Safety Assessment of Saccharide Esters as Used in Cosmetics

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All interested persons are provided 60 days from the above date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Director, Dr. Lillian J. Gill.

The 2016 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This safety assessment was prepared by Laura N. Scott, Scientific Writer/Analyst.

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INTRODUCTION

This safety assessment includes the 42 saccharide esters listed below. Only maltitol laurate has been reviewed previously by the Cosmetic Ingredient Review (CIR) Expert Panel (Panel); in 2008, the Panel concluded that this ingredient is safe as used in cosmetics.[1] The saccharide esters below are listed in alphabetical order; they are also shown in Table 1, ordered by sub-groups according to chain length.

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

Sucrose Palmitate/ Stearate, Sucrose Dipalmitate, and Sucrose Stearate-Palmitate Ester are not found in the *International Cosmetic Ingredient Dictionary and Handbook (Dictionary),* but they are included in the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP) as ingredients used in cosmetic products. Therefore, they are included in this safety assessment.

The saccharide esters have various reported functions in cosmetics, including use as emollients, emulsion stabilizers, and plasticizers.[2] Xylityl Sesquicaprylate, for example, 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 Xylityl, have been evaluated by the Panel (2014) and found to be safe as used in cosmetics; the conclusion for each of these saccharide moieties are presented in Table 3.[1,3-14] 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 non-irritating.[15] Several of the constituent acids that are used to synthesize some of the saccharide esters in this report have been previously reviewed by the Panel; summaries of those safety conclusions are also presented in Table 3.[1,3-14]

Sucrose Acetate Isobutyrate is generally recognized as safe (GRAS) for use as a direct food additives in the United States.[16] Given its GRAS status, the focus of this assessment for Sucrose Acetate Isobutyrate will be on dermal effects, primarily dermal irritation and sensitization.

Study reports and unpublished data included in this safety assessment were found on the European Chemicals Agency (ECHA) website, on the Australian Government Department of Health's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) website, and in a report published by the World Health Organization (WHO). The ECHA and NICNAS websites provide data summaries from industry. The WHO report is cited when unpublished data from that report 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 either glucose (monosaccharide), sucrose (disaccharide composed of glucose and fructose), the sugar alcohol maltitol derived from maltose (disaccharide composed of two glucose molecules; α-1,4 bond), trehalose (disaccharide composed of two 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 chainlength, degree of esterification, and/or regiospecificity of subsititution. For example, Maltitol Laurate contains a monoester of maltitiol and lauric acid but, without further specification, it is unknown whether it also contains 1) other chain length fatty acid residues (e.g., myristate), 2) di-, tri-, or tetra-esters, or 3) esterification at a different active site (free hydroxyl group). (Figure 1.)

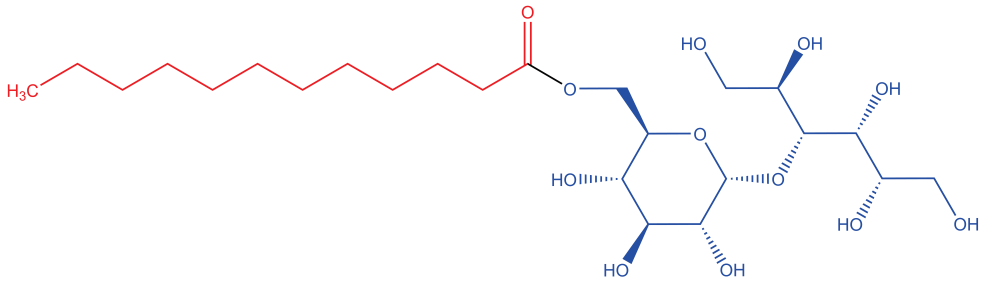


Figure 1. Maltitol Laurate, a saccharide ester

The wide range of hydrophilic-lipophilic balance (HLB), characteristic of sucrose esters, allow these chemicals to function as oil-in-water (high HLB values) and water-in-oil emulsifiers (low HLB values).[17] The hexa-, hepta-, and octa- substituted esters are used as fat replacers in food. The lower substituted esters (e.g. 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 higher HLB values. Secondary to that effect is the fatty acid chain length; the shorter the chain, the higher the HLB value.

The ingredients included in this safety assessment are listed in order by sub-groups according to chain length in Table 2 along with their definintions, structures, and functions in cosmetics, according to the *Dictionary*.

Chemical and Physical Properties

Sucrose fatty acid esters (e.g., Sucrose Laurate) may be stiff gels, soft solids, or white/slightly gray powders.[18] Generally, they are sparingly soluble in water, depending on the percentage of mono esters, and soluble in ethanol. The chemical and physical properties of the saccharide esters evaluated in this safety assessment are listed in Table 4.

Method of Manufacture

The Food Chemical Codex also recites that sucrose fatty acid esters (e.g., Sucrose Laurate) may be prepared from sucrose, the methyl and ethyl esters of edible fatty acids, or edible, naturally-occurring vegetable oils, using food-grade solvents such as ethyl acetate, methyl ethyl ketone, dimethyl sulfoxide, or isobutanol.[18]

Impurities

Lead impurities are acceptable at not more than (NMT) 1 mg/kg in sucrose acetate isobutyrate used in food, according to the Food Chemicals Codex.[18] The following acceptance criteria apply for sucrose fatty acid esters in food: lead (NMT 2 mg/kg in 10 g sample); dimethyl sulfoxide (NMT 2 mg/kg in a 5 g sample); ethyl acetate (NMT 350 mg/kg), isobutanol (NMT 10 mg/kg), methanol (NMT 10 mg/kg), and methyl ethyl ketone (NMT 10 mg/kg) in a 1 g powdered sample.

Sucrose Polycottonseedate contains mixtures of cottonseed acid esters[2]. Impurities known to be toxic that may be found in these ingredients include gossypol, aflatoxin, and cyclopropenoid fatty acids. In a CIR safety assessment published in 2001 evaluating Hydrogenated Cottonseed Oil, Cottonseed (Gossypium) Oil, Cottonseed Acid, Cottonseed Glyceride, and Hydrogenated Cottonseed Glyceride, the Panel concluded that Hydrogenated 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 ≤ 0.1 mg/kg; arsenic ≤ 3 ppm; mercury ≤1 ppm), and pesticide concentrations (NMT 3 ppm with NMT 1 ppm for any specific residue) are not exceeded.[19]

USE

Cosmetic

The safety of the cosmetic ingredients included in this assessment is evaluated on the basis of the expected use in cosmetics and potential exposure. The Panel utilizes data received from the FDA and from the cosmetics industry in determining the expected cosmetic use and potential exposure. The data received from the FDA are those collected from manufacturers on the use of individual ingredients in cosmetics, by product category, in its VCRP. Data from the cosmetic industry are submitted in response to a survey of maximum use concentrations, by product category, conducted by the Personal Care Products Council (Council). VCRP data obtained from the FDA in 2016[20] indicated that saccharide esters are being used in cosmetic formulations. In this safety assessment of 42 saccharide esters, according to the VCRP data, 24 are currently reported to be used in 970 cosmetic formulations. Among the ingredients most frequently used are Sucrose Acetate Isobutyrate (274 reported uses), Sucrose Cocoate (139 reported uses), and Sucrose Stearate (156 reported uses). All the other in-use saccharide esters are reported to have less than 75 uses, individually. The 2015-2016 concentration of use survey data [21] indicate the highest maximum reported concentrations of use are as follows: 0.0084-31% Sucrose Acetate Isobutyrate (up to 31% in eye shadow and foundation; up to 27% in lipstick); 0.21-14.3% Sucrose Benzoate (up to 14.3% in nail polish and enamel); 0.0001-20.6 % Sucrose Cocoate (up to 20.6% in shaving soap); 0.5-87.7% Sucrose Polycottonseedate (up to 87.7% in lipstick); 0.0086-15% Sucrose Tetrastearate Triacetate (up to 10% in lipstick and up to 15% in mascara).

The frequency and concentration of use data are summarized, alphabetically by ingredient, in Table 5. Only one ingredient (Maltitol Laurate) has been previously reviewed by the Panel, but in the 2008 report, there were no frequency or concentration of use data reported for this ingredient.[1] According to 2016 VCRP data, there is one reported use of this ingredient in the hair non-coloring product category[20].

The 15 saccharide esters included in this safety assessment but not currently in use, according to the VCRP and Council industry survey, are recited in Table 6.

In some cases, reported uses of saccharide esters were available in the VCRP, but concentration of use data was not provided. For example, Sucrose Dipalmitate is reported to be used in 1 cosmetic formulation, but no use concentration data were reported.[20] Conversely, there were instances in which no reported uses were received in the VCRP, but a use concentration was provided in the industry survey. For example, Trehalose Undecylenoate was not reported in the VCRP to be in use, but the industry survey indicated that it is used in leave-on formulations up to 0.05% and rinse-off formulations up to 0.25%.[21] It should be presumed in these cases that there is at least one use in every category for which a concentration is reported.

Saccharide esters were reported to be used in perfumes, hair sprays, deodorants, and powders, and could possibly be inhaled. As examples, Sucrose Laurate is reportedly used in pump hair sprays at concentrations up to 1.2%; Sucrose Stearate is reportedly used in aerosol deodorant sprays at concentrations up to 0.23%; Sucrose Tristearate is reportedly used in powders at concentrations up to 2%.[21] 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.[22,23,24,25] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[22,23] 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.[23] 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.

Saccharide esters were reported to be used in products indicating potential eye exposure, possible mucous membrane exposure, possible ingestion, and baby products.

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.[26]

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 Title 21. Sucrose fatty acid esters are listed as direct food additives (21CFR172.859). Sucrose Octaacetate is used in over the counter (OTC) drugs as nail-biting and thumb-sucking deterrents, however due to the lack of adequate safety data Sucrose Octaacetate cannot be generally recognized as safe and effective in this application (21CFR310.536).

TOXICOKINETICS

Absorption, Distribution, Metabolism, Excretion

Absorption, distribution, metabolism, and excretion studies are summarized in Table 8.

Experiments conducted *in vitro* showed that a mixture of Sucrose Palmitate and Sucrose Stearate (1 μmol/ml, ^{14}C-labelled) was not transported from mucosal to serosal solution in intestinal tissues of rat homogenates; hydrolysis by mucosal rat homogenates was 10%

to 30% with little hydrolysis in whole blood.[27] Results from another rat test *in vitro* indicated that Sucrose Acetate Isobutyrate (up to 250 µg/ml, ^{14}C-labelled) was 75% hydrolyzed by intestinal mucosa in 6 hours; little hydrolysis noted in the stomach and liver.[28] In an *in vitro* study testing human fecal homogenates, 1 mg/ml and 0.1 mg/ml Sucrose Acetate Isobutyrate (^{14}C-labelled) were 40% and 60%, respectively, hydrolyzed in 16 hours.[28] In an *in vitro* study evaluating human nasal epithelial cells, 0.01 to 3 mg/ml Sucrose Laurate and Sucrose Myristate were found to substantially enhance paracellular permeability using a labelled dextran marker; effects were dose dependent.[29]

Tests conducted in rats revealed the following: Glucose Pentaacetate (20% aqueous solution) was rapidly absorbed (>90%) in 4 hours[30]; a mixture of Sucrose Palmitate and Sucrose Stearate (up to 250 mg/kg, ^{14}C-labelled) was excreted in feces (30% to 67% of dose), exhaled (11% to 49% of dose), and not detected in urine or blood at 120 hours post-dosing[27]; a mixture of sucrose esters (250 mg/kg, ^{14}C-labelled), including Sucrose Hexastearate, were hydrolyzed prior to intestinal absorption (lesser esterification compounds were better absorbed) and largely excreted in feces (>95% of dose) at 120 hours post-dosing[31]; 200 mg/kg of ^{14}C-labelled Sucrose Octaisobutyrate (a component of Sucrose Acetate Isobutyrate) was excreted in feces (78% to 93% of dose), excreted as a volatile product (3% to 15% of dose), and eliminated in urine (1% to 2% of dose).[32] In dogs and monkeys dosed with 200 mg/kg of ^{14}C-Sucrose Octaisobutyrate no radioactivity was detected in whole blood or plasma and excretion in feces was 77% to 94% of dose and 62% to 85% of dose, respectively.[32] In dogs, ^{14}C-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.[32] Human subjects administered a single, oral dose of 1.0 to 1.2 mg/kg ^{14}C-Sucrose Acetate Isobutyrate showed 41% to 66% of the dose was expired in the breath, 15% to 21% of the dose was eliminated in urine, and 10% of the dose was excreted in feces within 30 days post-administration.[33]

Dermal Penetration

Sucrose Laurate (30% mono-, 40% di-, 30% tri-) in an elastic vesicle formulation (50:50:5; Sucrose Laurate: micelle-forming surfactant PEG-8-L: stabilizer sulfosuccinate) was evaluated in human subjects ($n \geq 3$) for duration, volume, and occlusion.[34] In the duration test, the vesicles were applied non-occlusively (20 µL to a 1-cm^2 skin surface area) and tape stripping was performed 1 and 4 hours after the solution had dried. After the 1 and 4-hour treatments, vesicles were observed up to the 9th and 15th strips, respectively, with extensive vesicle fusion at the skin surface and stratum corneum. 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 between the 20 µL and 100 µL volumes, however, in the stratum corneum the 100 µL volume increased the amount of vesicle material (intact and fused) in the 9th strip. The occlusion test was performed by applying 100 µL of vesicle formulation, both occlusively and non-occlusively, 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) and lipid plaques; 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; there was fast penetration of vesicles into the stratum corneum; very few intact vesicles were present in the deeper layers of the stratum corneum.

Penetration Enhancement

Penetration experiments are summarized in Table 9.

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[35], and in rat skin Sucrose Laurate (30% aqueous solution) was found to be a penetration enhancer for the drug cyclosporine.[36] In a nanoemulsion Sucrose Stearate (1%) was a permeation enhancer for progesterone in an *in vitro* porcine skin test.[37] Animal tests *in vivo* revealed that Sucrose Laurate (5% in a hydrogel) increased skin hydration and penetration of the drug ibuprofen in a mouse tape-stripping experiment[38]; 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 oestradiol.[39] In a unique 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.[40]

Sucrose Palmitate (2%) and Sucrose Stearate (0.5%) in a tape-stripping (12x) experiment in human subjects showed increased skin absorption of the drug aceclofenac, which was detected at all depths of the stratum corneum.[41] Sucrose Oleate and Sucrose Laurate, both tested at 2% and 10% in human subjects, showed increased skin penetration of the drug 4-hydroxy-benzonitrile.[42]

TOXICOLOGICAL STUDIES

Single and repeated dose toxicity studies are summarized in Table 10.

An $LD_{50} > 20$ g/kg was reported for a study in which a single dose of Sucrose Acetate Isobutyrate was dermally applied to rats.[26] For rats and monkeys orally administered single doses of Sucrose Acetate Isobutyrate an $LD_{50} > 5$ g/kg and an $LD_{50} > 20$ g/kg, respectively, were reported.[26] In dogs orally administered a single dose of 2 g/kg Sucrose Acetate Isobutyrate an increase in plasma bromosulfophthalein (BSP) levels was reported.[43]

Repeated dose studies conducted in animals that were orally administered Sucrose Acetate Isobutyrate resulted in the following: in a 4 week study in mice fed 5 g/kg/day in their diet no effects were reported[43]; in a 12 week study in dogs dosed up to 4%/day in their diet no NOAEL was reported, but an increase in serum alkaline phosphatase (SAP) levels was observed[44]; reported in a 90 day study

in dogs was a NOAEL > 20 g/kg/day (2%), an increase in SAP (with 2% dose), and an increase in liver weights (with 0.6% and 2% doses)[26]; reported in a 1 year study in monkeys was a No Observed Adverse Effect Level (NOAEL) of 2.4 g/kg/day[45]; reported in a 1 year study in rats was a NOAEL of 2 g/kg/day.[46] Studies in which Sucrose Polysoyate was orally administered to dogs and rats in their diets for 28 and 90 days, respectively, reported a NOEL of 15%/day for each species and was found not to be absorbed by the gastrointestinal tract in either species.[47,48] Human subjects orally administered 0.02 g/kg/day of Sucrose Acetate Isobutyrate for 14 days experienced no blood chemistry or hematological abnormalities.[43]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

Reproductive and developmental toxicity studies are summarized in Table 11.

In animals orally exposed to Sucrose Acetate Isobutyrate test results showed the following: in a 3-generation study in rats teratogenic and developmental toxic effects were not observed and a NOAEL of 2 g/kg/day was reported[49]; in a study in which rabbits were dosed on days 7-19 of gestation by gavage a NOAEL of 1.2 g/kg/day was reported, 2 of 16 rabbits dosed at this level died on day 17 of gestation, and teratogenic or developmental toxic effects were not observed[38]; rats fed 9.38% in their diet for 5 weeks showed fewer pregnancies and fewer pup births with survival to weaning, however this was attributed to a potentially compromised nutritive value.[43]

GENOTOXICITY

Summary data from genotoxicity studies are presented in Table 12.

Sucrose Acetate Isobutyrate was evaluated *in vitro* and *in vivo*. An Ames test conducted in *Salmonella typhimurium* cells was non-toxic at concentrations up to 10,000 µg/plate.[50] 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. A chromosomal aberration assay in CHO cells showed no increase in aberrations up to 2000 µg/ml. An unscheduled DNA synthesis assay in rat hepatocytes was non-toxic at concentrations up to 10,000 µg/ml. An *in vivo* study in which male rats were administered a single dose (2000 mg/kg) by gavage and subsequently mated with untreated females was negative for dominant lethal mutations.[26]

CARCINOGENICITY

Animal

In a 2-year carcinogenicity study, F344 rats (n=50/sex/dose group) were fed a diet containing Sucrose Acetate Isobutyrate (available *ad lib.*). The nominal dose levels were 0 (control group 1), 0 (control group 2), 0.5, 1.0, and 2.0 g/kg/day .[46] 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. Hematology samples were collected from all surviving animals at study week 4.

Results of the 2-year study were: no Sucrose Acetate Isobutyrate 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 weeks at 0.5 g/kg/day and up to 73 weeks at 1.0 or 2.0 g/kg/day were observed; there was a decrease in male mean body weight at 2.0 g/kg/day compared to the first control group (but not compared to the second control group); gross and microscopic observations were unaffected by treatment; tumors found were typical of those that occur spontaneously in the F344 rat and were not treatment-related; organ weights of treated animals were similar to controls.[46] For 0, 0, 0.5, 1.0 and 2.0 g/ kg/day, the survival rates of males were 46%, 50%, 58%, 58%, and 60%, respectively, and of females 74%, 68%, 78%, 62%, and 68%, respectively. A NOAEL of 2 g/kg/day Sucrose Acetate Isobutyrate was reported.

A 2-year carcinogenicity study was also conducted in $B6C3F_1$ mice (n=50/sex/dose group).[46] A range finding study was conducted at 0, 0.625, 1.25, 2.5, and 5.0 g/kg/day Sucrose Acetate Isobutyrate (n=10/sex/dose) for 4 weeks. Results indicated that Sucrose Acetate Isobutyrate was well tolerated. Dose rates selected for the 2-year carcinogenicity study were 0, 0, 1.25, 2.5, and 5.0 g/kg/day Sucrose Acetate Isobutyrate (highest dietary concentration of Sucrose Acetate Isobutyrate at 4.4%). Hematology samples were collected from 15 animals/sex in the 5.0 g/kg/day group(s) and the control groups during weeks 28, 53, 79, and 105 of the study.

Results of the 2-year experiment in mice were: no Sucrose Acetate Isobutyrate 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/day compared to both control groups (not observed at 5.0 g/kg/day); occasional substantially different body weights in females with 1.25 g/kg/day and 5.0 g/kg/day (not found at 2.5 g/kg/day), which did not appear to be treatment related (there was no dose-response trend); tumors found were typical of those that occur spontaneously in the $B6C3F_1$ mouse and were not treatment-related; Sucrose Acetate Isobutyrate treatment-related decrease in mean absolute and relative kidney weights were noted at necropsy in males (not at all in females) fed 5.0 g/kg/day compared to controls; no gross or microscopic kidney changes were observed in males or females; microscopic findings were not caused by treatment.[46] For 0, 0, 1.25, 2.5 and 5.0 g/kg/day, the survival rates of males were 80%, 80%, 80%, 80%, and 74%, respectively, and 68%, 68%, 78%, 66%, and 78% for females, respectively. A NOAEL of 2.5 g/kg/day Sucrose Acetate Isobutyrate was reported for males and females.

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 104 weeks.[43] Although in the 9.38% treatment group 4 males died (with massive hemorrhages in multiple organs; no further information specified as to the cause of these) within 10 weeks of the study, this was not attributed to Sucrose Acetate Isobutyrate treatment. There were no substantial body weight differences among the groups at the end of the first year. However, 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% Sucrose Acetate Isobutyrate exhibited decreased body weight compared to controls in the second year of the study. Absolute and relative kidney weights in both males and females were noted at study termination. However, 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 Sucrose Acetate Isobutyrate treatment-related lesions were found upon histological examination.

IRRITATION AND SENSITIZATION

Irritation and Sensitization

Dermal irritation and sensitization studies are summarized in Table 13.

The skin irritation testing of Sucrose Laurate in animals resulted in the following: a hydrogel formulation (concentration of Sucrose Laurate unknown) containing 5% ibuprofen was non-irritating to mouse skin[38]; 5% and 15% hydrophilic gel formulations (also containing drug estradiol) showed increased epidermal thickness and some irritation potential when tested in rabbits[39]; a 2% solution was non-irritating when tested in guinea pigs[36]. In a guinea pig maximization test evaluating Sucrose Acetate Isobutyrate (10% solution at challenge), no sensitization was observed .[26]

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, showed a decrease in stratum corneum hydration, but was tolerable to the skin.[41] Sucrose Acetate Isobutyrate (20% solution) in a human repeat insult patch test (HRIPT) was non-irritating and non-sensitizing.[26] Sucrose Polycottonseedate (up to 1% formulation) was slightly irritating in a 21 day occlusive patch test in human subjects.[47] Sucrose Polycottonseedate (up to 13% solution) and Sucrose Polybehenate (up to 3% solution) was non-irritating in a 5 day occlusive patch test in human subjects.[47,48] Sucrose Polycottonseedate (16-17% in facial cleansing cloths) was non-irritating and non-sensitizing in a HRIPT.[47] In a HRIPT, Sucrose Polycottonseedate (88% in solid form) was non-sensitizing in human subjects.[51]

Ocular Irritation

A study in Japanese white female rabbits was conducted to evaluate the effects of Sucrose Laurate on rabbit eyes.[52] 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 sace of the left eye (right eye served as untreated control) of each of three 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.

A study evaluating the irritation of Sucrose Acetate Isobutyrate in New Zealand White rabbit eyes was conducted.[26] The guidelines followed in this study were similar to OECD 405 (Acute Eye Irritation/ Corrosion), using good laboratory practice (GLP). To the eyes of three rabbits 0.1 ml of a 50% Sucrose Acetate Isobutyrate dilution in corn oil was instilled into the conjunctival sac of all six eyes (3 washed and 3 unwashed, following application). Observations were noted for 72 hours post-application. Controls performed as expected. Moderate erythema of conjunctivae and nictitating membranes were noted in all unwashed eyes 1 hour post-application; slight erythema of conjunctivae and nictitating membranes observed in 2 of 3 unwashed eyes 24 hours post-application. At 48 hours post-application 2 of 3 unwashed eyes were normal and at 72 hours post-application 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 post-application. All washed eyes were normal at 24 hours post-application. Sucrose Acetate Isobutyrate was slightly irritating to rabbit eyes.

SUMMARY

The 42 saccharide esters included in this safety assessment have a variety of reported functions in cosmetics, i.e. surfactants, humectants, emulsion stabilizers, emollients, and skin conditioning agents.

VCRP data obtained from the FDA in 2016 indicate that 24 of the 42 saccharide esters named in this safety assessment are used in 970 cosmetic formulations. Sucrose Acetate Isobutyrate has the highest reported uses (274) with the next highest reported uses for Sucrose Stearate (156 reported uses) and Sucrose Cocoate (139 reported uses). Concentration of use industry survey data obtained by the Council in 2015-2016 indicate that the highest maximum reported concentrations of use are for Sucrose Polycottonseedate (up to 87.7% in lipstick), Sucrose Acetate Isobutyrate (up to 31% in eye shadow and foundation; up to 27% in lipstick), Sucrose Cocoate (up to 20.6% in shaving soap), Sucrose Benzoate (up to 14.3% in nail polish and enamel), and Sucrose Tetrastearate Triacetate (up to 15% in mascara and up to 10% in lipstick).

Saccharide esters are known to be used as penetration enhancers in pharmaceutical applications. They are also incorporated in foods as direct and indirect food additives (i.e. flavoring substances and emulsion stabilizers). Sucrose Acetate Isobutyrate is a GRAS direct food additive.

Toxicokinetics studies *in vitro* showed that Sucrose Palmitate, Sucrose Stearate, and Sucrose Acetate Isobutyrate were hydrolyzed in the intestinal mucosa of rats.

Toxicokinetics studies conducted in rats orally exposed to saccharide esters showed that: 90% of Glucose Pentaacetate (20% Glucose Pentaacetate dose) was absorbed in the gastrointestinal tract rapidly over 4 hours; 120 hours post-dosing, 30%-67% of Sucrose Palmitate (100-250 mg/kg doses) and Sucrose Stearate (100-250 mg/kg doses) were excreted in feces; 78-93% of Sucrose Octaisobutyrate, a constituent of Sucrose Acetate Isobutyrate (200 mg/kg dose), was excreted in feces; >90% Sucrose Acetate Isobutyrate remained in the intestinal tract at 6 hours post-dosing (50 mg/kg dose) with evidence of hydrolysis in the intestinal tract prior to absorption; lower doses of Sucrose Acetate Isobutyrate (27 mg/kg) were better absorbed than higher doses (100 mg/kg). For monkeys and dogs orally administered Sucrose Octaisobutyrate (200 mg/kg dose) 62%-85% and 77%-94% were excreted in feces, respectively. Generally in rats, dogs, and monkeys, sucrose esters were not found in whole blood or plasma following oral administration. 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) nine-fold (nasal) and four-fold (ocular).

Toxicokinetic studies in human subjects orally administered Sucrose Acetate Isobutyrate (0.1-1.0 g) showed partially hydrolyzed Sucrose Acetate Isobutyrate in urine. In another experiment (oral dose of 1.0-1.2 mg Sucrose Acetate Isobutyrate), the following excretions were observed in percentages of the applied doses: 41%-66% in breath, 15%-21% in urine, and 10% in feces within 30 days of dosing.

Human dermal penetration studies showed at 1- hour post dermal (non-occlusive) application of elastic vesicles containing Sucrose Laurate (50:50:5; Sucrose Laurate: micelle-forming surfactant PEG-8-L: stabilizer sulfosuccinate) that Sucrose Laurate was observed up to the 9^{th} tape strip and after 4 hours up to the 15^{th} 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 Stearate was shown to be an emulsifier and dermal drug (e.g. 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 (oestradiol) bioavailability by 15%; Sucrose Laurate was a percutaneous absorption enhancer in single dose drug (oestradiol) 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. 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.

The acute toxicology 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 one 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 an LD_{50} > 20 g/kg for oral administration of Sucrose Acetate Isobutyrate was reported.

Repeated dose toxicological studies using Sucrose Acetate Isobutyrate reported the following results: NOAEL of 2 g/kg/day for 1 year in rats; NOAEL of 2.4 g/kg/day for 1 year in monkeys; 10 g/kg/day for 15 days was well tolerated in monkeys; NOAEL 20 g/kg/day for 90 days in dogs; mice were unaffected by 5 g /kg/day for 4 weeks in diet. Experiments in rats (for 90 days) and in dogs (for 28 days) orally exposed to Sucrose Polysoyate revealed a NOEL of 15%/day. A study in which Sucrose Acetate Isobutyrate was orally administered up to 0.020 g/kg/day for 14 days to human subjects reported that blood chemistry, hematological parameters, and BSP retention were unaffected by treatment.

Reproductive and developmental toxicology studies reported a NOAEL of 2 g Sucrose Acetate Isobutyrate/kg/day in rats and a NOAEL of 1.2 g Sucrose Acetate Isobutyrate/kg/day in rabbits. 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 resulted in decreased pregnancies and decreased number of pups surviving to weaning, but this may have been attributed to compromised nutritional value at high Sucrose Acetate Isobutyrate concentrations.

Bacterial reverse mutation assay experiments (*in vitro*) in *S. typhimurium* up to 2000 µg Sucrose Acetate Isobutyrate/plate showed no mutagenic activity; an unscheduled DNA synthesis assay was negative for genotoxicity in rat hepatocyte cells up to 1000 µg Sucrose Acetate Isobutyrate/ml; an animal study in rats tested for dominant lethal mutations was negative up to 2000 mg Sucrose Acetate Isobutyrate/kg (male rats dosed once by gavage 2 hours prior to mating with untreated females). An Ames test in Chinese Hamster Ovarian/Hypox-anthine-Guanine Phosphoribosyl Transferase cells treated with up to 10,000 µg Sucrose Acetate Isobutyrate/plate was negative for genotoxicity.

Carcinogenicity bioassays were conducted in rats and mice. These studies reported oral NOAELs of 2 g/kg/day Sucrose Acetate Isobutyrate and 2.5 g/kg/day Sucrose Acetate Isobutyrate, for rats and mice respectively (5 g/kg/day was associated with a decrease in kidney weights and body weights in male mice). Another test in rats dosed up to 9.38% Sucrose Acetate Isobutyrate in the diet for 2 years indicated no treatment-related lesions.

Dermal exposure studies in test animals indicated that Sucrose Laurate (unknown concentration) in a hydrogel was non-irritating, and 5% to 15% was moderately irritating, but well tolerated. A 20% Sucrose Acetate Isobutyrate solution caused slight, transient irritation. A 1% solution of Sucrose Acetate Isobutyrate was non-sensitizing in a Guinea Pig Maximization Test. A 10% Sucrose Laurate solution and a 50% Sucrose Acetate Isobutyrate solution were slightly irritating to rabbit eyes.

Dermal exposure studies in human subjects produced the following results: 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; Sucrose Acetate Isobutyrate (20% in a HRIPT) was found to be non-irritating and non-sensitizing; Sucrose Polybehenate (~3%) was non-irritating and non-sensitizing; Sucrose Polycottonseedate at 0.5-1.0% was slightly irritating; Sucrose Polycottonseedate at 88% in a HRIPT was found to be non-sensitizing.

TABLES

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	Sucrose Acetate Isobutyrate	Sucrose Benzoate
Sucrose Octaacetate	Xylityl Sesquicaprylate (C8)	Sucrose Disinapate
Trehalose Undecylenoate (C11:1)	Sucrose Polylaurate (C12)	
Maltitol Laurate (C12)	Sucrose Polystearate (C18)	
Sucrose Laurate (C12)	Sucrose Polyoleate (C18:1)	
Sucrose Dilaurate 2(C12)	Sucrose Polylinoleate (C18:2)	
Sucrose Trilaurate 3(C12)	Sucrose Tetraisostearate (C18 branched)	
Sucrose Myristate (C14)	Sucrose Acetate/Stearate (C2, C18)	
Raffinose Myristate (C14)	Sucrose Tetrastearate Triacetate (C18, C2)	
Sucrose Palmitate (C16)	Sucrose Palmitate/ Stearate (C16, C18)	
Sucrose Dipalmitate (C16)	Sucrose Palmitate/ Stearate Ester (C16, C18)	
Raffinose Isostearate (C16 branched)	Sucrose Polysoyate (Soybean Oil fatty acid distribution: Oleic Acid, C18:1, 11.5-60.0%; Linoleic Acid, C18:3, 2.9-12.1%)[13]	
Sucrose Hexapalmitate 6(C16)		
Sucrose Stearate (C18)		
Sucrose Oleate (C18:1)	Sucrose Hexaoleate/ Hexapalmitate/ Hexastearate (C16, C18, C18:1)	
Trehalose Isostearate Esters (C18 branched)	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%)[13]	
Raffinose Oleate (C18)		
Sucrose Distearate 2(C18)		
Sucrose Tristearate 3(C18)		
Sucrose Tetrahydroxystearate 4(C18:OH)		
Sucrose Pentahydroxy-Stearate 5(C18:OH)		
Sucrose Polybehenate (C22)		
Sucrose Tribehenate 3(C22)	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)[13]	
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

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

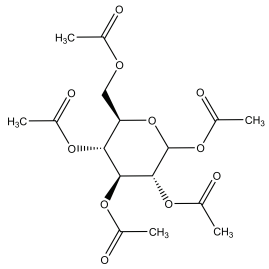
Name & CAS No.	Definition & Structure	Function(s)
	Alkyl Fatty Acid Esters (single chain length)	
Glucose Pentaacetate 3891-59-6 604-68-2	Glucose Pentaacetate is the pentaester of Glucose and Acetic Acid. 	Emulsion Stabilizers; Fragrance Ingredients

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

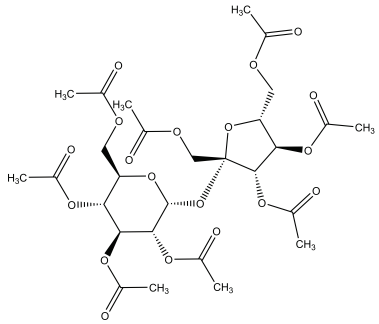
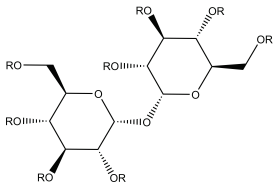
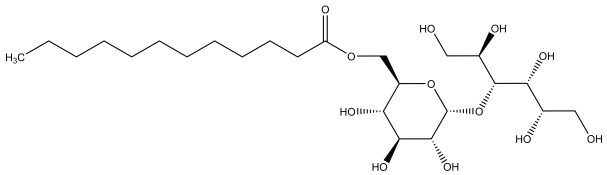
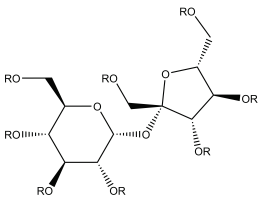
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Octaacetate 126-14-7	Sucrose Octaacetate is an acetylation product of Sucrose. It conforms to the formula:  where R represents the Acetic Acid radical.	Denaturants; Fragrance Ingredients
Trehalose Undecylenoate	Trehalose Undecylenoate is the ester formed by the reaction of Trehalose with undecylenic acid.  [wherein R is hydrogen or the residue of undecylenic acid (C11:1), where one R group is a 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
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 one R group is a Lauric Acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

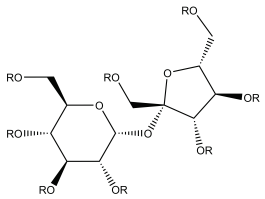
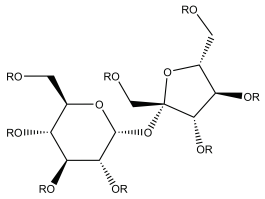
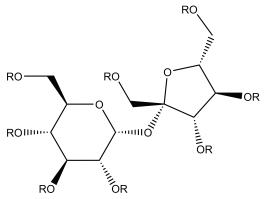
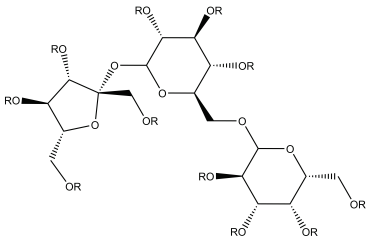
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Dilaurate 25915-57-5	Sucrose Dilaurate is the diester of Lauric Acid and Sucrose.  [wherein R is hydrogen or the residue of Lauric Acid (C12), where two R groups are Lauric Acid residues]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying 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 three 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 Myrisitic Acid (C14), where one 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 one R is the residue of Myristic Acid]	Skin-Conditioning Agents; Emollient; Surfactants-Emulsifying Agents

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

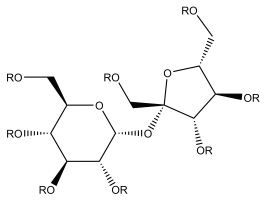
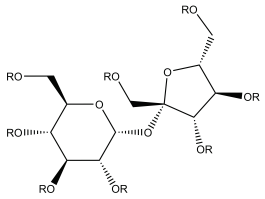
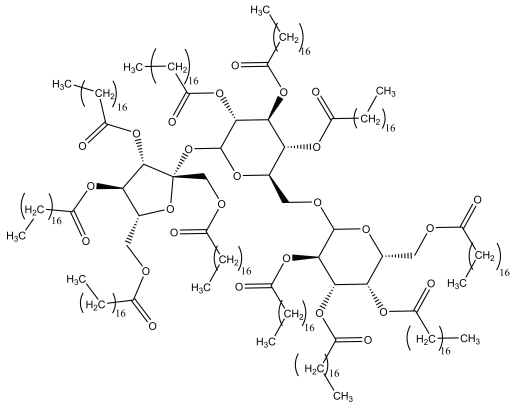
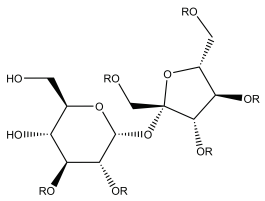
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Palmitate 26446-38-8 39300-95-3	Sucrose Palmitate is the monoester of Palmitic Acid and Sucrose.  [wherein R is hydrogen or the residue of Palmitic Acid (C16), where one R group is a Palmitic Acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
[Sucrose Dipalmitate] ***Reported to the FDA's VCRP, but not recited in the INCI Dictionary	[Sucrose Dipalmitate is the diester of Palmitic Acid and Sucrose.  wherein R is hydrogen or the residue of Palmitic (C16) Acid, where two 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 residue of Palmitic (C16) Acid]	Surfactants-Dispersing Agents; Surfactants-Emulsifying Agents

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

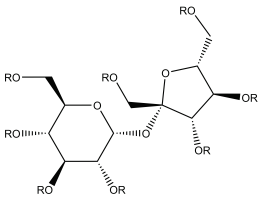
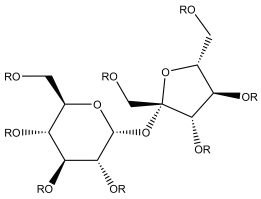
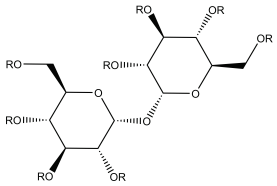
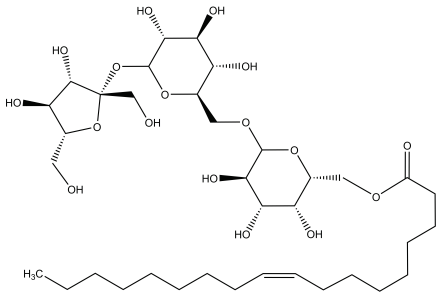
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Stearate 25168-73-4 37318-31-3	Sucrose Stearate is the monoester of Stearic Acid and Sucrose.  [wherein R is hydrogen or the residue of Stearic Acid (C18), where one R group is a Stearic Acid residue]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying 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 one R group is a Oleic Acid residue]	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. 	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

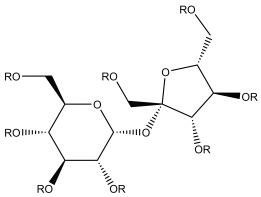
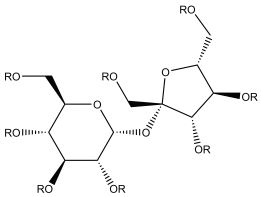
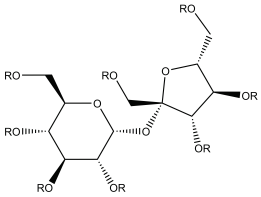
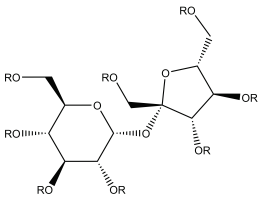
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Distearate 27195-16-0	Sucrose Distearate is a mixture of sucrose esters of Stearic Acid consisting primarily of the diester.  [wherein R is hydrogen or the residue of Stearic Acid, where two R groups are Stearic Acid residues]	Skin-Conditioning 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 three R groups are Stearic Acid residues]	Skin-Conditioning Agents-Emollient
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 five R groups are Hydroxystearic Acid residues]	Skin-Conditioning Agents-Humectant

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

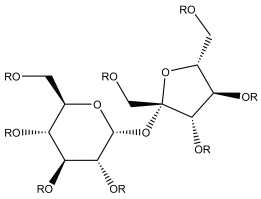
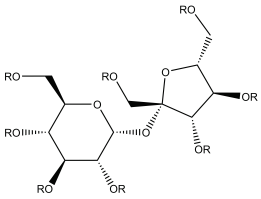
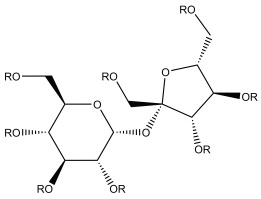
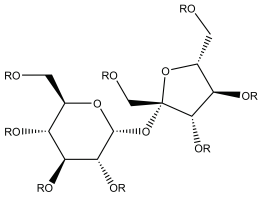
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Polybehenate 93571-82-5	Sucrose Polybehenate is a mixture of esters of behenic acid and Sucrose.  [wherein R is hydrogen or the residue of behenic acid (C22)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Tribehenate 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 three 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 five 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 six R groups are erucic acid residues]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Alkyl Fatty Acid Esters (mixed chain lengths)		

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

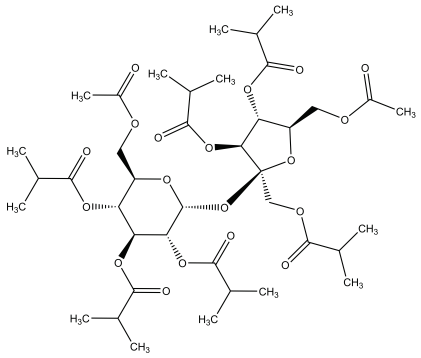
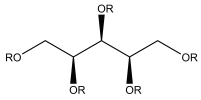
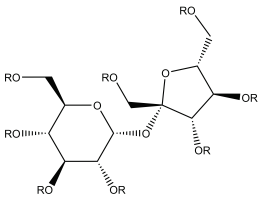
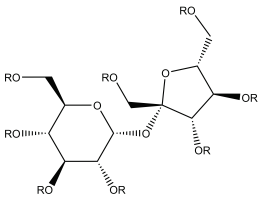
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Acetate Isobutyrate 126-13-6	Sucrose Acetate Isobutyrate is the mixed ester of Sucrose and Acetic and isobutyric Acids. 	Plasticizers
Xylityl Sesquicaprylate 181632-90-6	Xylityl Sesquicaprylate is a mixture of mono- and diesters of caprylic acid and the hexitol anhydrides derived from xylitol.  [wherein R is hydrogen or the residue of caprylic acid (C8), where one or two R groups are caprylic acid residues]	Antimicrobial Agents; Skin-Conditioning Agents-Humectant; 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 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

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

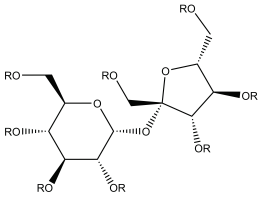
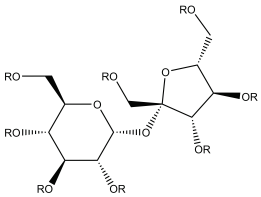
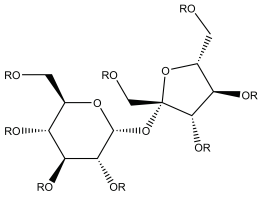
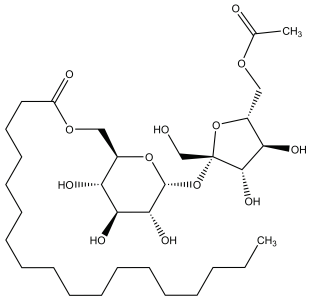
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Polyoleate	Sucrose Polyoleate is a mixture of esters of Oleic Acid and Sucrose.  [wherein R is hydrogen or the residue of Oleic Acid (C18:1)]	Skin-Conditioning Agents-Emollient; Surfactants-Emulsifying Agents
Sucrose Polylinoleate	Sucrose Polylinoleate 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
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 Acetate/Stearate 52439-69-7	Sucrose Acetate/Stearate is the mixed ester of Sucrose with Acetic and Stearic Acids.  [**one example of a mixed ester]	Skin-Conditioning Agents-Emollient

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

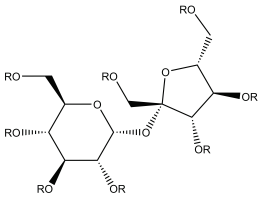
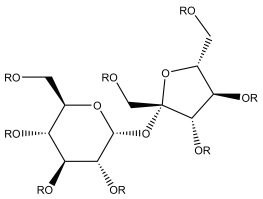
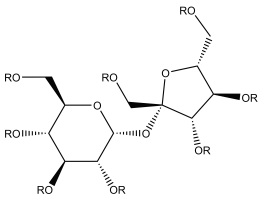
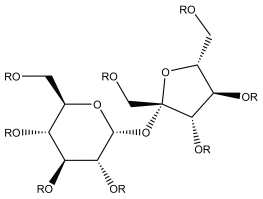
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Tetrastearate Triacetate	Sucrose Tetrastearate Triacetate is a mixture of esters of Stearic Acid, Acetic Acid and Sucrose.  [wherein R is hydrogen or the residue of Stearic (C18) or Acetic (C2) Acid, where three R groups are Stearic Acid residues and three R groups are Acetic Acid residues]	Skin-Conditioning Agents-Emollient
[Sucrose Palmitate/Stearate] ***Reported to the FDA's VCRP, but not recited in the INCI Dictionary	[Sucrose Palmitate/Stearate is the monoester of Palmitic Acid or Stearic Acid, and Sucrose.  wherein R is hydrogen or the residue of Palmitic (C16) or Stearic (C18) Acid, where one R group is an acid residue]	N/A
[Sucrose Palmitate-Stearate Ester] ***Reported to the FDA's VCRP, but not recited in the INCI Dictionary	[Sucrose Palmitate-Stearate Ester is the monoester of Palmitic Acid or Stearic Acid, and Sucrose.  wherein R is hydrogen or the residue of Palmitic (C16) or Stearic (C18) Acid, where one 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

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

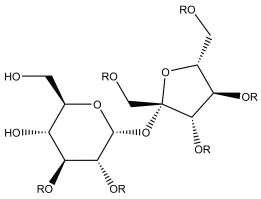
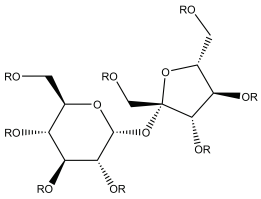
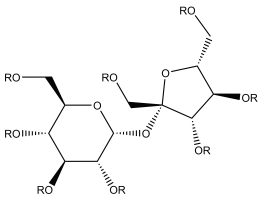
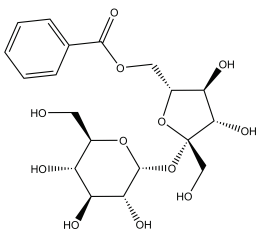
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Hexaoleate/ Hexapalmitate/Hexastearate	Sucrose Hexaoleate/Hexapalmitate/Hexastearate is the hexaester of Sucrose and Oleic, Palmitic, and Stearic acids.  [wherein R is residue of Oleic (C18:1), Palmitic (C16), or Stearic (C18) Acid]	Surfactants-Dispersing 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 one, and in most cases only one, 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
	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: 	Plasticizers

Table 2. Definitions, structures, and functions of the ingredients in this safety assessment.[2;CIR Staff]

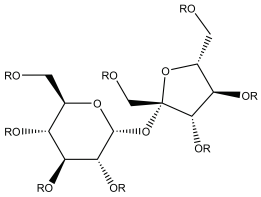
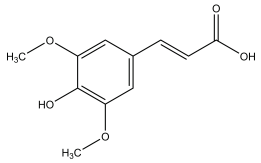
Name & CAS No.	Definition & Structure	Function(s)
Sucrose Disinapate	Sucrose Disinapate is the diester of Sucrose and sinapic acid  [wherein R is hydrogen or the residue of sinapic acid, where two R groups are sinapic acid residues]  [sinapic acid]	Skin-Conditioning Agents-Miscellaneous

Table 3. Constituent sugars, alcohols, and acids with CIR 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)	14
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)	1,14
Sucrose	Safe as used (2014; 58% in leave-ons; 65% in rinse-offs)	14
Trehalose	Safe as used (2014; 2% in leave-ons; 1% in rinse-offs)	14
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)	14
	ACID	
Acetic Acid	Safe as used (2012; 0.0004% in leave-ons; 0.3% in rinse-offs)	12
Benzoic Acid	Safe as used (2011; 5% in leave-ons; 5% in rinse-offs)	10,11
Coconut Acid	Safe as used (2011; not reported in leave-ons; 14% in rinse-offs)	9,13,53
Cottonseed Acid	Safe as used (2011; no reported use)	13,19
Hydroxystearic Acid	Safe as used (1999; 10% in leave-ons; not reported in rinse-offs)	8
Isostearic Acid	Safe as used (1983; 10% leave-ons; 5% rinse-offs); Reaffirmed in 2005	6,7
Lauric Acid	Safe as used (1987; 1% in leave-ons; 25% in rinse-offs); Reaffirmed 2006	4,5
Myristic Acid	Safe as used (2010; 10% in leave-ons; 19% in rinse-offs)	3-5
Oleic Acid	Safe as used (1987; 25% in leave-ons; 50% in rinse-offs); Reaffirmed in 2006	4,5
Palmitic Acid	Safe as used (1987; 25% in leave-ons; 25% in rinse-offs); Reaffirmed in 2006	4,5
Soy Acid	Safe as used (2011; no reported use)	13
Stearic Acid	Safe as used (1987; 50% in leave-ons; 50% in rinse-offs); Reaffirmed in 2006	4,5

*Not previously reviewed by the Panel

Table 4. Chemical and physical properties

Property	Value	Reference

Table 4. Chemical and physical properties

Property	Value	Reference
Glucose Pentaacetate		
Molecular Weight	390.34 g/mol	54
Density (predicted)	1.30±0.1 g/ml	54
Melting Point (experimental)	130-131.5 °C	55
Log P (predicted)	0.634±0.488	54
Water Solubility	Slightly soluble in water @ pH 7, 25 °C	54
Raffinose Oleate		
Molecular Weight	785.89 g/mol	56
Sucrose Acetate Isobutyrate		
Physical Form	Clear, pale yellow, viscous liquid	18
Molecular Weight	846.91 g/mol	56
Density (predicted)	1.22±0.1 g/ml	54
Water Solubility	Slightly soluble	18
Other Solubility	Very soluble in essential oils (orange); soluble in ethanol, ethyl acetate	18
Log P (predicted)	6.619±0.825	54
Sucrose Benzoate		
Melting Point (from patent)	98 °C	57
Sucrose Dilaurate		
Molecular Weight	706.90 g/mol	56
Sucrose Distearate		
Molecular Weight	875.22 g/mol	56
Melting Point (experimental)	76-78 °C	58
Sucrose Hexapalmitate		
Molecular Weight	1772.75 g/mol	56
Sucrose Laurate		
Molecular Weight	524.60 g/mol	56
Sucrose Myristate		
Molecular Weight	569.66 g/mol	56
Melting Point (experimental)	180-186 °C	59
Sucrose Octaacetate		
Molecular Weight	678.59 g/mol	56
Density (predicted)	1.37±0.1 g/ml	54
Melting Point (experimental)	89-93 °C	60
Water Solubility	0.909 g/L (hygroscopic)	61
Other Solubility	Very soluble in methanol, chloroform; soluble in ether	61
Log P (predicted)	1.440±0.812	54
Sucrose Oleate		
Melting Point (experimental)	54-56 °C	58
Sucrose Polybehenate		
Appearance	White waxy solid @ 20°C, 760 mmHg	48
Density	900-950 g/ml@72°C	48
Melting Point	72°C	48
Water Solubility	$\leq 4.26 \times 10^{-5}$ g/L @ 24°C	48
Log Pow (n-octanol/water)	3.55±0.16 @ 20°C	48
Sucrose Polycottonseedate		
Appearance	Amber, viscous liquid	47
Density	900-950 g/L at 71°C	47
Water Solubility	4.96×10^{-6} to 4.26×10^{-5} g/L @ 24°C	47
Log Pow (n-octanol/water)	3.55±0.16 @20°C	47
Sucrose Stearate		
Molecular Weight	608.76 g/mol	56
Melting Point (experimental)	67-71 °C	62
Sucrose Trilaurate		
Molecular Weight	889.20 g/mol	56
Sucrose Tristearate		
Molecular Weight	1141.68 g/mol	56

Table 4. Chemical and physical properties

Property	Value	Reference
Xylityl Sesquicaprylate		
Molecular Weight (predicted)	278.34 g/mol	[54]
Density (predicted)	1.170±0.06 g/ml	[54]
Water Solubility (predicted)	Slightly soluble @ pH 7, 25 °C	[54]
Log P (predicted)	1.387±0.735	[54]
pka (predicted)	13.02±0.20	[54]

Table 5. Current frequency and concentration of use of saccharide esters according to duration and exposure[20,21]

	# 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/ Hexastearte**	
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
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

Table 5. Current frequency and concentration of use of saccharide esters according to duration and exposure[20,21]

	# of Uses	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*	*# of Uses*	*Max Conc Use (%)*
	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
	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

Table 5. Current frequency and concentration of use of saccharide esters according to duration and exposure[20,21]

	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)	# of Uses	Max Conc Use (%)
	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
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

[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[20]

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

Table 7. Non-Cosmetic Uses

Ingredient	Non-Cosmetic Use	References
Glucose Pentaacetate	Direct food additive, synthetic flavoring substance	21CFR172.515; [63]
Sucrose Acetate Isobutyrate	Direct food additive, stabilizer of flavoring oil emulsions used in nonalcoholic beverages, Sucrose Acetate Isobutyrate content in beverage ≤ 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/day; WHO established ADI up to 20 mg/kg/day	21CFR172.833; 21CFR175.105; [16, 64, 65]
Sucrose Benzoate	Indirect food additive-component of adhesives; FDA reported cumulative estimated daily intake 0.00035 mg/kg/day	21CFR175.105; [66]
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	[63]; 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

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
				IN VITRO				
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	Not applicable	Yes	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; cells treated and transepithelial electrical resistance measured; paracellular permeability experiments performed using fluorescein isothiocyanate labelled dextran as a marker across epithelial cells	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 to 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); 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	[29]
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	1 µmol/ml ^{14}C-Sucrose Ester (intestinal absorption studies); 2mM ^{14}C-Sucrose Ester (pancreatic fluid hydrolysis); 20 mM ^{14}C-Sucrose Ester (liver and mucosa hydrolysis); 5 mM ^{14}C-sucrose esters (whole blood hydrolysis)	Not applicable	Yes	Intestinal absorption studies-bicarbonate buffer solutions were incubated for 1 h; serosal fluid, mucosal fluid and tissue were assayed for radioactivity; Artificial Pancreatic Fluid Hydrolysis-artificial pancreatic fluid aliquots were removed at 0, 0.5, 1, 2, and 4 h and assayed; Hydrolysis by Liver Homogenates and Intestinal Mucosa- incubation for up to 4 h for liver homogenates and 1 h for mucosal homogenates; 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 transport of ^{14}C-labelled 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 (10% of Sucrose Mono-Stearate, 30% of Sucrose Mono-Palmitate) considerably faster than by artificial pancreatic juice (9% of Sucrose Mono-Stearate, 15% of Sucrose Mono-Palmitate); liver homogenates hydrolyzed 20% of Sucrose Mono-Stearate or Sucrose Mono-Palmitate; hydrolysis of sucrose esters in whole blood showed 10% hydrolysis of Sucrose Mono-Palmitate and 2.4% of Sucrose Mono-Stearate	[27]

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
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)	Not applicable	Yes	Rat homogenates of the gut contents, liver, and intestinal mucosa were prepared and assayed	^{14}C-Sucrose Acetate Isobutyrate was hydrolyzed in intestinal mucosa (75% in 6 h) by non-specific esterases, but little hydrolysis in stomach and liver	[28]
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)	Not applicable	Yes	Human fecal homogenates were prepared and assayed; human feces bacteria cultured, hydrolysis was measured	40% of 1 mg/ml in fecal homogenates was hydrolyzed by 16 h (<2% hydrolyzed completely to sucrose); 60% of 0.1 mg/ml in fecal homogenates was hydrolyzed (5% completely de-esterified) by 16 h; only 2 strains each of E. *coli*, Streptococcus and Bacteroides and 1 strain of bifidobacteria resulted in > 15% degradation of ^{14}C-Sucrose Acetate Isobutyrate in 20 h (many E. *coli* and Lactobacillus strains yielded <5% hydrolysis)	[28]
ANIMAL								
Oral								
Glucose Pentaacetate	Rat (Wistar)	Male rats, fasted prior to dosing; n=37 total for all studies	Aqueous non-radioactive 20% Glucose Pentaacetate (intestinal absorption study); 10% radioactive Glucose Pentaacetate (repeated dose study); 10% radioactive Glucose Pentaacetate (metabolism study)	Oral intubation	Yes	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; Repeated Dose Retention Study-rats were dosed (1-ml) daily for 2, 7, or 14 days then were killed and carcass assayed for radioactivity; 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 $C^{14}O_2$ for 48 h post-dosing; urine and feces collect during this 48 h period	Gastrointestinal tract absorption is rapid (>90% in 4 h); 2% recovered from feces at 48 h; radioactive equilibrium by 7days; rats exposed to 10% Glucose Pentaacetate for 2 yr excreted 76% as CO_2 compared to rats not previously exposed to Glucose Pentaacetate (excreted 65% as CO_2); Glucose Pentaacetate is hydrolyzed to lesser acetylated metabolites which are detected in urine	[30]

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Palmitate (mono-) and Sucrose Stearate (mono-, di-); >95% purity	Rat (Wistar)	Male rats fasted prior to dosing	100 or 250 mg/kg ^{14}C-sucrose esters (excretion study); 250 mg/kg ^{14}C-sucrose esters (lymph evaluation); 250 mg/kg ^{14}C-sucrose esters (portal system study)	Oral	Yes	Excretion Study-single dose, $^{14}CO_2$, urine, feces were analyzed for radioactivity; Absorption Via Mesenteric Lymphatic System-performed by cannulating thoracic ducts of anaesthetized rats, fasting then dosing (single) rats, lymph collected at 2, 4, 6, 10, 24 h; Absorption Via Portal System-single dose, blood samples from portal and femoral veins taken at 1, 2, and 4 h then assayed for radioactivity	Within 120 h post-dosing 30%-67% ^{14}C-sucrose esters were excreted in feces and 11%-49% exhaled; urinary excretion of radioactivity was 0.7%-4.9% of the dose; no intact Sucrose Ester was found in the urine; very little intact Sucrose Stearate was transported from the intestinal tract to lymph; 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	[27]
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)	Oral gavage (corn oil)	Yes	24 h fast, rats dosed (single); expired CO_2, urine, feces collected 120 h post-dosing; blood, tissue, and lymph analyzed	>95% of the dose of sucrose esters was found in feces; lesser esterification compounds were better absorbed; sucrose esters were hydrolyzed before absorbed in the intestines; by 120 h post-dosing ^{14}C sucrose esters were found in fat, lymph node, liver, and blood samples	[31]
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	Oral gavage (corn oil)	Yes	Animals fasted prior to dosing; single dose; evaluations of CO_2, urine, feces, bile, and blood analysis were performed	3%-15% excreted as volatile products, 1%-2% in urine, 78%-93% in feces; peak CO_2 radioactivity 24-36 h post-dosing suggested delayed absorption, <0.2% excreted in bile, evidence of extensive gut hydrolysis; no radioactivity found in whole blood or plasma post-dosing	[32]
Sucrose Octaisobutyrate-(a component of Sucrose Acetate Isobutyrate)	Dog (Beagle)	male dogs, n=3	200 mg/kg ^{14}C-Sucrose Octaisobutyrate	Oral gavage (corn oil)	Yes	Animals fasted prior to dosing; single dose; evaluations of CO_2, urine, feces, bile, and blood analysis were performed	^{14}C recovered 1% in 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 post-dosing	[32]
Sucrose Octaisobutyrate-(a component of Sucrose Acetate Isobutyrate)	Monkey (Cynomolgus)	male monkeys, n=3	200 mg/kg ^{14}C-Sucrose Octaisobutyrate	Oral gavage (corn oil)	Yes	Animals fasted prior to dosing; single dose; evaluations of CO_2, urine, feces, bile, and blood analysis were performed	62%-85% excreted in feces, <2% eliminated in CO_2,1% or less in urine, not hydrolyzed in gut or absorbed, 0.1%-0.2% excreted in bile, little intestinal metabolism occurred; no radioactivity found in whole blood or plasma post-dosing	[32]

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Wistar)	Both sexes	50 mg/kg ^{14}C-Sucrose Acetate Isobutyrate (female rats); 20 mg/kg ^{14}C-Sucrose (one 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	Oral intubation (corn oil)	Yes	Metabolism studies were conducted in female rats; caecum absorption/hydrolysis tested in anaesthetized male rats; intestinal absorption studies conducted in anaesthetized rats	>90% radioactivity remained in intestinal tract 6 h post-dosing (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 gastro-intestinal tract); 50% excreted radioactivity 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	[28]
Sucrose Acetate Isobutyrate	Rat	For ^{14}C-Sucrose Acetate Isobutyrate treatments n=6	26, 28, 89, 98 mg/kg ^{14}C-Sucrose Acetate Isobutyrate in corn oil; 5.8 and 11.2 mg/kg ^{14}C-Sucrose Acetate Isobutyrate in aqueous emulsion; 400 mg/kg ^{14}C-Sucrose and 112 mg Sucrose/4 ml by stomach tube	Intragastric intubation	Yes	Metabolic parameters (CO_2, urine, feces) were evaluated after single dose	For 5.8 and 11.2 mg/kg ^{14}C-Sucrose Acetate Isobutyrate 59% and 52% detected in breath, 11% and 13% in urine, 23% and 27% in feces within 3 days post-dosing; 6.0% and 6.6% in carcass after 3 days post-dosing; ^{14}C-Sucrose rapidly absorbed and metabolized to $^{14}CO_2$	[33]
Sucrose Acetate Isobutyrate	Dog	n=2	4.8 and 3.0 mg/kg ^{14}C-Sucrose Acetate Isobutyrate in aqueous emulsion	Intragastric intubation	Yes	Metabolic parameters (CO_2, urine, feces) were evaluated after single dose	28% and 27% detected in breath, 7% and 5% in urine, 53% and 46% in feces within 7 days post-dosing	[33]

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
^{14}C-Sucrose Acetate Isobutyrate	Rat	n=3	Oral doses: 19.8 (rat 1), 41.5 (rat 2), or 50.6 (rat 3) mg/kg; no dose available for intragastric intubation	Oral (gavage)	No	Non-Good Laboratory Practice (GLP) study; Single oral dose; rat bile ducts cannulated and bile collected (after intragastric intubation) continuously for 65 h (rat 1) and 2-3 days (rats 2 and 3)	Material passed slowly through gastrointestinal tract (no feces) for rat 1 (78% in intestines 3 days post dose); rapid peak in bile elimination 1-2 h post dose, falling off 3-4 h post dose for rats 2 and 3; 12.4% and 35.1% dose 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	[26]
Sucrose Acetate Isobutyrate	Rat, Dog (Beagle)	Rats n=3; Dog , male n=1	4.0 mg/kg ^{14}C-Sucrose Acetate Isobutyrate	Oral (gavage)	No	Non-GLP study; test animals were fed unlabeled Sucrose Acetate Isobutyrate for 7 days (2nd trial) and 4 days (3rd trial) before dosing with ^{14}C-Sucrose Acetate Isobutyrate emulsion; 15 g unlabeled Sucrose Acetate Isobutyrate in corn oil administered to dog just prior to 3rd trial; bile ducts of rats and dog cannulated and bile collected 11-16 h following single oral dose; feces analyzed; no details of 1st trial provided	Dog: 67-75% Sucrose Acetate Isobutyrate eliminated in feces within 7.5-9 h; 2%-6% excreted in bile after 11-16 h; Results from rat tests not provided	[26]
Sucrose Acetate Isobutyrate	Rat (Holtzman)	Rat-male, corn oil administration n=2/dose level; aqueous emulsion n=2 for ^{14}C-Sucrose Acetate Isobutyrate; n=2 for ^{14}C-Sucrose	Unlabeled 2.5, 5 g/kg (prelim study); ^{14}C-Sucrose Acetate Isobutyrate in corn oil 26,28,89,98 mg/kg ; ^{14}C-Sucrose Acetate Isobutyrate in aqueous emulsion 5.8,11.2 mg/kg; 371, 405 mg/kg ^{14}C-Sucrose	Oral gavage	No	Non-GLP study; unlabeled Sucrose Acetate Isobutyrate administered in preliminary study; single doses administered; post-dosing (corn oil) metabolism parameters monitored for 4 days; post-dosing (aqueous emulsion) parameters monitored for 3 days	Rats fed unlabeled Sucrose Acetate Isobutyrate eliminated ethanol-extractable acetate and isobutyrate 16%-60% of dose within 6 days, at 2.5 mg/kg increased urinary excretion of combined acetic acid equivalent to 36%-46% of dose; Rats-corn oil dosed showed 45%-50% absorbed at higher doses, 74%-82% at lower doses from intestinal tract; Sucrose Acetate Isobutyrate rapidly eliminated at all doses, 90%-93% eliminated within 4 days with 97% of the total elimination occurring within 2 days; 55-67% 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 in gut; aqueous emulsion dose Sucrose Acetate Isobutyrate largely absorbed from gut; unabsorbed material in feces was highly acylated sucrose; >73% excreted as CO_2 in exhaled air in 3 days; 14%-18% eliminated in urine; no fat incorporation of Sucrose Acetate Isobutyrate detected	[26]

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Holtzman)	Male, n=?	27 or 100 mg/kg ^{14}C-Sucrose Acetate Isobutyrate	Oral intubation (corn oil)	Not specified	Single dose administered and CO_2 in exhaled air, urine, feces, blood, liver, and kidney evaluated	Gastrointestinal tract absorption was 74%-82% (27 mg/kg) and 45%-50% (100 mg/kg); eliminated 88%-90% by 48 h; 100 mg/kg dose eliminated 54%-56% as CO_2 and 26%-28% in urine; 27 mg/kg dose eliminated 63%-67% as CO_2 and 23%-25% in urine; <1% remaining in gastrointestinal tract, blood, liver, kidney at 4 days post admin; 24 h feces samples had Sucrose Acetate Isobutyrate + metabolites; most of radioactivity in urine was identified as sucrose with other unidentified compounds present	[43]
Sucrose Acetate Isobutyrate	Rat (Holtzman)	Male, n=?	100 mg/kg ^{14}C-Sucrose Acetate Isobutyrate	Oral gavage (corn oil)	Not specified	Single dose administered and metabolic parameters monitored	3-3.5 h post administration: 78%-84% recovered from gastrointestinal tract; 7%-9% from stomach, intestinal, caecal tissues; <4% excreted in breath, urine, feces; gastrointestinal tract + organ extracts contained sucrose, partially-acylated sucrose esters, and unchanged Sucrose Acetate Isobutyrate	[43]
Sucrose Acetate Isobutyrate	Rat	Not specified	^{14}C-Sucrose Acetate Isobutyrate, no further details provided	Oral	Not specified	Single dose administered	Eliminated 7%-10% in urine within 30-46 h post-dosing; ^{14}C molecules larger than sucrose not detected in urine (sucrose, glucose, and fructose absent)	[43]
Sucrose Acetate Isobutyrate	Dog	Not specified	^{14}C-Sucrose Acetate Isobutyrate, no further details provided	Oral	Not specified	Single dose administered	Eliminated 2.8%-5.2% in urine within 29-30 h post-dosing; ^{14}C molecules larger than sucrose not detected in urine (sucrose, glucose, and fructose absent)	[43]
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 via a pipetter; IV through right femoral vein of anesthetized rats; ocular via pipetter in left eye of anesthetized rat	Yes	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% to 0.5% increased (not linearly, i.e. physiological response to insulin has an effect maximum) compared to controls; Sucrose Cocoate increased absorption of insulin through the ocular route from 5µU/ml to 59 µU/ml (0.5% Sucrose Cocoate); nasal absorption of insulin with Sucrose Cocoate caused larger increase in plasma insulin levels (9x) than ocular delivery of the same insulin concentration (4x); 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	[67]
HUMAN								

Table 8. Toxicokinetic Studies-Absorption, Distribution, Metabolism, Excretion (ADME)

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Human	Males n=2 (single dose); Males n=2 (multi-dose); 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 x7 days (multi-dose study); 0.1g x7 days (fecal excretion study); 100, 250, and 500 mg sucrose iv as 10% (w/v)	Oral, IV	Not specified	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 multi-dose study urine was assayed for total sucrose); For 3 days feces collected post-dosing and assayed for glucose; Urine collected at 3, 12, and 24 h and assayed for glucose after acid hydrolysis (sucrose clearance study)	0.1 g or 1 g showed <0.4% excreted in urine as parent compound or metabolites w/disaccharide moiety; with 1 g x 7 days, similar result as above; with 0.1 g in 1 subject x 7 days, no unchanged Sucrose Acetate Isobutyrate or metabolite detected in fecal samples; urinary excretion following iv showed 50% sucrose recovered in urine after 3 h at all three dose levels; partially hydrolyzed Sucrose Acetate Isobutyrate in urine; absorption of partially esterified sucrose molecules from intestinal tract is insignificant	[28]
Sucrose Acetate Isobutyrate	Human	n=7 subjects total	1.0-1.2 mg/kg ^{14}C-Sucrose Acetate Isobutyrate (n=6) and 0.2 mg/kg (n=1) in non-carbonated beverage; ^{14}C-Sucrose administered @ 400 mg/kg ^{14}C-Sucrose; ^{14}C-Sucrose and unlabeled sucrose (25 or 28 g in 200 ml) administered to 2 subjects	Oral	Not specified	Human subjects administered single dose; breath and urine samples collected for 25-30 days and fecal samples collected for 5 days post-treatment	Subjects eliminated in breath 41-66%, urine 15-21%, feces 10% of dose within 30 days; subjects dosed ^{14}C-Sucrose eliminated 50% in breath, 2.7% in urine, <0.3% 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 elimination; in humans urinary elimination species are more polar (mostly sugar esters, very little free sucrose)	[33]
Sucrose Acetate Isobutyrate	Human	Male, n=1	1.18 mg/kg ^{14}C-Sucrose Acetate Isobutyrate	Oral	Not specified	Single dose administered; urine samples collected at 0 and 6.2 h post-dosing and assayed	Glucose, fructose, and the esters of fructose and sucrose were not detected in urine; metabolites (2 unidentified chromatographic peaks) thought to be principal metabolites of Sucrose Acetate Isobutyrate	[43]

Table 9. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
IN VITRO								

Table 9. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
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	Yes	At time zero 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	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	[35]
Sucrose Laurate	Yucatan Micropig	Yucatan Micropig skin	oil-in-water microemulsion containing Sucrose Laurate used for drug delivery; composition ratio 25:19:5:60, Sucrose Laurate:ethanol :iso-propyl 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	Yes	Skin was exposed to microemulsion containing polyphenols (chlorogenic acid/resveratrol), buffered for 6, 20, and 40 h then assayed	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 vehicle to epidermis, but slower distribution from epidermis to dermis	[68]
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)	Not Specified	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 15x; remaining skin was homogenized and assayed	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 (i.e. 2% Sucrose Laurate in micellar solution or 2% Sucrose Laurate in hydrogel) demonstrated that SL is an effective dermal penetration enhancer for hydrophilic substances	[36]

Table 9. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Stearate	Pig	Porcine skin	Nanoemulsions (used for dermal drug delivery); 2.5% w,w Sucrose Stearate in aqueous phase w/hydrdophilic 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 acceptor chambers of Franz-type diffusion cells	Yes	Receptor compartment 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 acceptor chamber at intervals for analysis (of drug content) and replaced by fresh receptor medium	Sucrose Stearate was shown to be an emulsifier with physical and chemical stability; pH decreased with increasing Sucrose Stearate concentrations due to residual, non-esterified fatty acids (up to 10%, based on manufacturer supplied info); drug permeation enhancement comparable to that of lecithin-based emulsions	[69]
Sucrose Stearate	Pig	Porcine 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 acceptor chambers of Franz-type diffusion cells	Yes	Receptor compartment 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 acceptor chamber at intervals for analysis (of drug content) and replaced by fresh receptor medium	Sucrose Stearate was a skin permeation enhancer for progesterone and helped to stabilize the nanoemulsion	[37]
ANIMAL								
Sucrose Laurate	Mouse (SKH-1 hairless mice)	15-wk old male mice	Sucrose Laurate (unknown concentration) in hydrogel containing 5% ibuprofen	Dermal	Yes	Tape stripping (up to 18x) used to collect corneocytes from uppermost layer of dorsal skin 30 min post treatment	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	[38]

Table 9. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Laurate	Rabbit (White New Zealand)	Male rabbits, n=9	5% and 15%, w/w Sucrose Laurate in hydrophilic gels (also containing 60 µg oestradiol and a preservative), pH 6	Dermal	Yes	Rabbits fasted 24 h pre-treatment and during treatment; 100 mg gels were applied on days 1 and 7 to hairless 3x3 cm skin area; days 2-6 placebos applied; blood samples taken from marginal ear vein 0.5 thru 12 h post administration; skin biopsies (taken from application site and untreated skin) evaluated for epidermal thickness	Bioavailability parameters were substantially higher after single application of oestradiol with 15% compared to oestradiol with 5%; epidermal skin-fold thickness and infiltration was 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 indicate that Sucrose Laurate is a percutaneous absorption enhancer	[39]
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, IV	Yes	*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; *in vivo* studies performed by microsyringe administration into nasal cavity and IV administration via tail vein, blood samples collected 2 h post-dosing	Intranasal absorption-enhancing effect (increasing with time and concentration); absolute drug bioavailability of 30% (*in vivo* rat experiment)	[40]
HUMAN								

Table 9. Penetration Enhancement Studies

Test Substance(s)	Species	Sample Type/Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
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	Yes	Tape-Stripping Study: Nanoemulsions (25 $\mu L/cm^2$) applied to 4 cm^2 forearm surface area for 2 h, after which residual test substance removed, tape stripping performed at least 12x	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)	[41]
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	Yes	Test formulation (1.5ml) applied via filter paper (11.5 x 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 post admin; 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)	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	[42]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
ACUTE								
Dermal								
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n=5/sex/dose	20 ml/kg Sucrose Acetate Isobutyrate (vehicle not specified)	Dermal	Single dose; 24 h	Dose applied to hairless skin, occlusively wrapped for 24 h, post-dose 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}>20,000 mg/kg for male and female rats	[26]
Oral								
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n=5/sex/dose	5000 mg/kg Sucrose Acetate Isobutyrate, in corn oil	Oral (gavage)	Single dose	Dose administered, 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 post-dosing); no treatment-related effects at necropsy	[26]
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)	Oral	Single dose	Dose administered; use of controls not specified	Oral doses produced no mortality in mice and mortality in 1 of 7 rats	[70]
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n=2 male, 2 female	1.25, 2.50, 5.00, 10.00, 20.00 g/kg Sucrose Acetate Isobutyrate (vehicle: orange juice concentrate)	Oral (gavage)	Incremental with 72 h in between	Doses administered incrementally (72 h between) until 20 g/kg reached or toxicity occurred; no controls	LD_{50}>20,000 mg/kg for male and female monkeys; yellow/ watery emesis or stools observed (at doses 1.25, 2.5, 5.0 g/kg); 24 h post-dosing with 20.0 g/kg loose stools noted; body weight and gross pathology were unaffected; food consumption was slightly less during treatment	[26]
Sucrose Acetate Isobutyrate, Sucrose Octaisobutyrate	Monkey (Cynomolgus)	n=10	5 g/kg Sucrose Acetate Isobutyrate, 5 g/kg Sucrose Octaisobutyrate (corn oil vehicle)	Oral	Single dose	Dose administered, 30 min bromosulfophthalein (BSP) retention and serum alkaline phosphatase (SAP) measured 5 h post-dosing; controls were used	BSP and SAP measurements, clinical observations, and body weight were unaffected by treatment (intervals for hepatic function measurements not optimized)	[43]
Sucrose Acetate Isobutyrate	Dog (Beagle)	Male, n=3 (dosed), n=2 (controls)	2 g/kg Sucrose Acetate Isobutyrate in corn oil	Oral	Single dose	Dose administered, BSP clearance measured 0.5, 2, 4, 6, 10, 12, 18 or 24 h post-dosing; controls were used (delayed BSP clearance rates are indicative of inhibited liver function)	Plasma BSP levels increased at all post-dosing measurements compared to pre-dosing values (5 h post-dosing was max BSP retention)	[43]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
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)	Oral	Single dose	Dose administered, BSP and SAP measured; controls were used	Sucrose Hexaacetate Diisobutyrate increased BSP (5-7x) at all doses tested vs. pretreatment values; Sucrose Octaisobutyrate increased BSP (4-5x) 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	[43]
REPEATED DOSE								
Animal								
Sucrose Acetate Isobutyrate	Rat (Wistar)	n=5	4% Sucrose Acetate Isobutyrate	Oral	7 days	Dosed daily in diet for 7 days; BSP measured at 0 (pretreatment) and 24, 48 h following withdrawal from treated feed ; use of controls not specified	BSP clearance unaffected	[43]
Sucrose Acetate Isobutyrate	Squirrel monkeys (*Saimiri sciureus*)	n=3 males/group (6 total animals)	1 g Sucrose Acetate Isobutyrate in 2 ml cottonseed oil	Oral	1 week	Dosed daily in diet; 24 h post-treatment BSP clearance measured; 7 days rest then treatment for groups reversed; controls were used	BSP clearance was normal in 2 of 3 monkeys in each group	[43]
Sucrose Acetate Isobutyrate	Squirrel monkeys (*Saimiri sciureus*)	n=3 males/group (6 total animals)	2 g Sucrose Acetate Isobutyrate in 4 ml cottonseed oil	Oral	1 week	Dosed daily in diet; 24 h post-treatment BSP clearance measured; 7 days rest then treatment for groups reversed; controls were used	High plasma BSP detected in 3 controls, however authors considered this to be a technical error when BSP clearance following Sucrose Acetate Isobutyrate treatment was normal in all animals	[43]
Sucrose Acetate Isobutyrate	Dog (Beagle)	n=2/sex	0.1, 0.3, 0.5% Sucrose Acetate Isobutyrate	Oral	2 weeks	Dosed daily in diet; tested for BSP clearance 24 and 48 h post-feeding; rest period of 1 week 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%	[43]
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/day; orange juice vehicle	Oral (gavage)	15 days	Dosed daily in diet for 15 days; controls were used	Body weight and food consumption unaffected; postmortem exam showed no change; no alteration in ultrastructural organization of hepatocytes	[43]
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	n=1/sex/group (4 groups, 8 total animals)	0, 2.0, 5.0, 10.0 g/kg /day; orange juice vehicle	Oral (gavage)	15 days	Dosed daily in diet for 15 days; controls were used	Body weight, food consumption, and clinical parameters (including BSP retention) unaffected	[43]
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n=15/sex/ group	0, 5000, 50,000 ppm Sucrose Acetate Isobutyrate	Oral	3 weeks	Dosed daily in diet for 3 weeks; 5 rats/sex/group killed after 1, 2, and 3 weeks treatment; controls were used	No effects on gross necropsy, liver weights, body weight, or food consumption	[43]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Mouse (B6C3F1/ Cr1BR)	n=10/sex/ group	0, 0.625, 1.25, 2.5, 5.0 g kg/day Sucrose Acetate Isobutyrate	Oral	4 weeks	Dosed daily in diet for 4 weeks; controls were used	No effect on biological performance; no treatment related effects observed at necropsy	[43]
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n=not specified	4% Sucrose Acetate Isobutyrate + corn oil	Oral	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; controls were used	ICG plasma clearance rates no different from controls	[43]
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	Rats n=40/sex/ group	Group 1 (basal diet); Group 2 (basal diet + sodium phenobarbital 100 mg/kg/day by gavage); Groups 3-5=2.5, 5.0, 10.0%/day Sucrose Acetate Isobutyrate in diet, respectively	Oral	6 and 12 weeks	Rat study: Dose administered daily as indicated; each group divided into 2 subgroups (n=20/subgroup) that were treated for 6 and 12 weeks; in each subgroup n=10 rats were used for zoxazolamine test (after which fed basal diet for 4 week 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; controls were used	NOAEL reported at 10%/day in diet; no deaths from treatment; mean body weights decreased in males at all dose levels 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 zoxaolamine hypnotic activity were unaffected by treatment; liver glycogen levels increased in males and females fed 10%/day; absolute mean heart weights decreased in all treated males	[44]
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%/day Sucrose Acetate Isobutyrate in diet, respectively	Oral	12 weeks	Dose administered daily as indicated for 12 weeks; additional dogs n=4/sex fed Sucrose Acetate Isobutyrate at 2.0% in diet for 12 weeks followed by 2 weeks withdrawal period (basal diet without Sucrose Acetate Isobutyrate); 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%/day for 12 weeks 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; no NOAEL reported	[44]
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%	Oral	90 days	Dosed daily in diet for 90 days; 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	[43]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose 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, 2.00%/day Sucrose Acetate Isobutyrate in diet, cottonseed oil vehicle	Oral	90 days	OECD Guideline 409 (repeated dose 90-day oral tox in non-rodents) followed (non-GLP); dosed daily in diet for 90 days; controls were used	NOAEL male and female dogs>20,000 mg/kg/day (2.00%); food consumption, hematological parameters, urinary exam, and gross pathology/ necropsy unaffected; increase in SAP at 2%; increase in liver weight at 0.6% and 2%	[26]
Sucrose Acetate Isobutyrate	Dog (Beagle)	Males n=10 (2 groups of 5)	5%/day Sucrose Acetate Isobutyrate,c orn oil vehicle	Oral	91 days	OECD Guideline 409 (repeated dose 90-day oral tox in non-rodents) followed (non-GLP); dosed daily in diet for 91 days; 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	[26]
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)	Oral	13 weeks	Dosed daily in diet for 13 weeks; 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	[43]
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	Males and females, n=10/sex/ group; n=10/sex for controls	0.38, 1.88, 9.38% /day Sucrose Acetate Isobutyrate (vegetable oil vehicle)	Oral	13 weeks	Non-GLP; dosed daily in diet for 13 weeks; controls were used	No toxic effects observed; at 9.38% no specific tissue changes in various organs, slight vacuolization of liver cells (control & treated groups) could be caused by 9.38% vegetable oil vehicle in diet; slight diarrhea for rats at higher doses	[26]
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%/day Sucrose Acetate Isobutyrate in 6% cottonseed oil); Exp 2 (5%/day Sucrose Acetate Isobutyrate in corn oil); Exp 3 (5%/day Sucrose Acetate Isobutyrate + 5% corn oil)	Oral	12 weeks; 86 days; 91 days	Exp 1 (36 dogs randomly assigned to each treatment group; dosed daily in diet for 12 weeks); 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); controls were used	Exp 1 (slight increase in SAP levels at 2%/day, increase dog liver weights with 0.6%/day and 2.0%/day); Exp 2 (increase in SAP and prolongation of ICG plasma clearance by liver with 5%/day for 4 weeks, after withdrawal of Sucrose Acetate Isobutyrate effects reversed in 2-5 weeks, when fed 5%/day again and tested 24 h post-dosing SAP unaffected, ICG clearance prolonged); Exp 3 (increase in SAP, prolongation of ICG clearance, increase in liver weight, increase in liver glycogen/ phospholipids)	[70]
Sucrose Acetate Isobutyrate	Rat (Holtzman)	n=25/sex/ group	0, 1.0, 5.0% Sucrose Acetate Isobutyrate (w/w)	Oral	95 days	Dosed daily in diet for 95 days; controls were used	Slight weight loss in males with 5%; slight increase in liver weight of females fed 5%; histopathological changes were unaffected	[43]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	Rats: Exp 1 n=25/sex; Exp 2 n=140/sex; Exp 3 n=not specified, males	Exp 1 (0.0, 1.0, 5.0%/day Sucrose Acetate Isobutyrate); Exp 2 (1.0, 2.0, 4.0%/day Sucrose Acetate Isobutyrate); Exp 3 (4.0% Sucrose Acetate Isobutyrate + 5.0% corn oil/day)	Oral	95 days; 28 or 56 days; 36 days	Exp 1 (25 rats randomly assigned to each treatment group; dosed daily in diet for 95 days); Exp 2 (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); Exp 3 (dosed daily in diet for 36 days to determine indocyanine green (ICG) clearance rates indicating liver functionality); controls were used	Exp 1 (with 5%/day showed lower body weight for males and slight increase in liver weight for females); Exp 2 (no toxicological effects); Exp 3 (no hepatic microsomal activity, slight depression of G-6-PTase activity)	[70]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Monkey (Cynomolgus)	Range finding study n=4/sex; 1yr Toxicological Study n=16/sex	For Range finding and 1-yr Toxicological study: 0, 500, 1450, 2400 mg/kg/day Sucrose Acetate Isobutyrate in corn oil	Oral (gavage)	4 weeks; 1 year	For 4 weeks (range-finding study) treatment was administered to 1 monkey/sex/dose/day; For 1 year (Toxicological study) treatment was administered to 4 monkeys/sex/dose/day; controls were used	No effect on hepatobiliary function; No Observed Adverse Effect Level (NOAEL) reported at 2400 mg/kg/day Range finding study (4 wks): 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/day), hematological values and BSP unaffected (no dose dependent effects), low terminal serum phosphorus in 1 female at 2400 mg/kg/day, no lesions, gross changes typical of spontaneous disease 1 Year Toxicological study: all doses were well tolerated, opthalmoscopic exam 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/day at 6 and12 months; statistically significant increase in prothrombin for all treated groups with 2400 mg/kg/day at 3 and 12 months; statistically significant increase in mean leucocyte count in females with 1450 mg/kg/day; statistically significant increase in mean segmented neutrophil in females with 1450 and 2400 mg/kg/day at 3 months; statistically significant decrease in serum phosphorus in males with 2400 mg/kg/day at 6 months; statistically significant decrease in alanine aminotransferase in males with 2400 mg/kg/day at 9 and 12 months; statistically significant decrease in serum glucose in males with 1450 mg/kg/day at 6 months and statistically significant increase in males with 2400 mg/kg/day at 6 months; statistically significant decrease in aspartate aminotransferase and serum glucose in females with 1450 mg/kg/day at 6 months; at necropsy statistically significant decrease in mean weight thyroid/parathyroid glands in males with 500 mg/kg/day; statistically significant decrease in mean absolute weight of ovaries and ovary/brain weight ratio in females with 2400 mg/kg/day	[45]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (F344)	n=20/sex/dose level	Highest doses fed were up to 5% of diet (beyond which risks nutritional deficiency); acetone vehicle, 1 Year study: 0, 0 (two control groups), 0.5, 1.0, 2.0 g/kg/day Sucrose Acetate Isobutyrate	Oral	1 year	Dose administered daily in diet for 1 year; controls were used	NOAEL reported at 2 g/kg/day for males and females; body weight gain decreased likely from nutritional deficiencies in females with 2 g/kg/day at week 17 and beyond and in males with 2 g/kg/day at weeks 13 and 54; 1 female died with 0.5 g/kg/day group, 1 female killed in moribund condition with 2 g/kg/day group, 1 control and 2 treated rats died during blood collection; clinical and ophthalmic observations unaffected; food consumption decreased in females with 2g/kg/day; clinical chemistry, urine analysis, BSP retention unaffected with 2g/kg/day; statistically significant hematology values occurred in doses <2g/kg/day at varying times in study but were normal again by 54 weeks; at necropsy absolute organ weights unaffected; no neoplastic or non-neoplastic microscopic changes; no gross or microscopic changes in liver	[46]
Sucrose Acetate Isobutyrate	Rat (Fischer 344)	Males and females, n=20/sex/dose level	0.5, 1.0, 2.0 g/kg/day Sucrose Acetate Isobutyrate (acetone vehicle); controls fed plain diet	Oral	1 year	OECD Guideline 452 (chronic tox studies) followed (GLP); dosed daily in diet for 52 weeks; controls were used	No Observed Effect Level (NOEL) males > 2g/kg/day; females 1 g/kg/day; body weight in females decreased at all levels, decreased food consumption in females with 2g /kg/day compared to controls at 52 weeks; body weight decreased in males with 2 g/kg/day vs. controls; no deaths; no ophthalmic observations; clinical pathology and liver function unaffected	[26]
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)	Oral	28 days	Dosed daily in diet for 28 days; animals killed on days 29 and 30; controls were used	NOAEL 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)	[47,48]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
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)	Oral	28 days	Dosed daily in diet for 28 days; animals killed beginning on day 29; controls were used	NOEL 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	[47,48]
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)	Oral	28 or 91 days	Dosed daily in diet for 28 or 91 days; 10 rats killed on day 28 and remainder killed on day 91; controls were used	NOEL 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 but not those killed on day 91 (completely hydrogenated soybean oil treatment led to decreased heart weight); lipid levels unaffected	[47,48]
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)	Oral	90 days	Dosed daily in diet for 90 days; animals killed on day 95; controls were used	NOEL 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	[47,48]
Human								
Sucrose Acetate Isobutyrate	Human	n=10/sex	10 mg/kg /day Sucrose Acetate Isobutyrate taken in a bolus	Oral	14 days	Dosed daily for 14 days; blood chemistry measured prior to treatment and on days 7 and 18; controls were used	Blood chemistry values were unaffected	[43]

Table 10. Acute and Repeated Dose Toxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population- Gender	Vehicle/ Concentration	Exposure Route	Dose Duration	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Human	n=12/sex/ group (3 groups, 24 total subjects)	7.0 or 20.0 mg/kg /day Sucrose Acetate Isobutyrate dissolved in a carbonated drink	Oral	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 /day 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; controls were used	Blood chemistry and BSP retention were unaffected	[43]
Sucrose Acetate Isobutyrate	Human	n=27 (13 males, 14 females)	20 mg/kg/day Sucrose Acetate Isobutyrate; orange juice vehicle	Oral	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; controls were used	Hematological parameters and blood chemistry (including hepatobiliary function) unaffected	[43]

Table 11. Developmental and Reproduction Toxicity (DART) Studies

Test Substance(s)	Species	Sample Type/ Test Population- Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Fischer 344)	n=30/sex/dose level F_0 generation (3 generation reproduction study; teratology study)	0, 0.5, 1.0, 2.0 g/kg/day Sucrose Acetate Isobutyrate; acetone vehicle	Oral	Yes	F_0 generation males fed Sucrose Acetate Isobutyrate for 10 weeks and females fed Sucrose Acetate Isobutyrate for 2 weeks 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 re-mated 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	NOAEL 2.0g /kg/day; pre-mating period treated males showed decreased food consumption; body weights lower for treated F_0 females during gestation and lactation with 1 and 2g /kg/day and F_1 females with 0.5 and 2g /kg/day during lactation; variability in fertility index (# females pregnant/ # females mated x100) not considered to be treatment related; reproduction unaffected; negative for teratogenic/ developmental toxic effects	[49]

Table 11. Developmental and Reproduction Toxicity (DART) Studies

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Exposure Route	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rabbit (New Zealand White)	n=5/dose level (range finding study); n=16/dose level (teratology studies)	Range finding-600 and 1200 mg /kg/day; for teratology-0, 0.5, 0.85, 1.2 g/kg/day; corn oil vehicle	Oral (gavage)	Yes	Range finding: 2x 1200 mg /kg/day or 1x 600 mg/kg/day for 14 days; Teratology study: dosed on days 7-19 gestation, animals killed day 29 of teratology study	NOAEL 1.2 g/kg/day; Range finding study-no mortality occurred, corn oil caused soft stools, treatment well-tolerated; Teratology study-2 high dose treated rabbits died on day 17 gestation, results indicated no difference in treated vs control rabbits for caesarean section exams, food consumption, weight gain, and gross morphology; negative for teratogenic/ developmental toxic effects	[49]
Sucrose Acetate Isobutyrate	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	Oral	Yes	Non-GLP; dosed during the breeding of 2 generations	NOAEL reported for maternal toxicity of 1250 mg/kg /day (actual dose received); 5.0% (w/w) in diet of 2 generations produced no effect on viability; no observable toxic effects; F_1 generation had respiratory outbreak resulting in the death of several young, several control rats, and 2 treated rats; none of young weaned in treatment group lived for 2 weeks (deaths attributed to respiratory outbreak)	[26]
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n=10/sex/ group	0, 0.38, 9.38% (w/w) Sucrose Acetate Isobutyrate	Oral	Yes	Dosed in diet daily for 5 weeks; pairs of rats from each dose group caged together for 19 days; females allowed to wean young to 21 days; parent rats bred 3x in weeks 9-36 with different male per mating	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	[43]

Table 12. Genotoxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population	Vehicle/ Concentration	Controls	Procedure	Results	Reference
IN VITRO							

Table 12. Genotoxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population	Vehicle/ Concentration	Controls	Procedure	Results	Reference
Sucrose Laurate	Hamster	Chinese Hamster Lung cells	10% Sucrose Laurate solution (prepared from 38% Sucrose Laurate solution) diluted in water	Yes	Neutral Red Effective Concentration$_{50}$ (NR-EC$_{50}$): 100 µL suspension of 4x10^3 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 h at which time NR-medium was added and incubated for 2 h, cells assayed and NR-EC$_{50}$ calculated *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 non-treated 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)	[52,71]
Sucrose Laurate	Human	Human Skin Fibroblasts Cells	10% Sucrose Laurate solution (prepared from 38% Sucrose Laurate solution) diluted in water	Yes	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 *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 dehydrogenses of metabolically active/ viable cells convert MTT to insoluble formazan); formazan was solubilized with isopropanol and its absorbance measured; the ratio of treated to non-treated 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)	[52,72]
Sucrose Acetate Isobutyrate	*Salmonella typhimurium*	Histidine auxotrophs TA98, TA100, TA1535, TA1537, TA1538	333-10,000 µg/plate Sucrose Acetate Isobutyrate, control-dimethyl sulfoxide	Yes	Ames Test (*Salmonella* reverse mutation assay): Following preliminary toxicity test with TA100 six doses from 333-10,000 µg/plate were selected, with and without metabolic activation	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; non-toxic; positive control outcomes were as expected	[50]

Table 12. Genotoxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population	Vehicle/ Concentration	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Hamster	Chinese Hamster Ovarian/Hypox-anthine-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	Yes	CHO/HGPRT Mutation Assay: Preliminary cytotoxicity test performed; $6x10^6$ cells/monolayer exposed to each concentration (25-1000 µg/ml) for 4 h with and without met activation and assayed	*Preliminary Results*-Sucrose Acetate Isobutyrate became toxic between 100-1000 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	[50]
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)	Yes	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)	Non-toxic to hepatocytes	[50]
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	Yes	CHO Chromosomal Aberration Assay: Cultures exposed to treatment for 7.5 h (without metabolic activation) and 2 h (with metabolic activation) and assayed	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 dose-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	[50]
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	Yes (+)	Bacterial Reverse Mutation Assay: This assay was performed with and without metabolic activation	Negative for mutagenic activity	[26]
Sucrose Acetate Isobutyrate	Hamster	CHO/HGPRT	10-1000 µg/ml Sucrose Acetate Isobutyrate	Not Specified	CHO/HGPRT Mutation Assay performed with and without metabolic activation	Negative for genotoxicity (no further details provided)	[43]
Sucrose Acetate Isobutyrate	Rat	Hepatocyte cells	250 ng/ml-1000 µg/ml Sucrose Acetate Isobutyrate	Not Specified	Unscheduled DNA Synthesis Assay performed	Negative for genotoxicity (no further details provided)	[43]
Sucrose Acetate Isobutyrate	Hamster	Chinese Hamster Ovarian Cells	200-2000 µg/ml Sucrose Acetate Isobutyrate	Not Specified	Chromosomal Aberration Assay performed with and without metabolic activation	Negative for genotoxicity (no further details provided)	[43]
IN VIVO							

Table 12. Genotoxicity Studies

Test Substance(s)	Species	Sample Type/ Test Population	Vehicle/ Concentration	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Rat (Sprague-Dawley)	n=20/sex/dose	20, 200, 2000 mg/kg Sucrose Acetate Isobutyrate in corn oil	Yes (+/-)	Oral administration by gavage as a single dose to male rats; 2 h post-dosing males mated with untreated females for 1 week; subsequent matings occurred during 3rd (post-meiotic), 5th (meiotic), and 7th (pre-meiotic spermatogenesis) week post-dosing	Negative for dominant lethal mutations; positive control outcomes were as expected	[26]

Table 13. Irritation and Sensitization Studies (Dermal)

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Controls	Procedure	Results	Reference
ANIMAL							
Sucrose Laurate	Mouse (SKH-1 hairless mice)	15 week old males, n=not specified	Sucrose Laurate (unknown concentration) in hydrogel containing 5% ibuprofen	Yes	Tape stripping (up to 18x) used to collect corneocytes from uppermost layer of dorsal skin 30 min post-treatment	The results of the tape stripping test are located in Table 9; the authors stated that the treatment was non-irritating	[38]
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	Yes	Fasted 24 h pre-administration and during administration; 100 mg gels were applied on days 1 and 7 to hairless 3 x 3 cm skin area; days 2-6 placebos applied; blood samples collected from marginal ear vein 0.5 thru 12 h post-administration; skin biopsies (taken from application site and untreated skin) evaluated for epidermal thickness	Authors 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	[39]
Sucrose Laurate	Rabbit (Japanese white)	Females, n=6	10% Sucrose Laurate (prepared from a 38% solution) diluted in water	Not Specified	*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	Max Primary Draize Skin Irritation Score is 3.0 (no further details provided)	[52]
Sucrose Laurate	Guinea Pig (Dunkin Hartley)	Females, n=3	2% Sucrose Laurate solution	Not Specified	*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 post- challenge (no further details provided)	Skinfold thickness unaffected by repeated applications; non-irritating	[36]

Table 13. Irritation and Sensitization Studies (Dermal)

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Controls	Procedure	Results	Reference
Sucrose Acetate Isobutyrate	Guinea Pig	Skin	*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)	Not specified	*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 post-administration for irritation; 3 more applications administered in 5 days followed by 3 week rest period; challenging doses (not specified) applied to right shoulder and 1 week later to left shoulder	Skin Irritation Test: Slight, transient irritation noted Delayed Sensitivity Test: No increased reactivity observed	[70]
Sucrose Acetate Isobutyrate	Guinea Pig (Hartley Guinea Pig)	n=5	0.5 ml Sucrose Acetate Isobutyrate (concentration and vehicle not specified)	No	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	Non-irritating; weight gain normal; no percutaneous absorption evident	[26]
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)	Yes	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 post-challenge	Light erythema at exposure site for 5 of 10 controls and 6of 10 animals previously induced with treatment; non-sensitizer	[26]
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	Yes	*Irritation Profile Test*: 25 µL/cm^2 nanoemulsions (nanoemulsions tested on human skin all contained acecofenac; controls used were non-treated skin both with and without occlusion) applied to 3 x 3cm^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	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 non-treatment controls; stratum corneum hydration showed substantial decrease in all treated sites compared to baselines and non-treated control under occlusion; nanoemulsions tested were tolerable to the skin	[41]

Table 13. Irritation and Sensitization Studies (Dermal)

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Controls	Procedure	Results	Reference
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 (one of 6 substances tested, others were plasticizers/lubricants)	Not Specified	Human Repeat Insult Patch Test (HRIPT) was performed using GLP (more specific details not provided)	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 96h) post-administration and 1 report slight erythema first appearing at 96 h post-administration; Non-irritating, no evidence of sensitization	[26]
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	Not Specified	HRIPT protocol followed (occlusive patch, 4 cm^2) using undiluted test material (0.2 g); induction phase was approximately 3 weeks; rest period was approximately 2 weeks	Staining of skin was observed in one subject during induction phase; no reactions were observed during rest period; no reactions at challenge; non-sensitizing	[51]
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	Yes	Treatment applied each day occlusively (to back for 24 h) in a 21 day study	Erythema observed (4 subjects) in test group, erythema noted (23 subjects) in control group; slightly irritating	[47]
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	Yes	Lotion containing treatment was applied daily at 100%, 50%, and 20% (v/v) occlusively for a 5-day cumulative study; same dosages were applied semi-occlusively to back for 24 h, 4x	Non-irritating	[47,48]

Table 13. Irritation and Sensitization Studies (Dermal)

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Controls	Procedure	Results	Reference
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	Not Specified	Treatment administered 2x/day for 4weeks in a single blind study (uncontrolled conditions)	1 subject discontinued study on day 8 (mild erythema and dryness with 17.19%); at 4 weeks 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 re-tested 3 weeks later after 4 days of application and determined to be treatment related; 1 subject re-tested 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	[47]
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	Not Specified	HRIPT was performed by applying treatment occlusively (to back for 24 h) at 72 h intervals x 9 applications; the rest period was 10-26 days; challenge patches similarly applied to a previously untreated area and removed at 24 h post-application	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; non-irritating	[47]
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	Not Specified	HRIPT was performed by applying treatment occlusively (to back for 24 h) at 72 h intervals x 9 applications; the rest period was 10-14 days; challenge patches similarly applied to a previously untreated area and removed at 24 h post-application	During induction definite erythema noted in 1 subject; at challenge 4 doubtful responses at 24h; no challenge responses at 48 h; no sensitization due to responses at challenge generally lower than single induction treatment; non-irritating	[47,48]

Table 13. Irritation and Sensitization Studies (Dermal)

Test Substance(s)	Species	Sample Type/ Test Population-Gender	Vehicle/ Concentration	Controls	Procedure	Results	Reference
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	Not Specified	HRIPT was performed by applying treatment occlusively (to back for 24 h) at 72 h intervals x 9 applications; the rest period was 10-14 days; challenge patches similarly applied to a previously untreated area and removed at 24 h post-application	Up to 1 subject at any observation time for either product showed definite erythema; no challenge responses at 48 h post-application, at 24 h post-application 2 subjects showed definite erythema; no sensitization since numbers at challenge were lower than after single induction treatment; non-irritating	[47]

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