Safety Assessment of Polysorbates as Used in Cosmetics

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The 2015 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 report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

1620 L Street, NW, Suite 1200 ♢ Washington, DC 20036-4702 ♢ ph 202.331.0651 ♢ fax 202.331.0088 ♢ cirinfo@cir-safety.org

ABSTRACT

This is a safety assessment of 80 polysorbates as used in cosmetics. These ingredients mostly function as surfactants in cosmetics. The safety assessment combined the polysorbates reviewed in 3 former safety assessments and polysorbates that had not been assessed for safety into 1 report. The Cosmetic Ingredient Review (CIR) Expert Panel (Panel) reviewed relevant data related to these ingredients, including the data in the previous reports. The Panel concluded that polysorbates were safe as cosmetic ingredients in the practices of use and concentration of this safety assessment when formulated to be nonirritating. This conclusion supersedes the conclusions reached in the 3 former safety assessments.

INTRODUCTION

This is a re-review of the available scientific literature and unpublished data relevant to assessing the safety of polysorbates as used in cosmetics; these ingredients mostly function as surfactants in cosmetics (Table 1). This safety assessment combines polysorbates reviewed in 3 previous safety assessments with other polysorbates that have not been reviewed by the CIR Panel into a group of 80 polyethoxylated sorbitan or sorbitol esters of fatty acids (Table 2). These ingredients have a common core structure of sorbitan or sorbitol, etherified with polyethyoxy (PEG) chains, and esterified with fatty acids.

In a safety assessment published in 1984, the CIR Panel concluded that the following 9 polysorbates were safe as used:

Polysorbate 20
Polysorbate 21
Polysorbate 40
Polysorbate 60
Polysorbate 61
Polysorbate 65
Polysorbate 80
Polysorbate 81
Polysorbate 85[1]

Other polysorbates, which are also polyethoxylated sorbitan or sorbitol esters of fatty acids and contain a PEG moiety, have been reviewed by the CIR Panel. In 2000, a safety assessment was published with a safe as used conclusion for the following 33 PEG sorbitan/sorbitol fatty acid esters:

PEG-20 sorbitan cocoate
PEG-40 sorbitan diisostearate
PEG-2 sorbitan isostearate
PEG-5 sorbitan isostearate
PEG-20 sorbitan isostearate
PEG-40 sorbitan lanolate
PEG-75 sorbitan lanolate
PEG-10 sorbitan laurate
PEG-40 sorbitan laurate
PEG-44 sorbitan laurate
PEG-75 sorbitan laurate
PEG-80 sorbitan laurate
PEG-3 sorbitan oleate
PEG-6 sorbitan oleate
PEG-80 sorbitan palmitate
PEG-40 sorbitan perisostearate
PEG-40 sorbitan peroleate
PEG-3 sorbitan stearate
PEG-6 sorbitan stearate
PEG-40 sorbitan stearate
PEG-60 sorbitan stearate
PEG-20 sorbitan tetraoleate
PEG-30 sorbitan tetraoleate
PEG-40 sorbitan tetraoleate
PEG-60 sorbitan tetraoleate
PEG-60 sorbitan tetrastearate
PEG-20 sorbitan triisostearate
PEG-160 sorbitan triisostearate
PEG-18 sorbitan trioleate
Sorbeth-40 hexaoleate (previously PEG-40 sorbitol hexaoleate)
Sorbeth-50 hexaoleate (previously PEG-50 sorbitol hexaoleate)
Sorbeth-30 tetraoleate laurate (previously PEG-30 sorbitol tetraoleate laurate)
Sorbeth-60 tetrastearate (previously PEG-60 sorbitol tetrastearate)[2]

There were 2 ingredients that were included in the 2000 report, but were not listed in the *International Cosmetic Ingredient Dictionary and Handbook*[3] (*Dictionary*) at the time of the original review, and are not listed as cosmetic ingredients in the current *Dictionary*.[4] One is PEG-18 sorbitan trioleate, which has 1 use listed in the 2015 Food and Drug Administration's (FDA) Voluntary Cosmetic Registration Program (VCRP)[5] and is therefore included in this safety assessment. However, the other, PEG-20 sorbitan tetraoleate, has no uses listed in the VCRP, so is not included in this safety assessment.

In 2001, a safety assessment was published with a safe as used conclusion for the following sorbitan beeswaxes:

Sorbeth-6 beeswax (previously PEG-6 sorbitan beeswax)
Sorbeth-8 beeswax (previously PEG-8 sorbitan beeswax)
Sorbeth-20 beeswax (previously PEG-20 sorbitan beeswax)[6]

At the time of the safety assessment on these sorbeth beeswaxes, the Panel had recommended that cosmetic formulations that included PEGs (specifically PEG-6, PEG-20, and PEG-75) not be used on damaged skin due to the possible connection between the use of PEGs on burn patients and renal toxicity. Since then, PEGs have been re-reviewed and the additional data demonstrated minimal dermal penetration of low-molecular weight PEGs. The amount of PEGs that would penetrate the stratum corneum barrier, even if damaged, from the use of cosmetics was well below the no observable effects level. Therefore, the Panel has removed the caveat that PEGs should not be used on damaged skin.[7]

The following 35 ingredients from the *Dictionary*, which are also polyethoxylated sorbitan or sorbitol esters of fatty acids, have not been reviewed by the Panel previously and are included in this group because of their common core structure of sorbitan or sorbitol etherified with PEG chains and esterified with fatty acids:

PEG-20 sorbitan oleate
PEG-40 sorbitan oleate
PEG-4 sorbitan stearate
PEG-4 sorbitan triisostearate
PEG-2 sorbitan trioleate
PEG-3 sorbitan tristearate
Sorbeth-2 beeswax
Sorbeth-2 cocoate
Sorbeth-2 hexacaprylate/caprate
Sorbeth-12 hexacocoate
Sorbeth-2 hexaisostearate
Sorbeth-2 hexalaurate
Sorbeth-2 hexaoleate
Sorbeth-6 hexastearate
Sorbeth-150 hexastearate
Sorbeth-3 isostearate
Sorbeth-6 laurate
Sorbeth-2/oleate/dimer dilinoleate crosspolymer
Sorbeth-20 pentaisostearate
Sorbeth-30 pentaisostearate
Sorbeth-40 pentaisostearate
Sorbeth-50 pentaisostearate
Sorbeth-40 pentaoleate
Sorbeth-20 tetraisostearate
Sorbeth-30 tetraisostearate
Sorbeth-40 tetraisostearate
Sorbeth-50 tetraisostearate
Sorbeth-4 tetraoleate
Sorbeth-6 tetraoleate
Sorbeth-30 tetraoleate
Sorbeth-40 tetraoleate
Sorbeth-60 tetraoleate
Sorbeth-3 tristearate
Sorbeth-160 tristearate
Sorbeth-450 tristearate[4]

The VCRP reported a single use for PEG-30 sorbitan beeswax, which is not listed in the *Dictionary*.[4,5] Since there is a use reported, this ingredient is included in this safety assessment.

CIR has conducted safety assessments of the acids and related chemical structure moieties of the ingredients in this safety assessment (Table 2). The Panel concluded that beeswax, coconut acid, isostearic acid, lanolin acid, lauric acid, myristic acid, oleic acid, stearic acid, and multiple stearates were safe as used.[8-16] An array of alkyl esters and numerous PEGs were also assessed to be safe as used.[7,17,18] Sorbitan esters have been reviewed, and safe as used conclusions were reached.[19-21]

Much of the new data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[22-24] The ECHA website provides robust summaries of information generated by industry, and it is those summary data that are reported in this safety assessment when ECHA is cited. Some of this data are for sorbitan monolaurate, ethoxylated, sorbitan monostearate, ethoxylated, and sorbitan monooleate, ethoxylated; these 3 chemicals fit the general definition of several of the ingredients in this report with the same CAS No. (ie, polysorbate 21, PEG-10 sorbitan laurate, PEG-40 sorbitan laurate, polysorbate 20, PEG-44 sorbitan laurate, PEG-75 sorbitan laurate, and PEG-80 sorbitan laurate all have the CAS No. 9005-64-5). It is expected that data under these chemicals names are for one or some mixture of the ingredients with that CAS No. and are useful for read across information.

CHEMISTRY

Definition and Method of Manufacture

The ingredients in this report (several of which are often referred to by the commercial trade name of Tween in the literature) are polyethoxylated sorbitan or sorbitol esters of fatty acids. Each ingredient has a common core structure of sorbitan or sorbitol, etherified with PEG chains, and esterified with fatty acids (Figure 1). Sorbitan is related to sorbitol as the simple dehydration product.

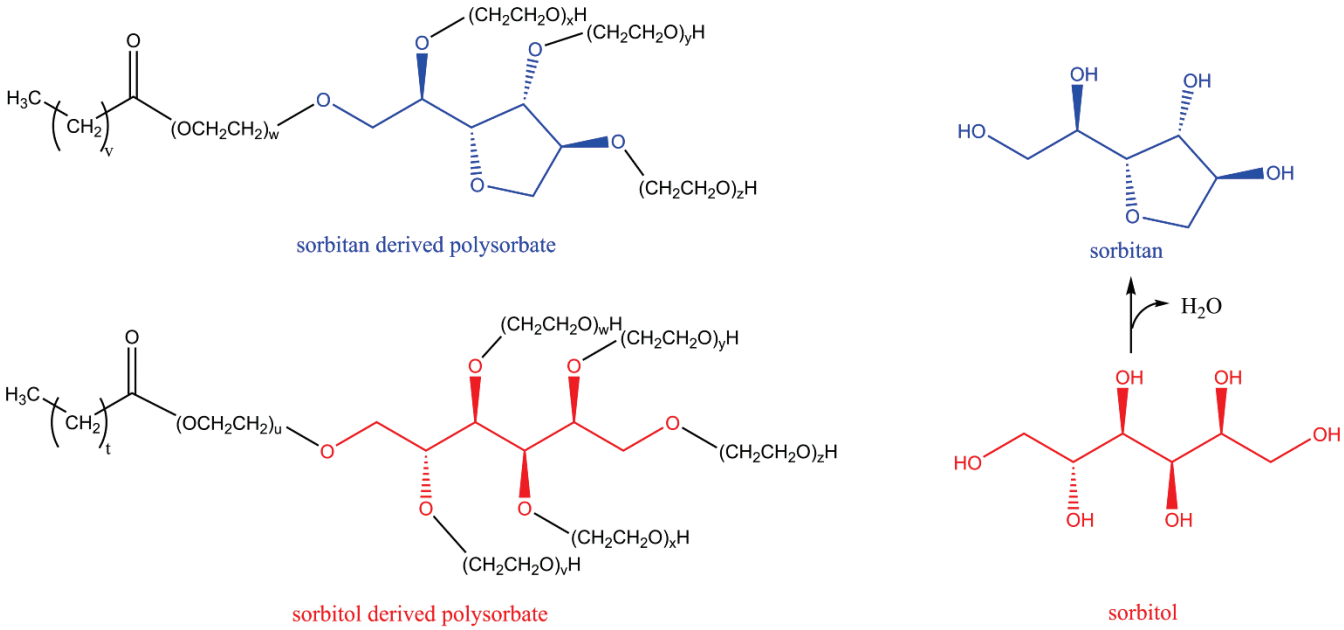


Figure 1. Polysorbates, sorbitan ("polysorbate #" or "PEG-x sorbitan nomenclature) and sorbitol ("sorbeth-#" nomenclature) derivatives.

While those ingredients with the nomenclature "polysorbate #" form sorbitan by dehydration of sorbitol during the above reactions (which is consequently ethoxylated and esterified), those ingredients herein with the nomenclature "PEG-x sorbitan fatty ester" are the product of the ethoxylation of a preformed sorbitan ester. Regardless of the nomenclature, the ingredients under these two nomenclature schemes are related as polyethoxylated sorbitan esters. The ingredients with the nomenclature "sorbeth-#" are not the product of dehydration, but are the ethoxylated and esterified products of sorbitol. While these ingredients are predominately either sorbitan derivatives or sorbitol derivatives, each may be mixtures resulting from some dehydration, isomerization, degree of ethoxylation, or degree of esterification. Accordingly, the ingredients in this report are closely related in that they have similar chemical structures and potential metabolism products (eg, via esterases known to be present in the skin). It should be noted that the number in ingredients with the nomenclature "polysorbate #" has no relationship to the size of the molecule but to the associated fatty acid from which the ingredient is derived (20, laurate; 40, palmitate; 60, stearate; 80, oleate).

Presented here are 2 possible routes for the synthesis of polysorbates.[25] In the first, sorbitol is esterified with fatty acids or their anhydrides, which reaction is typically carried out with acid catalysis at 130-180˚C. At the temperature required for the esterification, water is eliminated from sorbitol to form 3 possible isomers of sorbitan and (with elimination of another water molecule) isosorbide. These dehydration products react with a fatty acid to form corresponding sorbitan esters. These products, which are known as "spans", are ethoxylated to produce polysorbates.

In the other common method of manufacture, sorbitol is reacted with ethylene oxide and a basic catalyst at 200-250°C. Under these conditions, sorbitol is isomerized as above. Addition of ethylene oxide yields ethoxylated products, which are called carbowaxes, and which are subsequently esterified with fatty acids to produce oligomers of polyoxyethylene sorbitan esters (aka polysorbates).

Chemical and Physical Properties

Polysorbates are amphiphilic molecules, which are fatty esters of polyoxyethylated sorbitan or sorbitol.[25] The polysorbates are, for the most part, viscous liquids to waxy solids that range in color from yellow to orange to tan (Table 3).[1] They possess a faint, characteristic odor and a warm, somewhat bitter taste. The reported physical and chemical properties of generic sorbitan monolaurate, ethoxylated and sorbitan monostearate, ethoxylated are provided in Table 4.

Since the fatty acids used in the production of cosmetic ingredients frequently contain fatty acids other than the principal acid named (ie, a mixture), each of the polysorbates may contain a complex mixture of fatty acid moieties.[1,26] Table 5 provides an example of the approximate ester content of polysorbate 20, 21, 40, 60, and 80. Polysorbate 21 is reported to be 30%-80% monoesters, <50% diesters, and <20% triesters.[22] Sorbitan monolaurate is reported to be a mixture of esters of different lengths, with the highest percentage being C12, at 40%-60%.

Impurities

During the manufacturing process, the polysorbates are steam-stripped to remove unwanted water-soluble by-products such as 1,4-dioxane.[1] Since PEGs are the condensation products of ethylene oxide and water, with the chain length

controlled by the number of moles of ethylene oxide that are polymerized, they may contain trace amounts of 1,4-dioxane, a by-product of ethoxylation. 1,4-Dioxane is a known animal carcinogen.[27] The FDA has been periodically monitoring the levels of 1,4-dioxane in cosmetic products, and the cosmetic industry reported that it is aware that 1,4-dioxane may be an impurity in PEGs and, thus, uses additional purification steps to limit it in these ingredients before blending into cosmetic formulations.[28,29]

USE

Cosmetic

The Panel assesses the safety of cosmetic ingredients based on the expected use of these ingredients in cosmetics. The Panel reviews data received from the FDA and the cosmetics industry to determine the expected cosmetic use. The data received from the FDA are collected from manufacturers on the use of individual ingredients in cosmetics, by cosmetic product category, through the FDA VCRP, and the data from the cosmetic industry are submitted in response to a survey of the maximum reported use concentrations, by category, conducted by the Personal Care Products Council (Council).

In 2015, the polysorbates included in the current safety assessment with the highest number of uses reported were polysorbate 20 at 3013 (an increase from 770 in 1998), polysorbate 60 at 1589 (an increase from 332 in 1998), and polysorbate 80 at 932 (an increase from 231 in 1998; Table 6).[1,2,5,6,14] Almost all of the previously reviewed ingredients had increases in the number of reported uses. All of the ingredients not previously reviewed had less than 15 reported uses (Table 7).

In the survey conducted by the Council in 2014 (2015 for PEG-4 sorbitan stearate) of the maximum use concentrations for ingredients in this group, the highest concentrations of use were reported for polysorbate 20 at 19.6% in bath soaps and detergents (a decrease from >50% in 1984), polysorbate 80 at 18.1% in paste masks and mud packs (a decrease from up to 25% in 1984), polysorbate 81 at 25.6% in skin cleansing products (an increase from up to 5% in 1984), and polysorbate 85 at 21.9% skin cleansing products (a decrease from >50% in 1984).[1,2,30-32] The highest maximum concentration of use for leave-on products was 11.9% polysorbate 80 in perfumes.

In the 2000 published report, the only concentration of use data that were provided was the following: "…PEG-60 sorbitan tetraoleate, PEG-40 sorbitan tetraoleate, and PEG-160 sorbitan triisostearate are used in cosmetics at concentrations of 0.5% to 10%...".[2] Since the data from the 2000 report are limited, the concentration of use data from the 1984 report were provided in Table 6 to give a better historical perspective.

PEG-18 sorbitan trioleate is not listed as a cosmetic ingredient in the *Dictionary*.[4] However, the VCRP reported 1 use in a moisturizer, which is a decrease from 10 uses reported in 1998.[5] PEG-30 sorbitan beeswax is also not listed in the *Dictionary*, but is reported to have 1 use in mascara by the VCRP.

The VCRP also reported single uses for PEG-20 sorbitan laurate (used in 1 other personal cleanliness product) and PEG-20 sorbitan stearate (used in 1 night skin product).[5] However, these names are not listed in the *Dictionary* as INCI (International Nomenclature of Cosmetic Ingredients) names or technical terms.[4] The Council has reported that PEG-20 sorbitan laurate is another term for polysorbate 20 and PEG-20 sorbitan stearate is another term for polysorbate 60.[33] Since it cannot be confirmed that the reporting companies intended to refer to polysorbate 20 and polysorbate 60, this use information on these 2 ingredients are reported separately.

The 41 ingredients with no reported uses or concentrations of use are listed in Table 8.

In some cases, reports of uses were received in the VCRP, but no concentration of use data were available.[5,31] For example, PEG-3 sorbitan stearate was reported to be used in 3 formulations, but no use concentration data were reported. In other cases, no reported uses were received in the VCRP, however a use concentration was provided in the industry survey. For example, PEG-40 sorbitan laurate was not reported in the VCRP to be in use, but the industry survey indicated that it is used in leave-on formulations at up to 2% (skin care preparations) and rinse-off formulations up to 0.25% (shampoos and hair dyes and colors). It should be presumed that PEG-40 sorbitan laurate was used in at least 3 cosmetic formulations.

Several of these polysorbate ingredients are used at concentrations up to 5.8% in cosmetic products that may be ingested, in cosmetics used around the eyes at concentrations up to 11%, or in baby products at concentrations up to 12.6%.[30,31]

Polysorbates were reported to be used in cosmetic sprays, including aerosol and pump hair sprays, spray deodorants, spray body and hand products, and spray moisturizing products, and could possibly be inhaled. The highest concentrations of use were reported to be 11.9% polysorbate 80 in perfumes and polysorbate 20 in spray deodorants at up to 4%. 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.[34-37] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[34,36] 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.[34] 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.

All of the polysorbates named in this report are listed in the European Union inventory of cosmetic ingredients.[38]

Non-Cosmetic

The Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Food Additives (JECFA) estimated the acceptable daily intake for humans to be 0-25 mg/kg/d for total polyoxyethylene (20) sorbitan esters.[39] The Science Committee on Food (SCF) issued a group acceptable daily intake (ADI) of 10 mg/kg/d for polysorbate 80, polyoxyethylene sorbitan mono-esters of lauric and palmitic acids, and the mono- and the tri-ester of stearic acids.[40]

The largest food sources of polysorbates are confectionery, ices, desserts, fine bakery wares, milk analogues, emulsified sauces, chewing gums, and fat emulsions for baking.[25]

The polysorbates are used in the drug, food, and animal feed industries; several have been approved by the FDA as direct and indirect food additives for human consumption with certain restrictions (Table 9). The FDA drug inactive ingredients database lists polysorbate 80 and polysorbate 20 as being used in nasal metered sprays at concentrations of 10% and 2.5%, respectively.[41]

TOXICOKINETICS

Following oral administration of polysorbate 20 to rats, ester bonds of polysorbates are hydrolyzed within the digestive tract by pancreatic lipase.[24] Free fatty acids were absorbed from the digestive tract and oxidized and excreted, mainly as carbon dioxide in exhaled breath. No migration of the polyoxyethylene sorbitan into the thymus lymph nodes has been demonstrated. No sex difference has been detected in the disposition of polysorbates in rats.

Following oral ingestion of polysorbate 20 in humans, 90% or more of the administered substance was excreted in the feces as metabolites, with the polyoxyethylene sorbitan structure maintained, and 2%-3% of these metabolites were excreted in the urine.[24]

Penetration Enhancement

Polysorbate 20, polysorbate 65, and polysorbate 80 enhanced the dermal penetration of albuterol sulfate through hairless mouse skin in assays using Franz cells (Table 10).[42]

Cytotoxicity

POLYSORBATE 20

In a series of "cyto/genotoxicity" assays described below, polysorbate 20 induced apoptosis in human umbilical vein endothelial cells (HUVEC) and A549 lung cancer cells, which was manifested by chromatin fragmentation and DNA cleavage.[43]

In an MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, there was a dose- and time-dependent reduction in cell growth for both the HUVEC and A549 cells, with IC_{50}s of approximately 0.3 and 0.4 µL/mL polysorbate 20, respectively. There was >90% cell death observed after treatment with 2 µL/mL, and the greatest cell death was observed in the highest test group. For the assay, the cells were incubated with various concentrations of polysorbate 20 (2, 4, 6, 8, or 10 µL/mL) for 24, 48, and 72 h, and then washed.

In a DAPI (4',6-diamidino-2-phenylindole) staining assay, morphological changes and fragmentation in the chromatin and DNA rings within the nucleus were observed in the polysorbate-treated cells of both cell lines, but morphology was unaltered in untreated cells. Polysorbate 20-treated cells showed chromatin and DNA fragmentation as high as the positive control of 5% dimethyl sulfoxide (DMSO). For the assay, the cells were treated with polysorbates 20 (4 µL/mL) for various durations (not provided), then fixed and stained with DAPI.

In a DNA fragmentation assay analyzed by agarose gel electrophoresis, polysorbate 20 (concentration not clear) induced apoptosis, as evidenced by DNA fragmentation after incubation for 24 h. The gel showed the formation of DNA ladders in cells of both treated lines.

An alkaline comet assay showed that polysorbate 20 (2 µL/mL)-treated A549 cells exhibited increased DNA cleavages compared to untreated cells and similar DNA cleavages to the positive control, hydrogen peroxide (200 mM)-treated cells. Only A549 cells were used in this assay; HUVEC cells were not used.

When polysorbate 20 (2 µL/mL)-treated A549 cells were analyzed with a fluorescein isothiocyanate (FITC)-labeled annexin V apoptosis assay and flow cytometry analysis was used to estimate early and late apoptosis, the results were similar to the results of the DAPI staining assay. Almost all of the treated cells were in early and late stages of apoptosis after 24 h; less than half of DMSO-treated control cells were in early and late stages of apoptosis for the same period of exposure. Only A549 cells were used in this assay; HUVEC cells were not used.[43]

TOXICOLOGICAL STUDIES

Acute Toxicity

Oral – Non-Human

POLYSORBATE 81

The oral LD_{50} of polysorbate 81 was reported to be >20 000 mg/kg for rats (n=11).[23]

Oral - Human

SORBITAN MONOSTEARATE, ETHOXYLATED

No toxic effects were observed in human subjects (n=6) orally administered sorbitan monostearate, ethoxylated (20 g).[24] The amount of gastric acid was slightly reduced. It was concluded that sorbitan monostearate, ethoxylated was not acutely toxic when orally administered to humans.

Dermal – Non-Human

SORBITAN MONOSTEARATE, ETHOXYLATED

The acute dermal LD_{50} of sorbitan monostearate, ethoxylated in Wistar albino rats (n=10/sex) was reported to be >2000 mg/kg.[24]

Inhalation – Non-Human

SORBITAN MONOLARUATE, ETHOXYLATED

The inhalation LC_{50} was reported to be 5.1 mg/L air for sorbitan monolaurate, ethoxylated administered to Crl:Wl(Han) rats (n=5) for 4 h in a nose-only apparatus.[22] No clinical signs of systemic toxicity were observed up to the end of the 14-day observation period. No abnormalities were observed at macroscopic post mortem examination of the rats.

Intravenous – Non-Human

POLYSORBATE 20

The intravenous LD_{50} for polysorbate 20 in mice was reported to be 1420 mg/kg.[22]

Repeated Dose Toxicity

In a survey of 4 laboratories of the historical use of vehicles for in vivo experiments, the highest no-observed-adverse-effect levels (NOAEL) for various routes of administration were assembled (Table 11).[44] The highest oral NOAELs for polysorbate 20 were 250 and 500 mg/kg/d for 1 month and 90 days in rats, respectively, and 10 mg/kg/d for 1 month in mice. For polysorbate 80, the highest oral NOAEL for 90 days in dogs was 5 mL/kg/d, and for 4 weeks in rats was 5 mL/kg/d. The NOAEL for intranasal administration of polysorbates 80 for 3 days to mice was 10 µL/nostril/d at 0.2%.

Oral – Non-Human

POLYSORBATE 20, 40, 60, and 80

In a 22-month feeding study, the NOAEL of polysorbate 20 in male C57BL/6 Jax mice was 14285.71 mg/kg/d (10% in feed).[24] Decreased hematologic values were observed but not specified. No characteristic morphologic anemia was observed. The test substance was administered in the feed at 5% or 10% polysorbate 20. No further details were provided.

There were no adverse effects or mortalities related to polysorbate 80 (0.005, 0.05, or 0.15 g/kg/d) when administered by gavage to Sprague-Dawley rats (n=5) for 5 days.[45] There were no clinical signs and no significant findings at necropsy. Serum glucose levels were decreased and serum sodium levels increased at all concentration tested, as well as decreases in uric acid in the mid- and high-dose groups. The high-dose group exhibited a modest reduction in serum calcium levels.

There were no adverse effects or mortalities reported when Sprague-Dawley rats (n=6/sex) were orally administered polysorbate 80 (148, 740, or 3700 mg/kg/d in saline) for 28 days after 28 days of a high-fat diet.[46] It was not clear if the rats continued on the high-fat diet during treatment with polysorbate 80.

In the same study, there were no adverse effects or mortalities reported when C57BL/6J mice (n=6/sex) were orally administered polysorbates 80 (400, 1600, or 6400 mg/kg/d in saline) for 28 days after 28 days of a high-fat diet. In additional studies, there were no adverse effects or mortalities reported when the same strain of mice (n=5/sex) were orally administered polysorbate 20, polysorbate 40, or polysorbate 60 (1600 mg/kg/d in saline) for 28 days, also after 28 days of a high-fat diet. It was not clear if the mice continued on the high-fat diet during treatment with the polysorbates.[46]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

POLYSORBATE 60

The teratogenic and reproductive NOAEL was reported to be 7693 mg/kg/d when polysorbate 60 (0, 0.1%, 1.0% or 10% in feed; 0, 99 mg/kg, 960 mg/kg, 7693 mg/kg) was administered to pregnant Wistar rats on gestations days 7-14.[24] There were no effects by polysorbate 60 on the number, sex ratio, and body weights of live fetuses. There were no differences between the polysorbate 60-treated and control groups observed in the numbers of resorptions, dead fetuses and live fetuses per litter, the sex ratio of live fetuses, and the fetal body weight of both sexes. External, skeletal, and internal examinations of the fetuses revealed no evidence of teratogenesis. It was concluded that polysorbate 60 had no harmful effects on the prenatal development of the rat offspring.

POLYSORBATE 80

In a reproductive and developmental study where polysorbate 80 (500 and 5000 mg/kg/d in distilled water; 5 mL) was administered by gavage to Crl:CD BR VAF/PlusTM outbred albino rats (n=25) on gestation days 6-15, the maternal and

the developmental NOAELs were reported to be >5000 mg/kg/d.[23] The control group was administered 5 mL/kg distilled water. No maternal mortalities or treatment-related clinical signs of toxicity were observed. There were no effects on weight gain, organ weights (except non-adverse increased relative liver weights), and feed and water consumption observed. There were no differences in the number of corpora lutea per dam, number of implantations per litter, percent preimplantation loss per litter, percent resorptions per litter, and percent litters with resorptions. No adverse fetal effects were observed, including growth, viability, or development of the fetuses. There were no observed differences in malformations between treatment groups and controls.[23]

GENOTOXICITY

In Vitro

POLYSORBATE 80

Polysorbate 80 was not genotoxic to *Salmonella typhimurium* (strains TA98, TA100, TA1535, and TA1537) at up to 10 000 μg/plate (in distilled water) with and without metabolic activation.[23] The controls had the expected results.

Polysorbate 80 was not genotoxic to *S. typhimurium* (strains TA1535, TA1537, TA98 and TA100) and *Escherichia coli* (strain WP2 uvr A) at up to 5000 μg/plate (in ethanol) with and without metabolic activation.[23] The controls had the expected results.

SORBITAN MONOLAURATE, ETHOXYLATED

Sorbitan monolaurate, ethoxylated was not mutagenic, with or without metabolic activation, in an Ames assay using *S. typhimurium* (strains TA98, TA100, TA1535, and TA1537) and *E. coli* (strain WP2 uvr A) in 3 separate experiments.[22] In experiment 1, *S. typhimurium* (strains TA98, TA1535, TA1537) was tested at 10-3330 μg/plate in ethanol; and *S. typhimurium* (strain TA100) and *E. coli* were also tested at 3 and 5000 μg/plate with and without metabolic activation. In experiment 2, *S. typhimurium* (strains TA98 and TA1535) was tested at 33-5000 μg/plate in ethanol with and without metabolic activation. In experiment 3, all strains were tested again at 33-5000 μg/plate in ethanol with and without metabolic activation. Controls had the expected results.

In a chromosomal aberration assay using human lymphocytes, sorbitan monolaurate, ethoxylated was not genotoxic up to 100 μg/mL in ethanol, with and without metabolic activation, but was cytotoxic at 300 μg/mL.[22] Assays were run for 3, 24, and 48 h. Controls had the expected results.

In 2 mammalian cell gene mutation assays using mouse lymphoma L5178Y cells, sorbitan monolaurate, ethoxylated was not found to be genotoxic.[22] In the first experiment, the cells were tested for 3 h at 0.3-275 μg/mL without metabolic activation and at 0.3-300 μg/mL with metabolic activation in ethanol. In the second experiment, the cells were tested for 3 h at: 0.3-150 μg/mL without metabolic activation and at 0.3-350 μg/mL with metabolic activation in ethanol. Controls had the expected results.

SORBITAN MONOOLEATE, ETHOXYLATED

Sorbitan monooleate, ethoxylated produced ambiguous results in a chromosome aberration assay using Chinese hamster ovary (CHO; CHO-W-B1) cells.[23] The number and percentages of aberrations did not change in a concentration-dependent manner. Sorbitan monooleate, ethoxylated was tested at 300-1600 μg/mL without metabolic activation and 100-1000 μg/mL in DMSO. The positive controls were mitomycin and cyclophosphamide, which elicited the expected results.

Sorbitan monooleate, ethoxylated was not genotoxic in a chromosome aberration assay using CHO (CHO-W-B1) cells.[47] Sorbitan monooleate, ethoxylated was tested at 300-1600 μg/mL without metabolic activation and at 16-500 μg/mL in DMSO. The positive controls were mitomycin and cyclophosphamide. The controls elicited the expected results.

SORBITAN MONOSTEARATE, ETHOXYLATED

Sorbitan monostearate, ethoxylated (concentration and vehicle were not specified) was not mutagenic in a bacterial gene mutation assay using *S. typhimurium* (strain TA 98) with metabolic activation.[24]

CARCINOGENICITY

The Panel considered the carcinogenicity data presented in the previous safety assessments of polysorbates.[1,2,6] No new carcinogenicity data on polysorbates were found in the published literature, nor were unpublished data provided.

IRRITATION AND SENSITIZATION

Irritation

Summaries of dermal and ocular studies are provided in Tables 12 and 13, respectively.

Dermal – Non-Human

Polysorbate 60 was a moderate irritant at 5%, and skin necrosis occurred at 10%, when administered to rabbits for 30 days.[24] In another study, polysorbate 60 was not an irritant at 15% but a mild irritant in rabbits at 100%. Local inflammation was observed in mouse skin when polysorbate 60 was administered in a long-term study.

Sorbitan monolaurate, ethoxylated (100%; 0.5mL) resulted in a Draize score of 0.89 out of 4 when administered to rabbits.[22]

When sorbitan monostearate, ethoxylated was dermally administered to rabbits for 30 days, the test substance caused necrosis of the skin at 10% but only moderate irritation at 5%.[24] Administration of sorbitan monostearate, ethoxylated (100%) for 60 days did not cause irritation in rabbits. Sorbitan monostearate, ethoxylated (100%) did not produce any skin reaction when administered to the shaved backs of rabbits.

Dermal – Human

In human irritation studies, polysorbate 60 (1%), polysorbate 80 (100%), and sorbitan monostearate, ethoxylated (25%) were not dermally irritating.[24,48-50] Polysorbate 60 (100%) caused urticaria on the foreheads of subjects, but not on the dorsal and arm skin.

Ocular – Non-Human

Tests of polysorbate 20 (10%) and polysorbate 81 (up to 100%) showed that these ingredients were not ocular irritants in rabbits.[51-53] Sorbitan monostearate, ethoxylated (0.1 g in water) and sorbitan monolaurate, ethoxylated (100%; 0.1 mL) were not ocular irritants to rabbits.[22,23]

Ocular – In Vitro

POLYSORBATE 20

In vitro ocular irritation tests of polysorbate 20 had mixed results. EpiOcular tests, a red blood cell hemolysis assay, and a k562 cell assay predicted polysorbate 20 to be a non- or minimal ocular irritant at 2% and 100%.[54,55] Polysorbate 20 was predicted to be an ocular irritant in a short time exposure (STE) assay using SIRC cells, Hen's Egg test-Chorioallantoic Membrane (HET-CAM) assays, and Bovine Corneal Opacity and Permeability (BCOP) assay.[54]

Sensitization

Non-Human

POLYSORBATE 81

Polysorbate 81 (2% or 4% in corn oil) was not sensitizing to female Dunkin-Hartley guinea pigs (n=10) when the guinea pigs were challenged at 100% (0.5 mL). [22,23] The induction was a single intradermal injection followed 48 h later with an epicutaneous induction; the epicutaneous challenge was administered 21 days after second induction. There were no signs of sensitization up to 72 h after the challenge. The positive control, α-hexyl cinnamic acid (20%), elicited the expected results.

SORBITAN MONOLAURATES, ETHOXYLATED

In a local lymph node assay of sorbitan monolaurates, ethoxylated (25%, 50% and 100% in acetone/olive oil [4:1 v/v]; 25 µL) using female CBA mice (n=5), the stimulation indexes (SI) were calculated to be 1.9, 6.0 and 5.0, respectively. The test substance was considered sensitizing.[22] The authors noted that the response of the 100% group did not follow the expected dose-response relationship, which they also noted was common in this kind of study. The response might be less severe due to differences in skin penetration (no vehicle present) or viscosity. The estimated concentration of polysorbates that would give an SI of 3 was calculated to be 34%. The positive control, hexyl cinnamic aldehyde, had the expected results.

Human

POLYSORBATE 81

In a human patch test (n=50), polysorbate 81 (100%) was not sensitizing.[23] There were no signs of irritation or sensitization observed in any subject. The test material was administered under a single occluded patch for 3 days. After 7 days, challenge patches were administered for 72 h.

In a human patch test (n=10), polysorbate 81 (100%) was not sensitizing.[23] There were no signs of irritation or sensitization observed in any subject. The test material was administered under a single occluded patch for 5 days. After 10 days, challenge patches were administered for 48 h.

In a human patch test (n=10), polysorbate 81 (12%; vehicle not specified) was not sensitizing.[23] There were no signs of irritation or sensitization observed in any subject. The test material was administered under a single occluded patch for 5 days. After 10 days, challenge patches were administered for 48 h.

SUMMARY

This is a re-review of the safety of polysorbates as used in cosmetics. Safety assessments of various polysorbates were published in 1984, 2000, and 2001. This safety assessment combines the ingredients from these safety assessments along with additional polysorbate ingredients have been identified for a total of 80 ingredients. All of these polysorbate ingredients are related in that they have a common core structure of sorbitan or sorbitol etherified with PEG chains, and esterified with fatty acids.

The highest number of uses in 2015 were reported for polysorbate 20 at 3013 (an increase from 770 in 1998), polysorbate 60 at 1589 (an increase from 332 in 1998), and polysorbates 80 at 932 (an increase from 231 in 1998). Almost

all of the previously reviewed ingredients had increases in the number of reported uses. The highest maximum concentrations of use in 2014 were reported for polysorbate 20 at 19.6% (a decrease from >50% in 1984), polysorbate 80 at 18.1% (a decrease from up to 25% in 1984), polysorbate 81 at 25.6% (an increase from up to 5% in 1984), and polysorbate 85 at 21.9% (a decrease from >50% in 1984) in rinse-off products. The highest maximum concentration of use for leave-on products was 11.9% polysorbate 80 in perfumes.

Polysorbate 20, polysorbate 65, and polysorbate 80 enhanced the dermal penetration of albuterol sulfate through hairless mouse skin.

In a series of "cyto/genotoxicity" assays (MTT, DAPI, DNA fragmentation, alkaline comet, and FITC-labeled annexin V apoptosis assays), polysorbate 20 induced apoptosis in HUVEC and A549 lung cancer cells, which was manifested by chromatin fragmentation and DNA.

The oral LD_{50} of polysorbate 81 was reported to be >20 000 mg/kg for rats. The acute dermal LD_{50} of sorbitan monostearate, ethoxylated in rats was reported to be >2000 mg/kg. The inhalation LC_{50} was reported to be 5.1 mg/L air for sorbitan monolaurate, ethoxylated administered to rats for 4 h. The intravenous LD_{50} for mice was reported to be 1420 mg/kg for polysorbate 20.

In a survey of 4 laboratories of the historical use of vehicles for in vivo experiments, the highest NOAEL of various routes of administration were assembled. The highest oral NOAELs for polysorbate 20 were 250 and 500 mg/kg/d for 1 month and 90 days in rats, respectively, and 10 mg/kg/d for 1 month in mice. For polysorbate 80, the highest oral NOAEL for 90 days in dogs was 5 mL/kg/d, and for 4 weeks in rats was 5 mL/kg/d. The NOAEL for intranasal administration of polysorbates 80 for 3 days to mice was 10 µL/nostril/d at 0.2%.

There were no adverse effects or mortalities related to polysorbate 80 (up to 0.15 g/kg) when administered by gavage to rats for 5 days or in rats orally administered polysorbate 80 (up to 3700 mg/kg/d) for 28 days. There were no adverse effects observed in mice orally administered polysorbate 80 (up to 6400 mg/kg/d), or polysorbate 20, polysorbate 40, or polysorbate 60 (1600 mg/kg/d) for 28 days.

The teratogenic and reproductive NOAEL of polysorbate 60 was reported to be 7693 mg/kg/d (ie, the highest dose tested) when administered to pregnant rats on gestations days 7-14 in feed. In a reproductive and developmental study where polysorbate 80 was administered by gavage to rats on gestation days 6-15, the maternal and the developmental NOAELs were reported to be >5000 mg/kg/d.

Polysorbate 80 was not genotoxic to *S. typhimurium*, up to 10 000 µg/plate, and *E. coli*, up to 5000 µg/plate, with and without metabolic activation.

Sorbitan monolaurate, ethoxylated was not mutagenic in an Ames assay using *S. typhimurium* up to 5000 µg/plate. In a chromosomal aberration assay using human lymphocytes, sorbitan monolaurate, ethoxylated was not genotoxic up to 100 µg/mL but was cytotoxic at 300 µg/mL. In 2 mammalian cell gene mutation assays using mouse lymphoma L5178Y cells, sorbitan monolaurate, ethoxylated was not found to be genotoxic up to 275 µg/mL without metabolic activation and up to 300 µg/mL with metabolic activation. Sorbitan monooleate, ethoxylated produced ambiguous results in a chromosome aberration assay using CHO cells, but was not genotoxic in a second chromosome aberration assay also using CHO cells.

In a 30-day skin-painting study of polysorbate 60 in rabbits, there was moderate irritation observed at 5% and skin necrosis at 10%. In a study in rabbits, there were no dermal effects from a 15% aqueous solution of polysorbate 60 administered for 60 consecutive days; there was mild irritation after administration of an undiluted solution. Local inflammation also occurred after long-term (time not specified) administration of an undiluted polysorbate 60 solution to mouse skin.

Sorbitan monolaurate, ethoxylated at 100% had a Draize score of 0.89 out of 4 when dermally administered to rabbits. When sorbitan monostearate, ethoxylated was dermally administered to rabbits for 30 days, the test substance caused necrosis of the skin at 10% but only moderate irritation at 5%. Administration of sorbitan monostearate, ethoxylated at 100% for 60 days did not cause irritation in rabbits. Sorbitan monostearate, ethoxylated at 100% did not produce any skin reaction when administered to the shaved backs of rabbits.

In a clinical test, polysorbate 60 at 100%, polysorbate 80 at 100%, and sorbitan monostearate, ethoxylated at 25% were not dermally irritating.

In vivo tests of polysorbate 20 (10%) and polysorbate 81 (up to 100%) showed that these ingredients were not ocular irritants. In vitro prediction tests gave mixed results. EpiOcular tests, a red blood cell hemolysis assay, and a k562 cell assay predicted polysorbate 20 to be a non- or minimal ocular irritant at 2% and 100%. STE at 5%, HET-CAM at 100%, and BCOP at 100% predicted that polysorbate 20 would be a mild to severe ocular irritant.

Polysorbate 81 up to 4% was not sensitizing to guinea pigs when challenged at 100% for 21 days.

Polysorbate 81 at 100% was not sensitizing in human patch tests.

DISCUSSION

This is a re-review of polysorbates from 3 previous safety assessments that have been combined, along with similar polysorbates that have not been reviewed, into one report. The Panel agreed that grouping these ingredients together was appropriate because of the common core structure of sorbitan or sorbitol, etherified with PEG chains, and esterified with fatty acids.

The Panel considered the data available to characterize the potential for polysorbates to cause systemic toxicity, irritation, sensitization, reproductive and developmental toxicity, and genotoxicity. They noted the lack of systemic toxicity

at low and moderate doses in several acute and repeated-dose oral exposure studies, and low toxicity at high doses; little or no irritation or sensitization in multiple tests of dermal and ocular exposure; the absence of genotoxicity in multiple Ames tests and chromosome aberration tests, and minimal irritation and lack of sensitization in tests of dermal exposure at concentration of use.

The Panel recognizes that there are data gaps regarding use and concentration of these ingredients. However, the overall information available on the types of products in which these ingredients are used, concentrations of use and the similar pattern of use raise no safety concerns.

The Panel note that polysorbate 20, polysorbate 65, and polysorbate 80 were shown to enhance dermal drug absorption. The Panel cautions that care should be taken in formulating cosmetic products that may contain these ingredients in combination with any ingredients whose safety was based on their lack of dermal absorption, or when dermal absorption was a concern. Especially, care should be taken when creating formulations intended for use on infants.

To address the possible presence of 1,4-dioxane and ethylene oxide impurities in these ingredients, the Panel stressed that the cosmetics industry should continue to use the necessary procedures to limit these impurities from the PEG ingredients before blending them into cosmetic formulations.

The Panel expressed concern about pesticide residues and heavy metals that may be present in botanical (ie, coconut-derived) ingredients. They stressed that the cosmetics industry should continue to use current good manufacturing practices (cGMPs) to limit impurities.

Data from the 1984 safety assessment suggested that polysorbates caused a slight enhancement of tumor development caused by 7,12-dimethyl-benz[a]anthracene (DMBA) and *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG); however, the data were not consistent. For other compounds, the tumorigenic properties of 3-methyl-cholanthrene (MCA) and 3,4-benz[*a*]pyrene (BP) were not enhanced by polysorbates. Since the tumor enhancement effects were inconsistent and depended on the simultaneous exposure to strong chemical carcinogens, which are not present in cosmetics, the Panel felt that the weak tumor enhancement effects were not relevant to cosmetic formulations.

Because some studies showed minimal irritation at concentrations that are used in cosmetics, the Panel cautioned that products containing these ingredients should be formulated to be non-irritating.

It was noted that at the time of the 2001 safety assessment on sorbeth beeswaxes, the Panel had recommended that cosmetic formulations containing PEGs not be used on damaged skin because of the possibility of renal toxicity when PEGs were applied to severely damaged skin, such as in burn patients. Since then, PEGs have been re-reviewed and the additional data demonstrated minimal dermal penetration of low-molecular weight PEGs. The amount of PEGs that would penetrate the stratum corneum barrier, even if damaged, from the use of cosmetics was well below the level of renal toxicity. Therefore, the Panel has removed the caveat that PEGs should not be used on damaged skin. The Panel strongly asserted that it is inappropriate to apply cosmetic products containing high concentrations of PEGs to individuals exhibiting barrier skin disruption through both the stratum corneum and the epidermis.

The Panel discussed the issue of incidental inhalation exposure from spray products, including aerosol and pump hair sprays, spray deodorants, spray body and hand products, and spray moisturizing products. The limited acute exposure data available from 1 new inhalation study and 1 historical tracheal study suggest little potential for respiratory effects at relevant doses. These ingredients are reportedly used at concentrations up to 4% in cosmetic products that may be aerosolized. The Panel noted that 95%-99% of droplets/particles would not be respirable to any appreciable amount. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. The Panel also considered the other data available to characterize the safety of polysorbates. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at http://www.cir-safety.org/cir-findings.

CONCLUSION

The CIR Expert Panel concluded that the polysorbates listed below are safe in cosmetics when formulated to be non-irritating. This conclusion supersedes the conclusion reached in the 1984, 2000, and 2001 CIR safety assessments.

Polysorbate 20
Polysorbate 21
Polysorbate 40
Polysorbate 60
Polysorbate 61
Polysorbate 65
Polysorbate 80
Polysorbate 81
Polysorbate 85
PEG-30 sorbitan beeswax
PEG-20 sorbitan cocoate
PEG-40 sorbitan diisostearate
PEG-2 sorbitan isostearate*
PEG-5 sorbitan isostearate*
PEG-20 sorbitan isostearate
PEG-40 sorbitan lanolate
PEG-75 sorbitan lanolate*
PEG-10 sorbitan laurate
PEG-40 sorbitan laurate
PEG-44 sorbitan laurate
PEG-75 sorbitan laurate
PEG-80 sorbitan laurate
PEG-3 sorbitan oleate
PEG-6 sorbitan oleate
PEG-20 sorbitan oleate*
PEG-40 sorbitan oleate*
PEG-80 sorbitan palmitate*
PEG-40 sorbitan perisostearate*
PEG-40 sorbitan peroleate
PEG-3 sorbitan stearate
PEG-4 sorbitan stearate
PEG-6 sorbitan stearate
PEG-40 sorbitan stearate

PEG-60 sorbitan stearate*
PEG-30 sorbitan tetraoleate
PEG-40 sorbitan tetraoleate
PEG-60 sorbitan tetraoleate
PEG-60 sorbitan tetrastearate*
PEG-4 sorbitan triisostearate*
PEG-20 sorbitan triisostearate*
PEG-160 sorbitan triisostearate
PEG-2 sorbitan trioleate*
PEG-18 sorbitan trioleate
PEG-3 sorbitan tristearate*
Sorbeth-2 beeswax*
Sorbeth-6 beeswax
Sorbeth-8 beeswax*
Sorbeth-20 beeswax
Sorbeth-2 cocoate*
Sorbeth-2 hexacaprylate/caprate*
Sorbeth-12 hexacocoate*
Sorbeth-2 hexaisostearate*
Sorbeth-2 hexalaurate*
Sorbeth-2 hexaoleate*
Sorbeth-40 hexaoleate*
Sorbeth-50 hexaoleate*
Sorbeth-6 hexastearate*
Sorbeth-150 hexastearate*
Sorbeth-3 isostearate*
Sorbeth-6 laurate*
Sorbeth-2/oleate/dimer dilinoleate crosspolymer*
Sorbeth-20 pentaisostearate*
Sorbeth-30 pentaisostearate*
Sorbeth-40 pentaisostearate*
Sorbeth-50 pentaisostearate*
Sorbeth-40 pentaoleate*
Sorbeth-20 tetraisostearate*
Sorbeth-30 tetraisostearate
Sorbeth-40 tetraisostearate*
Sorbeth-50 tetraisostearate*
Sorbeth-4 tetraoleate
Sorbeth-6 tetraoleate
Sorbeth-30 tetraoleate
Sorbeth-40 tetraoleate
Sorbeth-60 tetraoleate
Sorbeth-30 tetraoleate laurate*
Sorbeth-60 tetrastearate*
Sorbeth-3 tristearate*
Sorbeth-160 tristearate*
Sorbeth-450 tristearate*

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

TABLES AND FIGURES

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

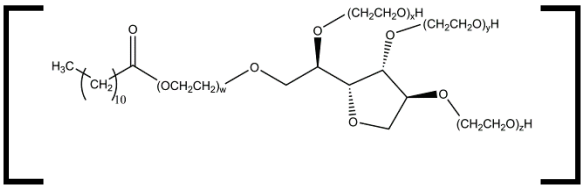
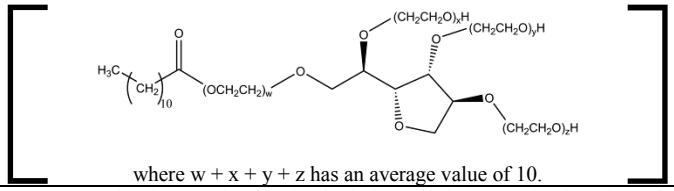
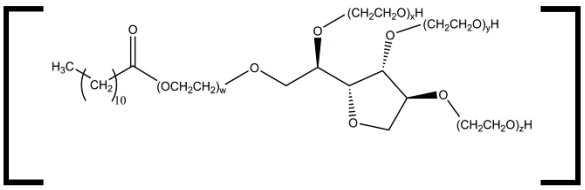
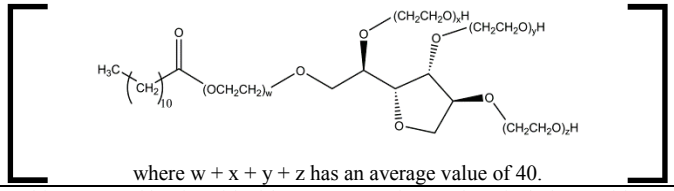
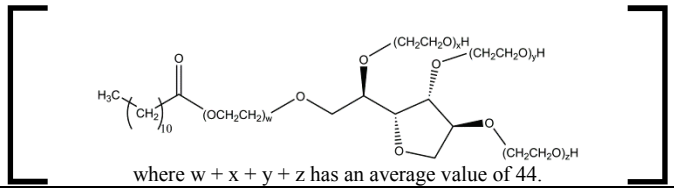
Ingredient and CAS No.	Definition	Function
Polysorbate Monoesters *Sorbitan derivatives*		
Polysorbate 21 9005-64-5 (generic)	A mixture of laurate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 4 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 4.	Fragrance ingredient; surfactant-emulsifying agent
PEG-10 sorbitan laurate 9005-64-5 (generic)	PEG-10 Sorbitan Laurate is an ethoxylated sorbitan ester of lauric acid with an average of 10 moles of ethylene oxide.  where w + x + y + z has an average value of 10.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent
Polysorbate 20 9005-64-5 (generic)	A mixture of laurate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 20.	Fragrance ingredient; surfactant-emulsifying agent; surfactant-solubilizing agent
PEG-40 sorbitan laurate 9005-64-5 (generic)	An ethoxylated sorbitan ester of lauric acid with an average of 40 moles of ethylene oxide.  where w + x + y + z has an average value of 40.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent
PEG-44 sorbitan laurate 9005-64-5 (generic)	An ethoxylated sorbitan ester of lauric acid with an average of 44 moles of ethylene oxide.  where w + x + y + z has an average value of 44.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

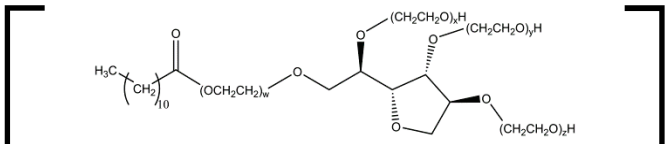
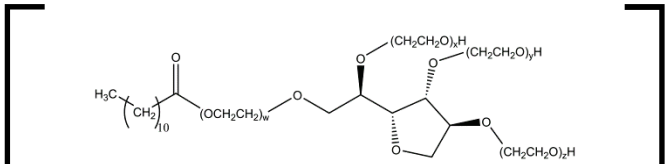
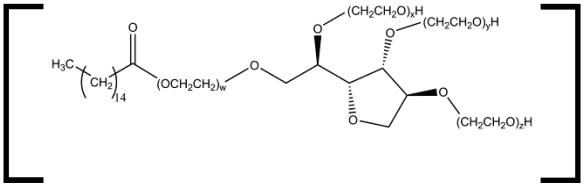
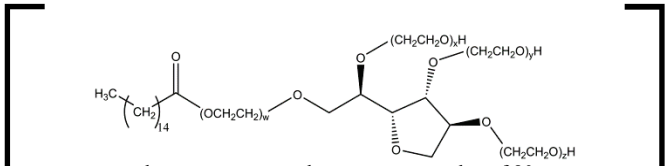
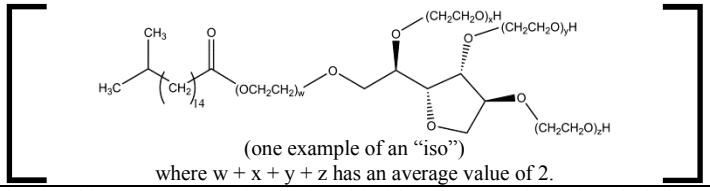
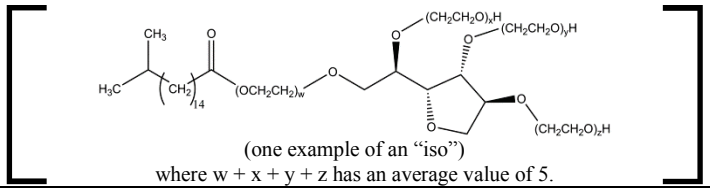
Ingredient and CAS No.	Definition	Function
PEG-75 sorbitan laurate 9005-64-5 (generic)	An ethoxylated sorbitan ester of lauric acid with an average of 75 moles of ethylene oxide.  where w + x + y + z has an average value of 75.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent
PEG-80 sorbitan laurate 68154-33-6 (generic) 9005-64-5 (generic)	An ethoxylated sorbitan ester of lauric acid with an average of 80 moles of ethylene oxide.  where w + x + y + z has an average value of 80.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent
Polysorbate 40 9005-66-7	A mixture of palmitate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 20.	Surfactant-emulsifying agent; surfactant-solubilizing agent
PEG-80 sorbitan palmitate 9005-66-7 (generic)	An ethoxylated sorbitan monoester of palmitic acid with an average of 80 moles of ethylene oxide.  where w + x + y + z has an average value of 80.	Surfactant-cleansing agent; surfactant solubilizing agent
PEG-2 sorbitan isostearate 66794-58-9 (generic)	An ethoxylated sorbitan monoester of isostearic acid with an average of 2 moles of ethylene oxide.  (one example of an "iso") where w + x + y + z has an average value of 2.	Surfactant-emulsifying agent
PEG-5 sorbitan isostearate 66794-58-9 (generic)	An ethoxylated sorbitan monoester of isostearic acid with an average of 5 moles of ethylene oxide.  (one example of an "iso") where w + x + y + z has an average value of 5.	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

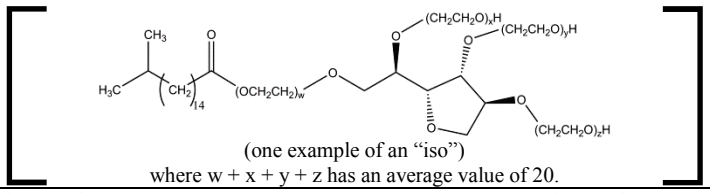
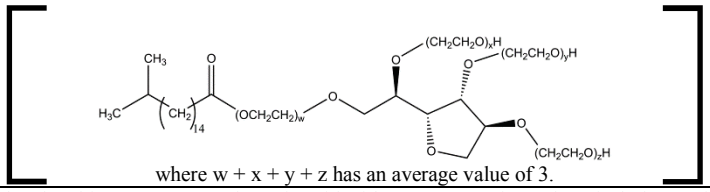
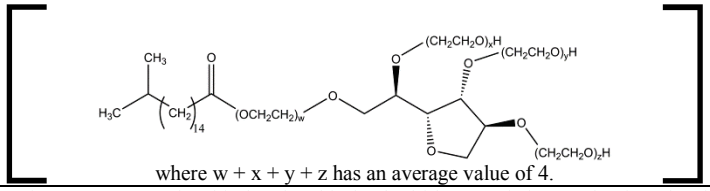
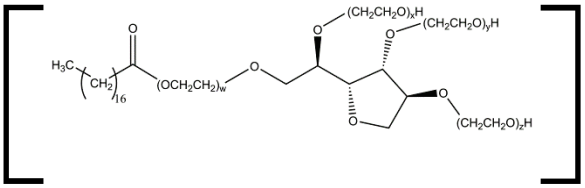
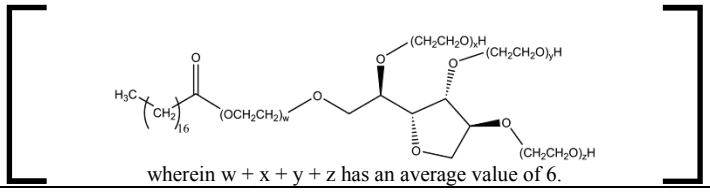
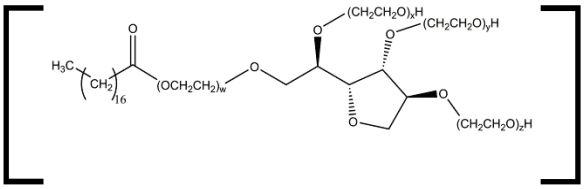
Ingredient and CAS No.	Definition	Function
PEG-20 sorbitan isostearate 66794-58-9 (generic)	An ethoxylated sorbitan monoester of isostearic acid with an average of 20 moles of ethylene oxide.  (one example of an "iso") where w + x + y + z has an average value of 20.	Surfactant-cleansing agent; surfactant-emulsifying agent; surfactant solubilizing agent
PEG-3 sorbitan stearate 9005-67-8 (generic)	An ethoxylated sorbitan monoester of stearic acid with an average of 3 moles of ethylene oxide.  where w + x + y + z has an average value of 3.	Fragrance ingredient; surfactant-emulsifying agent
PEG-4 sorbitan stearate 9005-67-8 (generic)	An ethoxylated sorbitan monoester of stearic acid with an average of 4 moles of ethylene oxide.  where w + x + y + z has an average value of 4.	Fragrance ingredient; surfactant-emulsifying agent
Polysorbate 61 9005-67-8 (generic)	A mixture of stearate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 4 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 4.	Fragrance ingredient; surfactant-emulsifying agent
PEG-6 sorbitan stearate 9005-67-8 (generic)	An ethoxylated sorbitan monoester of stearic acid with an average of 6 moles of ethylene oxide.  wherein w + x + y + z has an average value of 6.	Fragrance ingredient; surfactant-emulsifying agent
Polysorbate 60 9005-67-8 (generic)	A mixture of stearate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 20.	Fragrance ingredient; surfactant-emulsifying agent; surfactant-solubilizing agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

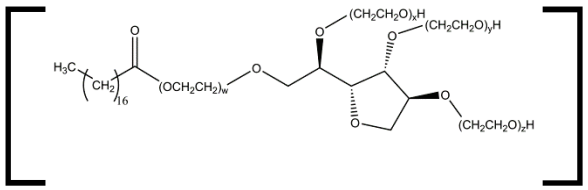
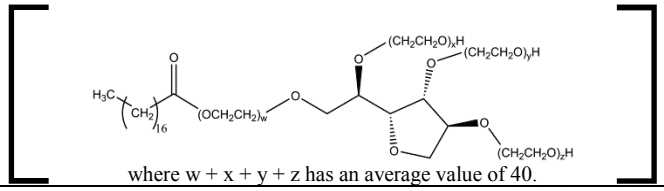
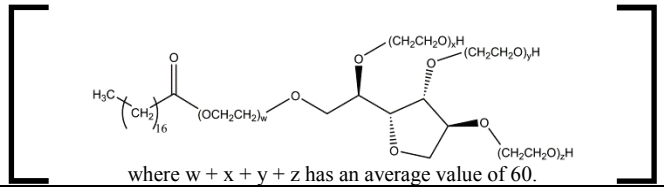
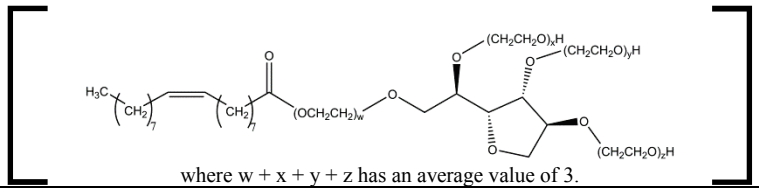
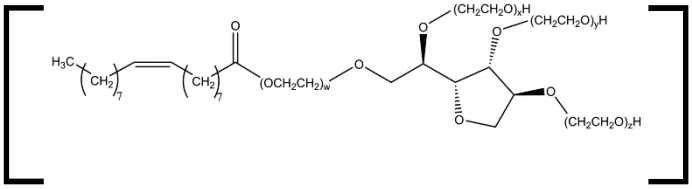
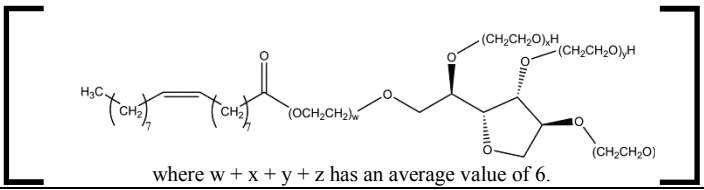
Ingredient and CAS No.	Definition	Function
Polysorbate 65 9005-71-4	A mixture of stearate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the triester, condensed with approximately 20 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 20.	Surfactant-emulsifying agent
PEG-40 sorbitan stearate 9005-67-8 (generic)	An ethoxylated sorbitan ester of stearic acid with an average of 40 moles of ethylene oxide.  where w + x + y + z has an average value of 40.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent
PEG-60 sorbitan stearate 9005-67-8 (generic)	An ethoxylated sorbitan ester of stearic acid with an average of 60 moles of ethylene oxide.  where w + x + y + z has an average value of 60.	Fragrance ingredient; surfactant-cleansing agent; surfactant-solubilizing agent
PEG-3 sorbitan oleate 9005-65-6 (generic)	An ethoxylated sorbitan ester of oleic acid with an average of 3 moles of ethylene oxide.  where w + x + y + z has an average value of 3.	Fragrance ingredient; surfactant-emulsifying agent
Polysorbate 81 9005-65-6 (generic)	A mixture of oleate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 5 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 5.	Fragrance ingredient; surfactant-emulsifying agent
PEG-6 sorbitan oleate 9005-65-6 (generic)	An ethoxylated sorbitan ester of oleic acid with an average of 6 moles of ethylene oxide.  where w + x + y + z has an average value of 6.	Fragrance ingredient; surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

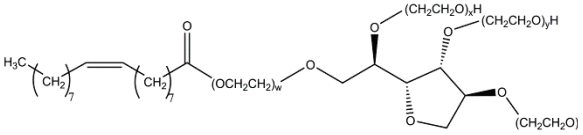
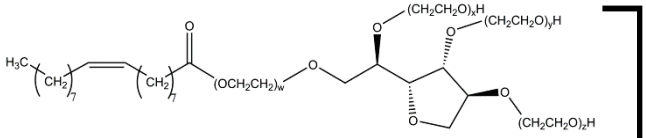
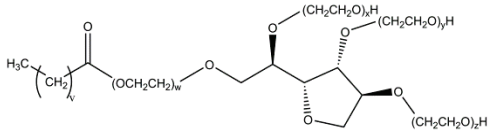
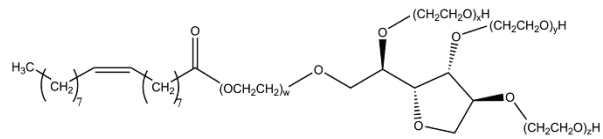
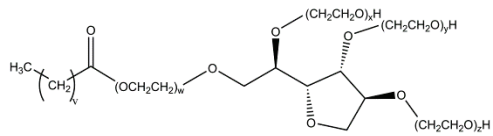
Ingredient and CAS No.	Definition	Function
PEG-20 sorbitan oleate	An ethoxylated sorbitan ester of oleic acid with an average of 20 moles of ethylene oxide.  where w + x + y + z has an average value of 20.	Surfactant-cleansing agent; surfactant-emulsifying agent; surfactant solubilizing agent
Polysorbate 80 9005-65-6 (generic)	A mixture of oleate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the monoester, condensed with approximately 20 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 20.	Denaturant; fragrance ingredient; surfactant-emulsifying agent; surfactant solubilizing agent
PEG-30 sorbitan beeswax	[Not listed as a cosmetic ingredient in the *Dictionary*. An ethoxylated sorbitan ester of beeswax acid with an average of 30 moles of ethylene oxide.]  where $CH_3(CH_2)_vC(O)$- represents the fatty acids derived from beeswax and w + x + y + z has an average value of 30. The composition of beeswax is a variable mixture of glycerides and fatty acids containing 24 to 36 carbons in alkyl chain length (beeswax acid).[18]	[1 use in VCRP[56]]
PEG-40 sorbitan oleate	An ethoxylated sorbitan ester of oleic acid with an average of 40 moles of ethylene oxide.  where w + x + y + z has an average value of 40.	Surfactant-cleansing agent; surfactant-emulsifying agent; surfactant solubilizing agent
PEG-20 sorbitan cocoate	An ethoxylated sorbitan ester of coconut acid with an average of 20 moles of ethylene oxide.  where $CH_3(CH_2)_vC(O)$- represents the fatty acids derived from cocos nucifera (coconut) oil and w + x + y + z has an average value of 20. The fatty acid distribution of coconut oil is 0-1% caproic, 5-9% caprylic, 6-10% capric, 44-52% lauric, 13-19% myristic, 0-1% palmitoleic, 1-3% stearic, 5-8% oleic, and trace-2.5% linoleic acid.[57]	Surfactant-cleansing agent; surfactant-solubilizing agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

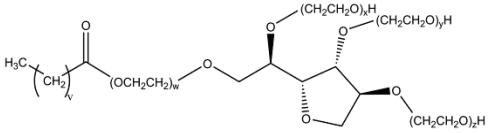
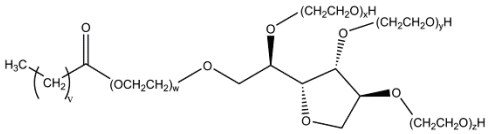
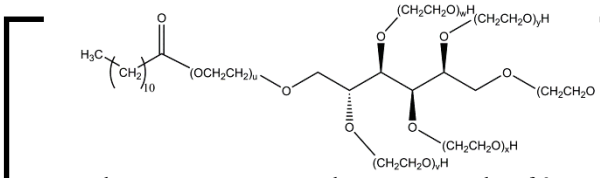
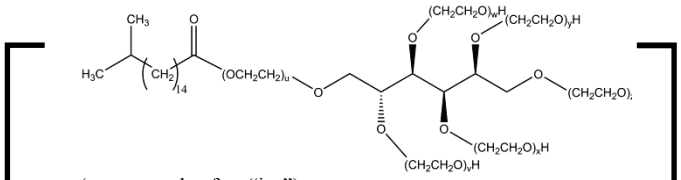
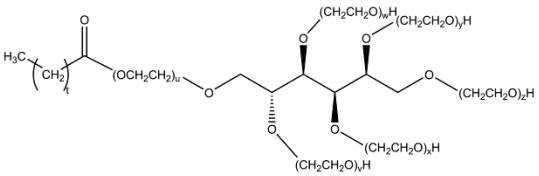
Ingredient and CAS No.	Definition	Function
PEG-40 sorbitan lanolate 8036-77-9	An ethoxylated sorbitan derivative of lanolin acid with an average of 40 moles of ethylene oxide.  where $CH_3(CH_2)_vC(O)$- represents the fatty acids derived from lanolin acid and w + x + y + z has an average value of 40. The length of the lanolin fatty acid chain varies from 7 to 41 carbon atoms. The main fatty acids are palmitic (C16), stearic (C18) and longer molecules (C20 to C 32).[12]	Surfactant-cleansing agent; surfactant solubilizing agent
PEG-75 sorbitan lanolate 8051-13-6	An ethoxylated sorbitan derivative of lanolin acid with an average of 75 moles of ethylene oxide.  where $CH_3(CH_2)_vC(O)$- represents the fatty acids derived from lanolin acid and w + x + y + z has an average value of 75. The length of the lanolin fatty acid chain varies from 7 to 41 carbon atoms. The main fatty acids are palmitic (C16), stearic (C18) and longer molecules (C20 to C 32).[12]	Surfactant-cleansing agent; surfactant solubilizing agent
Polysorbate Monoesters *Sorbitol derivatives*		
Sorbeth-6 laurate [66686-72-4]	The ester of lauric acid and a polyethylene glycol ether of sorbitol containing an average of 6 moles of ethylene oxide.  where u + v + w + x + y + z has an average value of 6.	Surfactant-emulsifying agent; surfactant-solubilizing agent
Sorbeth-3 isostearate	The ester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 3 moles of ethylene oxide.  (one example of an "iso") where u + v + w + x + y + z has an average value of 3.	Surfactant-emulsifying agent
Sorbeth-2 cocoate	The ester of the fatty acids derived from cocos nucifera (coconut) oil and a polyethylene glycol ether of Sorbitol containing an average of 2 moles of ethylene oxide.  where $CH_3(CH_2)_tC(O)$- represents the fatty acids derived from cocos nucifera (coconut) oil and u + v + w + x + y + z has an average value of 2. The fatty acid distribution of coconut oil is 0-1% caproic, 5-9% caprylic, 6-10% capric, 44-52% lauric, 13-19% myristic, 0-1% palmitoleic, 1-3% stearic, 5-8% oleic, and trace-2.5% linoleic acid.[57]	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

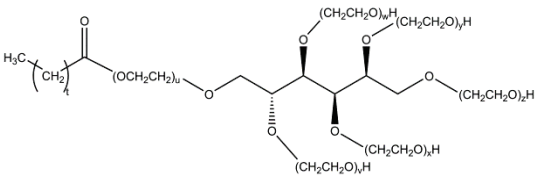
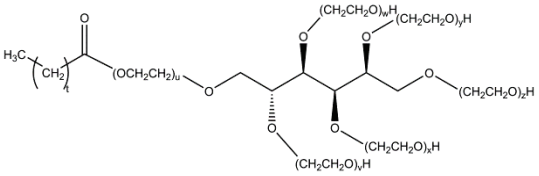
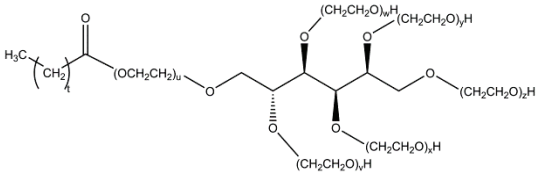
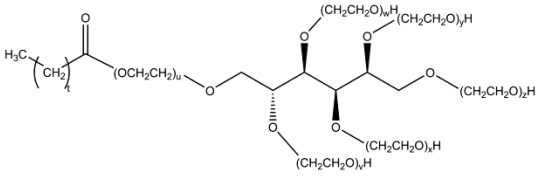
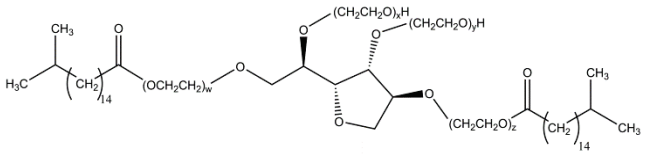
Ingredient and CAS No.	Definition	Function
Sorbeth-2 beeswax	An ethoxylated sorbitan derivative of beeswax with an average of 2 moles of ethylene oxide.  where $CH_3(CH_2)_tC(O)$- represents the fatty acids derived from beeswax and u + v + w + x + y + z has an average value of 2. The composition of beeswax is a variable mixture of glycerides and fatty acids containing 24 to 36 carbons in alkyl chain length (beeswax acid).[18]	Surfactant-emulsifying agent
Sorbeth-6 beeswax 8051-15-8	An ethoxylated sorbitan derivative of beeswax with an average of 6 moles of ethylene oxide.  where $CH_3(CH_2)_tC(O)$- represents the fatty acids derived from beeswax and u + v + w + x + y + z has an average value of 6. The composition of beeswax is a variable mixture of glycerides and fatty acids containing 24 to 36 carbons in alkyl chain length (beeswax acid).[18]	Surfactant-emulsifying agent
Sorbeth-8 beeswax	An ethoxylated sorbitan derivative of beeswax with an average of 8 moles of ethylene oxide.  where $CH_3(CH_2)_tC(O)$- represents the fatty acids derived from beeswax and u + v + w + x + y + z has an average value of 8. The composition of beeswax is a variable mixture of glycerides and fatty acids containing 24 to 36 carbons in alkyl chain length (beeswax acid).[18]	Surfactant-emulsifying agent
Sorbeth-20 beeswax	An ethoxylated sorbitan derivative of beeswax with an average of 20 moles of ethylene oxide.  where $CH_3(CH_2)_tC(O)$- represents the fatty acids derived from beeswax and u + v + w + x + y + z has an average value of 20. The composition of beeswax is a variable mixture of glycerides and fatty acids containing 24 to 36 carbons in alkyl chain length (beeswax acid).[18]	Surfactant-emulsifying agent; surfactant-solubilizing agent
Polysorbate Diester *Sorbitan Derivative*		
PEG-40 sorbitan diisostearate	An ethoxylated sorbitan diester of isostearic acid with an average of 40 moles of ethylene oxide.  (one example of an "iso"; one example of a diester) where w + x + y + z has an average value of 40.	Surfactant-emulsifying agent; surfactant solubilizing agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

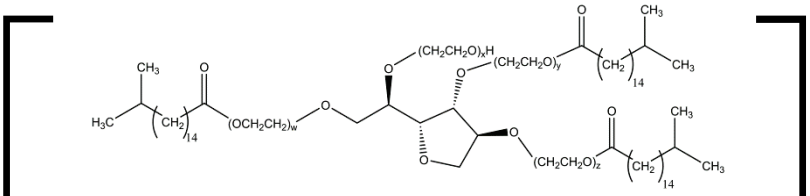
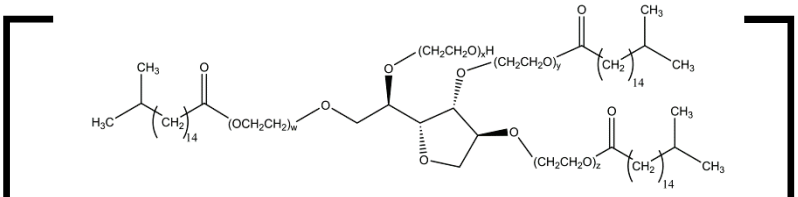
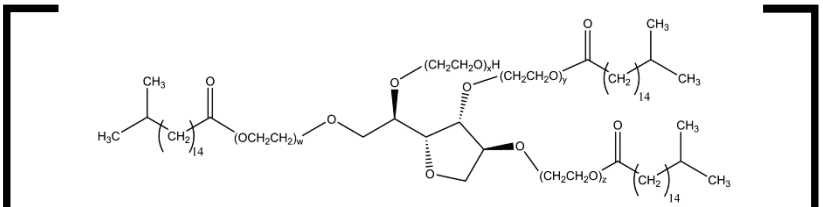
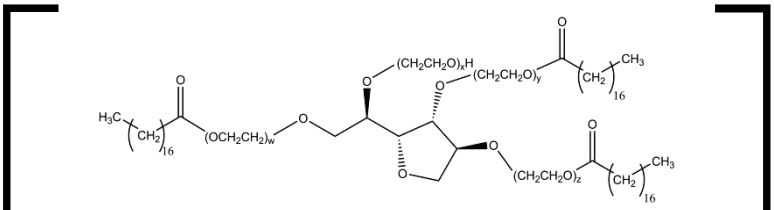
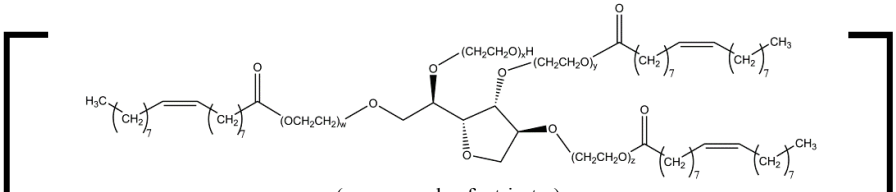
Ingredient and CAS No.	Definition	Function
Polysorbate Triesters *Sorbitan Derivatives*		
PEG-4 sorbitan triisostearate	The triester of isostearic acid and a polyethylene glycol ether of sorbitol with an average of 4 moles of ethylene oxide.  (one example of an "iso"; one example of a triester) where w + x + y + z has an average value of 4.	Surfactant-emulsifying agent
PEG-20 sorbitan triisostearate	The triester of isostearic acid and a polyethylene glycol ether of sorbitol with an average of 20 moles of ethylene oxide.  (one example of an "iso"; one example of a triester) where w + x + y + z has an average value of 20.	Surfactant-emulsifying agent
PEG-160 sorbitan triisostearate	The triester of isostearic acid and a polyethylene glycol ether of sorbitol with an average of 160 moles of ethylene oxide.  (one example of an "iso"; one example of a triester) where w + x + y + z has an average value of 160.	Surfactant-cleansing agent; surfactant-solubilizing agent
PEG-3 sorbitan tristearate	The triester of stearic acid and a polyethylene glycol ether of sorbitol with an average of 3 moles of ethylene oxide.  (one example of a triester) where w + x + y + z has an average value of 3.	Skin-conditioning agent-emollient
PEG-2 sorbitan trioleate	A triester of oleic acid and a polyethylene glycol ether of sorbitol with an average of 2 moles of ethylene oxide.  (one example of a triester) where w + x + y + z has an average value of 2.	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

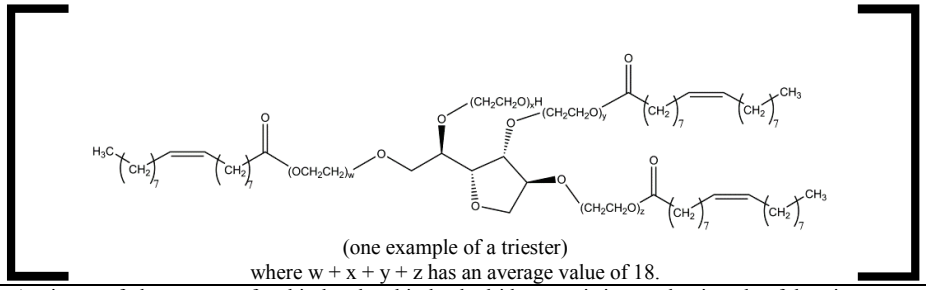
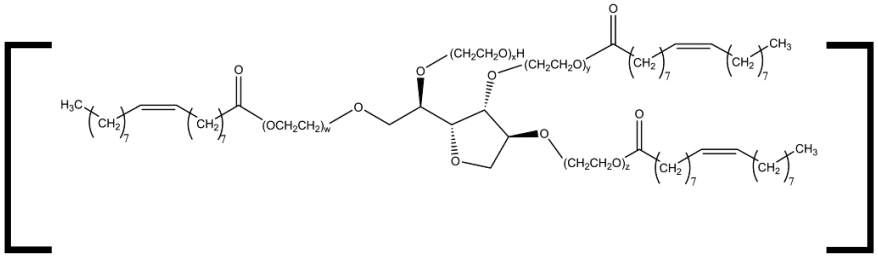
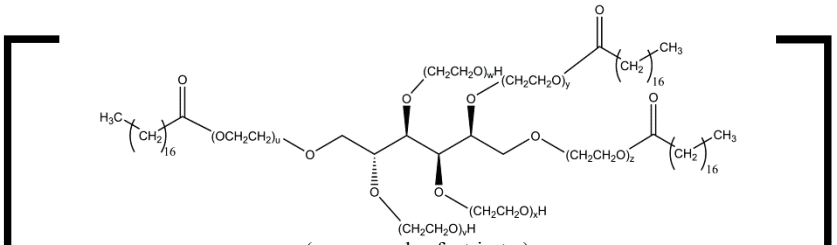
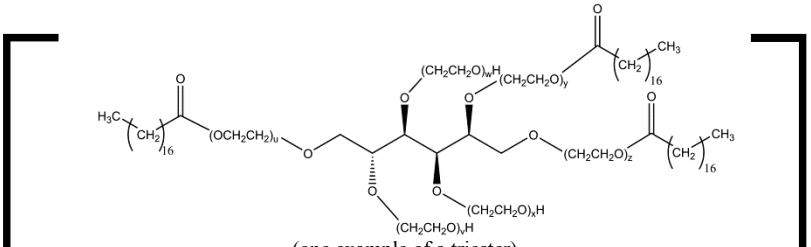
Ingredient and CAS No.	Definition	Function
PEG-18 sorbitan trioleate	[Not listed as a cosmetic ingredient in the *Dictionary*. A triester of oleic acid and a polyethylene glycol ether of sorbitol with an average of 18 moles of ethylene oxide.]  (one example of a triester) where w + x + y + z has an average value of 18.	[1 use in VCRP[56]]
Polysorbate 85 9005-70-3	A mixture of oleate esters of sorbitol and sorbitol anhydrides, consisting predominantly of the triester, condensed with approximately 20 moles of ethylene oxide. It conforms generally to the formula:  where w + x + y + z has an average value of 20.	Surfactant-dispersing agent; surfactant-emulsifying agent
Polysorbate Triesters *Sorbitol Derivatives*		
Sorbeth-3 tristearate	The triester of stearic acid and a polyethylene glycol ether of sorbitol containing an average of 3 moles of ethylene oxide.  (one example of a triester) where u + v + w + x + y + z has an average value of 3.	Surfactant-emulsifying agent
Sorbeth-160 tristearate	The triester of stearic acid and a polyethylene glycol ether of sorbitol with an average of 160 moles of ethylene oxide.  (one example of a triester) where u + v + w + x + y + z has an average value of 160.	Surfactant-cleansing agent; surfactant-solubilizing agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

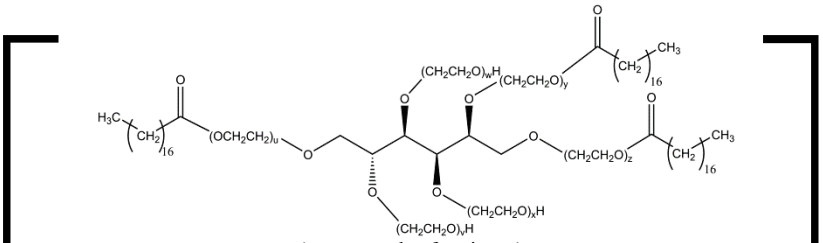
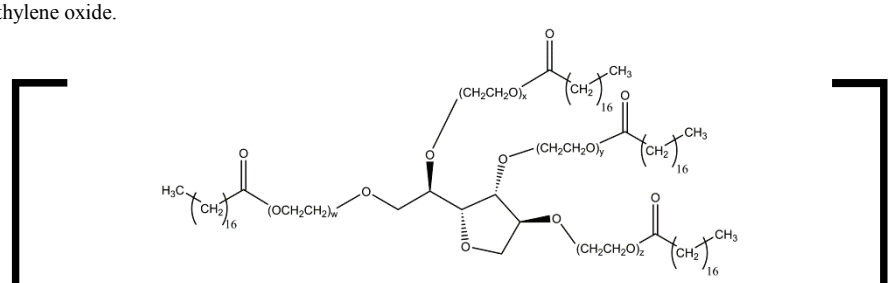
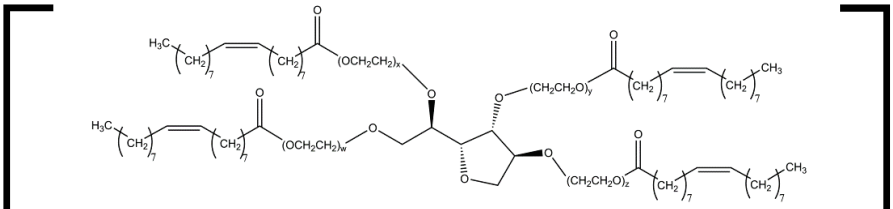
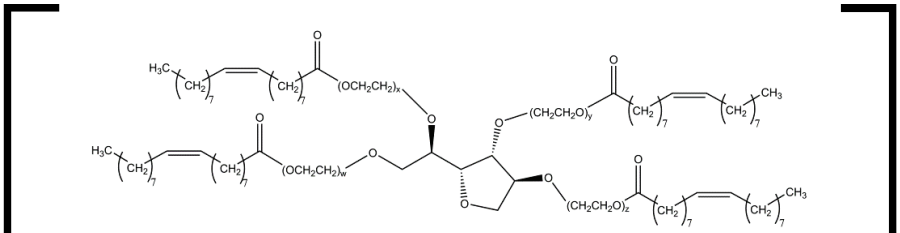
Ingredient and CAS No.	Definition	Function
Sorbeth-450 tristearate	The triester of stearic acid and a polyethylene glycol ether of sorbitol with an average of 450 moles of ethylene oxide.  (one example of a triester) where u + v + w + x + y + z has an average value of 450.	Surfactant-dispersing agent; surfactant - emulsifying agent; surfactant – foam booster; viscosity increasing agent – aqueous
Polysorbate Tetraesters *Sorbitan Derivatives*		
PEG-60 sorbitan tetrastearate	The tetraester of stearic acid and a polyethylene glycol ether of sorbitol, with an average of 60 moles of ethylene oxide.  (one example of a tetraester) where w + x + y + z has an average value of 60.	Surfactant-emulsifying agent
PEG-30 sorbitan tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol, with an average of 30 moles of ethylene oxide.  where w + x + y + z has an average value of 30.	Surfactant-emulsifying agent
PEG-40 sorbitan tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol, with an average of 40 moles of ethylene oxide.  where w + x + y + z has an average value of 40.	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

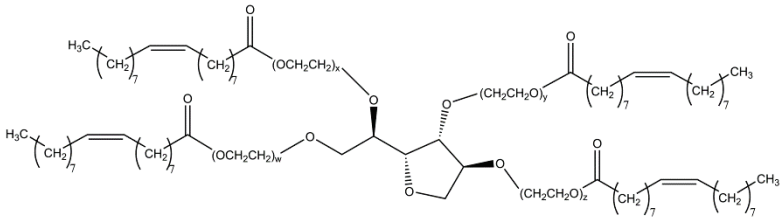
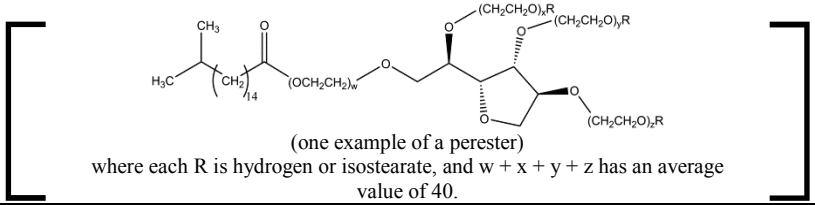
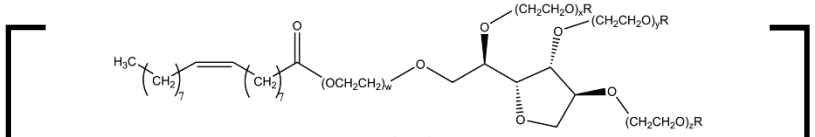
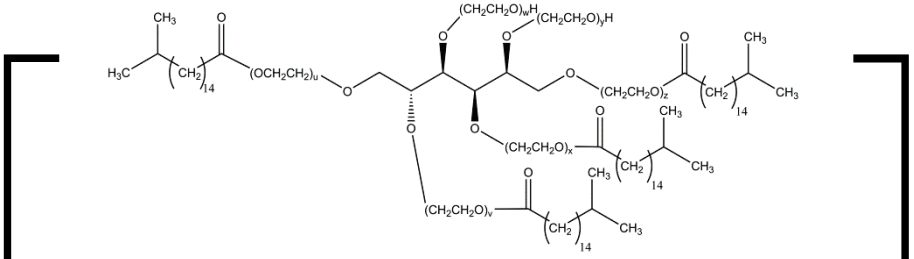
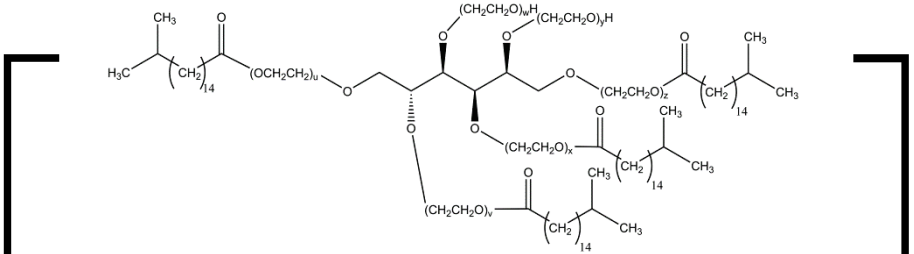
Ingredient and CAS No.	Definition	Function
PEG-60 sorbitan tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol, with an average of 60 moles of ethylene oxide.  [where w + x + y + z has an average value of 60.]	Surfactant-emulsifying agent
Polysorbate Esters - mixtures *Sorbitan Derivatives*		
PEG-40 sorbitan perisostearate	A mixture of isostearic acid esters of sorbitol condensed with an average of 40 moles of ethylene oxide.  (one example of a perester) where each R is hydrogen or isostearate, and w + x + y + z has an average value of 40.	Surfactant-emulsifying agent
PEG-40 sorbitan peroleate	A mixture of oleic acid esters of sorbitol condensed with an average of 40 moles of ethylene oxide.  (one example of a perester) where each R is hydrogen or oleate, and w + x + y + z has an average value of 40.	Surfactant-emulsifying agent; surfactant solubilizing agent
Polysorbate Tetraesters *Sorbitol Derivatives*		
Sorbeth-20 tetraisostearate	The tetraester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 20 moles of ethylene oxide.  (one example of an "iso"; one example of a tetraester) where u + v + w + x + y + z has an average value of 20.	Surfactant-emulsifying agent
Sorbeth-30 tetraisostearate	The tetraester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 30 moles of ethylene oxide.  (one example of an "iso"; one example of a tetraester) where u + v + w + x + y + z has an average value of 30.	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

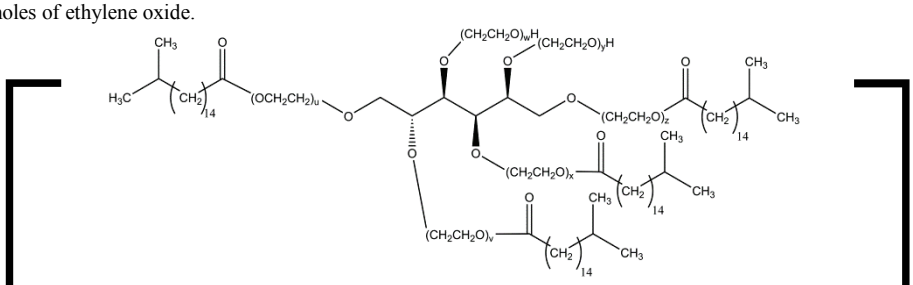
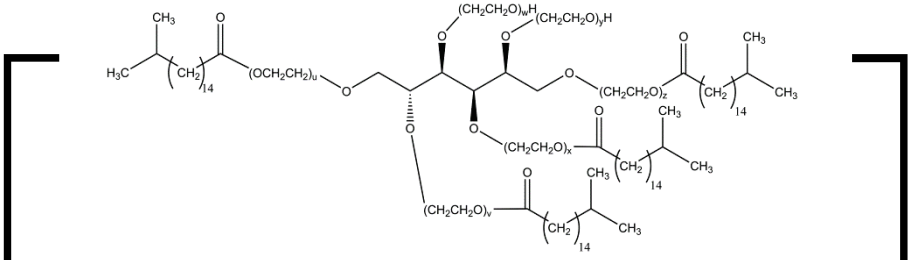
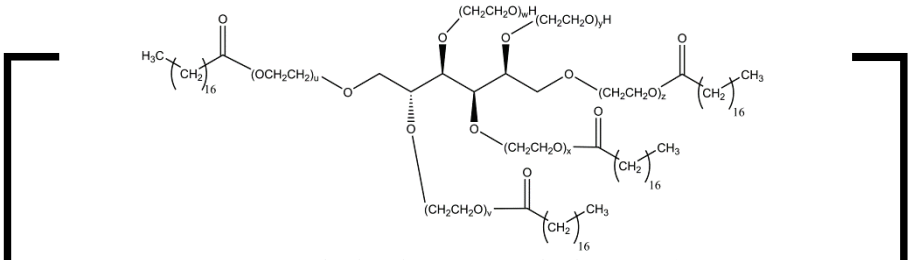
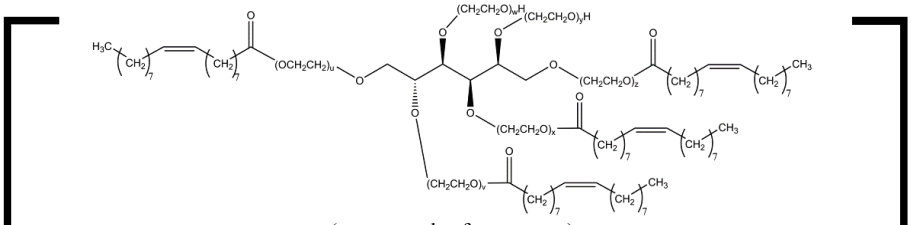
Ingredient and CAS No.	Definition	Function
Sorbeth-40 tetraisostearate	The tetraester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 40 moles of ethylene oxide.  (one example of an "iso"; on example of a tetraester) where u + v + w + x + y + z has an average value of 40.	Surfactant-emulsifying agent
Sorbeth-50 tetraisostearate	The tetraester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 50 moles of ethylene oxide.  (one example of an "iso"; one example of a tetraester) where u + v + w + x + y + z has an average value of 50.	Surfactant-emulsifying agent
Sorbeth-60 tetrastearate	The tetraester of stearic acid and a polyethylene glycol ether of sorbitol containing an average of 60 moles of ethylene oxide.  (one example of an "iso"; one example of a tetraester) where u + v + w + x + y + z has an average value of 60.	Surfactant-emulsifying agent
Sorbeth-4 tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol containing an average of 4 moles of ethylene oxide.  (one example of a tetraester) where w + x + y + z has an average value of 4.	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

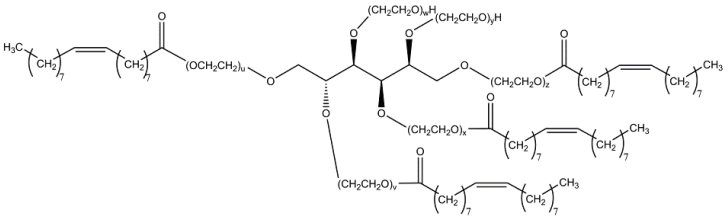
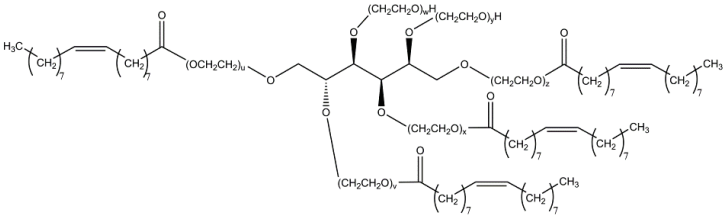
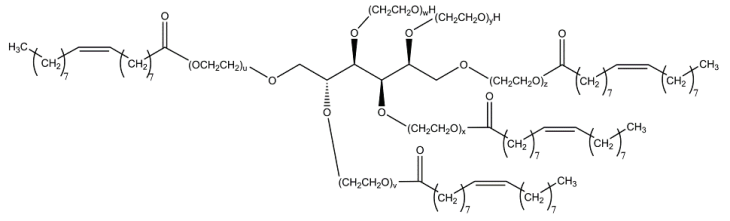
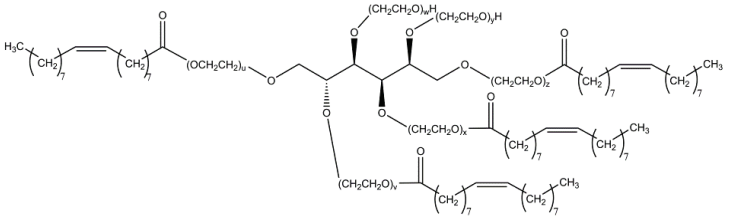
Ingredient and CAS No.	Definition	Function
Sorbeth-6 tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol containing an average of 6 moles of ethylene oxide.	Surfactant-emulsifying agent
	 (one example of a tetraester) where w + x + y + z has an average value of 6.	
Sorbeth-30 tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol containing an average of 30 moles of ethylene oxide.	Surfactant-emulsifying agent
	 (one example of a tetraester) where w + x + y + z has an average value of 30.	
Sorbeth-40 tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol with an average of 40 moles of ethylene oxide.	Surfactant-emulsifying agent
	 (one example of a tetraester) where w + x + y + z has an average value of 40.	
Sorbeth-60 tetraoleate	The tetraester of oleic acid and a polyethylene glycol ether of sorbitol with an average of 60 moles of ethylene oxide.	Surfactant-emulsifying agent
	 (one example of a tetraester) where w + x + y + z has an average value of 60.	

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

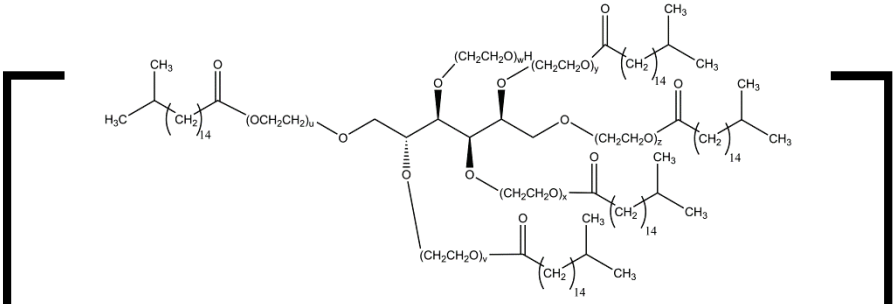
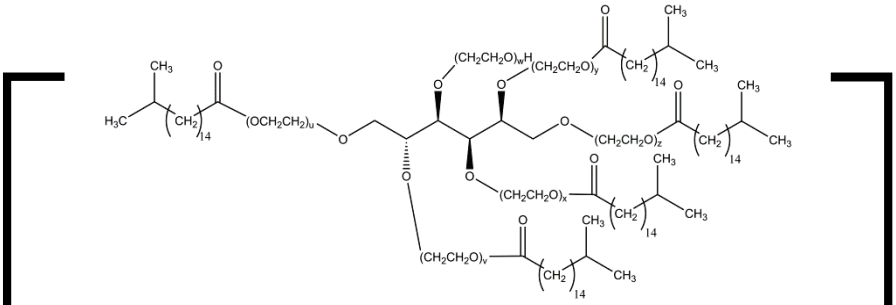
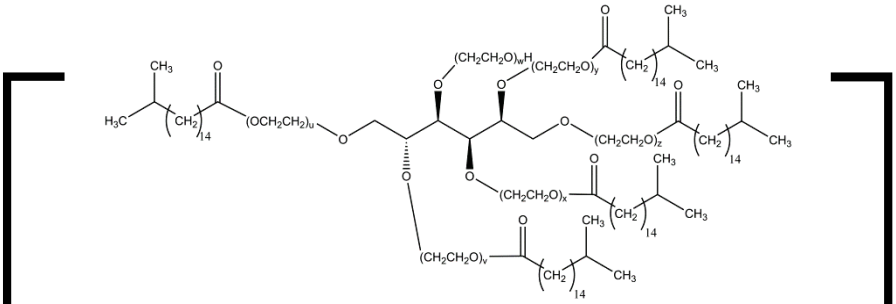
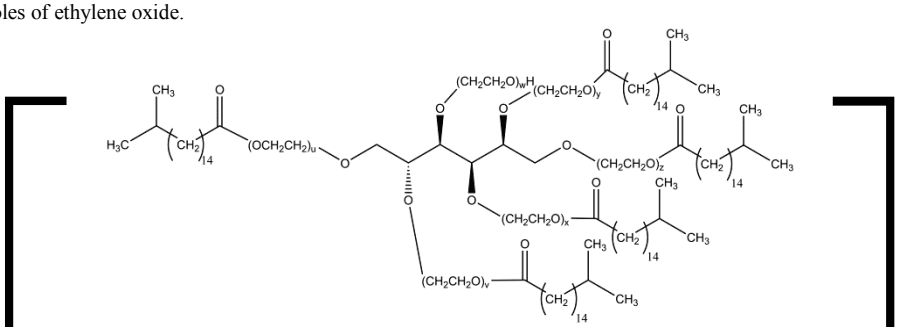
Ingredient and CAS No.	Definition	Function
Polysorbate Pentaesters *Sorbitol Derivatives*		
Sorbeth-20 pentaisostearate	The pentaester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 20 moles of ethylene oxide.  (one example of an "iso"; one example of a pentaester) where u + v + w + x + y + z has an average value of 20.	Surfactant-emulsifying agent
Sorbeth-30 pentaisostearate	The pentaester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 30 moles of ethylene oxide.  (one example of an "iso"; one example of a pentaester) where u + v + w + x + y + z has an average value of 30.	Surfactant-emulsifying agent
Sorbeth-40 pentaisostearate	The pentaester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 40 moles of ethylene oxide.  (one example of an "iso"; one example of a pentaester) where u + v + w + x + y + z has an average value of 40.	Surfactant-emulsifying agent
Sorbeth-50 pentaisostearate	The pentaester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 50 moles of ethylene oxide.  (one example of an "iso"; one example of a pentaester) where u + v + w + x + y + z has an average value of 50.	Surfactant-emulsifying agent

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

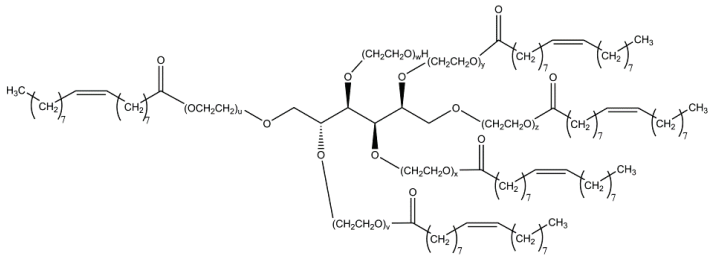
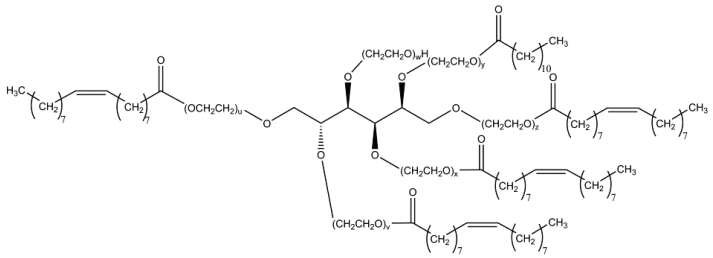
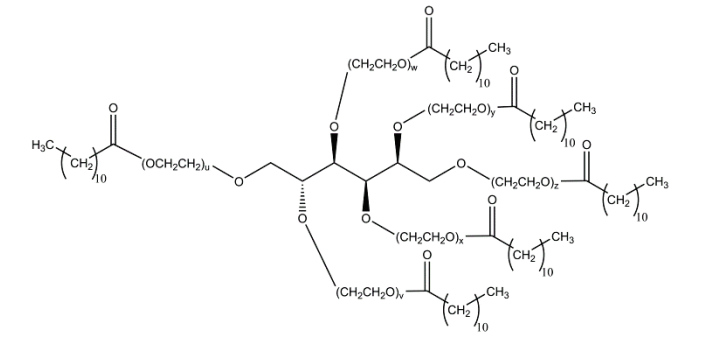
Ingredient and CAS No.	Definition	Function
Sorbeth-40 pentaoleate	The pentaester of oleic acid and a polyethylene glycol ether of sorbitol containing an average of 40 moles of ethylene oxide.	Surfactant-emulsifying agent
	 (one example of a pentaester) where u + v + w + x + y + z has an average value of 40.	
Sorbeth-30 tetraoleate laurate	The oleic acid tetraester and lauric acid ester of sorbitol ethoxylated with an average of 30 moles of ethylene oxide.	Surfactant-emulsifying agent
	 (one example of an "iso"; one example of a pentaester) where u + v + w + x + y + z has an average value of 30.	
Polysorbate Hexaesters *Sorbitol Deriviatives*		
Sorbeth-2 hexalaurate	The hexaester of lauric acid and a polyethylene glycol ether of sorbitol containing an average 2 moles of ethylene oxide.	Skin-conditioning agent-emollient
	 (one example of a pentaester) where u + v + w + x + y + z has an average value of 2.	

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

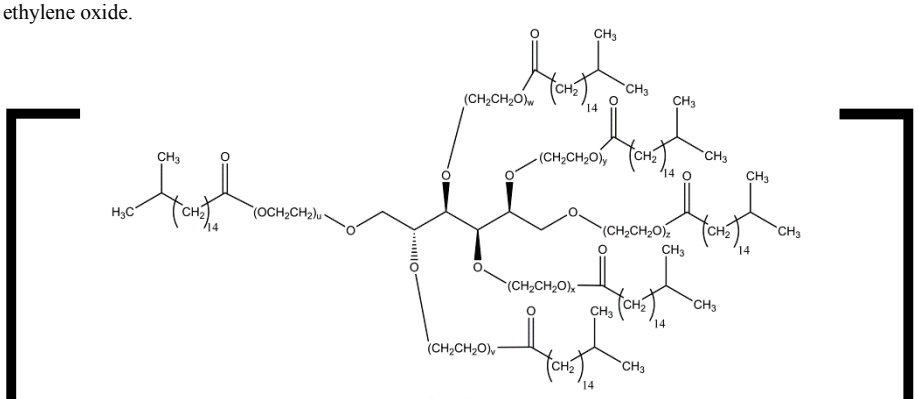
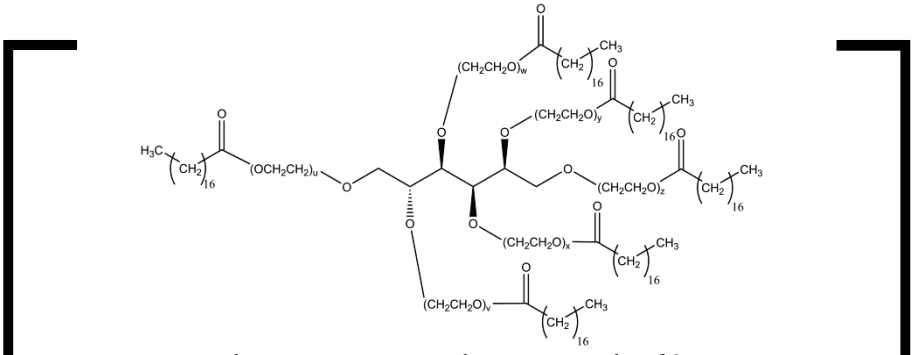
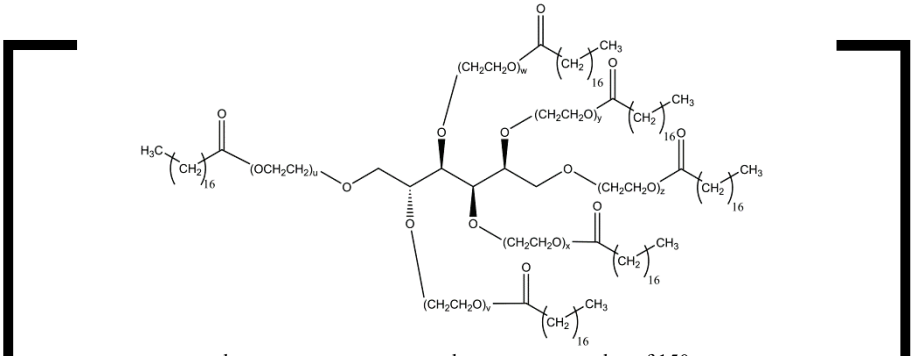
Ingredient and CAS No.	Definition	Function
Sorbeth-2 hexaisostearate	The hexaester of isostearic acid and a polyethylene glycol ether of sorbitol containing an average of 2 moles of ethylene oxide.  (one example of a pentaester) where u + v + w + x + y + z has an average value of 2.	Skin-conditioning agent-emollient
Sorbeth-6 hexastearate	The hexaester of stearic acid and a polyethylene glycol ether of sorbitol containing an average of 6 moles of ethylene oxide.  where u + v + w + x + y + z has an average value of 6.	Surfactant-emulsifying agent
Sorbeth-150 hexastearate	The hexaester of stearic acid and a polyethylene glycol ether of sorbitol containing an average of 150 moles of ethylene oxide.  where u + v + w + x + y + z has an average value of 150.	Viscosity increasing agent-aqueous

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

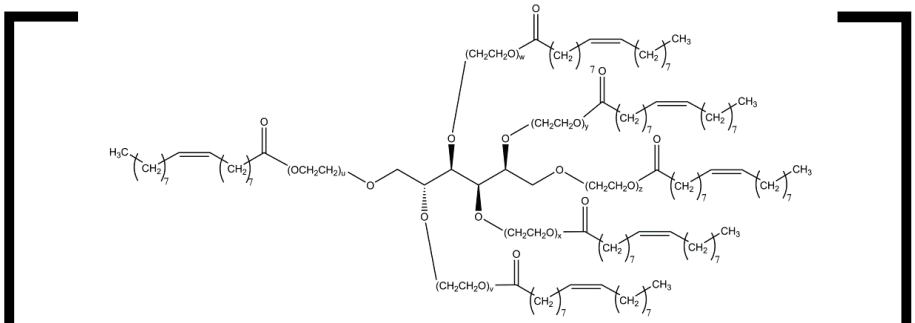
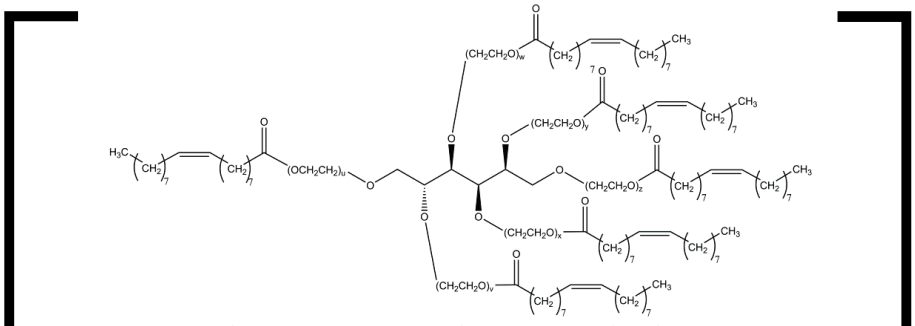
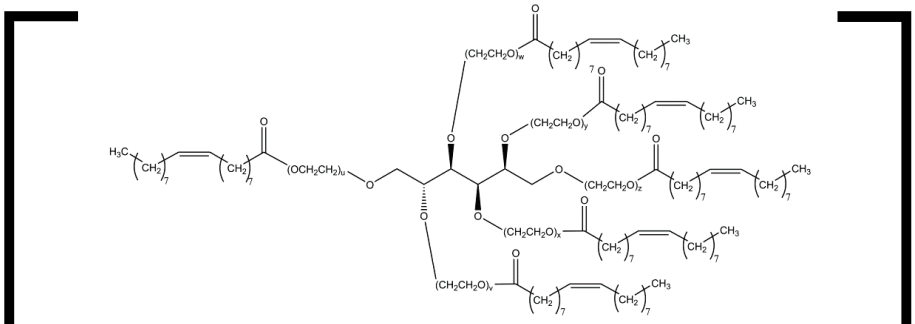
Ingredient and CAS No.	Definition	Function
Sorbeth-2 hexaoleate	The hexaester of oleic acid and a polyethylene glycol ether of sorbitol containing an average of 2 moles of ethylene oxide.	Skin-conditioning agent-emollient
	 where u + v + w + x + y + z has an average value of 2.	
Sorbeth-40 hexaoleate	The hexaester of oleic acid and sorbeth-40.	Surfactant-emulsifying agent
	 where u + v + w + x + y + z has an average value of 40.	
Sorbeth-50 hexaoleate	The hexaester of oleic acid with a polyethylene glycol ether of sorbitol containing an average of 50 moles of ethylene oxide.	Surfactant-emulsifying agent
	 where u + v + w + x + y + z has an average value of 50.	

Table 1. The Definitions and Functions of the Polysorbates in This Safety Assessment.[4]
[Bracketed entries are the work product of CIR staff]

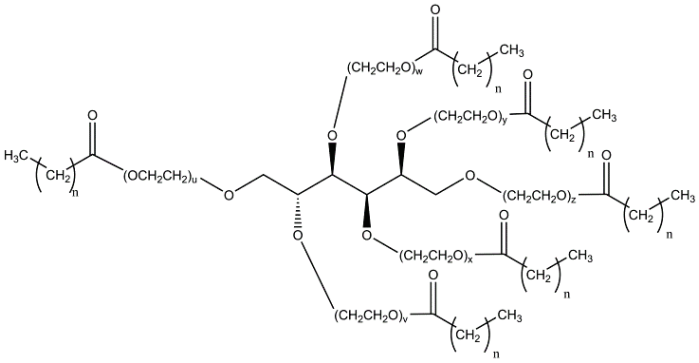
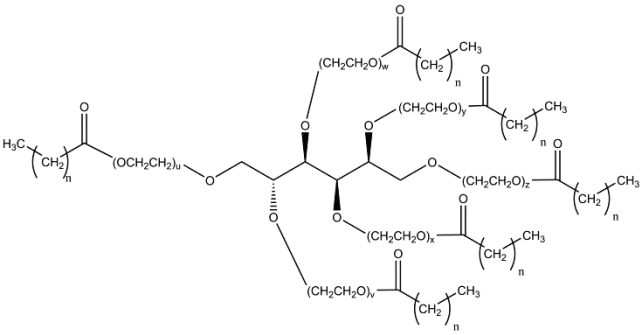
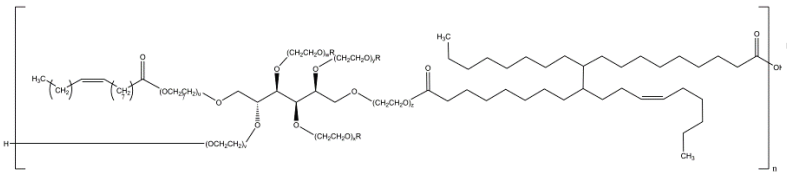
Ingredient and CAS No.	Definition	Function
Sorbeth-2 hexacaprylate/ caprate	The hexaester of a mixture of caprylic and capric acids with a polyethylene glycol ether of sorbitol containing an average of 2 moles of ethylene oxide.  where n is in each case 6 or 8, and u + v + w + x + y + z has an average value of 2.	Skin-conditioning agent-emollient
Sorbeth-12 hexacocoate	The hexaester of coconut acid with a polyethylene glycol ether of sorbitol containing an average of 12 moles of ethylene oxide.  where $CH_3(CH_2)_nC(O)$- represents the fatty acids derived from cocos nucifera (coconut) oil and u + v + w + x + y + z has an average value of 12. The fatty acid distribution of coconut oil is 0-1% caproic, 5-9% caprylic, 6-10% capric, 44-52% lauric, 13-19% myristic, 0-1% palmitoleic, 1-3% stearic, 5-8% oleic, and trace-2.5% linoleic acid.[57]	Skin-conditioning agent-emollient
Other		
Sorbeth-2/oleate/ dimer dilinoleate crosspolymer	The crosslinked polymer of a 2-mole ethoxylate of sorbitol, oleic acid, and dilinoleic acid.  where R is hydrogen, oleate, or dimer dilinoleate, and u + v + w + x + y + z has an average value of 2.	Skin-conditioning agent – emollient

Table 2. Previous safety assessment of polysorbates and component moieties of the ingredients in this safety assessment.

Ingredients	Conclusion	Maximum concentration in report	Reference
Previous safety assessment of polysorbates			
Polysorbates – polysorbate 20, 21, 40, 60, 61, 65, 80, 81, 85	Safe as used.	>50%	[1]
Polysorbates – PEG-20 sorbitan cocoate, PEG-40 sorbitan diisostearate, PEG-2 sorbitan isostearate, PEG-5 sorbitan isostearate, PEG-20 sorbitan isostearate, PEG-40 sorbitan lanolate, PEG-75 sorbitan lanolate, PEG-10 sorbitan laurate, PEG-40 sorbitan laurate, PEG-44 sorbitan laurate, PEG-75 sorbitan laurate, PEG-80 sorbitan laurate, PEG-3 sorbitan oleate, PEG-6 sorbitan oleate, PEG-80 sorbitan palmitate, PEG-40 sorbitan perisostearate, PEG-40 sorbitan peroleate, PEG-3 sorbitan stearate, PEG-6 sorbitan stearate, PEG-40 sorbitan stearate, PEG-60 sorbitan stearate, PEG-30 sorbitan tetraoleate, PEG-40 sorbitan tetraoleate, PEG-60 sorbitan tetraoleate, PEG-60 sorbitan tetrastearate, PEG-20 sorbitan triisostearate, PEG-160 sorbitan triisostearate, PEG-40 sorbitol hexaoleate (currently sorbeth-40 hexaoleate), PEG-50 sorbitol hexaoleate(currently sorbeth-50 hexaoleate), PEG-30 sorbitol tetraoleate laurate (currently sorbeth-30 tetraoleate laurate), PEG-60 sorbitol tetrastearate (currently sorbeth-60 tetrastearate)	Safe as used.	10%	[2]
Sorbeth-6 beeswax, Sorbeth-8 beeswax, Sorbeth-20 beeswax	Safe for use as cosmetic ingredients under the present practices of use. The Expert Panel recommends that cosmetic formulations containing PEG-6, PEG-20, or PEG-75 not be used on damaged skin.*	11%	[6]
Safety assessments of components			
Beeswax, candelilla wax, carnauba wax, and Japan wax	Safe as used.	56%	[8,14]
Coconut oil, acid and related ingredients	Safe as used	100%	[8,10,11,58]
Isostearic acid	Safe as used.	26%	[8,13]
Lanolin acid	Safe as used	65%	[8,12]
Oleic acid, lauric acid, myristic acid, stearic acid	Safe in the present practices of use and concentration.	> 50% in 1987; 43% in 2006	[9,16]
Polyethylene glycols (PEG) - triethylene glycol and polyethylene (PEGs) -4, -6, -7, -8, -9, -10, -12, -14, -16, -18, -20, -32, -33, -40, -45, -55, -60, -75, -80, -90, -100, -135, -150, -180, -200, -220, -240, -350, -400, -450, -500, -800, -2M, -5M, -7M, -9M, -14M, -20M, -23M, -25M, -45M, -65M, -90M, -115M, -160M, and -180M and any PEG >= 4	Safe in the present practices of use and concentration.*	85%	[7,17]
Sorbitan esters - sorbitan caprylate, sorbitan cocoate, sorbitan diisostearate, sorbitan dioleate, sorbitan distearate, sorbitan isostearate, sorbitan laurate, sorbitan oleate, sorbitan olivate, sorbitan palmitate, sorbitan sesquiisosotearate, sorbitan stearate, sorbitan sesquioleate, sorbitan triisostearate, sorbitan trioleate, and sorbitan tristearate	Safe as used.	9.1%	[19-21]
Stearates - butyl stearate, cetyl stearate, isobutyl stearate, isocetyl stearate, isopropyl stearate, myristyl stearate, and octyl stearate	Safe as used.	87%	[8,15]
Alkyl Esters	Safe as used	78%	[18]

* In 2010, the Panel concluded that PEGs were safe as used and removed the caveat that PEGs should not be used on damaged skin.[7]

Table 3. Chemical and physical properties of some polysorbates.

Property	Value	Reference
Polysorbate 21		
Physical Form	Liquid/oily liquid	[22]
Molecular Weight g/mol	390.5	[22]
PEG-10 sorbitan laurate		
Physical Form	Unctuous liquid	[59]
Color	Clear yellow	[59]
Odor	Mild	[59]
Water Solubility	Soluble	[59]
Other Solubility		
Acetone	Soluble	[59]
Ethyl acetate	Soluble	[59]
Mineral oil	Insoluble	[59]

Table 3. Chemical and physical properties of some polysorbates.

Property	Value	Reference
Polysorbate 20		
Physical Form	Liquid	22,60
	Oily liquid	61
Color	Lemon-amber	22,60,61
Odor	Characteristic	22,60
Molecular Weight g/mol	~1228	60
Density/Specific Gravity @ 25ºC	1.095	22,60
Water Solubility	Soluble	59,60
Other Solubility		
Ethanol	Soluble	59,60
Ethyl acetate	Soluble	59,60
Mineral oil	Insoluble	61
Polysorbate 40		
Physical Form	Oily liquid or Vaseline-like	62-65
Color	Lemon-orange	66
Odor	Characteristic	2,59,66
Density/Specific Gravity	1.05	65
Water Solubility	Soluble	59,66
Other Solubility		
Methanol	Soluble	59,66
Ethanol	Soluble	59,66
Mineral oil	Insoluble	59,66
Polysorbate 61		
Physical Form	Waxy solid	59,62,67
Color	Tan	59
Water Solubility	Dispersible	68
Other Solubility		
Ethylene glycol	Insoluble	68
Propylene glycol	Insoluble	68
Polysorbate 60		
Physical Form	Oily liquid	62,69
	Semigel	69,70
	Wax	71
Color	Lemon yellow	59
	Yellow-orange	69
Odor	Characteristic	69
Water Solubility	Soluble	69
Other solubility		
Ethyl acetate	Soluble	69
Tolulene	Soluble	69
Vegetable and mineral oil	insoluble	69
Polysorbate 65		
Physical Form	Waxy solid	62,63,72
Color	Tan	59,72
Odor	Faint, characteristic	59,72
Water Solubility	Dispersible	59
Other Solubility		
Acetone	Soluble	72
Ethanol	Soluble	59
Methanol	Soluble	59
Vegetable and mineral oil	Soluble	59

Table 3. Chemical and physical properties of some polysorbates.

Property	Value	Reference
Polysorbate 81		
Physical Form	Liquid	[23]
	May gel at room temperature	[63]
Color	Clear	[23]
Odor	Faint	[59]
Density/Specific Gravity @ 20ºC	1.0356	[23]
@ 25 ºC	1.032	[23]
@ 20 ºC	10299	[23]
@ 25 ºC	1.0264	[23]
Viscosity kg/(s m) @ 20ºC	0.672	[23]
	0.84	[23]
@ 25ºC	0.328	[23]
	0.383	[23]
Vapor pressure mmHg	0.002	[23]
Melting Point ºC	-33.9	[23]
	-32.7	[23]
Water Solubility g/L	~0.100	[23]
	~0.035	[23]
@ 20ºC & pH 8.29-9.39	>0.500	[23]
Other Solubility		
Ether	Dispersible	[59]
Ethylene glycol	Dispersible	[59]
Ethanol	Soluble	[59]
PEG-20 sorbitan oleate		
Density/Specific Gravity	1.1/1.064	[2]
Other Solubility		
Dimethyl sulfoxide	Soluble	[59]
Ethanol	Soluble	[59]
Mineral oil	Soluble	[59]
Toluene	Soluble	[59]
Polysorbate 80		
Physical Form	Viscous, oily liquid	[62,64,65,70,71,73-75]
Color	Lemon to orange/amber	[59,75,76]
Odor	Characteristic	[59,75]
Density/Specific Gravity	1.08	[73]
	1.06-1.10	[74,76]
	1.07-1.09	[65]
Viscosity kg/(s m)	0.3-0.5	[76]
Water Solubility	Soluble	[59]
Other Solubility		
Ethanol	Soluble	[75]
Methanol	Soluble	[75]
Toluene	Soluble	[75]
Mineral oil	Insoluble	[75]
Petroleum ether	Insoluble	[75]
PEG-40 sorbitan lanolate		
Physical Form	Soft paste	[68]
Water Solubility @ 65ºC	Soluble	[68]
Other Solubility @ 65ºC		
Dioxane	Soluble	[68]
Carbon tetrachloride	Soluble	[68]
Sorbeth-6 beeswax		
Physical Form	Waxy solid	[77]
Color	Tan	[77]
Odor	Fatty	[77]
Water Solubility	Insoluble	[77]
Other Solubility		
Corn oil	Soluble	[77]
Ethylene glycol	Insoluble	[77]
Mineral oil	Insoluble	[77]
Sorbeth-20 beeswax		
Physical Form	Waxy solid	[77]
Color	Tan	[77]
Odor	Mild, fatty	[77]
Water Solubility	Insoluble	[77]
Other Solubility		[77]
Warm corn oil	Soluble	
Mineral oil	Dispersible	

Table 3. Chemical and physical properties of some polysorbates.

Property	Value	Reference
Polysorbate 85		
Physical Form	Liquid May gel at room temperature	62,64 59,63
Color	Clear amber	59
Odor	Characteristic	59
Water Solubility	Dispersible	59
Other Solubility Vegetable and mineral oils	Soluble	59
PEG-40 sorbitan peroleate		
Physical Form	Viscous, oily liquid	68
Color	Clear yellow	68
Odor	Faint characteristic	68
Water Solubility	Dispersible	68
Other Solubility Mineral oil	Soluble	68

Table 4. Chemical and physical properties of generic Sorbitan monolaurate, ethoxylated ingredients.

Property	Value	Reference
Sorbitan monolaurate, ethoxylated		
Physical Form	Liquid	22
Water Solubility g/L @ 20 ºC & pH 6.3 and 7.9	<2.0	22
Sorbitan monostearate, ethoxylated		
Physical Form	Solid (wax)	24
Color	Colorless	24
Odor	Odorless	24
Density/Specific Gravity @ 23ºC @ 25ºC	1.007 1.07	24 24
Vapor pressure mmHg @ 20ºC @ 20ºC	<0. 0.75 <0.1	24 24
Melting Point ºC	45-50 39.6	24 24
Boiling Point ºC	90.4	24
Water Solubility g/L @ 23ºC	0.300	24
Other Solubility g/L Petroleum ether @ 23ºC Methanol @ 23ºC	 1.800 0.200	 24 24
log K_{ow} @ 23 ºC & pH 6.4	0.03	24
Disassociation constants pKa @ 23ºC	0.199 x 10^{-9}	24

Table 5. The approximate ester content of some polysorbates.[22,26]

Ingredient	Laurate (%)	Myristate (%)	Palmitate (%)	Stearate (%)	Oleate (%)	Other esters (%)
Polysorbate 20	39±2	26±1	12±1	12±2	ND	11±2
Polysorbate 21	40-60	14-25	6-15	0-7	0-11	0-24
Polysorbate 40	<1	2	87±2	10±1	ND	<1
Polysorbate 60	2±1	4±1	43±1	51±2	ND	<1
Polysorbate 80	<1	2	22±2	11±2	66±1	<1

ND=none detected

Table 6. Current and historical frequency and concentration of use of polysorbates according to duration and exposure.[1,2,5,6,14,31]

	# of Uses		*Max Conc of Use (%)*		*# of Uses*		*Max Conc of Use (%)*	
	2015	**1998****	**2014**	**1981*****	**2015**	**1998**	**2014**	**1981**
	Polysorbate 20				**Polysorbate 21**			
Totals*	**3013**	**770**	**0.00001-19.6**	**0.09->50**	**55**	**4**	**0.33-8**	**0.1-1**
Duration of Use								
Leave-On	*1639*	*446*	*0.00001-9.1*	*0.09->50*	*17*	*4*	*0.33-2*	*0.1-1*
Rinse-Off	*1275*	*297*	*0.0006-19.6*	*0.09-25*	*38*	*NR*	*0.5-8*	*NR*
Diluted for (Bath) Use	*99*	*27*	*0.0097-8.9*	*0.1-50*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	226	39	0.00015-3.5	0.1-10	4	NR	0.5	NR
Incidental Ingestion	32	12	0.01-5.8	0.09-5	NR	NR	NR	NR
Incidental Inhalation-Spray	35; 546[a]; 397[c]	22; 169[a]; 50[c]	0.00001-3[d]; 0.0019-3[a]; 0.76-2[c]	0.09-1; <0.1->50[a]; 0.09-5[c]	6[a]	4[a]	0.33[g]	0.1-1[a]
Incidental Inhalation-Powder	52; 5[b]; 397[c]	43; 50[c]	0.00075-3; 0.0006-9.1[b]; 0.76-2[c]	0.1-1; 0.09-5[c]	NR	NR	0.38[b]	NR
Dermal Contact	2299	493	0.00001-19.6	0.09-5	14	4	0.38-2	NR
Deodorant (underarm)	9[a]	3[a]	0.00018-4[e]; 0.00082-3[f]	0.1-5[a]	NR	NR	NR	NR
Hair - Non-Coloring	555	205	0.006-12.6	0.09-25	14	NR	0.33-8	NR
Hair-Coloring	92	50	0.4-3.8	0.09-5	24	NR	2.4	NR
Nail	11	6	0.000041-3.3	0.09-5	NR	NR	NR	NR
Mucous Membrane	822	66	0.0006-19.6	0.09->50	3	NR	NR	NR
Baby Products	32	3	0.00078-12.6	0.1-25	NR	NR	NR	NR

	2015	**1998**	**2014**	**1981**	**2014**	**1998**	**2014**	**1981**
	Polysorbate 40				**Polysorbate 60**			
Totals*	**80**	**32**	**0.008-5**	**0.09-10**	**1589**	**332**	**0.0000001-6**	**0.09-25**
Duration of Use								
Leave-On	*65*	*24*	*0.008-5*	*0.09-10*	*1228*	*255*	*0.00009-4*	*0.09-25*
Rinse-Off	*15*	*8*	*1.5-3*	*0.09-5*	*358*	*77*	*0.0000001-6*	*0.09-5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*3*	*NR*	*0.0015-0.06*	*0.1-10*
Exposure Type								
Eye Area	12	1	0.015-3.75	1-5	75	35	0.0021-3.8	0.09-10
Incidental Ingestion	1	NR	NR	NR	13	NR	0.2-0.4	0.09-5
Incidental Inhalation-Spray	24[a]; 21[c]	13[a]; 3[c]	0.5-2.5[a]	0.1-10[a]; 0.1-5[c]	2; 635[a]; 338[c]	93[a]; 59[c]	0.0025-0.8[h]; 0.0005-4[a]; 2.4[c]	0.1-10[a]
Incidental Inhalation-Powder	21[c]	3[c]	0.019-5[b]	0.1-5[c]	7; 10[b]; 338[c]	59[c]	0.053; 0.018-3.7[b]; 2.4[c]	0.09-5
Dermal Contact	76	29	0.008-5	0.09-10	1302	297	0.00009-6	0.09-10
Deodorant (underarm)	NR	NR	NR	NR	1[a]	NR	0.02[f]	NR
Hair - Non-Coloring	1	2	0.8-2.5	0.09-5	156	22	0.0000001-5	0.1-25
Hair-Coloring	NR	NR	NR	NR	107	1	0.002-2.5	1-5
Nail	NR	1	NR	0.1-5	2	5	3.5	0.1-5
Mucous Membrane	4	NR	3	NR	52	NR	0.0008-2	0.09-10
Baby Products	NR	NR	NR	NR	11	3	0.00009-1.5	NR

Table 6. Current and historical frequency and concentration of use of polysorbates according to duration and exposure.[1,2,5,6,14,31]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2015	**1998**	**2014**	**1981**	**2015**	**1998**	**2014**	**1981**
	Polysorbate 61				**Polysorbate 65**			
Totals*	**16**	**8**	**1-1.8**	**0.1-5**	**24**	**2**	**0.0003-3**	**1-5**
Duration of Use								
Leave-On	*16*	*8*	*1-1.8*	*0.1-5*	*21*	*NR*	*0.0003-3*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*0.1-5*	*3*	*2*	*0.002-0.15*	*1-5*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	5	NR	0.5	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	9[a]; 5[c]	4[c]	NR	1-5[a]; 0.1-1[c]	7[a]; 8[c]	NR	NR	NR
Incidental Inhalation-Powder	1[b]; 5[c]	3[b]; 4[c]	1.8[b]	1-5[b]; 0.1-1[c]	8[c]	NR	0.003-3[b]	NR
Dermal Contact	16	8	1-1.8	0.1-5	24	1	0.0003-3	1-5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	0.0003[f]	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	1	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	0.002-0.003	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	1	4	NR	1-5	NR	NR	NR	NR

	2015	**1998**	**2014**	**1981**	**2015**	**1998**	**2014**	**1981**
	Polysorbate 80				**Polysorbate 81**			
Totals*	**932**	**231**	**0.00031-18.1**	**0.01-25**	**NR**	**4**	**0.4-25.6**	**0.1-5**
Duration of Use								
Leave-On	*759*	*132*	*0.00031-11.9*	*0.01-10*	*NR*	*4*	*0.5-7.5*	*0.1-5*
Rinse-Off	*166*	*89*	*0.0038-18.1*	*0.09-10*	*NR*	*NR*	*0.4-25.6*	*0.1-5*
Diluted for (Bath) Use	*7*	*10*	*NR*	*0.1-25*	*NR*	*NR*	*5-7.5*	*NR*
Exposure Type								
Eye Area	114	16	0.0024-11	0.09-5	NR	NR	0.5	NR
Incidental Ingestion	45	15	0.00031-1.5	0.09-1	NR	NR	NR	NR
Incidental Inhalation-Spray	15; 315[a]; 196[c]	16; 71[a]; 13[c]	0.02-11.9[i]; 0.0038-2[a]	0.1-1; 0.09-10[a]; 0.09-10[c]	NR	1[a]	5	0.1-5[a]; 0.1-1[c]
Incidental Inhalation-Powder	18;2[b]; 196[c]	7; 13[c]	0.42-2; 0.005-2[c]	1-10; 0.09-10[b]; 0.09-10[c]	NR	NR	5[b]	0.1-1[c]
Dermal Contact	731	122	0.00075-18.1	0.01-25	NR	3	0.5-25.6	0.1-1
Deodorant (underarm)	1[a]	NR	NR	0.09-1[a]	NR	NR	NR	NR
Hair - Non-Coloring	118	80	0.02-10	0.09-10	NR	1	0.4	0.1-5
Hair-Coloring	25	10	0.36	NR	NR	NR	NR	NR
Nail	7	2	NR	0.1-1	NR	NR	7.5	NR
Mucous Membrane	75	29	0.00031-1.5	0.09-25	NR	NR	5-7.5	NR
Baby Products	4	4	10	0.1-10	NR	NR	NR	NR

	2015	**1998**	**2014**	**1981**	**2015**	**1998**	**2014**	**1998**
	Polysorbate 85				**PEG-20 sorbitan isostearate**			
Totals*	**51**	**35**	**0.03-21.9**	**0.01->50**	**3**	**2**	**0.3**	**NR**
Duration of Use								
Leave-On	*23*	*28*	*0.03-6*	*0.01-10*	*3*	*2*	*0.3*	*NR*
Rinse-Off	*15*	*7*	*5.5-21.9*	*0.09->50*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*13*	*NR*	*0.03-0.055*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	4	5	NR	0.09-5	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1; 6[a]; 5[c]	NR	NR	0.01-10[a]; 0.1-1[c]	1[a]; 2[c]	1[a]	NR	NR
Incidental Inhalation-Powder	1; 5[c]	NR	0.06-0.54[b]	0.01-1[b]; 0.1-1[c]	2[c]	NR	0.3[b]	NR
Dermal Contact	51	30	0.03-21.9	0.01-10	3	NR	0.3	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	4	NR	0.01-5	NR	NR	NR	NR
Hair-Coloring	NR	1	NR	>50	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	1	NR	NR
Mucous Membrane	14	NR	0.03-0.55	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 6. Current and historical frequency and concentration of use of polysorbates according to duration and exposure.[1,2,5,6,14,31]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2014	**1998**	**2014**	**1998**	**2015**	**1998**	**2014**	**1998**
	PEG-40 sorbitan lanolate				**PEG-10 sorbitan laurate**			
Totals*	**NR**	**7**	**NR**	**NR**	**2**	**2**	**NR**	**NR**
Duration of Use								
Leave-On	*NR*	*4*	*NR*	*NR*	*1*	*NR*	*NR*	*NR*
Rinse-Off	*NR*	*3*	*NR*	*NR*	*1*	*2*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	1[a]	NR	NR	1[a]	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	NR	NR
Dermal Contact	NR	NR	NR	NR	2	NR	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	5	NR	NR	NR	1	NR	NR
Hair-Coloring	NR	2	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	1	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

	2015	1998	2014	1998	2015	1998	2014	1998
	PEG-44 sorbitan laurate				**PEG-80 sorbitan laurate**			
Totals*	**3**	**8**	**0.5-2**	**NR**	**93**	**34**	**0.0002-4.2**	**NR**
Duration of Use								
Leave-On	*1*	*6*	*2*	*NR*	*20*	*6*	*0.0002-0.059*	*NR*
Rinse-Off	*2*	*2*	*0.5*	*NR*	*60*	*28*	*2-4.2*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*13*	*NR*	*2.5*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	1	NR	0.059	NR
Incidental Inhalation-Spray	1[a]	1[a]	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	NR	NR	0.0002-0.0098[b]	NR
Dermal Contact	3	8	2	NR	70	14	0.0002-4.2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	0.5	NR	22	20	4.2	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	36	2	0.059-4.2	NR
Baby Products	NR	NR	NR	NR	33	15	4.2	NR

	2015	1998	2014	1998	2015	1998	2014	1998
	PEG-3 sorbitan oleate				**PEG-40 sorbitan peroleate**			
Totals*	**1**	**4**	**NR**	**NR**	**53**	**13**	**0.16-4**	**NR**
Duration of Use								
Leave-On	*1*	*4*	*NR*	*NR*	*51*	*8*	*0.16-4*	*NR*
Rinse-Off	*NR*	*NR*	*NR*	*NR*	*2*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*5*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	8	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	1[a]	1[a]	NR	NR	14[a]; 13[c]	6[a]; 1[c]	4[a]	NR
Incidental Inhalation-Powder	NR	NR	NR	NR	13[c]	1; 1[c]	0.3-0.9[b]	NR
Dermal Contact	1	3	NR	NR	50	13	0.16-1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	1	NR	NR	3	NR	4	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	5	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR	NR	NR

Table 6. Current and historical frequency and concentration of use of polysorbates according to duration and exposure.[1,2,5,6,14,31]

	# of Uses		Max Conc of Use (%)		# of Uses		Max Conc of Use (%)	
	2015	**1998**	**2014**	**1998**	**2015**	**1998**	**2014**	**1998**
	PEG-40 sorbitan stearate				**PEG-40 sorbitan tetraoleate**			
Totals*	**1**	**1**	**NR**	**NR**	**1**	**1**	**NR**	**NR**
Duration of Use								
Leave-On	*1*	*NR*	*NR*	*NR*	*1*	*1*	*NR*	*NR*
Rinse-Off	*NR*	*1*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*	*NR*
Exposure Type								
Eye Area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	NR	NR	NR	NR	1[c]	1[c]	NR	NR
Incidental Inhalation-Powder	1[a]	NR	NR	NR	1[c]	1[c]	NR	NR
Dermal Contact	1	1	NR	NR	1	1	NR	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby Products	1	NR	NR	NR	NR	NR	NR	NR
	2015	**1998**	**2014**	**1999**				
	Sorbeth-20 beeswax							
Totals*	**9**	**16**	**0.5-2.8**	**0.5-2.8**				
Duration of Use								
Leave-On	*9*	*1*	*0.5-2.8*	*NR*				
Rinse-Off	*NR*	*NR*	*NR*	*NR*				
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*				
Exposure Type								
Eye Area	7	11	2.8	2.8				
Incidental Ingestion	1	4	2.5	2.5				
Incidental Inhalation-Spray	NR	NR	NR	NR				
Incidental Inhalation-Powder	NR	NR	0.5-1[b]	NR				
Dermal Contact	1	4	0.5-1	0.5-1				
Deodorant (underarm)	NR	NR	NR	NR				
Hair - Non-Coloring	NR	NR	NR	NR				
Hair-Coloring	NR	NR	NR	NR				
Nail	NR	NR	NR	NR				
Mucous Membrane	1	4	2.5	2.5				
Baby Products	NR	NR	NR	NR				

NR – no reported use

* 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.

** The year that the Council survey was conducted in the previous report. In the report published in 2000, the only concentration of use data that were provided was the following: "…PEG-60 sorbitan tetratoleate, PEG-40 sorbitan tetraoleate, and PEG-160 sorbitan Triisostearate are used in cosmetics at concentrations of 0.5% to 10%..." in 1998. Since the data from the 2000 report is limited, the concentration of use data from the 1984 report are provided here to give a better historical perspective.

*** At the time of the 1984 safety assessment, concentration of use data were not reported by the FDA; 1981 data were presented. These data were presented in ranges so the limits of the ranges are represented here.

[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.

[b] It is possible these products are powders, but it is not specified whether the reported uses are powders.

[c] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories.

[d] Aerosol hair spray 0.027%-3%; pump hair spray 0.4%-1%; spray body and hand products 0.00001%-1.2%; spray moisturizing products 0.1%.

[e] Spray deodorants.

[f] Not spray deodorants.

[g] Aerosol hair spray.

[h] Spray body and hand products 0.083%-0.8%.

[i] Aerosol hair spray 0.078%-1.6%; pump hair spray 0.02%-0.2%; spray face and neck products 0.39%.

Table 7. Frequency of use according to duration and exposure of polysorbates that are reviewed for the first time in this safety assessment.[5,31,32]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PEG-30 sorbitan beeswax		PEG-20 sorbitan cocoate		PEG-40 sorbitan diisostearate		PEG-20 sorbitan laurate	
Total/range	**1**	**NR**	**14**	**0.03-0.3**	**2**	**1**	**1**	**NS**
Duration of use								
Leave-on	1	NR	12	0.03-0.3	2	1	NS	NS
Rinse-off	NR	NR	2	0.06	NR	NR	1	NS
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NS	NS
*Exposure type**								
Eye area	1	*NR*	1	NR	NR	NR	NS	NS
Incidental ingestion	*NR*	*NR*	NR	NR	NR	NR	NS	NS
Incidental Inhalation-sprays	*NR*	*NR*	6[a]; 3[c]	NR	2[a]	1[a]	NS	NS
Incidental inhalation-powders	*NR*	*NR*	3[c]	0.03-0.3[b]	NR	NR	NS	NS
Dermal contact	1	*NR*	14	0.03-0.3	2	NR	1	NS
Deodorant (underarm)	*NR*	*NR*	NR	NR	NR	NR	NS	NS
Hair-noncoloring	*NR*	*NR*	NR	NR	NR	1	NS	NS
Hair-coloring	*NR*	*NR*	NR	NR	NR	NR	NS	NS
Nail	*NR*	*NR*	NR	NR	NR	NR	NS	NS
Mucous Membrane	*NR*	*NR*	NR	NR	NR	NR	NS	NS
Baby	*NR*	*NR*	NR	NR	NR	NR	NS	NS

	PEG-40 sorbitan laurate		PEG-75 sorbitan laurate		PEG-6 sorbitan oleate		PEG-4 sorbitan stearate	
Total/range	**NR**	**0.25-2**	**NR**	**0.5-2**	**NR**	**0.43**	**NR**	**0.00025-1.5**
Duration of use								
Leave-on	NR	2	NR	NR	NR	0.43	NR	0.028-1.5
Rinse-off	NR	0.25-0.5	NR	0.5-2	NR	NR	NR	0.00025
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	NR	NR	NR	NR	0.028; 0.1[a]
Incidental inhalation-powders	NR	NR	NR	NR	NR	NR	NR	NR
Dermal contact	NR	2	NR	2	NR	0.43	NR	0.028-1.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	0.2[d]
Hair-noncoloring	NR	0.5	NR	0.5	NR	NR	NR	0.00025-0.29
Hair-coloring	NR	0.25	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	1.5

Table 7. Frequency of use according to duration and exposure of polysorbates that are reviewed for the first time in this safety assessment.[5,31,32]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PEG-3 sorbitan stearate		PEG-6 sorbitan stearate		PEG-20 sorbitan stearate		PEG-30 sorbitan tetraoleate	
Total/range	**3**	**NR**	**2**	**3.4**	**1**	**NS**	**1**	**10**
Duration of use								
Leave-on	2	NR	NR	NR	1	NS	NR	NR
Rinse-off	1	NR	2	3.4	NR	NS	1	10
Diluted for (bath) use	NR	NR	NR	NR	NR	NS	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NS	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NS	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	NR	NR	NS	NR	NR
Incidental inhalation-powders	NR	NR	NR	NR	NR	NS	NR	NR
Dermal contact	3	NR	2	3.4	1	NS	1	10
Deodorant (underarm)	NR	NR	NR	NR	NR	NS	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NS	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NS	NR	NR
Nail	NR	NR	NR	NR	NR	NS	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NS	NR	NR
Baby	NR	NR	NR	NR	NR	NS	NR	NR

	PEG-60 sorbitan tetraoleate		PEG-160 sorbitan triisostearate		Sorbeth-6 beeswax		Sorbeth-30 tetraisostearate	
Total/range	**NR**	**0.5-0.9**	**4**	**NR**	**7**	**2**	**1**	**NR**
Duration of use								
Leave-on	NR	0.5-0.9	NR	NR	7	2	1	NR
Rinse-off	NR	NR	4	NR	NR	NR	NR	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	3	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	0.5-0.8[a]	NR	NR	NR	NR	1[c]	NR
Incidental inhalation-powders	NR	0.9[c]	NR	NR	NR	NR	1[c]	NR
Dermal contact	NR	0.8-0.9	1	NR	7	2	1	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	0.5	3	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	1	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

Table 7. Frequency of use according to duration and exposure of polysorbates that are reviewed for the first time in this safety assessment.[5,31,32]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	Sorbeth-4 tetraoleate		**Sorbeth-6 tetraoleate**		**Sorbeth-30 tetraoleate**		**Sorbeth-40 tetraoleate**	
Total/range	**4**	**NR**	**NR**	**0.21**	**10**	**0.11-10.8**	**2**	**0.5**
Duration of use								
Leave-on	4	NR	NR	0.21	4	NR	1	0.5
Rinse-off	NR	NR	NR	NR	6	0.11-10.8	1	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	NR	NR	NR	NR	NR	1[b]	NR
Incidental inhalation-powders	NR	NR	NR	0.21	NR	NR	1[b]	0.5[c]
Dermal contact	4	NR	NR	0.21	10	0.11-10.8	2	0.5
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	NR	NR	NR	NR	NR	NR
Hair-coloring	NR	NR	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

	Sorbeth-60 tetraoleate	
Total/range	**1**	**NR**
Duration of use		
Leave-on	1	NR
Rinse-off	NR	NR
Diluted for (bath) use	NR	NR
Exposure type		
Eye area	NR	NR
Incidental ingestion	NR	NR
Incidental Inhalation-sprays	1[a]	NR
Incidental inhalation-powders	NR	NR
Dermal contact	1	NR
Deodorant (underarm)	NR	NR
Hair-noncoloring	NR	NR
Hair-coloring	NR	NR
Nail	NR	NR
Mucous Membrane	NR	NR
Baby	NR	NR

NR = Not Reported; NS = Not Surveyed; Totals = Rinse-off + Leave-on Product Uses.
Note: Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure type uses may not equal the sum total uses.
*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] It is possible these products may be sprays, but it is not specified whether the reported uses are sprays.
[b] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.
[c] It is possible these products may be powders, but it is not specified whether the reported uses are powders.
[d] Not spray products.

Table 8. Ingredients for which there were no reported current or historic uses from the VCRP or the Council.[5,31]

PEG-2 sorbitan isostearate	Sorbeth-40 hexaoleate
PEG-5 sorbitan isostearate	Sorbeth-50 hexaoleate
PEG-75 sorbitan lanolate	Sorbeth-6 hexastearate
PEG-20 sorbitan oleate	Sorbeth-150 hexastearate
PEG-40 sorbitan oleate	Sorbeth-3 isostearate
PEG-80 sorbitan palmitate	Sorbeth-6 laurate
PEG-40 sorbitan perisostearate	Sorbeth-2/oleate/dimer dilinoleate crosspolymer
PEG-60 sorbitan stearate	Sorbeth-20 pentaisostearate
PEG-60 sorbitan tetrastearate	Sorbeth-30 pentaisostearate
PEG-4 sorbitan triisostearate	Sorbeth-40 pentaisostearate
PEG-20 sorbitan triisostearate	Sorbeth-50 pentaisostearate
PEG-2 sorbitan trioleate	Sorbeth-40 pentaoleate
PEG-3 sorbitan tristearate	Sorbeth-20 tetraisostearate
Sorbeth-2 beeswax	Sorbeth-40 tetraisostearate
Sorbeth-8 beeswax	Sorbeth-50 tetraisostearate
Sorbeth-2 cocoate	Sorbeth-30 tetraoleate laurate
Sorbeth-2 hexacaprylate/caprate	Sorbeth-60 tetrastearate
Sorbeth-12 hexacocoate	Sorbeth-3 tristearate
Sorbeth-2 hexaisostearate	Sorbeth-160 tristearate
Sorbeth-2 hexalaurate	Sorbeth-450 tristearate
Sorbeth-2 hexaoleate	

Table 9. U. S. regulations controlling the use of polysorbates.

Ingredient	Regulation	Citation
Polysorbate 20, 60, 65, and 80	Approved as diluents in color additives for drug use.	21CFR73.1; 21CFR73.1001
Polysorbates 20, 60, and 80	Approved for direct use in all food types as synthetic flavorings.	21CFR172.623
Polysorbate 80	Approved to be used with carrageenan to make chewing gum bases and related substances.	21CFR172.623
Polysorbate 60, 65, and 80	Approved as multipurpose additives.	21CFR172.836; 21CFR172.838; 21CFR172.840
Polysorbate 20	Permitted as a secondary direct food additive for human consumption.	21CFR173.310
Polysorbate 60, 65, and 80	Approved as defoaming agents in food for human consumption.	21CFR173.340
Polysorbate 20, 40, 60, and 80; PEG-3 sorbitan stearate; and PEG-3 sorbitan oleate	Approved for indirect addition to all food types as components of adhesives.	21 CFR 175.105
PEG-40 sorbitan laurate, PEG-6 sorbitan stearate, PEG-40 sorbitan stearate, PEG-6 sorbitan oleate, PEG-40 sorbitan tetraoleate, and PEG-40 sorbitan peroleate	May be used as indirect food additives as a defoaming agent in the manufacture of paper and paperboard.	21CFR176.210
Polysorbate 20, 40, 60, 65, 80, and 85, and PEG-3 sorbitan oleate	Approved for indirect addition to all food types as emulsifiers and/or surfactants.	21CFR178.3400
PEG-3 sorbitan oleate	May be used as a component of paper and paperboard in contact with dry food.	21CFR180
Polysorbate 80	Approved as an ophthalmic demulcent.	21CFR349.12
Polysorbate 60 and 80	Approved for use in animal feed and drinking water.	21CFR573.840; 21CFR573.860
Polysorbate 80	May be used to denature spirits.	27CFR21.68; 27CFR21.151

Table 10. Penetration enhancement studies of some polysorbates. [42]

Ingredient (concentration)	Chemical/drug tested	Results; notes
Polysorbate 20 (5%)	Albuterol sulfate	ER compared to control (saline buffer)=3.43±0.52; ER compared to vehicle (ethanol)=1.26±0.32. Thawed, hairless mouse skin pretreated with test substance using Franz cells.
Polysorbate 65 (5%)	Albuterol sulfate	ER compared to control (saline buffer)=4.74±0.23; ER compared to vehicle (ethanol)=1.75±0.29. Thawed, hairless mouse skin pretreated with test substance using Franz cells.
Polysorbate 80 (5%)	Albuterol sulfate	ER compared to control (saline buffer)=2.95±0.45; ER compared to vehicle (ethanol)=1.09±0.17. Thawed, hairless mouse skin pretreated with test substance using Franz cells.

ER=Enhancement ratio

Table 11. Highest reported historic NOAELs for polysorbate 20 and polysorbate 80 reported in a survey of 4 research laboratories.[44]

Animal	Route	Duration	Dose	Comments
		Polysorbate 20		
Rat	Oral	1 month	250 mg/kg	Well tolerated
	Oral	90 days	500 mg/kg	Diarrhea
Mouse	Oral	1 month	10 mg/kg	Well tolerated
		Polysorbate 80		
Dog	Oral	90 days	5 mL/kg	As 1% of formulation; well tolerated
Rat	Oral	Not reported	350 mg/kg	Well tolerated
	Oral	4 weeks	5 mL/kg	1%; well tolerated
	Oral	7 days	10 mL/kg	1%; well tolerated
	Intravenous	Not reported	100 mg/kg	Well tolerated
Mouse	Intraperitoneal	1 month	10 mL/kg	2%; well tolerated
	Intranasal	3 days	10 µL/nostril	0.2%; well tolerated
Primate	Oral	Efficacy (distinct time not indicated.)	5 mL/kg	1%; well tolerated

Table 12. In vivo animal and human irritation studies of some polysorbates.

Ingredient (concentration)	Assay	Results; notes	Reference
	Animal studies		
Polysorbate 60 (5% and 10% aqueous)	Daily skin-painting study for 30 days on rabbits	Moderate irritation observed at 5%; skin necrosis occurred at 10%.	[24]
Polysorbate 60 (15% aqueous)	Daily skin-painting study for 60 days on rabbits	No dermal effects at 15%; mild irritation at 100%.	[24]
Polysorbate 60 (100%)	Long-term (time not specified) dermal administration on mice	Local inflammation.	[24]
Sorbitan monolaurate, ethoxylated (100%; 0.5mL)	Draize test using New Zealand White Rabbits (n=3). The test sites were observed at 1, 24, 48, and 72 h and 7 days.	Draize score of 0.89. Scaliness was observed in all 3 animals at 72 h after exposure and in 1 rabbit at 7 days after exposure.	[22]
Sorbitan monostearate, ethoxylated (5% and 10% aqueous)	Dermally administered to rabbits (n not specified) for 30 days.	Necrosis of the skin at 10%. Necrosis was reversible after stopping treatment. Moderate irritation was observed at 5%.	[24]
Sorbitan monostearate, ethoxylated (100%)	Dermally administered to rabbits (n not specified) for 60 days.	Did not cause irritation.	[24]
Sorbitan monostearate, ethoxylated (100%; 0.5 g)	Dermally administered to the shaved backs (approximately 6 cm^2) of New Zealand white rabbits (n=3) for 4 h under occlusion. The test site was observed for 14 days after removal.	Did not produce any skin reaction. The irritation score was 0.8 out of 8.	[24]
	Human studies		
Polysorbate 60 (concentration not specified in a cream or 100%)	Administered to the forehead, dorsal, and arm skin. Amount and n not specified.	Urticaria observed at application sites at 20 min caused by both polysorbate 60-based cream and polysorbate 60. There was no effect of either the polysorbate 60 or the cream on the dorsal and arm skin	[24]
Polysorbate 60 (1% in DMEM)	Human patch test scored according to ICDRG. Patches were in place for 2 days in Haye's chambers. n=30.	Irritation score=0.4 out of 4.	[49]
Polysorbate 80 (100%)	Test substance administered for increasing time periods: 15 min-4 h and observed at 24, 48, and 72 h. n=29	1 positive reaction. Control of 20% sodium dodecyl sulfate exhibited 24 of 29 reactions.	[48]
Polysorbate 80 (100%)	Test substance administered for increasing time periods to the upper outer arm in a 25 mm Hill Top Chamber: 15 min-4 h and observed at 24, 48, and 72 h. n=24	1 positive reaction. Control of 20% sodium dodecyl sulfate exhibited 8 of 27 reactions.	[50]
Sorbitan monostearate, ethoxylated (25% aqueous)	10 drops of the solution administered to the scalp twice/d for 16 weeks. n=68	Irritation score 1 out of 68. Mild redness observed in 1 subject. Not irritating.	[24]

DMEM – Dulbecco's minimal essential medium; ICDRG - International Contact Dermatitis Research Group.

Table 13. Ocular irritation assays of some polysorbates.

Ingredient (concentration)	Assay	Results; notes	Reference
	Non-human		
Polysorbate 20 (10%)	Draize test using New Zealand White rabbits (n=3)	Maximal average score=0.7 out of 4; 24-h average score=0.0	[52, 53]
Polysorbate 81 (10% in light mineral oil)	Draize test using New Zealand White Rabbits (n=9)	Irritation score=0 out of 4; not irritating.	[23]
Polysorbate 81 (100%)	Draize test using New Zealand White Rabbits (n=9). Eyes were washed 2 sec after administration in 3 rabbits. Eyes were observed at 1, 24, 48, 72 h and 7 days.	Irritation score=0 out of 4; not irritating.	[23]
Sorbitan monostearate, ethoxylated (0.1 g in water)	Draize test using New Zealand White Rabbits (n=3)	Irritation score-0 out of 110; not irritating. Did not produce any eye irritation or any eye discharge throughout the 72-h observation period. No lesions such as pannus or staining were observed.	[24]
Sorbitan monolaurate, ethoxylated (100%; 0.1 mL)	Draize test using New Zealand White rabbits (n=9). Eyes were washed 2 sec after administration in 3 rabbits.	Irritation score=0 out of 4; not irritating.	[22]
	In vitro		
Polysorbate 20 (not provided)	EpiOcular test over 7 laboratories	Not predicted to be an ocular irritant. Average mean cell viability 97.40±6.49% of distilled water control.	[55]
Polysorbate 20 (2%)	Red blood cell hemolysis assay	Predicted to be a minimal ocular irritant.	[51]
Polysorbate 20 (2%)	K562 cell assay	Predicted to be a minimal ocular irritant.	[51]
Polysorbate 20 (5% in saline; 200 µL)	STE using SIRC cells (CCL-60). Exposure for 5 min.	Predicted to be an irritant.	[54]
Polysorbate 20 (100%; 50 µL)	EpiOcular assay	Predicted to be a non-irritant.	[54]
Polysorbate 20 (100%; 200 µL)	HET-CAM assay (Fertilized chicken eggs (white leghorn breed) with microscopic evaluation of hemorrhage, lysis, and coagulation at 0.5, 2, and 5 min.	Predicted to be an irritant.	[54]
Polysorbate 20 (100%)	HET-CAM assay (Same as above but evaluation of time to hemorrhage, lysis, and coagulation)	Predicted to be a severe irritant.	[54]
Polysorbate 20 (100%)	BCOP assay	Predicted to be a mild irritant.	[54]

BCOP=Bovine Corneal Opacity and Permeability assay; DMEM= Dulbecco's modified Eagle's medium; HET-CAM=Hen's Egg Test-Chorioallantoic Membrane assay; ICDRG=International Contact Dermatitis Research Group; STE=Short Time Exposure test.

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