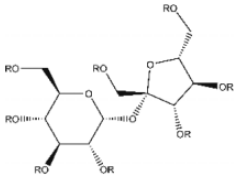
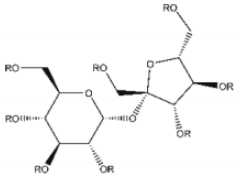
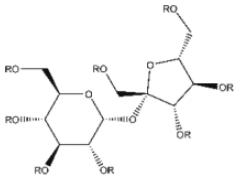
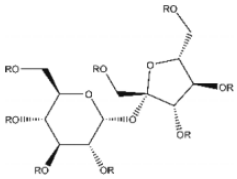
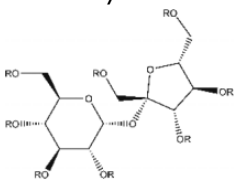
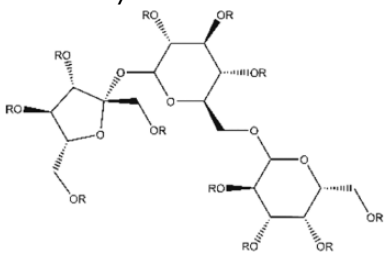
FDA = Food and Drug Administration; VCRP = Voluntary Cosmetic Registration Program.

Table 2. Definitions, Structures, and Functions of the Ingredients in This Safety Assessment.[2, CIR Staff]

Name and CAS No.	Definition and Structure	Function(s)
	Alkyl Fatty Acid Esters (single chain length)	
Glucose Pentaacetate 3891-59-6 604-68-2	Glucose Pentaacetate is the pentaester of glucose and acetic acid. 	Emulsion Stabilizers; Fragrance Ingredients
Sucrose Octaacetate 126-14-7	Sucrose Octaacetate is an acetylation product of sucrose. It conforms to the formula: 	Denaturants; Fragrance Ingredients
Xylityl Sesquicaprylate 181632-90-6	Xylityl Sesquicaprylate is a mixture of mono- and diesters of caprylic acid and the hexitol anhydrides derived from xylitol.  [wherein R is hydrogen or the residue of caprylic acid (C8), where 1 or 2 R groups are caprylic acid residues]	Antimicrobial Agents; Skin-Conditioning Agents-Humectant; Surfactants-Emulsifying Agents
Trehalose Undecylenoate	Trehalose Undecylenoate is the ester formed by the reaction of trehalose with undecylenic acid.  [wherein R is hydrogen or the residue of undecylenic acid (C11:1), where 1 R group is an undecylenic acid residue]	Emulsion Stabilizers; Skin-Conditioning Agents
Maltitol Laurate 75765-49-0	Maltitol Laurate is the ester of maltitol and lauric acid that conforms to the formula: 	Skin-Conditioning Agents-Emollient; Slip Modifiers

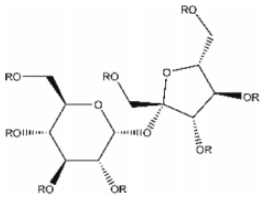
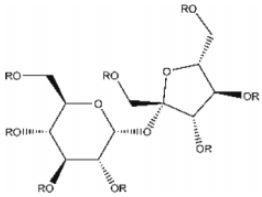
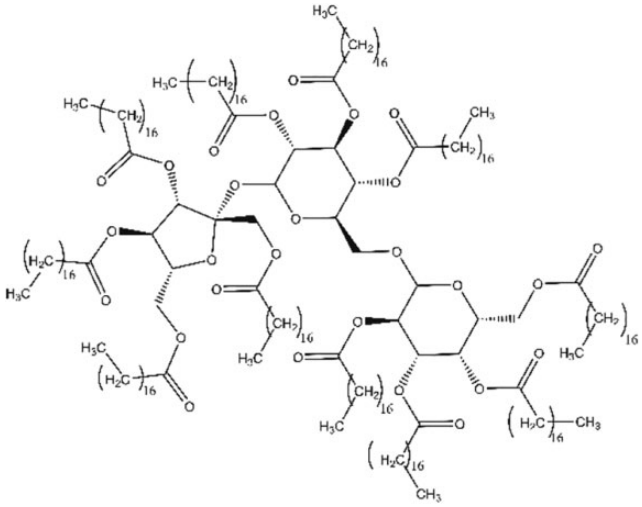
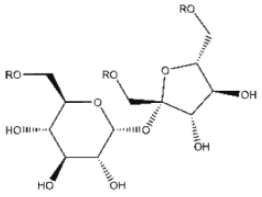
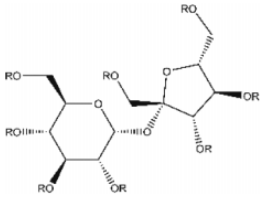
(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Sucrose Laurate 25339-99-5 37266-93-6	Sucrose Laurate is a mixture of sucrose esters of lauric acid consisting primarily of the monoester.  [wherein R is hydrogen or the residue of lauric acid (C12), where 1 R group is a lauric acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Polylaurate	Sucrose Polylaurate is a mixture of esters of lauric acid and sucrose.  [wherein R is hydrogen or the residue of lauric acid (C12)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Dilaurate 25915-57-5	Sucrose Dilaurate is the diester of lauric acid and sucrose.  [wherein R is hydrogen or the residue of lauric acid (C12), where 2 R groups are lauric acid residues]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Trilaurate 94031-23-9	Sucrose Trilaurate is the triester of lauric acid and sucrose.  [wherein R is hydrogen or the residue of Lauric Acid (C12), where 3 R groups are lauric acid residues]	Surfactants-Emulsifying Agents; Surfactants-Solubilizing Agents
Sucrose Myristate 27216-47-3 9042-71-1	Sucrose Myristate is the monoester of myristic acid and sucrose.  [wherein R is hydrogen or the residue of myristic acid (C14), where 1 R group is a myristic acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Raffinose Myristate 91433-10-2	Raffinose Myristate is the ester of raffinose and myristic acid.  [wherein R is hydrogen or the residue of myristic acid (C14), where at least 1 R is the residue of myristic acid]	Skin-Conditioning Agents; Emollient; Surfactants-Emulsifying Agents

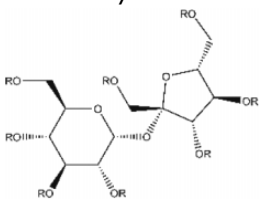
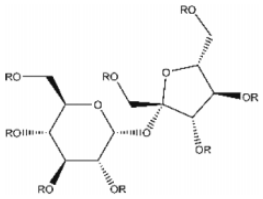
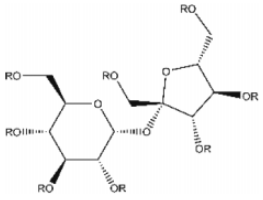
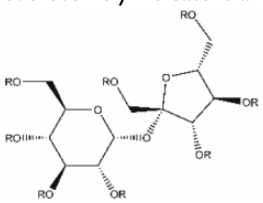
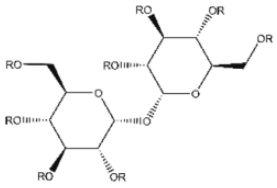
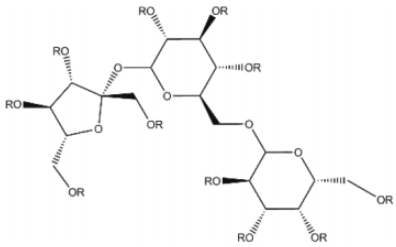
(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Sucrose Palmitate 26446-38-8 39300-95-3	Sucrose Palmitate is the monoester of palmitic acid and sucrose.  [wherein R is hydrogen or the residue of palmitic acid (C16), where 1 R group is a palmitic acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
[Sucrose Dipalmitate] ***Reported to the FDA's VCRP, but not recited in the INCI Dictionary 25637-97-2	[Sucrose Dipalmitate is the diester of palmitic acid and sucrose.  wherein R is hydrogen or the residue of palmitic (C16) acid, where 2 R groups are palmitic acid residues]	N/A
Raffinose Isostearate 1032182-34-5	Raffinose Isostearate is the ester of raffinose and isostearic acid. 	Skin-Conditioning Agents-Emollient; Slip Modifiers
Sucrose Hexapalmitate 29130-29-8	Sucrose Hexapalmitate is the hexaester of sucrose and palmitic acid.  [wherein R is hydrogen or palmitoyl, in which 6 instances of R are palmitoyl]	Surfactants-Dispersing Agents; Surfactants-Emulsifying Agents
Sucrose Stearate 25168-73-4 37318-31-3	Sucrose Stearate is the monoester of stearic acid and sucrose.  [wherein R is hydrogen or the residue of stearic acid (C18), where 1 R group is a stearic acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents

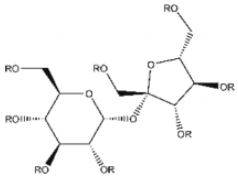
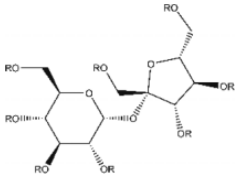
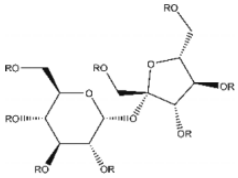
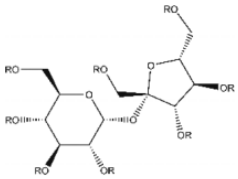
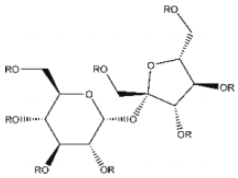
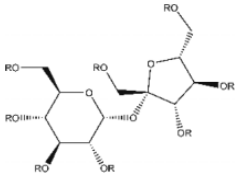
(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Sucrose Polystearate	Sucrose Polystearate is a mixture of esters of stearic acid and sucrose.  [wherein R is hydrogen or the residue of stearic acid (C18)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Oleate 52683-61-1	Sucrose Oleate is the monoester of oleic acid and sucrose.  [wherein R is hydrogen or the residue of oleic acid (C18:1), where 1 R group is a oleic acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Polyoleate	Sucrose Polyoleate is a mixture of esters of oleic acid and sucrose.  [wherein R is hydrogen or the residue of oleic acid (C18:1)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Polylinoleate	Sucrose Polylinoleate is a mixture of esters of linoleic acid and sucrose.  [wherein R is hydrogen or the residue of linoleic acid (C18:2)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Trehalose Isostearate Esters 861436-89-7 (generic)	Trehalose Isostearate Esters is the product obtained by the esterification of isostearic acid and trehalose.  [wherein R is hydrogen or the residue of isostearic acid (C18: branched)]	Skin-Conditioning Agents-Emollient
Raffinose Oleate 96352-58-8	Raffinose Oleate is the ester of raffinose and oleic acid.  [wherein R is oleate in one instance, and hydrogen in all other instances]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents

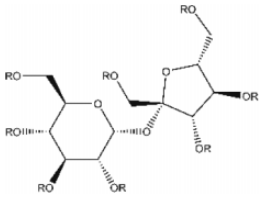
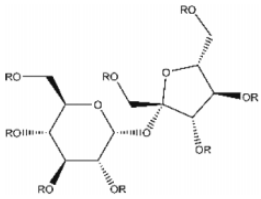
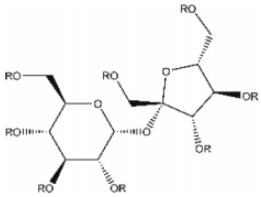
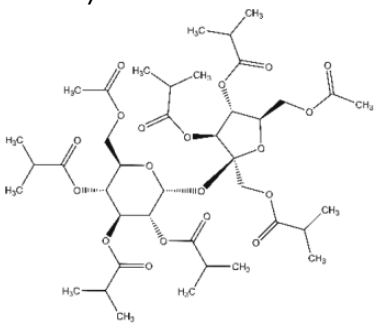
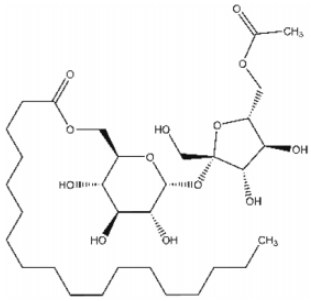
(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Sucrose Distearate 27195-16-0	Sucrose Distearate is a mixture of sucrose esters of stearic acid consisting primarily of the diester.  [wherein R is hydrogen or the residue of stearic acid, where 2 R groups are stearic acid residues]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Tristearate 27923-63-3	Sucrose Tristearate is the triester of stearic acid and sucrose.  [wherein R is hydrogen or the residue of stearic acid (C18), where 3 R groups are stearic acid residues]	Skin-Conditioning Agents-Emollient
Sucrose Tetraisostearate 88484-21-3	Sucrose Tetraisostearate is a mixture of esters of isostearic acid and sucrose, consisting primarily of the tetraester.  [wherein R is hydrogen or the residue of isostearic acid (C18: branched), where four R groups are isostearic acid residues]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Tetrahydroxystearate	Sucrose Tetrahydroxystearate is the tetraester of sucrose and hydroxystearic acid.  [wherein R is hydrogen or the residue of hydroxystearic acid (C18: OH), where four R groups are hydroxystearic acid residues]	Skin-Conditioning Agents-Emollient
Sucrose Pentahydroxystearate	Sucrose Pentahydroxystearate is the pentaester of sucrose and hydroxystearic acid.  [wherein R is hydrogen or the residue of hydroxystearic acid (C18: OH), where 5 R groups are hydroxystearic acid residues]	Skin-Conditioning Agents-Humectant
Sucrose Polybehenate 93571-82-5	Sucrose Polybehenate is a mixture of esters of behenic acid and sucrose.  [wherein R is hydrogen or the residue of behenic acid (C22)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents

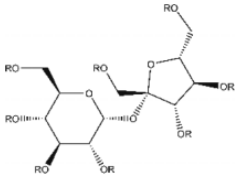
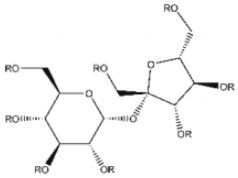
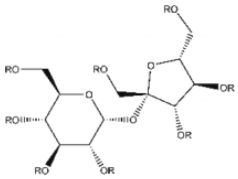
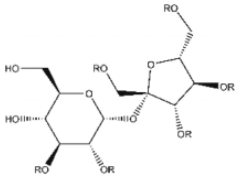
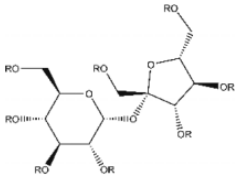
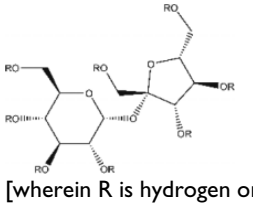
(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Sucrose Tribehenate 84798-44-7	Sucrose Tribehenate is the triester of behenic acid and sucrose.  [wherein R is hydrogen or the residue of behenic acid (C22), where 3 R groups are behenic acid residues]	Skin-Conditioning Agents-Emollient
Sucrose Pentaerucate	Sucrose Pentaerucate is the pentaester of sucrose and erucic acid.  [wherein R is hydrogen or the residue of erucic acid (C22:1), where 5 R groups are erucic acid residues]	Skin-Conditioning Agents-Emollient; Surfactants
Sucrose Hexaerucate	Sucrose Hexaerucate is the hexaester of sucrose and erucic acid.  [wherein R is hydrogen or the residue of erucic acid (C22:1), where 6 R groups are erucic acid residues]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Alkyl Fatty Acid Esters (mixed chain lengths)		
Sucrose Acetate Isobutyrate 126-13-6	Sucrose Acetate Isobutyrate is the mixed ester of sucrose and acetic and isobutyric acids.  [substitution pattern as described in the CAS file]	Plasticizers
Sucrose Acetate/Stearate 52439-69-7	Sucrose Acetate/Stearate is the mixed ester of sucrose with acetic and stearic acids.  [**1 example of a mixed ester]	Skin-Conditioning Agents-Emollient

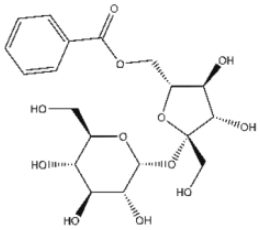
(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Sucrose Tetrastearate Triacetate	Sucrose Tetrastearate Triacetate is a mixture of esters of stearic acid, acetic acid, and sucrose.  [wherein R is hydrogen or the residue of stearic (C18) or acetic (C2) acid, where 4 R groups are stearic acid residues and 3 R groups are acetic acid residues]	Skin-Conditioning Agents-Emollient
[Sucrose Palmitate/Stearate or Sucrose Palmitate-Stearate Ester] ***Both of the above names are reported to the FDA VCRP, but are not recited in the INCI Dictionary; the 2 names refer to the same ingredient	[Sucrose Palmitate/Stearate is the monoester of sucrose and palmitic acid or stearic acid.  wherein R is hydrogen or the residue of palmitic (C16) or stearic (C18) acid, where 1 R group is an acid residue]	N/A
Sucrose Polysoyate 93571-82-5	Sucrose Polysoyate is a mixture of esters of soy acid and sucrose.  [wherein R is hydrogen or the residue of a fatty acid derived from soy]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Hexaoleate/ Hexapalmitate/Hexastearate	Sucrose Hexaoleate/Hexapalmitate/Hexastearate is the hexaester of sucrose and oleic, palmitic, and stearic acids.  [wherein R is residue of oleic (C18:1), palmitic (C16), or stearic (C18) acid]	Surfactants-Dispersing Agents; Surfactants-Emulsifying Agents
Sucrose Cocoate 91031-88-8	Sucrose Cocoate is a mixture of sucrose esters of coconut acid, consisting primarily of the monoesters.  [wherein R is hydrogen or the residue of a fatty acid derived from coconut acid, where at least 1, and in most instances only 1, R is a fatty acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Polycottonseedate 93571-82-5	Sucrose Polycottonseedate is a mixture of esters of cottonseed acid and sucrose.  [wherein R is hydrogen or the residue of a fatty acid derived from cotton seed]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents

(continued)

Table 2. (continued)

Name and CAS No.	Definition and Structure	Function(s)
Non-Alkyl Esters		
Sucrose Benzoate 12738-64-6	Sucrose Benzoate is the disaccharide ester [of benzoic acid and sucrose] that conforms generally to the formula:  [one example substitution pattern]	Plasticizers

*Carbon chain length is indicated in parentheses; the number of double bonds or the double bonded hydroxyl group (in structures where these exist) within the chain is preceded by a colon.
**In the FDA VCRP data, both names are listed, but they refer to the same ingredient.
FDA = Food and Drug Administration; INCI = *International Nomenclature Cosmetic Ingredient*; VCRP = Voluntary Cosmetic Registration Program.

Table 3. Constituent Sugars, Alcohols, and Acids With Panel Conclusions.

Constituents	Conclusion (year issued; maximum use concentration reported)	Reference
SUGAR or SUGAR ALCOHOL		
Glucose	Safe as used (2014; 91% in leave-ons; 97.8% in rinse-offs)	15
Maltitol (sugar alcohol derived from the sugar Maltose)	Maltitol: Safe as used (2008; 8% in leave-ons; 15% in rinse-offs) Maltose: Safe as used (2014; 0.5% in leave-ons; 0.5% in rinse-offs)	1,15
Sucrose	Safe as used (2014; 58% in leave-ons; 65% in rinse-offs)	15
Trehalose	Safe as used (2014; 2% in leave-ons; 1% in rinse-offs)	15
Xylose (Xylityl* is derived from the sugar alcohol xylitol*, which is derived from the sugar Xylose)	Safe as used (2014; 0.11% in leave-ons; 1% in rinse-offs)	15
ACID		
Acetic Acid	Safe as used (2012; 0.0004% in leave-ons; 0.3% in rinse-offs)	13
Benzoic Acid	Safe as used (2011; 5% in leave-ons; 5% in rinse-offs)	11,12
Coconut Acid	Safe as used (2011; not reported in leave-ons; 14% in rinse-offs)	10,14,63
Cottonseed Acid	Safe as used (2011; no reported use)	14,25
Hydroxystearic Acid	Safe as used (1999; 10% in leave-ons; not reported in rinse-offs)	9
Isostearic Acid	Safe as used (1983; 10% leave-ons; 5% rinse-offs); Reaffirmed in 2005	7,8
Lauric Acid	Safe as used (1987; 1% in leave-ons; 25% in rinse-offs); Reaffirmed 2006	5,6
Myristic Acid	Safe as used (2010; 10% in leave-ons; 19% in rinse-offs)	4-6
Oleic Acid	Safe as used (1987; 25% in leave-ons; 50% in rinse-offs); Reaffirmed in 2006	5,6
Palmitic Acid	Safe as used (1987; 25% in leave-ons; 25% in rinse-offs); Reaffirmed in 2006	5,6
Soy Acid	Safe as used (2011; no reported use)	14
Stearic Acid	Safe as used (1987; 50% in leave-ons; 50% in rinse-offs); Reaffirmed in 2006	5,6

*Not previously reviewed by the Panel.

Table 4. Chemical and Physical Properties.

Property	Value	Reference
Glucose Pentaacetate		
Molecular Weight (g/mol)	390.33	64
Density (g/mL)	1.30 ± 0.1[a]	65
Melting Point (°C)	130-131.5[b]	66
Water Solubility at pH 7, 25 °C	Slightly soluble	65
Log P	0.634 ± 0.488[a]	65
Maltitol Laurate		
Molecular Weight (g/mol)	527[a]	67
Raffinose Isostearate		
Molecular Weight (g/mol)	3435[a]	67
Raffinose Myristate		
Molecular Weight (g/mol)	687[a]	67
Raffinose Oleate		
Molecular Weight (g/mol)	785.89	64
Sucrose Acetate Isobutyrate		
Physical Form	Clear, pale yellow, viscous liquid	23
Molecular Weight (g/mol)	846.91	64
Density (g/mL)	1.22 ± 0.1[a]	65
Water Solubility	Slightly soluble	23
Other Solubility	Very soluble in essential oils (orange); soluble in ethanol, ethyl acetate	23
Log P	6.619 ± 0.825[a]	65
Sucrose Acetate/Stearate		
Molecular Weight (g/mol)	651[a]	67
Sucrose Benzoate		
Molecular Weight (g/mol)	446[a]	67
Melting Point (°C)	98 (from patent)	68
Sucrose Dilaurate		
Molecular Weight (g/mol)	706.90	64
Sucrose Dipalmitate		
Molecular Weight (g/mol)	819[a]	67
Sucrose Distearate		
Molecular Weight (g/mol)	875.22	64
Melting Point (°C)	76-78[b]	69
Sucrose Hexaerucate		
Molecular Weight (g/mol)	2265[a]	67
Sucrose Hexapalmitate		
Molecular Weight (g/mol)	1772.75	64
Sucrose Laurate		
Molecular Weight (g/mol)	524.60	64
Water Solubility (mg/L)	42.37[a]	24
Sucrose Myristate		
Molecular Weight (g/mol)	569.66	64
Melting Point (°C)	180-186[b]	70
Sucrose Octaacetate		
Molecular Weight (g/mol)	678.59	64
Density (g/mL)	1.37 ± 0.1[a]	65
Melting Point (°C)	89-93[b]	71
Water Solubility (g/L)	0.909 (hygroscopic)	72
Other Solubility	Very soluble in methanol, chloroform; soluble in ether	72
Log P	1.440 ± 0.812[a]	65
Sucrose Oleate		
Molecular Weight (g/mol)	607[a]	67
Melting Point (°C)	54-56[b]	69
Sucrose Palmitate		
Molecular Weight (g/mol)	552[a]	67
Sucrose Pentaerucate		
Molecular Weight (g/mol)	1945[a]	67
Sucrose Pentahydroxystearate		
Molecular Weight (g/mol)	2039[a]	67

(continued)

Table 4. (continued)

Property	Value	Reference
Sucrose Polybehenate		
Physical Form at 20 °C, 760 mm Hg	White waxy solid	19
Density (g/mL) at 72 °C	900-950	19
Melting Point (°C)	72	19
Water Solubility at 24 °C (g/L)	$\leq 4.26 \times 10^{-5}$	19
Log Pow (n-octanol/water) at 20 °C	3.55 ± 0.16	19
Sucrose Polycottonseedate		
Physical Form	Amber, viscous liquid	20
Density at 71 °C (g/L)	900-950	20
Water Solubility at 24 °C (g/L)	4.96×10^{-6} to 4.26×10^{-5}	20
Log Pow (n-octanol/water) at 20 °C	3.55 ± 0.16	20
Sucrose Stearate		
Molecular Weight (g/mol)	608.76	64
Melting Point (°C)	67-71[b]	73
Sucrose Tetrahydroxystearate		
Molecular Weight (g/mol)	1472[a]	67
Sucrose Tetraisostearate		
Molecular Weight (g/mol)	1408[a]	67
Sucrose Tetrastearate Triacetate		
Molecular Weight (g/mol)	1534[a]	67
Sucrose Tribehenate		
Molecular Weight (g/mol)	1310[a]	67
Sucrose Trilaurate		
Molecular Weight (g/mol)	889.20	64
Water Solubility (mg/L)	1.35×10^{-12}[a]	24
Sucrose Tristearate		
Molecular Weight (g/mol)	1141.68	64
Trehalose Undecylenoate		
Molecular Weight (g/mol)	509[a]	67
Xylityl Sesquicaprylate		
Molecular Weight (g/mol)	278.34[c]	65
Density (g/mL)	1.17 ± 0.06[c]	65
Water Solubility at pH 7, 25 °C	Slightly soluble[c]	65
Log P	1.387 ± 0.735[c]	65

[a]Computational.
[b]Measured.
[c]Computational, calculated from a monocaprylate-substituted Xylityl moiety.

Table 5. Current Frequency and Concentration of Use of Saccharide Esters According to Duration and Exposure.[3,26]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Maltitol Laurate		Sucrose Acetate Isobutyrate		Sucrose Acetate Stearate	
Totals*	1	NR	274	0.0084-31	2	0.3
Duration of Use						
Leave-On	*NR*	*NR*	*273*	*0.0084-31*	*2*	*0.3*
Rinse-Off	*1*	*NR*	*1*	*0.1*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	22	0.5-31	2	NR
Incidental Ingestion	NR	NR	18	0.41-27	NR	NR
Incidental Inhalation-Spray	NR	NR	Spray: 2 Possible: 1[b]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	Powder: 1 Possible: 1[b]	NR	NR	Possible: 0.3[c]
Dermal Contact	NR	NR	41	0.5-31	2	0.3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	1	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	210	0.0084-9	NR	NR
Mucous Membrane	NR	NR	18	0.41-27	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Sucrose Benzoate		Sucrose Cocoate		Sucrose Dilaurate	
Totals*	48	0.21-14.3	139	0.0001-20.6	13	0.00000004-0.45
Duration of Use						
Leave-On	*48*	*1.4-14.3*	*91*	*0.0001-4*	*10*	*0.00000004-0.45*
Rinse-Off	*NR*	*0.21*	*48*	*0.05-20.6*	*3*	*0.18*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	8	NR	2	0.00000004
Incidental Ingestion	NR	NR	14	0.0001-0.98	NR	0.013
Incidental Inhalation-Spray	NR	NR	Possible: 30[a]; 12[b]	Possible: 0.12[a]	Possible: 6[b]	NR
Incidental Inhalation-Powder	NR	NR	Powder: 1 Possible: 12[b]	Possible: 0.05-4[c]	Possible: 6[b]	Possible: 0.17-0.45[c]
Dermal Contact	NR	0.21	121	0.05-20.6	13	0.00000004-0.45
Deodorant (underarm)	NR	NR	11[a]	Not spray: 0.49	NR	NR
Hair—Non-Coloring	NR	NR	4	0.05-0.12	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	48	1.4-14.3	NR	NR	NR	NR
Mucous Membrane	NR	NR	29	0.0001-1.3	NR	0.013
Baby Products	NR	NR	1	NR	NR	NR
	Sucrose Dipalmitate		Sucrose Distearate		Sucrose Hexaoleate/Hexapalmitate/ Hexastearate	
Totals*	1	NR	67	0.0003-5.5	NR	5
Duration of Use						
Leave-On	*NR*	*NR*	*63*	*0.0003-5.5*	*NR*	*5*
Rinse-Off	*1*	*NR*	*4*	*1.1*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*0.011*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	20	1-5.5	NR	NR
Incidental Ingestion	NR	NR	1	0.57-1.8	NR	NR
Incidental Inhalation-Spray	NR	NR	Possible: 11[a]; 25[b]	Possible: 1.2[a]	NR	NR

(continued)

Table 5. (continued)

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
Incidental Inhalation-Powder	NR	NR	Possible: 25[b]	Powder: 0.015 Possible: 0.5-2[c]	NR	NR
Dermal Contact	1	NR	51	0.0003-2	NR	5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	NR	1	1.2	NR	NR
Hair-Coloring	NR	NR	NR	1.1	NR	NR
Nail	NR	NR	2	NR	NR	NR
Mucous Membrane	NR	NR	2	0.011-1.8	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR
	Sucrose Laurate		Sucrose Myristate		Sucrose Palmitate	
Totals*	42	0.0003-3	3	0.1-6	74	0.000012-3
Duration of Use						
Leave-On	*28*	*0.0003-3*	*NR*	*6*	*60*	*0.000012-3*
Rinse-Off	*12*	*0.05-3*	*3*	*0.1-0.3*	*14*	*0.00004-3*
Diluted for (Bath) Use	*2*	*NR*	*NR*	*NR*	*NR*	*0.008*
Exposure Type						
Eye Area	4	0.0003-3	1	NR	7	0.000012-3
Incidental Ingestion	1	0.05-0.1	NR	0.1	NR	0.02
Incidental Inhalation-Spray	Spray: 1; Possible: 3[a]; 12[b]	Spray: 0.6-1.2 Possible: 0.05[a]	NR	Possible: 0.1[a]	Spray: 1; Possible: 11[a]; 32[b]	Possible: 0.0004[a]
Incidental Inhalation-Powder	Powder: 1; Possible: 12[b]	Possible: 0.05-3[c]	NR	NR	Powder: 1 Possible: 32[b]	Powder: 0.008 Possible: 0.0008-1.5[c]
Dermal Contact	40	0.0003-3	3	6	70	0.000012-3
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	1	0.05-1.5	NR	0.3	4	0.00004-0.05
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	0.00002
Mucous Membrane	6	0.05-1	NR	0.1	NR	0.008-0.02
Baby Products	3	NR	NR	NR	3	NR
	Sucrose Palmitate/Stearate**		Sucrose Polybehenate		Sucrose Polycottonseedate	
Totals*	1	NR	2	1-6	23	0.5-87.7
Duration of Use						
Leave-On	*1*	*NR*	*2*	*1-6*	*22*	*0.5-87.7*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*1*	*2.8*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	1	4	3	1-1.5
Incidental Ingestion	NR	NR	NR	6	4	87.7
Incidental Inhalation-Spray	Possible: 1[b]	NR	NR	Spray: 1	Possible: 8[a]; 6[b]	NR
Incidental Inhalation-Powder	Possible: 1[b]	NR	NR	NR	Possible: 6[b]	Possible: 1[c]
Dermal Contact	1	NR	1	1	19	0.5-2.8
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	NR	6	4	87.7
Baby Products	NR	NR	NR	NR	NR	NR

(continued)

Table 5. (continued)

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	Sucrose Polylaurate		Sucrose Polyoleate		Sucrose Polysoyate	
Totals*	1	0.01-0.039	1	NR	19	0.51-4.9
Duration of Use						
Leave-On	*1*	*0.01-0.039*	*NR*	*NR*	*19*	*0.51-4.9*
Rinse-Off	*NR*	*NR*	*1*	*NR*	*NR*	*NR*
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	4.9
Incidental Inhalation-Spray	Possible: 1[a]	NR	NR	NR	17[a]; 2[b]	NR
Incidental Inhalation-Powder	NR	Possible: 0.01-0.039[c]	NR	NR	2[b]	NR
Dermal Contact	1	0.01-0.039	NR	NR	19	0.51-1
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	NR	1	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	4.9
Baby Products	NR	NR	NR	NR	NR	NR
	Sucrose Polystearate		Sucrose Stearate		Sucrose Stearate-Palmitate Ester**	
Totals*	16	0.7-6	156	0.0001-6	2	NR
Duration of Use						
Leave-On	*16*	*1-6*	*126*	*0.0001-6*	*2*	*NR*
Rinse-Off	*NR*	*0.7*	*30*	*0.04-3*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*0.069*	*NR*	*NR*
Exposure Type						
Eye Area	1	1-6	32	0.0003-6	NR	NR
Incidental Ingestion	3	1-2.5	1	0.079-0.2	NR	NR
Incidental Inhalation-Spray	Possible: 3[a]; 1[b]	NR	Spray: 1 Possible: 29[a]; 49[b]	Possible: 0.2-2.2[a]	NR	NR
Incidental Inhalation-Powder	Powder: 3 Possible: 1[b]	Possible: 1.7[c]	Powder: 1 Possible: 49[b]	Possible: 0.013-3.9[c]	Powder: 2	NR
Dermal Contact	12	1-1.7	137	0.0003-6	2	NR
Deodorant (underarm)	NR	NR	NR	spray: 0.23 not spray: 0.45	NR	NR
Hair—Non-Coloring	NR	NR	3	0.3-2.2	NR	NR
Hair-Coloring	NR	0.7	NR	NR	NR	NR
Nail	NR	NR	3	0.0001	NR	NR
Mucous Membrane	3	1-2.5	3	0.069-0.2	NR	NR
Baby Products	NR	NR	4	NR	2	NR
	Sucrose Tetraisostearate		Sucrose Tetrastearate Triacetate		Sucrose Trilaurate	
Totals*	3	0.01-5	61	0.0086-15	2	0.004
Duration of Use						
Leave-On	*3*	0.01-5	*61*	0.0086-15	*2*	*0.004*
Rinse-Off	*NR*	NR	*NR*	10	*NR*	*NR*
Diluted for (Bath) Use	*NR*	NR	*NR*	NR	*NR*	*NR*
Exposure Type						
Eye Area	3	0.01-5	38	0.55-15	2	NR
Incidental Ingestion	NR	1	7	0.0086-10	NR	0.004
Incidental Inhalation-Spray	NR	NR	Possible: 2[a]	NR	NR	NR

(continued)

Table 5. (continued)

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
Incidental Inhalation-Powder	NR	NR	NR	Possible: 1-2[c]	NR	NR
Dermal Contact	NR	0.01-5	49	0.5-10	2	NR
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	1	7	0.0086-10	NR	0.004
Baby Products	NR	NR	NR	NR	NR	NR
	Sucrose Tristearate		Trehalose Isostearate Esters		Trehalose Undecylenoate	
Totals*	19	0.38-2	NR	0.5	NR	0.0005-0.25
Duration of Use						
Leave-On	*17*	*0.38-2*	*NR*	*0.5*	*NR*	*0.05*
Rinse-Off	*2*	*NR*	*NR*	*NR*	*NR*	*0.0005-0.25*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	NR	NR	NR	NR	NR
Incidental Ingestion	1	0.38-0.75	NR	NR	NR	NR
Incidental Inhalation-Spray	Possible: 9[a]; 6[b]	NR	NR	NR	NR	Possible: 0.05[a]
Incidental Inhalation-Powder	Possible: 6[b]	Powder: 2 Possible: 2[c]	NR	NR	NR	NR
Dermal Contact	18	0.5-2	NR	0.5	NR	0.0005
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair—Non-Coloring	NR	NR	NR	NR	NR	0.05-0.25
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	1	0.38-0.75	NR	NR	NR	0.0005
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 may not equal the sum of total uses.
**Although structurally Sucrose Stearate-Palmitate Ester and Sucrose Palmitate/Stearate have the same definition, they are listed separately here because VCRP data for each is individually recited.
[a]Includes products that can be sprays, but it is not known whether the reported uses are sprays.
[b]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.
[c]Includes products that can be powders, but it is not known whether the reported uses are powders.
NR = no reported use.

Table 6. Ingredients not Currently Reported to be in Use.[3,26]

Glucose Pentaacetate	Sucrose Hexapalmitate	Sucrose Polylinoleate
Raffinose Isostearate	Sucrose Octaacetate	Sucrose Tetrahydroxystearate
Raffinose Myristate	Sucrose Oleate	Sucrose Tribehenate
Raffinose Oleate	Sucrose Pentaerucate	Xylityl Sesquicaprylate
Sucrose Hexaerucate	Sucrose Pentahydroxystearate	

Table 7. Non-Cosmetic Uses.

Ingredient	Non-Cosmetic Use	References
Glucose Pentaacetate	Direct food additive, synthetic flavoring substance	21CFR172.515; [74]
Sucrose Acetate Isobutyrate	Direct food additive, stabilizer of flavoring oil emulsions used in nonalcoholic beverages, Sucrose Acetate Isobutyrate content in beverage $\leq$ 300 mg/kg of finished beverage; indirect food additive-component of adhesives; GRAS as a stabilizer of flavoring oil emulsions used in alcoholic beverages; FDA established ADI (acceptable daily intake) up to 20 mg/kg/d; WHO established ADI up to 20 mg/kg/d	21CFR172.833; 21CFR175.105; [17; 75; 76]
Sucrose Benzoate	Indirect food additive component of adhesives; FDA reported cumulative estimated daily intake of 0.00035 mg/kg/d	21CFR175.105; [77]
Sucrose Cocoate, Sucrose Dilaurate, Sucrose Distearate	Direct food additive-multipurpose additives, sucrose fatty acid esters	21CFR172.859
Sucrose Hexaerucate, Sucrose Hexaoleate/ Hexapalmitate/Hexastearate, Sucrose Hexapalmitate	Direct food additive-multipurpose additives, Sucrose Oligoesters	21CFR172.869
Sucrose Laurate, Sucrose Myristate	Direct food additive-multipurpose additives, sucrose fatty acid esters	21CFR172.859
Sucrose Octaacetate	Direct food additive; synthetic flavoring substance; indirect food additive component of adhesives; drug product containing active ingredients offered OTC as nail-biting/thumb-sucking deterrent, however, due to the lack of safety data in this application, Sucrose Octaacetate is *not* GRAS in OTC drug products used as nail-biting/thumb-sucking deterrents	[74]; 21CFR172.515; 21CFR175.105; 21CFR310.536
Sucrose Oleate, Sucrose Palmitate	Direct food additive-multipurpose additives, sucrose fatty acid esters	21CFR172.859
Sucrose Pentaerucate	Direct food additive-multipurpose additives, Sucrose Oligoesters	21CFR172.869
Sucrose Stearate	Direct food additive-multipurpose additives, sucrose fatty acid esters	21CFR172.859
Sucrose Tetrahydroxystearate, Sucrose Tetraisostearate	Direct food additive-multipurpose additives, Sucrose Oligoesters	21CFR172.869
Sucrose Tribehenate, Sucrose Trilaurate, Sucrose Tristearate	Direct food additive-multipurpose additives, sucrose fatty acid esters	21CFR172.859

FDA = Food and Drug Administration; OTC = over the counter; WHO = World Health Organization.

Table 8. Penetration Enhancement Studies.

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Exposure Route	Procedure	Results	Reference
				IN VITRO			
Sucrose Laurate (mono-81%; di-, tri-, poly-19%)	Mouse	Full-thickness dorsal skin excised from female mice	Aqueous, 1.5% Sucrose Laurate at pH 6, 7, 8, 10	Stratum corneum (1 cm^2) mounted on flow-through teflon diffusion cell	At time 0, 0.5 mL of lidocaine solution (varying pH's) containing either 0 or 1.5% Sucrose Laurate was applied to skin, receptor fluid collected hourly for 6 h, negative controls used	For lidocaine with 1.5% Sucrose Laurate, permeability coefficient increased up to pH 8; permeability coefficients at pH 6 and 7 with Sucrose Laurate were larger than controls; at low lidocaine concentrations, Sucrose Laurate increased permeation rate at pH 6; for saturated lidocaine solutions at low pH, Sucrose Laurate was a potent percutaneous absorption enhancer but at high pH, Sucrose Laurate had almost no effect on permeation; permeation rate at pH 8 or 10 decreased due to interaction of unionized lidocaine with Sucrose Laurate micelles not participating in permeation	37
Sucrose Laurate	Yucatan Micropig	Skin	Oil-in-water microemulsion containing Sucrose Laurate used for drug delivery; composition ratio 25:19:5:60, Sucrose Laurate: ethanol: isopropyl myristate: water	Skin (0.83 cm^2 diffusion area) mounted in Franz-type diffusion (37 °C water jacket), 2-h pretreatment with 150 mM NaCl	Skin was exposed to microemulsion containing polyphenols (chlorogenic acid/resveratrol), buffered for 6, 20, and 40 h then assayed; for comparison, a microemulsion containing polyoxyethylene sorbitan monooleate (Tween 80) as the surfactant and no Sucrose Laurate was also evaluated	Sucrose Laurate (surfactant component in the microemulsion) enhanced skin incorporation of polyphenols at 6, 20, 40 h in epidermis and at 20 and 40 h in dermis; hydrophilic polyphenol distributed slightly more in epidermis, and hydrophobic (small molecular weight) polyphenol distributed mainly in dermis; rapid distribution from microemulsion to epidermis, but slower distribution from epidermis to dermis	39

(continued)

Table 8. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Exposure Route	Procedure	Results	Reference
Sucrose Laurate	Rat (ICO: OFA)	Hairless female rats, abdominal and dorsal skin (4 samples; 35-mm diameter; subcutaneous fat removed); dermis and epidermis skin thickness 0.30-0.35 mm	5 g cyclosporin A was dissolved in 100 mL of 30% Sucrose Laurate (aqueous)	Skin samples (2.54 cm^2 diffusion area) mounted in Franz-type diffusion cell (32 °C water jacket)	100 μL receptor-fluid samples taken at 4, 8, 24, 28, 32, and 48 h and replaced by equivalent saline/methanol solution; at 48 h, skin removed from cell and stratum corneum tape-stripped 15×; remaining skin was homogenized and assayed; negative controls were used	Skin penetration rate of cyclosporine A was 0.153 μg/mL·h in Sucrose Laurate solution; Sucrose Laurate exhibited intermediate skin penetration enhancing properties; efficacy experiment performed with cyclosporine A dissolved in Sucrose Laurate formulations (ie, 2% Sucrose Laurate in micellar solution or 2% Sucrose Laurate in hydrogel) demonstrated that Sucrose Laurate is an effective dermal penetration enhancer for hydrophilic substances	[38]
Sucrose Laurate and Sucrose Myristate	Human	RPMI 2650 human nasal epithelial cells	Variable between 0.01 and 3 mg/mL	Cells cultured in Transwell filter inserts (cells used to model absorption from the respiratory zone of human nasal epithelium, limitations include no cilia and no air–liquid interface)	Cells treated and transepithelial electrical resistance measured; paracellular permeability experiments performed using fluorescein isothiocyanate labeled dextran as a marker across epithelial cells; positive and negative controls were used	Sucrose Laurate and Sucrose Myristate showed a substantial transepithelial electrical resistance (characterizing the permeability of tight junctions for sodium ions in cell cultures) decrease at 0.1 mg/mL and irreversible drop at 0.3 mg/mL; substantial enhancement of paracellular permeability of nasal epithelial cell layers, effects were dose-dependent	[40]
Sucrose Stearate	Pig	Skin	Nanoemulsions (used for dermal drug delivery); 2.5% w/w Sucrose Stearate in aqueous phase w/ hydrophilic drugs (fluconazole and minoxidil); lecithin in oil-phase w/ lipophilic drugs (fludrocortisone acetate and flufenamic acid)	Hair-free porcine skin (area 1.13 cm^2) treated with dermatome (1.2 mm), frozen, thawed; skin patches clamped between donor and receptor chambers of Franz-type diffusion cells	Receptor chamber filled with phosphate buffer; diffusion cells at 32 °C for 24 h then 0.6 g of nanoemulsion (mixture of aqueous and oil phase described) placed on skin in donor chamber; 200 μL samples removed from the receptor chamber at intervals for analysis (of drug content) and replaced by fresh receptor medium; lecithin emulsions were used as a comparison to Sucrose Stearate emulsions; controls without drugs were used, but no controls without Sucrose Stearate were used	Sucrose Stearate was shown to be an emulsifier with physical and chemical stability; pH decreased with increasing Sucrose Stearate concentrations due to residual, nonesterified fatty acids (up to 10%, based on manufacturer supplied info); drug permeation enhancement comparable to that of lecithin-based emulsions	[78]

(continued)

Table 8. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Exposure Route	Procedure	Results	Reference
Sucrose Stearate	Pig	Abdominal skin	Nanoemulsions (used for dermal drug delivery); 1% w/w Sucrose Stearate in aqueous phase with cyclodextrin; tocopherol, phytosphingosine, and progesterone in oil phase	Hair-free porcine skin (area 1.13 cm^2) treated with dermatome (1.2 mm), frozen, thawed; skin patches clamped between donor and receptor chambers of Franz-type diffusion cells	Receptor chamber filled with propylene glycol/water; diffusion cells at 32 °C for 48 h then 0.6 g of nanoemulsion (mixture of aqueous and oil phase described) placed on skin in donor chamber; 200 μL samples removed from the receptor chamber at intervals for analysis (of drug content) and replaced by fresh receptor medium; negative controls used	Sucrose Stearate was a skin permeation enhancer for progesterone and helped to stabilize the nanoemulsion	[41]
				ANIMAL			
Sucrose Laurate	Mouse (SKH-1 hairless mice)	15-wk old male mice	Sucrose Laurate (unknown concentration) in hydrogel containing 5% ibuprofen	Dermal	Tape-stripping (up to 18×) used to collect corneocytes from uppermost layer of dorsal skin 30 min post-treatment; negative controls used	Minimal changes in lipid and protein structure of stratum corneum observed; stratum corneum took up lipophilic hydrocarbon components of the gel; biopsies from skin treated with 5% and 15% showed increased eosinophils, lymphocytes, and polymorphonuclear cells compared to untreated skin; Sucrose Laurate gel increased skin hydration and penetration of ibuprofen	[42]
Sucrose Laurate	Rabbit (White New Zealand)	Male rabbits, n = 9	5% and 15%, w/w Sucrose Laurate in hydrophilic gels (also containing 60 μg estradiol and a preservative), pH 6	Dermal	Rabbits fasted 24 h pretreatment and during treatment; 100 mg gels were applied on days 1 and 7 to hairless (shaved) 3 × 3 cm skin area; days 2-6 placebos applied; blood samples taken from marginal ear vein 0.5 through 12 h postadministration; skin biopsies (taken from application site and untreated skin) evaluated for epidermal thickness; negative controls used	Bioavailability parameters were substantially higher after single application of estradiol with 15% compared to estradiol with 5%; epidermal skin-fold thickness and infiltration were observed with 5% and 15%; elevated levels of eosinophils, lymphocytes, and polymorphonuclear cells were observed in biopsy samples of skin exposed to 5% and 15% compared to controls; multiple applications with 5% and 15% showed decreased penetration-enhancing effect compared to single application; results	[43]

(continued)

Table 8. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Exposure Route	Procedure	Results	Reference
						indicate that Sucrose Laurate is a percutaneous absorption enhancer	
Sucrose Laurate	Rat (Sprague – Dawley)	Male rats, n = 25 (in vivo study)	0.5% Sucrose Laurate (solution contained varying amounts of drug sumatriptan succinate)	Nasal	In situ nasal perfusion technique performed: trachea of anesthetized rats cannulated, tube inserted through esophagus into posterior of nasal cavity, drug solution containing Sucrose Laurate circulated, aliquots removed up to 2 h; positive and negative controls were used In vivo studies performed by microsyringe administration into nasal cavity and IV administration (drug only) via tail vein, blood samples collected 2 h postdosing; negative controls used	Intranasal absorption-enhancing effect (increasing with time and concentration); absolute drug bioavailability of 30% (in vivo rat experiment)	[44]
Sucrose Cocoate, sucrose monodecanoate, sucrose monododecanoate, sucrose monotridecanoate, sucrose monotetradecanoate	Rat (Sprague-Dawley)	Male, n = 3-6/experiment	For nasal formulations, 0.125%, 0.25%, or 0.5% Sucrose Cocoate containing either insulin or calcitonin; ocular formulation 0.5% Sucrose Cocoate w/insulin or calcitonin; vehicle (aqueous ethanol solution)	Nasal, Ocular	Dose was administered for nasal exposure via a pipette; IV (drug only) through right femoral vein of anesthetized rats; through ocular exposure via pipette in left eye of anesthetized rat; negative controls used. Following administration of Sucrose Cocoate solution, blood glucose and insulin levels were monitored	Sucrose monodecanoate was found to be the predominant sucrose ester in Sucrose Cocoate; plasma concentrations of insulin after nasal exposure to Sucrose Cocoate concentrations of 0.125%-0.5% increased (not linearly, ie, physiological response to insulin has an effect maximum) compared to controls; Sucrose Cocoate increased absorption of insulin through the ocular route from 5 μU/mL to 59 μU/mL (0.5% Sucrose Cocoate); nasal absorption of insulin with Sucrose Cocoate caused larger increase in plasma insulin levels (9×) than ocular delivery of the same insulin concentration (4×); similar effect observed for calcitonin nasal vs ocular absorption; sucrose esters with acyl chains of C_{12}-C_{14} were most effective nasal peptide-absorption enhancers	[45]

(continued)

Table 8. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Exposure Route	Procedure	Results	Reference
			HUMAN				
Sucrose Palmitate (80% mono-, 17% di-, 3% tri-), Sucrose Stearate (48% mono-, 34% di-, 14% tri-)	Human	Healthy, female subjects, n = 4 (tape-stripping study)	Nanoemulsions: oil phase-(drug aceclofenac), 1%-2% (w/w) egg lecithin, 10% medium chain triglycerides, 10% Castor oil, 0.05% butylhydroxy-toluene; aqueous phase- 0%-2% (w/w) Sucrose Palmitate; 0%-2% (w/w) Sucrose Stearate	Dermal	Tape-Stripping Study: Nanoemulsions (25 μL cm^2) applied to 4 cm^2 forearm surface area for 2 h, after which residual test substance removed, tape-stripping performed at least 12×; negative controls used	2% Sucrose Palmitate (hydrophilic), 0.5% Sucrose Stearate (intermediate lipophilicity), and 1.5% egg lecithin were superior in in vivo tape-stripping for increasing skin absorption of aceclofenac; aceclofenac detected at all depths into stratum corneum compared to controls (this attributed to small droplet size/large surface area for close and prolonged skin contact; lipid bilayer perturbation observed in stratum corneum from phospholipids and sucrose esters)	46
Sucrose Oleate, Sucrose Laurate	Human	Healthy, female subjects, n = 6	2% or 10% Sucrose Oleate, 2% or 10% Sucrose Laurate in Transcutol; 4-hydroxy-benzonitrile (drug evaluated)	Dermal	Test formulation (1.5 mL) applied via filter paper (11.5 × 4.5 cm), affixed to skin with occlusive film for 1 h, then filter paper removed and skin cleaned; Transepidermal water loss measured up to 4 h postadmin; Penetration of 4-hydroxy-benzonitrile evaluated by tape-stripping tests in a similar experiment as above (including pretreatment of skin with Sucrose Oleate and Sucrose Laurate for 1 h); negative controls used	Sucrose Oleate and Sucrose Laurate increased 4-hydroxy-benzonitrile penetration vs control (2% Sucrose Laurate with Transcutol synergistically increased penetration the most); C-H asymmetric and symmetric stretching bands of lipid methylene groups showed decreases in absorption and frequency shifts to higher wave numbers, temporarily altering stratum corneum barrier properties to increase penetration; no sustained increase in water loss from test formulation	47

IV = intravenous.

Table 9. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion.

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO			
Sucrose Palmitate (mono-) and Sucrose Stearate (mono-, di-); >95% purity	Rat (Wistar)	Male rats, three 10 cm segments of rat small intestine used to prepare everted sacs; also used in this study were rat liver homogenates, intestinal mucosa homogenates, artificial pancreatic fluids, and whole blood	*Intestinal Absorption Studies*: 1 μmol/mL ^{14}C-sucrose esters *Pancreatic Fluid Hydrolysis:* 2 mM ^{14}C-sucrose esters *Liver and Mucosa Hydrolysis:* 20 mM ^{14}C-sucrose esters *Whole Blood Hydrolysis*: 5 mM ^{14}C-sucrose esters (in the above experiments, a mixture of ^{14}C-sucrose esters was used, radiolabels were on sucrose or on the ester portion of the molecule)	*Intestinal absorption studies:* bicarbonate buffer solutions were incubated for 1 h; serosal fluid, mucosal fluid, and tissue were assayed for radioactivity; no controls used *Artificial Pancreatic Fluid Hydrolysis*: artificial pancreatic fluid aliquots were removed at 0, 0.5, 1, 2, and 4 h and assayed; no controls used *Hydrolysis by Liver Homogenates and Intestinal Mucosa:* incubation for up to 4 h for liver homogenates and 1 h for mucosal homogenates; no controls used *Hydrolysis by Whole Blood:* performed by adding 1 mL of 5 mM ^{14}C-sucrose esters to buffered solution of blood and incubated up to 1 h and assayed; no controls used	1 h after incubation, ^{14}C-sucrose esters concentrations decreased and sucrose, stearic acid, and palmitic acid concentrations increased showing that substantial hydrolysis occurred; substantial amount of ^{14}C-sucrose esters was absorbed into intestinal tissues; there was no notable transport of ^{14}C-labeled sucrose esters from mucosal to serosal solution via intestinal tissues; enzymes in intestinal mucosal more important in hydrolysis of sucrose esters than enzymes in digestive fluid Rate of hydrolysis by mucosal homogenates was faster than by artificial pancreatic juice; in 10 min hydrolysis of 10% administered radioactivity of Sucrose Mono-Stearate (radiolabel on sucrose) and 30% administered radioactivity of Sucrose Mono-Palmitate (radiolabel on ester); in 30 min hydrolysis of 9% administered radioactivity of Sucrose Mono-Stearate (radiolabel on ester) and 15% of Sucrose Mono-Palmitate (radiolabel on ester) In 1 h liver homogenates hydrolyzed 20% of Sucrose Mono-Stearate or Sucrose Mono-Palmitate (location of radiolabel not specified) In 1 h hydrolysis of ^{14}C-sucrose esters in whole blood showed 10% of Sucrose Mono-Palmitate and 2.4% of Sucrose Mono-Stearate (location of radiolabel not specified)	[48]
Sucrose Acetate Isobutyrate	Rat (Wistar)	Both sexes; homogenates of gut contents, liver, and intestinal mucosa	10 mg/mL ^{14}C-Sucrose Acetate Isobutyrate (gut content homogenates); 25 or 250 μg/mL ^{14}C-Sucrose Acetate Isobutyrate (liver/intestinal mucosa homogenates) (Radiolabel on the sucrose)	Rat homogenates of the gut contents, liver, and intestinal mucosa were prepared and assayed; negative controls used	^{14}C-Sucrose Acetate Isobutyrate was hydrolyzed (under anaerobic conditions) by intestinal homogenates (75% of administered radioactivity in 6 h); intestinal mucosa hydrolyzed (under aerobic conditions) ^{14}C-Sucrose Acetate Isobutyrate greater than liver homogenates, presence of low molecular weight esters increased as hydrolysis progressed; little hydrolysis in stomach	[49]

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Human	Fecal homogenate	0.1 or 1 mg/mL ^{14}C-Sucrose Acetate Isobutyrate (fecal homogenates); 100 μg/mL ^{14}C-Sucrose Acetate Isobutyrate (bacteria isolated from human feces) (Radiolabel on the sucrose)	Human fecal homogenates were prepared and assayed; human feces bacteria cultured, hydrolysis was measured; negative controls used	40% administered radioactivity (1 mg/mL) was hydrolyzed by fecal homogenates in 16 h (<2% administered radioactivity was hydrolyzed completely to sucrose); 60% administered radioactivity (0.1 mg/mL) was hydrolyzed by fecal homogenates (5% completely de-esterified) in 16 h; 2 strains each of *E coli*, Streptococcus and Bacteroides and 1 strain of bifidobacteria resulted in > 15% hydrolysis of ^{14}C-Sucrose Acetate Isobutyrate in 20 h (many *E coli* and Lactobacillus strains yielded < 5% hydrolysis)	[49]
			ANIMAL			
			Oral			
Glucose Pentaacetate	Rat (Wistar)	Male rats, fasted prior to dosing; n = 37 total for all studies	Aqueous nonradioactive 20% Glucose Pentaacetate (intestinal absorption study); 10% radioactive Glucose Pentaacetate (repeated-dose study, label on glucose); 10% radioactive Glucose Pentaacetate (metabolism study, label on glucose in dosages administered to some animals and label on acetate for dosing in others)	*Intestinal Absorption Study*: rats were dosed (2 mL, single) and at time intervals of ½, 1, 2, and 4 h were killed and gastrointestinal tract analyzed by saponification to determine residual Glucose Pentaacetate amounts; negative controls used *Repeated Dose Retention Study:* rats were dosed (1 mL) daily for 2, 7, or 14 days then were killed and carcass assayed for radioactivity; no controls used *Metabolism Study*: rats were dosed (2 mL, single) and placed in a metabolic chamber where a continuous radioactive gas analyzer recorded specific activity and integrated total $^{14}CO_2$ for 48 h postdosing; urine and feces collect during this 48 h period; no controls used	Gastrointestinal tract absorption is rapid (>90% in 4 h when measured by glucose and just under 90% in 4 h when measured by acetate); 2% of radioactivity recovered from feces at 48 h; radioactive equilibrium by 7 days; rats exposed to 10% Glucose Pentaacetate for 2 yr excreted 76% of dose (glucose labeled) as radiolabeled CO_2 compared to rats not previously exposed to Glucose Pentaacetate (excreted 65% of dose, glucose labeled, as radiolabeled CO_2); Glucose Pentaacetate is hydrolyzed to lesser acetylated metabolites which are detected in urine	[50]
Sucrose Palmitate (mono-) and Sucrose Stearate (mono-, di-); >95% purity	Rat (Wistar)	Male rats fasted prior to dosing	*Excretion Study:* 100 or 250 mg/kg ^{14}C-sucrose esters (water vehicle) with the radiolabel on sucrose or on either the palmitate or stearate; in some animals only radiolabeled sucrose, radiolabeled stearic acid, or radiolabeled palmitic acid were administered	*Excretion Study*: single dosage, $^{14}CO_2$, urine, feces were analyzed for radioactivity; negative controls used *Absorption Via Mesenteric Lymphatic System:* performed by cannulating thoracic ducts of anaesthetized rats, fasting then dosing (single)	Within 120 h postdosing, 30% (Sucrose Mono-Stearate with label on sucrose) to 67% (Sucrose Di-Stearate with label on di-stearate) ^{14}C-sucrose esters were excreted in feces and 11% (Sucrose Di-Stearate with label on di-stearate) to 49% (Sucrose Mono-Stearate	[48]

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
			Lymph Study: 250 mg/kg ^{14}C-sucrose esters (water vehicle) with the radiolabel on sucrose in Sucrose Mono-Stearate, on mono-stearate in Sucrose Mono-Stearate, on distearate in Sucrose Di-Stearate, on mono-palmitate in Sucrose Mono-Palmitate; in some animals only radiolabeled sucrose (140 mg/kg, water vehicle) or radiolabeled stearic acid (117 mg/kg, colza oil vehicle) were administered *Portal System Study*: 250 mg/kg ^{14}C-sucrose esters with the radiolabel on sucrose in Sucrose Mono-Stearate, radiolabel on the mono-stearate in Sucrose Mono-Stearate, or radiolabel on mono-palmitate in Sucrose Mono-Palmitate	rats, lymph collected at 2, 4, 6, 10, 24 h; negative controls used *Absorption Via Portal System*: single dosage, blood samples from portal and femoral veins taken at 1, 2, and 4 h then assayed for radioactivity; no controls used	with label on sucrose) of dosed radioactivity exhaled; urinary excretion of radioactivity was 0.7% (Sucrose Di-Stearate with label on di-stearate) to 4.9% (Sucrose Mono-Stearate with label on sucrose) of the dosage; no intact sucrose ester was found in the urine Little intact Sucrose Stearate was transported from the intestinal tract to lymph (1.8% recovery of Sucrose Mono-Stearate with label on sucrose, compared to 20% recovery of Sucrose Mono-Stearate with label on mono-stearate); sucrose esters were hydrolyzed to yield sucrose and fatty acids that were transferred from the intestine to lymph No intact sucrose esters were detected in blood	
Sucrose Octaisobutyrate- (a component of Sucrose Acetate Isobutyrate)	Rat (Fischer 344)	Male rats, n = 3 (metabolism studies) and n = 3 (blood study)	200 mg/kg ^{14}C-Sucrose Octaisobutyrate (label on sucrose)	Animals fasted prior to dosing; single dosage (by gavage); rats placed in metabolism cages for 5 days postdosing; food available *ad lib.*; collections from expired air traps to measure CO_2 were made at 2, 4, 6, 8, 10, 12, and 24 h and at successive 12 h intervals for 5 days postdosing; urine and feces were collected at 4, 8, 12, 24 h intervals for 5 days postdosing; bile collected (through catheter) 2-6 h intervals for 48 h postdosing, and blood analysis (collected from abdominal aorta) was performed 2, 4, 8, 12, and 24 h postdosing; no controls used	3%-15% of radioactivity was excreted as volatile products, 1%-2% of radioactivity was excreted in urine, 78%-93% of radioactivity was excreted in feces; peak excretion (in ^{14}CO2, urine, and feces) of radioactivity was 24-36 h postdosing suggested delayed absorption, $<$ 0.2% excreted in bile, evidence of extensive gut hydrolysis; no radioactivity found in whole blood or plasma postdosing	52
Sucrose Octaisobutyrate- (a component of Sucrose Acetate Isobutyrate)	Dog (Beagle)	Male dogs, n = 3	200 mg/kg ^{14}C-Sucrose Octaisobutyrate (label on sucrose)	Animals fasted prior to dosing; single dosage (by gavage); dogs placed in metabolism cages for 5 days postdosing and fed 2×/d; collections from expired air traps to measure CO_2 were made at 2, 4, 6, 8, 10, 12, and 24 h and at successive 12 h intervals for 5 days postdosing; urine and feces were collected at 4, 8, 12, 24 h intervals for 5 days postdosing; bile collected (through catheter) 2-6 h intervals	$\leq$1% radioactivity in $^{14}CO_2$, $<$ 2% in urine, 77%-94% in feces, 2%-10% in bile; no radioactivity recovered as volatile products within 24 h of treatment indicating a slow absorption rate, less extensive hydrolysis in gut; no radioactivity found in whole blood or plasma postdosing	52

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
				for 48 h postdosing, and blood analysis (collected from a saphenous vein) was performed 2, 4, 8, 12 h and longer intervals postdosing; no controls used		
Sucrose Octaisobutyrate- (a component of Sucrose Acetate Isobutyrate)	Monkey (Cynomolgus)	Male monkeys, n = 3	200 mg/kg ^{14}C-Sucrose Octaisobutyrate (label on sucrose)	Animals fasted prior to dosing; single dosage (by gavage); monkeys placed in metabolism cages for 5 days postdosing and fed 2×/d; collections from expired air traps to measure CO_2 were made at 2, 4, 6, 8, 10, 12, and 24 h and at successive 12 h intervals for 5 days postdosing; urine and feces were collected at 4, 8, 12, 24 h intervals for 5 days postdosing; bile collected (through catheter) 2-6 hr intervals for 48 h postdosing, and blood analysis (collected from a saphenous or radial vein) was performed 4, 8, 12, 24, 36, and 48 h postdosing; no controls used	62%-85% radioactivity excreted in feces, <2% radioactivity eliminated in $^{14}CO_2$, ≤1% radioactivity recovered in urine, not hydrolyzed in gut or absorbed, 0.1%-0.2% radioactivity excreted in bile, little intestinal metabolism occurred; no radioactivity found in whole blood or plasma postdosing	[52]
Sucrose Acetate Isobutyrate	Rat (Wistar)	Both sexes	50 mg/kg ^{14}C-Sucrose Acetate Isobutyrate (female rats); 20 mg/kg ^{14}C-Sucrose (1 female rat); 20 mg/kg ^{14}C-Sucrose Acetate Isobutyrate (male rats); 0.4 mg ^{14}C-Sucrose Acetate Isobutyrate or 0.15 mg ^{14}C-Sucrose/5 cm length of small intestines (label on sucrose in ^{14}C-Sucrose Acetate Isobutyrate label)	Metabolism studies were conducted in female rats dosed by oral intubation; rats housed in metabolism cages with free access to food and water; rats killed at 6 or 24 h postdosing and total radioactivity measured; no controls used A single female rat dosed by oral intubation (^{14}C-Sucrose 20 mg/kg) and urine collected over 24 h; this was a negative control Dosages administered directly into caecum (to evaluate absorption and hydrolysis of ^{14}C-Sucrose Acetate Isobutyrate) of anaesthetized male rats; rats placed in metabolism cage and killed at 3 or 6 h postdosing; negative controls used Intestinal absorption studies were conducted in anaesthetized male rats by administering dosage through 3 separate 5-cm sections of small intestine loops (absorptive durations postdosing were up to 1 h); after dosing loops were excised, washed with saline and wall homogenates and washings were assayed for radioactivity; negative controls used	> 90% radioactivity remained in intestinal tract 6 h postdosing (60% in small intestine); hydrolysis occurred with <30% radioactivity recovered from small intestine and caecum; urinary excretion of radioactivity 4.9% of dose; expired $^{14}CO_2$ showed complete hydrolysis to glucose and fructose at 2.4% of dose; 90% radioactivity excreted by 24 h (< 8% in gastrointestinal tract); 50% excreted from $^{14}CO_2$; fecal excretion was 33% of dose; 87% of dose in small intestine remained after 1 h, whereas control (^{14}C-sucrose) < 30% after 30 min; ^{14}C-Sucrose Acetate Isobutyrate hydrolyzed in gastrointestinal tract prior to absorption; hydrolysis decreases from duodenum to caecum (less hydrolysis in caecum with direct administration vs small intestine after oral dosing); end result of orally administered ^{14}C-Sucrose Acetate Isobutyrate similar to that of ^{14}C-Sucrose	[49]

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat	For Sucrose-*U*-^{14}C Acetate Isobutyrate treatments n = 6	26, 28, 89, 98 mg/kg Sucrose-*U*-^{14}C Acetate Isobutyrate in corn oil; 5.8 and 11.2 mg/kg Sucrose-*U*-^{14}C Acetate Isobutyrate in aqueous emulsion; 400 mg/kg Sucrose-^{14}C and 112 mg Sucrose/4 mL by stomach tube	Metabolic parameters (CO_2, urine, feces) were evaluated after a single dosage; postdosing the rats were placed in metabolic cages for 3 days (rats fed an aqueous emulsion of Sucrose-*U*-^{14}C Acetate Isobutyrate) or 4 days (rats fed Sucrose-*U*-^{14}C Acetate Isobutyrate in corn oil); for rats housed 3 days samples to measure metabolic parameters were collected every 24 hours; for rats housed 4 days samples to measure metabolic parameters were collected every 1.5 h for the first 15 h and then successively at 8-16 h intervals; negative controls used	For 5.8 and 11.2 mg/kg Sucrose-*U*-^{14}C Acetate Isobutyrate 59% and 52% of radioactivity was detected in breath, 11% radioactivity and 13% radioactivity were detected in urine, % and 27% radioactivity were detected in feces within 3 days postdosing; 6.0% and 6.6% in carcass after 3 days postdosing; Sucrose-^{14}C rapidly absorbed and metabolized to $^{14}CO_2$	[53]
Sucrose Acetate Isobutyrate	Dog	n = 2	4.8 and 3.0 mg/kg Sucrose-*U*-^{14}C Acetate Isobutyrate in aqueous emulsion	Metabolic parameters (CO_2, urine, feces) were evaluated after a single dosage; postdosing the dogs were placed in metabolic cages; samples to measure metabolic parameters were collected every 1.5 h for the first 15 h and then successively at 8-16 h intervals; negative controls used	28% and 27% radioactivity was detected in breath, 7% and 5% radioactivity detected in urine, 53% and 46% radioactivity detected in feces within 7 d postdosing	[53]
Sucrose Acetate Isobutyrate	Rat	n = 3	Oral dosages: 19.8 (rat 1), 41.5 (rat 2), or 50.6 (rat 3) mg/kg Sucrose-^{14}C(U) Acetate Isobutyrate; no dosage specified for intragastric intubation	Non-Good Laboratory Practice (GLP) study; Single oral dosage; rat bile ducts cannulated and bile collected (after intragastric intubation) continuously for 65 h (rat 1) and 2-3 days (rats 2 and 3); no controls used	Material passed slowly through gastrointestinal tract (no feces) for rat 1 (78% radioactivity in intestines 3 d postdosing); rapid peak in bile elimination 1-2 h postdosing, falling off 3-4 h postdosing for rats 2 and 3; 12.4% and 35.1% of radioactivity detected in feces at 96 h and 72 h with 19.4% and 5.0% in intestines at death for rats 2 and 3; low levels of radioactivity detected in blood of all 3 rats	[18]
Sucrose Acetate Isobutyrate	Rat, Dog (Beagle)	Rats n = 3; Dog, male n = 1	4.0 mg/kg Sucrose-^{14}C(U) Acetate Isobutyrate	Non-GLP study; test animals were fed unlabeled Sucrose Acetate Isobutyrate for 7 days (second trial) and 4 days (third trial) before dosing with Sucrose-^{14}C(U) Acetate Isobutyrate emulsion; 15 g unlabeled Sucrose Acetate Isobutyrate in corn oil administered to dog just prior to third trial; bile ducts of rats and dog cannulated and bile collected 11-16 h following single oral dosage; feces analyzed; no details of first trial provided; no controls used	Dog: 67%-75% of radioactivity was eliminated in feces within 7.5-9 h; 2%-6% radioactivity excreted in bile after 11-16 h; results from rat tests not provided	[18]

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Holtzman)	Rat-male, corn oil administration n = 2/dosage; aqueous emulsion n = 2 for ^{14}C-Sucrose Acetate Isobutyrate; n = 2 for ^{14}C-Sucrose	Unlabeled Sucrose Acetate Isobutyrate 2.5, 5 g/kg (prelim study); ^{14}C-Sucrose Acetate Isobutyrate (label on sucrose) in corn oil 26, 28, 89, 98 mg/kg; ^{14}C-Sucrose Acetate Isobutyrate (label on sucrose) in aqueous emulsion 5.8, 11.2 mg/kg; 371, 405 mg/kg ^{14}C-Sucrose (aqueous)	Non-GLP study; unlabeled Sucrose Acetate Isobutyrate administered in preliminary study; single dosages administered; postdosing (corn oil) metabolism parameters monitored for 4 days; postdosing (aqueous emulsion) parameters monitored for 3 days; no controls used	Rats fed unlabeled Sucrose Acetate Isobutyrate eliminated ethanol-extractable acetate and isobutyrate 16%-60% of administered dose within 6 days, at 2.5 mg/kg increased urinary excretion of combined acetic acid equivalent to 36%-46% of administered dose Corn oil dosed rats showed 45%-50% radioactivity was absorbed at higher dosages, 74%-82% radioactivity was absorbed from intestinal tract at lower dosages; Sucrose Acetate Isobutyrate rapidly eliminated (all dosages), 90%-93% radioactivity was eliminated within 4 days with 97% of the total radiolabeled elimination occurring within 2 days; 55-67% of dosage metabolized to $^{14}CO_2$ in 4 days; 23%-28% eliminated in urine in 4 days; unabsorbed material in feces was Sucrose Acetate Isobutyrate or highly acylated sucrose; Sucrose Acetate Isobutyrate metabolized to sucrose and partially acylated sucrose in gut and was absorbed; higher dosages were not as well absorbed as lower dosages Aqueous emulsion dosage of Sucrose Acetate Isobutyrate largely absorbed from gut; unabsorbed material in feces was highly acylated sucrose; > 73% radioactivity was excreted as CO_2 in exhaled air in 3 days; 14%-18% radioactivity was eliminated in urine; no fat incorporation of Sucrose Acetate Isobutyrate detected Rats dosed with ^{14}C-Sucrose exhaled 77%-83% of dosage as $^{14}CO_2$ in 3 days (elimination of radioactivity in urine and feces was very small); 10%-13% dosed radioactivity detected in carcass	[18]

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Holtzman)	Male, n = ?	27 or 100 mg/kg ^{14}C-Sucrose Acetate Isobutyrate (label on Sucrose) (vehicle = corn oil)	Single dosage administered and CO_2 in exhaled air, urine, feces, blood, liver, and kidney evaluated; use of controls not specified	Gastrointestinal tract absorption of administered radioactivity was 74%-82% (27 mg/kg) and 45%-50% (100 mg/kg); eliminated 88%-90% radioactivity by 48 h; 100 mg/kg radioactivity eliminated 54%-56% as CO_2 and 26%-28% radioactivity in urine; 27 mg/kg radioactivity eliminated 63%-67% as CO_2 and 23%-25% radioactivity in urine; <1% radioactivity remaining in gastrointestinal tract, blood, liver, kidney at 4 days postadmin; 24 h feces samples had Sucrose Acetate Isobutyrate + metabolites; most of radioactivity in urine was identified as sucrose with other unidentified compounds present	21
Sucrose Acetate Isobutyrate	Rat (Holtzman)	Male, n = ?	100 mg/kg ^{14}C-Sucrose Acetate Isobutyrate (label on Sucrose)	Single dosage administered and metabolic parameters monitored; use of controls not specified	3-3.5 h post administration: 78%-84% radioactivity was recovered from gastrointestinal tract; 7%-9% radioactivity from stomach, intestinal, caecal tissues; < 4% radioactivity was excreted in breath, urine, feces; gastrointestinal tract + organ extracts contained sucrose, partially-acylated sucrose esters, and unchanged Sucrose Acetate Isobutyrate	21
Sucrose Acetate Isobutyrate	Rat	Not specified	^{14}C-Sucrose Acetate Isobutyrate, no further details provided	Single dosage administered; use of controls not specified	Eliminated 7%-10% radioactivity in urine within 30-46 h postdosing; ^{14}C molecules larger than sucrose not detected in urine (sucrose, glucose, and fructose absent)	21
Sucrose Acetate Isobutyrate	Dog	Not specified	^{14}C-Sucrose Acetate Isobutyrate, no further details provided	Single dosage administered; use of controls not specified	Eliminated 2.8%-5.2% of radioactivity in urine within 29-30 h postdosing; ^{14}C molecules larger than sucrose not detected in urine (sucrose, glucose, and fructose absent)	21
Sucrose tetrastearate, Sucrose Hexastearate, sucrose octastearate	Rat (Wistar)	Male rats, n = 3 per formulation	250 mg/kg ^{14}C-sucrose esters (sucrose tetrastearate, Sucrose Hexastearate, sucrose octastearate; ^{14}C radiolabels were on either the sucrose or the ester portion of the molecule)	24 h fast, rats dosed (single); expired CO_2, urine, feces collected 120 h postdosing; blood, tissue, and lymph analyzed; use of controls not specified	At 120 h postdosing for radioactivity labeled on ester portion, ≥99% was found in feces, ≤1.6% in expired CO_2, and ≤0.3% in urine; lesser esterification compounds were better absorbed; for dosed radioactivity labeled on sucrose portion ≥96% was found in feces, ≤ 1.5% in expired CO_2, and ≤ 1.0% in	51

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
					urine; sucrose esters were hydrolyzed before absorbed in the intestines; by 120 h postdosing ^{14}C sucrose esters (label on ester) were found in fat, lymph node, liver, other organs and tissues, and blood samples; by 1 to 8 h postdosing, small levels of ^{14}C sucrose esters (label on sucrose) were detected in blood, tissues, and organs; in lymph samples analyzed 120 h postdosing (label on ester) $\leq$ 7.6% radioactivity detected and by 96 h postdosing (label on sucrose) $<$ 0.3% of radioactivity was detected	
			HUMAN			
			Oral			
Sucrose Acetate Isobutyrate	Human	Males n = 2 (single dose); Males n = 2 (multidose); n = 1 (fecal excretion study); n = 2 (sucrose clearance study)	All Sucrose Acetate Isobutyrate dissolved in butter: single dose of 0.1 or 1.0 g; 1g/d $\times$ 7 days (multidose study); 0.1 g/d $\times$ 7 days (fecal excretion study used); each subject administered 100, 250, and 500 mg sucrose IV as 10% (w/v) on different days	For 5 days, 24 h urine samples were collected in the single-dose study, urine was assayed for sucrose, free and esterified; For 7 days, 24 h urine sample collected (in the multidose study, urine was assayed for total sucrose); For 3 days, feces collected postdosing and assayed for glucose; Urine collected at 3, 12, and 24 h and assayed for glucose after acid hydrolysis (sucrose clearance study); negative controls were used	0.1 g or 1 g showed $<$ 0.4% was excreted in urine as parent compound or metabolites with disaccharide moiety; with 1 g/d $\times$ 7 d, similar result as above; with 0.1 g/d $\times$ 7 d in 1 subject, no unchanged Sucrose Acetate Isobutyrate or metabolite detected in fecal samples; absorption of partially esterified sucrose molecules from intestinal tract is insignificant; urinary excretion following IV dosing showed 50% sucrose recovered in urine after 3 h at all 3 dose levels	[49]
Sucrose Acetate Isobutyrate	Human	n = 7 subjects total	1.0-1.2 mg/kg Sucrose-*U*-^{14}C Acetate Isobutyrate (n = 6) and 0.2 mg/kg (n = 1) in noncarbonated beverage; Sucrose-^{14}C administered at 400 mg/kg Sucrose-^{14}C; Sucrose-^{14}C and unlabeled sucrose (25 or 28 g in 200 mL) administered to 2 subjects	Human subjects were administered a single dosage; breath samples were collected at 1-1.5 h intervals from 0.5 to 16 h postdosing and at various successive intervals up to 25-30 days; urine samples were collected *ad libitum* for 25-30 days and fecal samples collected *ad lib.* for 5 days posttreatment; negative controls were used	Subjects eliminated in breath 41%-66% radioactivity, urine 15%-21% of radioactivity, feces 10% of radioactivity within 30 days; subjects dosed with Sucrose-^{14}C eliminated 50% radioactivity in breath, 2.7% radioactivity in urine, $<$0.3% in radioactivity in feces within 31 days; studies were also conducted to examine the effect on elimination of Sucrose Acetate Isobutyrate with various dosing routine changes and results indicated no significant differences in patterns or routes of dose	[53]

(continued)

Table 9. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
					elimination; in humans urinary elimination species are more polar (mostly sugar esters, very little free sucrose)	
Sucrose Acetate Isobutyrate	Human	Male, n = 1	1.18 mg/kg ^{14}C-Sucrose Acetate Isobutyrate	Single dosage administered; urine samples collected prior to dosing and at 0 and 6.2 h postdosing and assayed; no controls used	Glucose, fructose, and the esters of fructose and sucrose were not detected in urine; metabolites (2 unidentified chromatographic peaks) were thought to be principal metabolites of Sucrose Acetate Isobutyrate	[21]

IV = intravenous.

Table 10. Acute Toxicity Studies.

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
			ANIMAL				
			Dermal				
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	N = 5/sex/dosage	20 mL/kg Sucrose Acetate Isobutyrate (vehicle not specified)	Single dosage; 24 h	Test substance applied to hairless skin, occlusively wrapped for 24 h, post-application residual material washed off with water (followed Organization for Economic Co-operation and Development [OECD] Guideline 434, Acute Dermal Tox-Fixed Dose); use of controls not specified	Skin unaffected by treatment during 14 days observation; weight gain, clinical signs, gross pathology unaffected (no evidence of percutaneous absorption); LD_{50} > 20000 mg/kg for male and female rats	18
Oral							
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 5/sex/dosage	5000 mg/kg Sucrose Acetate Isobutyrate in corn oil	Single dosage	Dosage administered orally by gavage, rats observed for 14 days; use of controls not specified	LD_{50} > 5000 mg/kg for male and female rats; body weight and gross pathology unaffected; diarrhea (likely from corn oil) observed day of dosing (resolved 1-2 days postdosing); no treatment-related effects at necropsy	18
Sucrose Acetate Isobutyrate	Rat, Mouse	Sample size details not specified	25.6 g/kg Sucrose Acetate Isobutyrate in corn oil (50% solution of Sucrose Acetate Isobutyrate)	Single dosage	Dosage administered; use of controls not specified	Oral dosages produced no mortality in mice and mortality in 1 of 7 rats	60
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n = 2 male, 2 female	1.25, 2.50, 5.00, 10.00, 20.00 g/kg bw Sucrose Acetate Isobutyrate (vehicle: orange juice concentrate)	Incremental with 72 h in between	Dosage administered (by gavage) incrementally (72 h between) until 20 g/kg reached or toxicity occurred; no controls used	LD_{50} > 20 000 mg/kg for male and female monkeys; yellow/watery emesis or stools observed (at dosages 1.25, 2.5, 5.0 g/kg); 24 h postdosing with 20.0 g/kg loose stools noted; body weight and gross pathology were unaffected; food consumption was slightly less during treatment	18
Sucrose Acetate Isobutyrate	Squirrel monkeys (*Saimiri sciureus*)	n = 3 males/group (6 total animals; 1 group received treatment and the other group served as a control)	1 g Sucrose Acetate Isobutyrate in 2 mL cottonseed oil	Single dosage	Dosage administered after fasting overnight (method of administration was not specified); 24 h posttreatment BSP clearance measured; 7 days rest then treatment for groups was reversed	BSP clearance was normal in 2 of 3 monkeys in each group	21
Sucrose Acetate Isobutyrate	Squirrel monkeys (*Saimiri sciureus*)	n = 3 males/group (6 total animals; 1 group received treatment and the other group served as a control)	2 g Sucrose Acetate Isobutyrate in 4 mL cottonseed oil	Single dosage	Dosage administered after fasting overnight (method of administration was not specified); 24 h posttreatment BSP clearance measured; 7 days rest then treatment for groups was reversed	High plasma BSP detected in 3 controls, however authors considered this to be a technical error when BSP clearance after Sucrose Acetate Isobutyrate treatment was normal in all animals	21

(continued)

Table 10. (continued)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration/ Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate, Sucrose Octaisobutyrate	Monkey (Cynomolgus)	n = 10	5 g/kg Sucrose Acetate Isobutyrate, 5 g/kg Sucrose Octaisobutyrate (corn oil vehicle)	Single dosage	Dosage administered, 30 min bromosulfophthalein (BSP)* retention and serum alkaline phosphatase (SAP)* measured 5 h postdosing; negative controls were used	BSP and SAP measurements, clinical observations, and body weight were unaffected by treatment (intervals for hepatic function measurements not optimized)	[21]
Sucrose Acetate Isobutyrate	Dog (Beagle)	Male, n = 3 (dosed), n = 2 (controls)	2 g/kg Sucrose Acetate Isobutyrate in corn oil	Single dosage	Dosage administered (by gavage), BSP clearance measured 0.5, 2, 4, 6, 10, 12, 18 or 24 h postdosing; negative controls were used (delayed BSP clearance rates are indicative of inhibited liver function)	Plasma BSP levels increased at all postdosing measurements compared to predosing values (5 h postdosing was max BSP retention)	[21]
Sucrose Hexaacetate Diisobutyrate, Sucrose Octaisobutyrate; both are constituent esters of Sucrose Acetate Isobutyrate	Dog (Beagle)	Males, Experiments 1-3: n = 12 (test animals), n = 2 (control animals); Experiment 4: n = 6 (test animals), n = 1 (control animal)	100-1000 mg/kg Sucrose Hexaacetate Diisobutyrate; 5-1000 mg/kg Sucrose Octaisobutyrate (corn oil vehicle)	Single dosage	Dosage administered, BSP and SAP measured; negative controls were used	Sucrose Hexaacetate Diisobutyrate increased BSP (5-7×) at all dosages tested vs pretreatment values; Sucrose Octaisobutyrate increased BSP (4-5×) at levels of 25 mg/kg and higher; no dose-response correlation; BSP retention at 5 mg/kg Sucrose Octaisobutyrate showed slight increase vs control and pretreatment values; SAP, body weight, and gross clinical observations unaffected	[21]

*BSP = bromosulfophthalein; SAP = serum alkaline phosphatase.

Table 11. Short-Term, Subchronic, and Chronic Toxicity Studies.

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
SHORT-TERM (<3 MONTHS EXPOSURE)							
ANIMAL							
Oral							
Sucrose Acetate Isobutyrate	Rat (Wistar)	n = 5	4% Sucrose Acetate Isobutyrate	7 days	Dosed daily in diet for 7 days; BSP* measured at 0 (pretreatment) 24, and 48 h following withdrawal from treated feed; use of controls not specified	BSP clearance unaffected	21
Sucrose Acetate Isobutyrate	Dog (Beagle)	n = 2/sex	0.1, 0.3, 0.5% Sucrose Acetate Isobutyrate	2 weeks	Dosed daily in diet; tested for BSP clearance 24 and 48 h postfeeding; rest period of 1 wk between dosing levels; use of controls not specified	No BSP retention with 0.1%, but reversible BSP retention did occur at 0.3% and 0.5%	21
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n = 1/sex/group (6 groups, 12 total animals)	0, 0.5, 1.0, 2.0, 5.0, 10.0 g/kg/d; orange juice vehicle	15 days	Dosed daily by gavage for 15 days; negative controls were used	Body weight and food consumption unaffected; postmortem examination showed no change; no alteration in ultrastructural organization of hepatocytes	21
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n = 1/sex/group (4 groups, 8 total animals)	0, 2.0, 5.0, 10.0 g/kg /d; orange juice vehicle	15 days	Dosed daily by gavage for 15 days; negative controls were used	Body weight, food consumption, and clinical parameters (including BSP retention) unaffected	21
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 15/sex/ group	0, 5000, 50000 ppm Sucrose Acetate Isobutyrate	3 weeks	Dosed daily in diet for 3 wk; 5 rats/sex/ group killed after 1, 2, and 3 wk of treatment; negative controls were used	No effects on gross necropsy, liver weights, body weight, or food consumption	21
Sucrose Acetate Isobutyrate	Mouse (B6C3F1/ Cr1BR)	n = 10/sex/group	0, 0.625, 1.25, 2.5, 5.0 g/kg bw/d Sucrose Acetate Isobutyrate	4 weeks	Dosed daily in diet for 4 wk; negative controls were used; this study was used for range finding to be applied to a 2-year toxicity (*see Chronic Toxicity section of this table*)/carcinogenicity study (*see Carcinogenicity in-text*)	Body weights/weight gains and food consumption were unaffected by treatment; no treatment-related effects observed at necropsy; treatment was well-tolerated	55
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n = 4/sex	0, 500, 1450, 2400 mg/kg/d Sucrose Acetate Isobutyrate in corn oil	4 weeks	For 4 wk, treatment was administered to 1 monkey/sex/dosage/d; negative controls were used; *see Chronic Toxicity section of this table for 1-year study conducted following this preliminary range-finding study*	All monkeys survived to termination, occasional decreased appetite in all monkeys, no change in body weight except for 1 female (12% loss at 2400 mg/kg/d), hematological values and BSP unaffected (no dose rate-dependent effects), low terminal serum phosphorus in 1 female at 2400 mg/kg/ d, no lesions, gross changes typical of spontaneous disease	56
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 140/sex	1.0%, 2.0%, 4.0%	28 or 56 days	280 rats randomly assigned to 14 treatment groups of each sex, 10/ group; dosed daily in diet for 28 or 56 days or for 28 days prior to or after which were fed a control diet for 28 days	No toxicological effects were observed	60

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = not specified	4% Sucrose Acetate Isobutyrate + corn oil	36 days	Dosed daily in diet as indicated for 36 days; ICG* clearance tested on ≥2 rats/group on days 1, 3, 5, 8, 10, 22, 26, and 36; negative controls were used	ICG plasma clearance rates no different from controls	21
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = not specified, males	4.0% Sucrose Acetate Isobutyrate + 5.0% corn oil/d	36 days	Dosed daily in diet for 36 days to determine ICG clearance rates indicating liver functionality	No hepatic microsomal activity, slight depression of G-6-PTase activity	60
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 40/sex/group	Group 1 (basal diet); group 2 (basal diet + sodium phenobarbital 100 mg/kg/d by gavage); groups 3-5 = 2.5, 5.0, 10.0% Sucrose Acetate Isobutyrate daily in diet, respectively	6 weeks	Dose administered daily as indicated; each group divided into 2 subgroups (n = 20/subgroup) that were treated for 6 and 12 wk (see Subchronic section of this table); in each subgroup n = 10 rats were used for zoxazolamine test (after which fed basal diet for 4 wk withdrawal period and then zoxazolamine test repeated), n = 10/subgroup used for clinical chemistry and pathology studies; effects of phenobarbital and Sucrose Acetate Isobutyrate on liver microsomal enzymes were determined by urinary ascorbic acid excretion, zoxazolamine hypnotic activity (Sucrose Acetate Isobutyrate's effect on the zoxazolamine biotransformation rate by liver enzymes may be an indication of toxicity), and liver biochemistry; negative controls were used	NOAEC reported at 10% daily in diet; no deaths from treatment; mean body weights decreased in males at all dosage rates for entire study vs controls potentially due to palatability of treatment; no effect on hepatobiliary function; no microsomal enzyme induction observed; carboxylesterase activity unaffected; urinary excretion of ascorbic acid and zoxazolamine hypnotic activity were unaffected by treatment; liver glycogen levels increased in males and females fed 10%; absolute mean heart weights decreased in all treated males	54
Sucrose Polysoyate	Rat (Sprague-Dawley)	Males, n = 20/group (5 groups, 100 animals total)	17% (w/w) lipid content mixed in diet; 0%, 4%, 8%, 15% Sucrose Polysoyate (sucrose polyester prepared from completely and partially hydrogenated soybean oil); 15% Sucrose Polysoyate (prepared from completely hydrogenated soybean oil)	28 days	Dosed daily in diet for 28 days (some animals in this study were dosed for 91 days, see Subchronic section of this table); 10 rats killed on day 28 and remainder killed on day 91; negative controls were used	NOEC of 15% reported; no toxicity observed; 8% and 15% groups noted softer feces and lower growth rates (dose-related); food consumption increased with dosage increase; no effects on histopathological findings (Sucrose Polysoyate not substantially absorbed from gastrointestinal tract); heart weight decreased (dose-dependent) in rats killed day 28 but not those killed on day 91 (see Subchronic section of this table, completely hydrogenated soybean oil treatment led to decreased heart weight); lipid levels unaffected	19,20

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Polysoyate	Dog (Beagle)	Males, n = 4/group (4 groups, 16 animals total)	17% (w/w) lipid content mixed in diet; 0%, 4%, 15% Sucrose Polysoyate (sucrose polyester prepared from completely and partially hydrogenated soybean oil); 15% Sucrose Polysoyate (prepared from completely hydrogenated soybean oil)	28 days	Dosed daily in diet for 28 days; animals killed on days 29 and 30; negative controls were used	NOAEC of 15% reported in male dogs; no toxicity observed; food consumption highest with 15% groups; hematology, urine, and organs unaffected; lower gastrointestinal tract contained more material with 15% groups; increased heart lipids and liver cholesterol in treated dogs (Sucrose Polysoyate identified in liver lipids)	19,20
Sucrose Polysoyate	Dog (Beagle)	n = 4/sex/group (4 groups, 32 animals total)	17% (w/w) lipid content mixed in diet; 0%, 4%, 15% Sucrose Polysoyate (sucrose polyester prepared from completely and partially hydrogenated soybean oil); 15% Sucrose Polysoyate (prepared from completely hydrogenated soybean oil)	28 days	Dosed daily in diet for 28 days; animals killed beginning on day 29; negative controls were used	NOEC reported as 15% for male and female dogs; no clinical toxicity observed; higher food consumption for treatment group vs control; hematology, organs, and urine unaffected by treatment; decrease in cholesterol/lipids in treatment groups (dose-related); Sucrose Polysoyate not absorbed from diet	19,20
				HUMAN			
				Oral			
Sucrose Acetate Isobutyrate	Human	n = 10/sex	10 mg/kg/d Sucrose Acetate Isobutyrate taken in a bolus	14 days	Dosed daily for 14 days; blood chemistry measured prior to treatment and on days 7 and 18; negative controls were used	Blood chemistry values were unaffected	21
Sucrose Acetate Isobutyrate	Human	n = 12/sex/group (3 groups, 24 total subjects)	7.0 or 20.0 mg/kg/d Sucrose Acetate Isobutyrate dissolved in a carbonated drink	14 days	Dosed daily for 14 days (blood chemistry measured prior to testing and on days 7 and 14); additional preliminary experiment performed in which 4 men received 20 mg /kg/d for 1 or 3 days only; 45-min BSP retention test performed on all subjects prior to and after completion of Sucrose Acetate Isobutyrate treatment; negative controls were used	Blood chemistry and BSP retention were unaffected	21
Sucrose Acetate Isobutyrate	Human	n = 27 (13 males, 14 females)	20 mg/kg/d Sucrose Acetate Isobutyrate; orange juice vehicle	14 days	7 days prior to treatment served as each subject's control with ingestion of placebo orange juice emulsion; dosed daily for 14 days, blood samples collected on days −6 (pretreatment), 0, 7, and 14; negative controls were used	Hematological parameters and blood chemistry (including hepatobiliary function) unaffected	21

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
SUBCHRONIC (3 TO 6 MONTHS EXPOSURE)							
ANIMAL							
Oral							
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 40/sex/ group	Group 1 (basal diet); group 2 (basal diet + sodium phenobarbital 100 mg/kg/d by gavage); groups 3-5 = 2.5%, 5.0%, 10.0% Sucrose Acetate Isobutyrate daily in diet, respectively	12 weeks	Dosage administered daily as indicated; each group divided into 2 subgroups (n = 20/subgroup) that were treated for 6 wk (see short-term section of this table) and 12 wk; in each subgroup n = 10 rats were used for zoxazolamine test (after which fed basal diet for 4 wk withdrawal period and then zoxazolamine test repeated), n = 10/ subgroup used for clinical chemistry and pathology studies; effects of phenobarbital and Sucrose Acetate Isobutyrate on liver microsomal enzymes were determined by urinary ascorbic acid excretion, zoxazolamine hypnotic activity (Sucrose Acetate Isobutyrate's effect on the zoxazolamine biotransformation rate by liver enzymes may be an indication of toxicity), and liver biochemistry; negative controls were used	NOAEC reported at 10% daily in diet; no deaths from treatment; mean body weights decreased in males at all dosages for entire study vs controls potentially due to palatability of treatment; no effect on hepatobiliary function; no microsomal enzyme induction observed; carboxylesterase activity unaffected; urinary excretion of ascorbic acid and zoxazolamine hypnotic activity were unaffected by treatment; liver glycogen levels increased in males and females fed 10%; absolute mean heart weights decreased in all treated males	[54]
Sucrose Acetate Isobutyrate	Dog (Pure-bred Beagle)	n = 68 total	Groups 1-5 (n = 6 males + 6 females/ group) 0%, 0.5%, 1.0%, 2.0%, and 4.0% Sucrose Acetate Isobutyrate in diet, respectively	12 weeks	Dose administered daily as indicated for 12 wk; additional dogs n = 4/sex fed Sucrose Acetate Isobutyrate at 2.0% in diet for 12 wk followed by 2 wk withdrawal period (basal diet without Sucrose Acetate Isobutyrate); negative controls were used	No deaths from treatment; no ocular lesions; no impaired growth; hematology and urinalysis unaffected; statistically significant increase in SAP* (dose- and time-related); serum bilirubin levels unaffected; 2% for 12 wk did not affect BSP retention; dilatation of bile canaliculi increased enzyme activity of bile canaliculi; treatment-induced liver changes were reversible; hepatobiliary effects indicate a pharmacological effect and not toxicity	[54]
Sucrose Acetate Isobutyrate	Dog (Beagle)	n = 4/sex in treatment groups; n = 6/sex for control group	0.2%, 0.6%, 2.0% Sucrose Acetate Isobutyrate in cotton seed oil; fat content of diet 12%	90 days	Dosed daily in diet for 90 days; negative controls were used	Food intake/weight gain, hematological/ urine parameters, organ weights unaffected; serum chemistry showed increase in SAP* in male and female dogs with 2% group; dose-related increase in relative liver weights in 0.6% and 2% groups of male and female dogs compared to controls	[21]

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Dog (Beagle)	Males and females, n = 4/sex/dose; 6/sex/dose (control group)	0.2%, 0.6%, 2.0% Sucrose Acetate Isobutyrate, cottonseed oil vehicle	90 days	OECD Guideline 409 (repeated-dose 90-day oral tox in nonrodents) followed (nonGLP); dosed daily in diet for 90 days; negative controls were used	NOAEL male and female dogs > 20000 mg/kg/d (2.0%); food consumption, hematological parameters, urinary examination, and gross pathology/necropsy unaffected; increase in SAP at 2%; increase in liver weight at 0.6% and 2%	18
Sucrose Acetate Isobutyrate	Dog (Beagle)	Males n = 10 (2 groups of 5)	5% Sucrose Acetate Isobutyrate, corn oil vehicle	91 days	OECD Guideline 409 (repeated-dose 90-day oral tox in nonrodents) followed (non-GLP); dosed daily in diet for 91 days; negative controls were used	Moderate elevation in SAP; prolongation of ICG cleared by liver; heavier liver weights vs controls; functional effect on liver which was reversed when removed from diet	18
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 10/sex/group	0%, 0.3%, 1.8%, 9.12% Sucrose Acetate Isobutyrate in vegetable oil (9.3% oil in diet)	13 weeks	Dosed daily in diet for 13 wk; negative controls were used	Slight diarrhea at 9.12%; no differences in weight gain for test and control groups; organ weight, blood chemistry, and histopathology unaffected	21
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	Males and females, n = 10/sex/group; n = 10/sex for controls	0.38%, 1.88%, 9.38% Sucrose Acetate Isobutyrate (vegetable oil vehicle)	13 weeks	Non-GLP; dosed daily in diet for 13 wk; negative controls were used	No toxic effects observed; at 9.38% no specific tissue changes in various organs, slight vacuolization of liver cells (control and treated groups) could be caused by 9.38% vegetable oil in diet; slight diarrhea for rats at higher doses	18
Sucrose Acetate Isobutyrate	Dog (Beagle)	*Exp 1*: n = 18/sex *Exp 2*: n = 6 males *Exp 3*: n = 10 males	*Exp 1* (0.2%, 0.6%, 2.00% Sucrose Acetate Isobutyrate in 6% cottonseed oil) *Exp 2* (5% Sucrose Acetate Isobutyrate in corn oil) *Exp 3* (5% Sucrose Acetate Isobutyrate + 5% corn oil)	12 weeks; 86 days; 91 days	*Exp 1* (36 dogs randomly assigned to each treatment group; dosed daily in diet for 12 wk) *Exp 2* (dosed daily in diet for 28 days, switched to control diet 57 days, on 86th day 4 dogs returned to treatment diet-ICG clearance rates/SAP test conducted at 24 and 48 h) *Exp 3* (10 dogs randomly assigned to 2 groups of 5; dosed daily in diet for 91 days); negative controls were used	*Exp 1* (slight increase in SAP levels at 2%, increase dog liver weights with 0.6% and 2.0%) *Exp 2* (increase in SAP and prolongation of ICG plasma clearance by liver with 5% for 4 wk, after withdrawal of Sucrose Acetate Isobutyrate effects reversed in 2-5 wk, when fed 5% again and tested 24 h postdosing SAP unaffected, ICG clearance prolonged) *Exp 3* (increase in SAP, prolongation of ICG clearance, increase in liver weight, increase in liver glycogen/phospholipids)	60
Sucrose Acetate Isobutyrate	Rat (Holtzman)	n = 25/sex/group	0%, 1.0%, 5.0% Sucrose Acetate Isobutyrate (w/w)	95 days	Dosed daily in diet for 95 days; negative controls were used	Slight weight loss in males with 5%; slight increase in liver weight of females fed 5%; histopathological changes were unaffected	21
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 25/sex	0.0%, 1.0%, or 5.0%	95 days	25 rats randomly assigned to each treatment group; dosed daily in diet for 95 days	With 5% showed lower body weight for males and slight increase in liver weight for females	60

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Polysoyate	Rat (Sprague-Dawley)	Males, n = 20/group (5 groups, 100 animals total)	17% (w/w) lipid content mixed in diet; 0, 4%, 8%, 15% Sucrose Polysoyate (sucrose polyester prepared from completely and partially hydrogenated soybean oil); 15% Sucrose Polysoyate (prepared from completely hydrogenated soybean oil)	91 days	Dosed daily in diet for 91 days (some animals in this study were also dosed for 28 days, see short-term section of this table); negative controls were used	NOEC of 15% reported; No toxicity observed; 8% and 15% groups noted softer feces and lower growth rates (dose-related); food consumption increased with dose increase; no effects on histopathological findings (Sucrose Polysoyate not substantially absorbed from gastrointestinal tract); heart weight decreased (dose-dependent) in rats killed day 28 (see short-term section of this table) but not those killed on day 91 (completely hydrogenated soybean oil treatment led to decreased heart weight); lipid levels unaffected	19,20
Sucrose Polysoyate	Rat (Sprague-Dawley)	n = 10/sex/group (5 groups, 100 animals total)	16% (w/w) lipid content mixed in diet; 0%, 4%, 8%, 15% Sucrose Polysoyate (sucrose polyester prepared from completely and partially hydrogenated soybean oil); 15% Sucrose Polysoyate (prepared from completely hydrogenated soybean oil)	90 days	Dosed daily in diet for 90 days; animals killed on day 95; negative controls were used	NOEC of 15% reported for males and females; no toxicity observed; lower weight gain in 8% and 15% groups; food consumption highest in groups with highest dose (15%) Sucrose Polysoyate prepared from completely hydrogenated soybean oil; organs, clinical chemistry, urinalysis, and hematology unaffected; Sucrose Polysoyate not substantially absorbed by gastrointestinal tract and not identified in liver lipids	19,20
CHRONIC (> 6 MONTHS EXPOSURE)							
ANIMAL							
Oral							
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n = 16/sex	0, 500, 1450, 2400 mg/kg/d Sucrose Acetate Isobutyrate in corn oil	1 year	For 1 year, treatment was administered to 4 monkeys/sex/dosage/d; negative controls were used; *see short-term toxicity section of this table for the 4-wk range-finding study conducted prior to this 1-yr study*	No effect on hepatobiliary function; NOAEL reported at 2400 mg/kg/d All dosage rates were well-tolerated, opthalmoscopic examination unremarkable; no lesions; few gross changes (typical of natural disease) observed in treated and control animals; statistically significant mean corpuscular hemoglobin decrease in males with 2400 mg/kg/d at 6 and 12 months; statistically significant increase in prothrombin for all treated groups with 2400 mg/kg/d at 3 and 12 months; statistically significant increase in mean	56

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
						leucocyte count in females with 1450 mg/kg/d; statistically significant increase in mean segmented neutrophil in females with 1450 and 2400 mg/kg/d at 3 months; statistically significant decrease in serum phosphorus in males with 2400 mg/kg/d at 6 months; statistically significant decrease in alanine aminotransferase in males with 2400 mg/kg/d at 9 and 12 months; statistically significant decrease in serum glucose in males with 1450 mg/kg/d at 6 months and statistically significant increase in males with 2400 mg/kg/d at 6 months; statistically significant decrease in aspartate aminotransferase and serum glucose in females with 1450 mg/kg/d at 6 months; at necropsy statistically significant decrease in mean weight thyroid/parathyroid glands in males with 500 mg/kg/d; statistically significant decrease in mean absolute weight of ovaries and ovary/brain weight ratio in females with 2400 mg/kg/d	
Sucrose Acetate Isobutyrate	Rat (F344)	n = 20/sex/dosage rate	Highest doses fed were up to 5% of diet (beyond which risks nutritional deficiency); acetone vehicle; 0, 0.5, 1.0, 2.0 g/kg/d	1 year	Dosage administered daily in diet for 1 year; hematology and urine analysis were conducted at 27 and 53 wk; negative controls were used	NOAEL reported at 2 g/kg/d for males and females; body weight gain decreased likely from nutritional deficiencies in females with 2 g/kg/d at wk 17 and beyond and in males with 2 g/kg/d at wk 13 and 54; 1 female died with 0.5 g/kg/d group, 1 female killed in moribund condition with 2 g/kg/d group, 1 control and 2 treated rats died during blood collection; clinical and ophthalmic observations unaffected; food consumption decreased in females with 2g /kg/d; clinical chemistry, urine analysis, BSP retention unaffected with 2 g/kg/ d; small, but statistically significant hematology differences compared to controls occurred in dosage rates <2 g/kg/d at varying times in study but were normal again by 54 wk; at necropsy absolute organ weights unaffected; no neoplastic or non-neoplastic microscopic changes; no gross or microscopic changes in liver	[55]

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (F344)	n = 50/sex/dosage rate	Highest doses fed were up to 5% of diet (beyond which risks nutritional deficiency); acetone vehicle; 0, 0 (2 control groups), 0.5, 1, 2 g/kg/d	2 year	Diet containing Sucrose Acetate Isobutyrate was administered daily for 2 years; hematology samples were collected from all surviving animals at study wk 104; negative controls were used; this study also evaluated carcinogenicity (see *Carcinogenicity section in-text*)	NOAEL of 2 g/kg/d reported; no treatment-related deaths or clinical effects; food consumption and hematological parameters were unaffected by treatment; occasional decreased mean body weight compared to controls in females up to 61 wk at 0.5 g/kg/d and up to 73 wk at 1 or 2 g/kg/d were observed; there was a decrease in male mean body weight at 2 g/kg/d compared to first control group (but not second control group); gross and microscopic observations were unaffected by treatment; tumors found were typical of those that occur spontaneously in F344 rat (not treatment-related); male survival rates were 46%, 50% 58%, 58%, and 60%; female survival rates were 74%, 68%, 78%, 62%, and 68% for dosage rates 0, 0, 0.5, 1, and 2 g/kg/d, respectively	[55]
Sucrose Acetate Isobutyrate	Mouse ($B6C3F_1$)	n = 50/sex/dosage rate	Highest doses fed were up to 5% of diet (beyond which risks nutritional deficiency); acetone vehicle; 0, 0 (2 control groups), 1.25, 2.5, 5 g/kg/d	2 year	Diet containing Sucrose Acetate Isobutyrate was administered daily for 2 years; hematology samples were collected from 15 animals/sex in 5 g/kg/d group and control groups at 28, 53, 79, and 105 wk; negative controls were used; this study also evaluated carcinogenicity (see *Carcinogenicity section in-text*)	NOAEL of 2.5 g/kg bw/d was reported; no treatment-related deaths or clinical effects; food consumption and hematological parameters were unaffected by treatment; occasional substantially decreased mean body weight in males at 2.5 g/kg/d compared to both control groups (not seen with 5 g/kg/d); occasional substantially different body weight in females with 1.25 g/kg/d and 5 g/kg/d (not seen with 2.5 g/kg/d) not thought to be treatment-related; tumors found were typical of those that occur spontaneously in the $B6C3F_1$ mouse and were not treatment-related; there was a treatment-related decrease in mean absolute and relative kidney weights observed at necropsy in males (with 5 g/kg/d) compared to controls; no gross or microscopic kidney changes were observed in males or females; male survival rates were 80%, 80%, 80%, 80%, and 74%; female survival rates were 68%, 68%, 78%, 66%, and 78% for dosage rates 0, 0, 1.25, 2.5, and 5 g/kg/d, respectively	[55]

(continued)

Table 11. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Dosage (Vehicle)	Exposure Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 10/sex/dose group	0%, 0.38%, 9.38% in diet	2 year	Diet containing Sucrose Acetate Isobutyrate was administered daily for 2 years; negative controls were used; this study also evaluated carcinogenicity (see *Carcinogenicity section in-text*)	No substantial body weight differences among the groups concluding the first study year; differences in body weight and food consumption appeared at varying times and doses (no further details provided); males exposed to 0.38% or 9.38% exhibited decreased body weight compared to controls in the second study year; absolute and relative kidney weights in both males and females were noted to have a dose-related increase; organ weight findings were inconclusive because of discrepancies in male body weights compared to controls and low survival numbers (2-3 rats/group; no further details provided); no treatment-related lesions were found upon histological examination; within 10 wk of the study 4 males died in 9.38% group (with massive hemorrhages in multiple organs, no further information specified as to the cause of these) but was not attributed to treatment	[21]

BSP = bromosulfophthalein; ICG = indocyanine Green plasma clearance rates indicating liver functionality; NOAEC = no-observed-adverse-effect concentration; NOEC = no-observed-effect concentration; NOAEL = no-observed-adverse-effect level; SAP = serum alkaline phosphatase.

Table 12. Developmental and Reproduction Toxicity Studies for Sucrose Acetate Isobutyrate.

Species/Strain	Test Population-Sex	Dosage (Vehicle)	Procedure	Results	Reference
			Oral		
Rat (Fischer 344)	n = 30/sex/dosage rate F_0 generation (3 generation reproduction study; teratology study)	0, 0.5, 1.0, 2.0 g/kg/d Sucrose Acetate Isobutyrate; acetone vehicle	F_0 generation males fed Sucrose Acetate Isobutyrate for 10 wk and females fed Sucrose Acetate Isobutyrate for 2 wk prior to mating (F_0 females treated through lactation); F_1 generation rats raised on test diet and mated to produce F_{2a} (treated through lactation; examined for fertility indices for F_3 pregnancy) litters then remated to produce F_{2b} litters (treated through day 20; examined for teratology); F_{2a} females treated until day 14 of gestation; animals killed day 29 of teratology study; negative controls were used	NOAEL 2.0 g /kg/d (maternal and developmental); premating period treated males showed decreased food consumption; body weights lower for treated F_0 females during gestation and lactation with 1 and 2 g /kg/d and F_1 females with 0.5 and 2 g /kg/d during lactation; variability in fertility index (# females pregnant/ # females mated × 100) not considered to be treatment related; reproduction unaffected; negative for teratogenic/ developmental toxic effects	[57]
Rabbit (New Zealand White)	n = 5/dosage rate (range finding study); n= 16/dose level (teratology studies)	Range finding-0.6 and 1.2 g /kg/d; for teratology-0, 0.5, 0.85, 1.2 g/kg/d; corn oil vehicle	Range finding: 2 × 1.2 g/kg/d or 1 × 0.6 g/kg/d for 14 days; Teratology study: dosed on days 7-19 gestation, animals killed day 29 of teratology study; negative controls were used	NOAEL 1.2 g/kg/d (maternal and developmental); Range finding study-no mortality occurred, corn oil caused soft stools, treatment well-tolerated; Teratology study-2 high dosage rate treated rabbits died on day 17 gestation, results indicated no difference in treated vs control rabbits for caesarean section examinations, food consumption, weight gain, and gross morphology; negative for teratogenic/developmental toxic effects	[57]
Rat (Holtzman)	n = 15 female/5 male in treatment group; n = 9 female/7 male in control group	5% Sucrose Acetate Isobutyrate in diet; acetone vehicle	Non-GLP; dosed during the breeding of 2 generations; negative controls used	NOAEL reported for maternal toxicity of 1250 mg/kg/d (actual dosage rate); 5.0% (w/w) in diet of 2 generations produced no effect on viability; no observable toxic effects; F_1 generation had respiratory infection resulting in the death of several young, several control rats, and 2 treated rats; none of young weaned in treatment group lived for 2 wk (deaths attributed to respiratory infection)	[18]
Rat (Sprague-Dawley)	n = 10/sex/group	0%, 0.38%, 9.38% (w/w) Sucrose Acetate Isobutyrate	Dosed in diet daily for 5 wk; pairs of rats from each dose group caged together for 19 days; females allowed to wean young to 21 days; parent rats bred 3× in wk 9-36 with different male per mating; negative controls used	At 0.38%, reproductive performance was slightly better vs controls; at 9.38%, fewer females became pregnant, fewer pups born and survived to weaning as observed over 3 breedings, this effect potentially attributable to compromised nutritive value of feed at high treatment levels	[21]

GLP = Good Laboratory Practice; NOAEL = no-observed-adverse-effect level.

Table 13. Genotoxicity Studies.

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
			IN VITRO			
Maltitol Laurate	*Salmonella typhimurium*	Not specified	Composition of test substance: 40% Maltitol Laurate, 50%-55% water, 5%-10% ethanol	Ames Test was performed (no further details specified)	Negative	58
Sucrose Acetate Isobutyrate	*Salmonella typhimurium*	Histidine auxotrophs TA98, TA100, TA1535, TA1537, TA1538	333-10000 μg/plate Sucrose Acetate Isobutyrate, control: dimethyl sulfoxide	Ames Test (*Salmonella* reverse mutation assay): Following preliminary toxicity test with TA100, 6 concentrations from 333-10000 μg/plate were selected, with and without metabolic activation; positive and negative control used	Negative for genotoxicity (as a mutagen, clastogen, and DNA-damaging agent); Solubility exceeded at 50 μg/mL in dimethyl sulfoxide Ames Test: Treatment was not effective at increasing revertant number per plate; nontoxic; positive control outcomes were as expected	59
Sucrose Acetate Isobutyrate	*Salmonella typhimurium*	Strains: TA 1535, TA 1537, TA 98, TA 100	10, 100, 500, 1000, 1500, 2000 μg/plate Sucrose Acetate Isobutyrate; dimethyl sulfoxide vehicle	Bacterial Reverse Mutation Assay: This assay was performed with and without metabolic activation; positive controls used	Negative for mutagenic activity	18
Sucrose Acetate Isobutyrate	Hamster	Chinese Hamster Ovarian/ Hypoxanthine-Guanine Phosphoribosyl Transferase (CHO/ HGPRT)	2.5 to 3350 μg/mL Sucrose Acetate Isobutyrate in dimethyl sulfoxide (preliminary); 25-1000 μg/mL Sucrose Acetate Isobutyrate in Mutation Assay	CHO/HGPRT Mutation Assay: Preliminary cytotoxicity test performed; 6×10^6 cells/ monolayer exposed to each concentration (25-1000 μg/mL) for 4 h with and without met activation and assayed; positive and negative controls used	*Preliminary Results*-Sucrose Acetate Isobutyrate became toxic between 100 and 1000 μg/mL; metabolic activation had no effect on toxicity; at max toxicity 40%-50% survival occurred at 1000 μg/mL (3350 μg/mL caused no further increase in toxicity); *HGPRT Mutation Assay*-No increase in mutant frequency from treatment; positive control outcomes were as expected	59
Sucrose Acetate Isobutyrate	Rat	Rat hepatocytes (Unscheduled DNA Synthesis test)	Sucrose Acetate Isobutyrate dissolved in acetone, solutions diluted 1:100 into William's medium E culture medium containing heat-inactivated fetal bovine serum at 1% v/v (Sucrose Acetate Isobutyrate concentrations of 25 ng/mL to 1000 μg/mL)	Unscheduled DNA Synthesis: Treatment applied to rat primary hepatocytes in 35-mm dishes within 2 h after attachment to coverslip and assayed (18 h exposure); positive and negative controls used	Nontoxic to hepatocytes	59
Sucrose Acetate Isobutyrate	Hamster	CHO	Preliminary test-Sucrose Acetate Isobutyrate in dimethyl sulfoxide diluted 1:100 for concentration range of 1900 μg/mL to 63 ng/mL; 1200, 1600, 2000 μg/mL Sucrose Acetate Isobutyrate in CHO Chromosomal Aberration Assay	CHO Chromosomal Aberration Assay: Cultures exposed to treatment for 7.5 h (without metabolic activation) and 2 h (with metabolic activation) and assayed; positive and negative controls used	In preliminary testing 2000 μg/mL caused monolayer confluency reduction of 37% (without metabolic activation) to 50% (with activation); 63-1900 μg/mL caused little cell cycle delay; 2000 μg/mL caused concentration-related decrease in monolayer confluency and max reduction in confluency of 33% (without activation) and 67% (with activation) but no increases in aberrations; positive control outcomes were as expected	59

(continued)

Table 13. (continued)

Test Substance(s)	Species/Strain	Sample Type/Test Population-Sex	Concentration/Dosage (Vehicle)	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Hamster	CHO/HGPRT	10-1000 μg/mL Sucrose Acetate Isobutyrate	CHO/HGPRT Mutation Assay performed with and without metabolic activation; use of controls not specified	Negative for genotoxicity (no further details provided)	21
Sucrose Acetate Isobutyrate	Rat	Hepatocyte cells	250 ng/mL-1000 μg/mL Sucrose Acetate Isobutyrate	Unscheduled DNA Synthesis Assay performed; use of controls not specified	Negative for genotoxicity (no further details provided)	21
Sucrose Acetate Isobutyrate	Hamster	CHO cells	200-2000 μg/mL Sucrose Acetate Isobutyrate	Chromosomal Aberration Assay performed with and without metabolic activation; not specified	Negative for genotoxicity (no further details provided)	21
IN VIVO						
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n = 20/sex/dosage	20, 200, 2000 mg/kg Sucrose Acetate Isobutyrate in corn oil	Oral administration by gavage as a single dosage to male rats; 2 h postdosing males mated with untreated females for 1 wk; subsequent matings occurred during third (post-meiotic), fifth (meiotic), and seventh (pre-meiotic spermatogenesis) wk postdosing; positive and negative controls used	Negative for dominant lethal mutations; positive control outcomes were as expected	18

Table 14. Cytotoxicity Studies.

Test Substance(s)	Species	Sample Type/ Test Population	Concentration (Vehicle)	Procedure	Results	Reference
				IN VITRO		
Sucrose Laurate	Hamster	Chinese Hamster Lung cells	10% Sucrose Laurate solution (prepared from 38% Sucrose Laurate solution) diluted in water	*Neutral Red Effective Concentration$_{50}$ (NR-EC$_{50}$):* 100 μL suspension of 4 $\times 10^3$ cells/mL added to 96-well plates, cells incubated at 37 °C for 3 days in 5% CO_2 incubator, 10% Sucrose Laurate added to 5 or 6 wells and incubated for 48 hours at which time NR-medium was added and incubated for 2 h, cells assayed and NR-EC$_{50}$ calculated; negative controls were used This cytotoxicity test measured the number of viable cells in a culture by evaluating the uptake of neutral red dye into Chinese hamster lung cells in Sucrose Laurate treated and untreated cells (the dye is only incorporated into the lysosomes of viable cells); absorbance of the dye in cells was measured and the ratio of treated to nontreated cells determined; NR-EC$_{50}$ was calculated based on concentration response curves	Cytotoxicity results: NR-EC$_{50}$ was reported to be 290.0 μg/mL or log (NR-EC$_{50}$) of 2.46 (no further details provided)	62,79
Sucrose Laurate	Human	Human Skin Fibroblasts Cells	10% Sucrose Laurate solution (prepared from 38% Sucrose Laurate solution) diluted in water	*MTT (tetrazolium dye) Effective Concentration$_{50}$ (MTT-EC$_{50}$):* Treated cells were incubated, after 2 h MTT-formazan crystals were solubilized in 200 μL isopropanol, cells assayed and MTT-EC$_{50}$ calculated; negative controls were used This cytotoxicity test measured the number of viable cells by evaluating the conversion of [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide], MTT, dye into human skin fibroblast cells both treated with Sucrose Laurate and untreated (mitochondrial dehydrogenases of metabolically active/viable cells convert MTT to insoluble formazan); formazan was solubilized with isopropanol and its absorbance measured; the ratio of treated to nontreated cells determined; MTT-EC$_{50}$ was calculated based on converted dye concentration of response curves	Cytotoxicity results: MTT-EC$_{50}$ was reported to be 680.0 μg/mL or log (MTT-EC$_{50}$) of 2.83 (no further details provided)	62,80
Sucrose Laurate and Sucrose Myristate	Human	RPMI 2650 human nasal epithelial cells (used to model absorption from the respiratory zone of human nasal epithelium, limitations include no cilia and no air–liquid interface)	Variable between 0.01 and 3 mg/mL	Cellular toxicity studies-1-h treatment on cells measured by lactate dehydrogenase release assay; 4-h treatment on cells measured by 3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay; positive and negative controls used	Cell death in the lactate dehydrogenase assay for Sucrose Laurate was <25% (0.1 mg/mL) and >75% (0.3 mg/mL) and for Sucrose Myristate was 50%-75% (0.1-0.3 mg/mL); cell viability in the 3-(4,5-dimethyltiazol-2-yl)-2,5-diphenyltetrazolium bromide reduction assay for Sucrose Laurate was near 100% (0.1 mg/mL) and <25% (0.3 mg/mL) and for Sucrose Myristate was near 100% (0.03 mg/mL) and 25% (0.3 mg/mL)	40

Table 15. Irritation Studies (Dermal).

Test Substance(s)	Species/Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
			ANIMAL			
Sucrose Laurate	Mouse (SKH-1 hairless mice)	15 wk old males, n = not specified	Sucrose Laurate (unknown concentration) in hydrogel containing 5% ibuprofen	Tape-stripping (up to 18×) used to collect corneocytes from uppermost layer of dorsal skin 30 min posttreatment; negative controls used	The results of the tape-stripping test are located in Table 8; the authors stated that the treatment was nonirritating	[42]
Sucrose Laurate	Rabbit (White New Zealand)	Males, n = 9	5% and 15%, w/w Sucrose Laurate hydrophilic gels (also containing 60 μg estradiol and a preservative), pH 6	Fasted 24 h preadministration and during administration; 100 mg gels were applied on days 1 and 7 to 3 × 3 cm shaved skin area; days 2-6 placebos applied; blood samples collected from marginal ear vein 0.5 through 12 h postadministration; skin biopsies (taken from application site and untreated skin) evaluated for epidermal thickness; negative controls used	Authors of this study stated that there was some skin irritation potential observed, but that treatment was well-tolerated and emphasized that the irritation effects of surfactants are influenced by the application method and parameters of investigation	[43]
Sucrose Laurate	Rabbit (Japanese white)	Females, n = 6	10% Sucrose Laurate (prepared from a 38% solution) diluted in water	*Max Primary Draize Rabbit Skin Irritation Score Test*: 0.15 mL of solution applied to shaved skin and secured with occlusive patches for 24 h, patches removed 24 h post-treatment and evaluated for erythema and edema; use of controls not specified	Max Primary Draize Skin Irritation Score is 3.0 (no further details provided)	[62]
Sucrose Laurate	Guinea Pig (Dunkin Hartley)	Females, n = 3	2% Sucrose Laurate solution	*Skin Irritant Potential Test*: 250 ± 10 mg of solution applied by repeated topical application to left and right flanks; skinfold thickness measured at 20 min, 8, 24, 32, and 48 h postchallenge (no further details provided); use of controls not specified	Skinfold thickness unaffected by repeated applications; nonirritating	[38]
Sucrose Acetate Isobutyrate	Guinea Pig (Hartley Guinea Pig)	n = 5	0.5 mL Sucrose Acetate Isobutyrate (concentration and vehicle not specified)	Irritation test similar to the Acute Dermal Irritation/Corrosion test (OECD Guideline 404) was conducted (GLP) by applying treatment to shaved skin (test material secured by occlusive wrap) for 24 h; skin observed for 14 days; controls were not used	Nonirritating; weight gain normal; no percutaneous absorption evident	[18]

(continued)

Table 15. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
HUMAN						
Sucrose Palmitate (80% mono-, 17% di-, 3% tri-) Sucrose Stearate (48% mono-, 34% di-, 14% tri-)	Human	Female subjects, n = 8 (irritation profile study)	Nanoemulsions: oil phase (drug aceclofenac), 1%-2% (w/w) egg lecithin, 10% medium chain triglycerides, 10% castor oil, 0.05% butylhydroxy-toluene -aqueous phase: 0%-2% (w/w) Sucrose Palmitate; 0%-2% (w/w) Sucrose Stearate	*Irritation Profile Test*: 25 μL/cm^2 nanoemulsions (nanoemulsions tested on human skin all contained aceclofenac; controls used were nontreated skin both with and without occlusion) applied to 3 × 3 cm^2 forearm surface area; erythema index, transepidermal water loss, and stratum corneum hydration evaluated prior to testing (to establish a baseline) and 3 h after removal of 24 h occlusion; negative controls used	3 h after occlusion was removed no cutaneous adverse reactions were visually observed; no change in erythema index values; transepidermal water loss increased substantially relative to baseline but not compared to nontreatment controls; stratum corneum hydration showed substantial decrease in all treated sites compared to baselines and nontreated control under occlusion; nanoemulsions tested were tolerable to the skin	46
Sucrose Pentahydroxystearate	Human	n 40	100%	Human Patch Test was performed (no further details specified)	Negative (0% after 24 h, no further details specified)	58
Sucrose Tetraisostearate	Human	n = 40	100%	Human Patch Test was performed (no further details specified)	Negative (0% after 24 h, no further details specified)	58
Sucrose Polycottonseedate	Human	n = 34 subjects, but only 27 completed study	4 UV protectant prototypes, 3 containing 0.5% Sucrose Polycottonseedate and 1 containing 1% Sucrose Polycottonseedate; no vehicle used	Treatment applied each day occlusively (to back for 24 h) in a 21-day study; negative controls used	Erythema observed (4 subjects) in test group, erythema noted (23 subjects) in control group; slightly irritating	20
Sucrose Polycottonseedate, Sucrose Polybehenate	Human	n = 11 (all subjects completed study)	Lotion squeezed from cleansing cloths containing 3.18% Sucrose Polybehenate and 12.73% Sucrose Polycottonseedate; water vehicle	Lotion containing treatment was applied daily at 100%, 50%, and 20% (v/v) occlusively for a 5-day cumulative study; same dosages were applied semiocclusively to back for 24 h, 4×; negative controls used	Nonirritating	19,20
Sucrose Polycottonseedate	Human	n = 55 subjects per product (49 using 17.19% Sucrose Polycottonseedate cloths and 50 using 15.79% Sucrose Polycottonseed cloths completed study)	Two facial cleansing cloths containing Sucrose Polycottonseedate at 17.19% and 15.79%; no vehicle used	Treatment administered 2×/d for 4 wk in a single blind study (uncontrolled conditions); use of controls not specified	1 subject discontinued study on day 8 (mild erythema and dryness with 17.19%); at 4 wk 5 subjects had mild to moderate conjunctival follicles, mild papillae, mild cysts, mild to moderate concretions, mild mucous lens deposits, and severe blurred vision; 2 subjects did not complete due to adverse reactions (severe itching, moderate erythema, papules, tightness, hives and skin dryness, difficulty focusing, conjunctival injection); symptoms in 1 subject were reproducible when retested 3 wk later after 4 days of application and determined to be	20

(continued)

Table 15. (continued)

Test Substance(s)	Species/Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
					treatment related; 1 subject retested on arm 12 days later with no symptoms, but symptoms returned upon facial application; 18 of 50 subjects (using 17.19%) and 12 of 50 subjects (using 15.79%) reported mild skin or eye conditions (dryness, redness, itching, stinging or burning, blurred vision); 4 of 30 reactions >mild but <severe and these effects may be related to constituents in formulation and not Sucrose Polycottonseedate	

GLP = Good Laboratory Practice; OECD = Organization for Economic Co-operation and Development.

Table 16. Irritation and Sensitization Studies (Dermal).

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
			ANIMAL			
Sucrose Acetate Isobutyrate	Guinea Pig	Unknown	*Skin Irritation Test*: 5-20 mL of 20% Sucrose Acetate Isobutyrate in acetone + corn oil (9:1) *Delayed Sensitivity Test*: Sucrose Acetate Isobutyrate in acetone/ dioxane/guinea pig fat (7:2:1)	*Skin Irritation Test*: Treatment was applied directly to hairless guinea pig skin and held in place by a secured gauze pad for 24 h *Delayed Sensitivity Test*: 10 drops of solution (concentration not specified) applied to hairless guinea pig skin and examined at 24 and 48 h postadministration for irritation; 3 more applications administered in 5 days followed by 3 wk rest period; challenge concentrations (not specified) applied to right shoulder and 1 wk later to left shoulder Use of controls not specified	Skin Irritation Test: Slight, transient irritation noted Delayed Sensitivity Test: No increased reactivity observed	[60]
Sucrose Acetate Isobutyrate	Guinea Pig (Hartley Guinea pig)	Males, n = 10	*Induction*: 1% Sucrose Acetate Isobutyrate in Freund's Complete Adjuvant *Challenge*: 10% Sucrose Acetate Isobutyrate; Vehicle = acetone + dioxane + guinea pig fat (7:2:1)	Guinea Pig Maximization Test performed, guidelines followed were similar to OECD 406 (Skin Sensitization), GLP, challenge used Kodak foot pad method) *Induction*: Treatment applied to shaved skin and occlusively secured (no further details specified) *Challenge*: Treatment applied topically; skin observed 24 h postchallenge Negative (vehicle) controls used	Light erythema at exposure site for 5 of 10 controls and 6 of 10 animals previously induced with treatment; nonsensitizer	[18]
			HUMAN			
Sucrose Acetate Isobutyrate	Human	N = 203 (40 males, 163 females) completed study; 38 additional subjects did not complete study	20% Sucrose Acetate Isobutyrate (industrial grade) in acetone (1 of 6 substances tested, others were plasticizers/lubricants)	Human Repeat Insult Patch Test (HRIPT) was performed using GLP (more specific details not provided); use of controls not specified	One subject reported enlarged lymph nodes (cervical area) and was discontinued in study (details do not indicate whether this was treatment related); 1 adverse event related and one possibly related to treatment reported (details not specified); during induction phase isolated reports of slight erythema and 2 reports of mild erythema; at challenge 3 reports of slight erythema at 48 h (resolved by 96 h) postadministration and 1 report slight erythema first appearing at 96 h postadministration; nonirritating, no evidence of sensitization	[18]

(continued)

Table 16. (continued)

Test Substance(s)	Species/ Strain	Test Population-Sex	Concentration (Vehicle)	Procedure	Results	Reference
Sucrose Polycottonseedate	Human	n = 113 (5 discontinued study for personal reasons, no reactions from treatment); 108 subjects completed study	88% Sucrose Polycottonseedate in a lipstick topcoat matrix	HRIPT protocol followed (occlusive patch, 4 cm^2) using undiluted test material (0.2 g); induction phase was approximately 3 wk; rest period was approximately 2 wk; use of controls not specified	Staining of skin was observed in 1 subject during induction phase; no reactions were observed during rest period; no reactions at challenge; nonsensitizing	61
Sucrose Polycottonseedate	Human	n = 233 (28 male, 205 female); 200 completed the study; 102-normal skin; 98-sensitive skin	4 UV protectant prototypes, 3 containing 0.5% Sucrose Polycottonseedate and 1 containing 1% Sucrose Polycottonseedate; no vehicle used	HRIPT was performed by applying treatment occlusively (to back for 24 h) at 72 h intervals × 9 applications; the rest period was 10-26 days; challenge patches similarly applied to a previously untreated area and removed at 24 h postapplication; use of controls not specified	No subjects discontinued the study due to treatment-related effects; during induction scattered positive findings for all formulations with up to 8 showing definite erythema especially in sensitive skin group; at challenge 1, subject showed definite erythema and 2 subjects had doubtful responses; no sensitization reported since numbers of responses at challenge were no higher than induction period treatment; researchers conducting this study reported that results were nonirritating	20
Sucrose Polycottonseedate, Sucrose Polybehenate	Human	n = 113 subjects (24 male and 89 female); 102 completed study	Lotion squeezed from cleansing cloths containing 3.18% Sucrose Polybehenate and 12.73% Sucrose Polycottonseedate; no vehicle used	HRIPT was performed by applying treatment occlusively (to back for 24 h) at 72 h intervals × 9 applications; the rest period was 10-14 days; challenge patches similarly applied to a previously untreated area and removed at 24 h postapplication; use of controls not specified	During induction definite erythema noted in 1 subject; at challenge 4, doubtful responses at 24 h; no challenge responses at 48 h; no sensitization due to responses at challenge generally lower than single induction treatment; researchers conducting this study reported that results were nonirritating	19,20
Sucrose Polycottonseedate	Human	n = 108 subjects (7 male and 101 female); 107 completed study	Two facial cleansing cloths containing Sucrose Polycottonseedate at 17.19% and 15.79%; no vehicle used	HRIPT was performed by applying treatment occlusively (to back for 24 h) at 72 h intervals × 9 applications; the rest period was 10-14 days; challenge patches similarly applied to a previously untreated area and removed at 24 h postapplication; use of controls not specified	Up to 1 subject at any observation time for either product showed definite erythema; no challenge responses at 48 h postapplication, at 24 h postapplication, 2 subjects showed definite erythema; no sensitization since numbers at challenge were lower than after single induction treatment; researchers conducting this study reported that results were nonirritating	20

GLP = Good Laboratory Practice; OECD = Organization for Economic Co-operation and Development.

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