Tentative Amended Report

Safety Assessment of Polyether Lanolins as Used in Cosmetics

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ABSTRACT

The CIR Expert Panel (Panel) assessed the safety of polyether lanolins as used in cosmetics. These ingredients function in cosmetics primarily as hair conditioning agents, skin-conditioning agent-emollients, and surfactant-emulsifying agents. The Panel reviewed available relevant animal and clinical data, from previous CIR safety assessments of related ingredients and components. The similar structure, properties, functions and uses of these ingredients enabled grouping them and using the available toxicological data to assess the safety of the entire group. The Panel concluded that the polyether lanolins are safe as used.

INTRODUCTION

This is an amended safety assessment of polypropylene glycol (PPG) and polyethylene glycol (PEG) lanolin ingredients, collectively termed polyether lanolins, as used in cosmetics. These ingredients function mostly as hair conditioning agents, skin-conditioning agent-emollients, and surfactant-emulsifying agents (Table 1).

Because of the similarity in chemical structures, this safety assessment combines previously reviewed PPG- and PEG-lanolins, with the previously unreviewed PPG- and PEG-lanolin ingredients for a total of 39 cosmetic ingredients. There were little data on the polyether lanolins from the prior reviews, so the Panel relied on data about PPGs, PEGs, and lanolin from other reports. The relevant data from these reports are summarized along with the new data.

The cosmetic ingredients from previous safety assessments are:

- PPG-5 lanolin wax,
- PPG-5 lanolin wax glyceride,
- PEG-5 hydrogenated lanolin,
- PEG-10 hydrogenated lanolin,
- PEG-15 hydrogenated lanolin,
- PEG-20 hydrogenated lanolin,
- PEG-24 hydrogenated lanolin,
- PEG-30 hydrogenated lanolin,
- PEG-40 hydrogenated lanolin,
- PEG-70 hydrogenated lanolin,
- PEG-5 lanolin,
- PEG-10 lanolin,
- PEG-20 lanolin,
- PEG-24 lanolin,
- PEG-25 lanolin,
- PEG-27 lanolin,
- PEG-30 lanolin,
- PEG-35 lanolin,
- PEG-40 lanolin,
- PEG-50 lanolin,
- PEG-55 lanolin,
- PEG-60 lanolin,
- PEG-70 lanolin,
- PEG-75 lanolin,
- PEG-85 lanolin,
- PEG-100 lanolin, and
- PEG-150 lanolin.

The cosmetic ingredients that have not been previously reviewed are:

- PEG-75 lanolin wax,
- PEG-75 lanolin oil,
- Polyglyceryl-2 lanolin alcohol ether,
- PPG-2 lanolin alcohol ether,
- PPG-5 lanolin alcohol ether,
- PPG-10 lanolin alcohol ether,
- PPG-20 lanolin alcohol ether,
- PPG-30 lanolin alcohol ether,
- PPG-20-PEG-20 hydrogenated lanolin,
- PPG-12-PEG-50 lanolin,
- PPG-12-PEG-65 lanolin oil, and
- PPG-40-PEG-60 lanolin oil.

PPG-5 lanolin wax and PPG-5 lanolin wax glyceride were reviewed by the Panel and published in 1997.[1] These ingredients were found to be safe as used in cosmetics (Table 2).

A safety assessment of PEG lanolins (PEG-20, 27, 30, 40, 50, 60, 75, and 85) was published in 1982.[2] These cosmetic ingredients were found to be safe as presently used in cosmetic products. In 1999, an addendum was published adding more PEG lanolins (PEG-5, 10, 24, 25, 35, 50, 55, 60, 85, 100, and 150) and hydrogenated lanolins (PEG-5, 10, 20, 24, 30, and 70) to the safety conclusion. These ingredients were found to be safe for use in cosmetic formulations under the present practices of use.[3]

Dipropylene glycol (PPG-2) was reviewed in 1985 and re-reviewed in 2005.[4,5] This ingredient was found to be safe as presently used in cosmetics.

In a 1999 special report that addressed alkyl ethers of polyethylene glycols, the Panel noted that such compounds, as used in cosmetics, have large or complex alkyl chains, suggesting little or no potential toxicity, and that reproductive and developmentally toxic metabolites were not expected to be formed.[6]

Lanolin, lanolin oil, lanolin wax, lanolin acid, lanolin alcohol, acetylated lanolin, acetylated lanolin alcohol, hydrogenated lanolin, and hydroxylated lanolin were reviewed in 1980 and re-reviewed in 2003.[7,8] These component compounds of polyether lanolins were found to be safe for topical application in the present practices of use and concentration

Alkyl PEG ethers, including PEG ethers of lanolin alcohol (e.g., laneths-5), were reviewed in 2010.[9] These ingredients were found to be safe as used in cosmetics when formulated to be non-irritating.

A review of laneths previously was published in 1982.[10] These ingredients were found to be safe for topical application in the present practices of use and concentration. This conclusion was re-evaluated in 2003 and the conclusion affirmed.[7]

A review of PPGs was published in 1994, with the conclusion of safe for use in cosmetic products at concentrations up to 50.0%.[1] In 2010, the report was amended to specify that propylene glycol, tripropylene glycol, and PPGs with chain lengths ≥ 3 are safe as used in cosmetic formulations when formulated to be non-irritating.[11]

A review of PEGs was completed by the Panel in 2010.[12] PEG-4 was one of the ingredients addressed in this safety assessment and, in so doing, the Panel acknowledged that PEG-4 was actually a mixture of PEGs in which the average number of ethylene glycol residues was 4, but which would include 2, 3, 4, 5 and even 6 based on the method of manufacture that does not end block the polymerization.

PEG-25 lanolin was included in the 1999 report but is currently not listed in the Council's database. A survey of use is being conducted for this ingredient and for PEG-75.

Unless otherwise noted, the data below are summaries of the above safety assessments.

The similar chemical structures, physicochemical properties, functions and concentrations used in cosmetics enable grouping these ingredients and reading across the available toxicological data to support the safety assessment of the entire group.

References to data used from previous reports cite the original safety assessment. CIR acknowledges the need to properly reference data related to descriptions of individual studies to their primary sources. At this time, that task of identifying those sources is only partially completed. The appropriate citations will be in the next version of this safety assessment for the next review by the Panel.

CHEMISTRY

Definition and Structure

The definitions and functions of the ingredients in this safety assessment are provided in Table 1.

The ingredients in this review are polyetherified derivatives of lanolin and lanolin sub-fractions.

Lanolin is the purified secretory product of the sheep sebaceous gland. Lanolin comprises 10% to 25% of the weight of sheared wool.[13] Lanolin is a complex mixture of a large number of compounds. High molecular weight esters make up approximately 87% of a typical lanolin sample.[14,15] The remainder of the mixture consists of 11% free compounds (aliphatic alcohols, sterols, fatty acids and hydrocarbons) and of 2% unidentified compounds. Since lanolin is composed predominantly of high molecular weight esters, it is classified chemically as a wax and not as a fat.[13]

Whole lanolin is a mixture of esters of sterols; triterpene alcohols; esters of aliphatic alcohols; monohydroxyesters of sterols, and of triterpene and aliphatic alcohols; di- and polyhydroxyesters; free diols; free aliphatic alcohols; free sterols; free fatty acids; and other free hydrocarbons (Table 3).[8] Lanolin wax derivatives come from the most solid sub-fraction of whole lanolin. For example, PEG-75 lanolin wax consists of the solid/semisolid constituents obtained from the low temperature fractional crystallization, or solvent fraction, of lanolin, which is then reacted with seventy-five stoichiometric equivalents of ethylene oxide. PEG-75 lanolin oil, therefore, consists of an oil sub-fraction obtained from the low temperature fractional crystallization, or solvent fraction, of lanolin, reacted with seventy-five stoichiometric equivalents of ethylene oxide. PEG-75 lanolin, then, is unfractionated, whole lanolin, reacted with seventy-five stoichiometric equivalents of ethylene oxide. A few examples of the discrete molecules that may be formed in these mixtures are drawn in Figure 1.

The PPG derivatives are described a little differently than the PEG derivatives. As noted above, PEG-75 lanolin refers to whole lanolin that has been reacted with seventy-five stoichiometric equivalents of ethylene oxide. The PPG derivatives, however, are defined as having "an average propoxylation value," suggesting that an ingredient such as PPG-2 lanolin alcohol ether is the polypropylene glycol ether of a lanolin alcohol sub-fraction, with polypropylene glycol chains averaging two propylene glycol repeat units in length.

Method of Manufacture

PEG lanolins are prepared by ethoxylating the hydroxy fatty acids, hydroxy esters, sterols, and alcohols present in whole lanolin. An average of n moles ethylene oxide are added to each equivalent of lanolin in the presence of an alkaline catalyst.[2]

Given the methods of manufacture of the PEGs lanolin,[3] there is no likelihood of methoxyethanol, ethoxyethanol, etc., being present as an impurity.[6] Although the exact structures of lanolin, hydrogenated lanolin, lanolin oil, or lanolin wax are not known, such extracts are usually long-chain or complex compounds. When combined via an ether linkage with polyethylene glycol, it is not likely that any of them would present the simple R-group appearance of methyl, ethyl, propyl, or even butyl. It is also unlikely that the lanolin moieties would be metabolized (e.g., via β-oxidation) to simple methyl, ethyl, etc., alkyl groups. In addition, most of the polyethylene glycol chain lengths used in making the various PEG lanolins are 10 glycol repeat units or longer, suggesting that there would be a very little chance of a monomer linked by an ether group to the lanolin moiety.

Impurities

A maximum of 2.5% inorganic salts has been found in PEG-75 lanolin. Trace amounts of 1,4-dioxane, a by-product of the ethoxylation process, may be present in PEG lanolins. Pesticides and trace metals found in crude lanolin may also be impurities.[2,16,17]

It was reported that PEG-6 may contain small amounts of monomer and dimers.[18] The amounts were not quantified. Peroxides, formed as a result of autoxidation, are found in PEG-32 and PEG-75.[19] The amount of peroxide in PEGs is dependent upon the molecular weight of the PEG and its age. In a colorimetric assay used to determine the peroxide concentrations in several production lots of PEGs, PEG-6 and PEG-8 were each added to acidified potassium iodide solution, and the iodine liberated was titrated against a standard thiosulfate solution. PEG-6 had peroxide concentrations ranging from 1.4 to 9.3 μEq PEG thiosulfate/ml glycol. PEG-8 had concentrations ranging from 3.24 - 5.7 μEq PEG thiosulfate/ml glycol. The specific peroxides present in the PEGs were not determined, but they were thought to be organic peroxides rather than hydrogen peroxide.[20]

USE

Cosmetic

Data on ingredient usage are provided to the Food and Drug Administration (FDA) Voluntary Cosmetic Registration Program (VCRP).[21] A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group (Table 4).[22] PEG-75 lanolin had the most uses at 168. Polyether lanolins are used at a range of 0.001%-15%

VCRP and Council data were available for:

- PPG-5 lanolin wax was reported to be used in 3 lipsticks. The Council reports use in leave-on cosmetic products at 2%-4% and in rinse off-products at 2%-3%.
- PEG-20 hydrogenated lanolin was reported to be used in hair products, 7 leave-on products (5%) and 10 rinse-off products (1%).
- PEG-20 hydrogenated lanolin was reported to be used in 17 noncoloring hair products (1% - 5%).
- PEG-24 hydrogenated lanolin was reported to be used in 1 hair conditioner. The Council reports use in hair dyes and colors (0.2%) and in skin care preparations (0.3%).
- PEG-30 lanolin was reported to be used in 2 leave-on products (2 aftershave lotions; 0.05%).
- PEG-40 lanolin was reported to be used in 8 leave-on products (hair care products; no concentration of use reported) and body and hand creams (0.25%).
- PEG-60 lanolin was reported to be used in 28 products (3 leave-on products, 0.05%-2%; 25 rinse-off products, 0.05%-1%).
- PEG-75 lanolin was reported to be used in 168 products (84 leave-on products, 0.001%-2%; 84 rinse-off products, 0.02%-15%) mostly in hair care products).
- PPG-12-PEG-50 lanolin was reported to be used in 44 products (25 leave-on, 0.3%-2%; 19 rinse-off, 0.2%-8%), mostly in hair care products).
- PPG-12-PEG-65 lanolin oil was reported to be used in 11 products (7 leave-on, 0.1%; 4 rinse-off, 0.002%-0.4%) mostly in hair care products.

VCRP data only were available for:

- PEG-5 lanolin was reported to be used in 3 rinse-off products (hair conditioners).
- PEG-50 was reported to be used in 3 rinse-off products (2 hair conditioners).
- PEG-85 lanolin was reported to be used in 1 rinse-off product (non-coloring shampoo).
- PEG-100 was reported to be used in 1 hair straightener.
- PEG-75 lanolin oil was reported to be used in 9 products (3 leave-on and 6 rinse-off products).

There were no uses reported for PPG-5 lanolin wax glyceride, PEG-75 lanolin wax, PEG-5 hydrogenated lanolin, PEG-10 hydrogenated lanolin, PEG-15 hydrogenated lanolin, PEG-30 hydrogenated lanolin, PEG-40 hydrogenated lanolin, PEG-70 hydrogenated lanolin, PEG-5 lanolin, PEG-10 lanolin, PEG-20 lanolin, PEG-24 lanolin, PEG-27 lanolin, PEG-35 lanolin, PEG-55 lanolin, PEG-70 lanolin, PEG-100 lanolin, PEG-150 lanolin, polyglyceryl-2 lanolin alcohol ether, PPG-2 lanolin alcohol ether, PPG-5 lanolin alcohol ether, PPG-10 lanolin alcohol ether, PPG-20 lanolin alcohol ether, PPG-30 lanolin alcohol ether, PPG-20 PEG-20 hydrogenated lanolin, and PPG-40 PEG-60 lanolin oil.

Council data on PEG-75 lanolin is expected soon.

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Dermal/Percutaneous

ALKYL PEG ETHERS

According to the original laureths report, in general, alkyl PEG ethers are readily absorbed through the skin of guinea pigs and rats and through the intestinal mucosa of rats, and they are quickly eliminated from the body through the urine, feces, and expired air.[10] A portion of the constituents of PEG lanolin ingredients are alkyl PEG ethers.

In rats, compounds analogous to laureth-9 are rapidly absorbed and excreted in the urine after oral, i.p., and s.c. dosing.[23] Two distinct polar metabolites were identified in the urine for each compound tested. The length of the alkyl chain appeared to have an effect on metabolism, with excretion of longer alkyl chains occurring at a higher proportion as CO_2 in expired air and less in urine. Similar results were found following oral administration in humans. Again, the major route of excretion was the urine. The metabolic product of each compound was a function of carbon chain length. However, the longer carbon chain ethoxylates produced more metabolic CO_2 and less urinary elimination products. The degradation of ether linkage and oxidation of the alkyl chain to form lower molecular weight PEG-like compounds, CO_2 and water appeared to be the major degradation products of alcohol ethoxylates.

In dermal metabolism studies with hairless mice, the 4-hour percutaneous absorption decreased from 22.9% for laureth-1 to 2.1% for laureth-10 solutions, administered at a concentration of 0.25% in ethanol.[23,24] The absorbed laureths were rapidly metabolized to CO_2. Compounds analogous to laureth-9 readily penetrated the skin of rats, and approximately 50% of the absorbed dose was excreted. In human subjects, the majority of the dose could be wiped away from the test site after 8 h; less than 2% was found in the urine. With atopic patients, the calculated dermal absorption for laureth-9 was 0.0017% for a diluted bath oil and 0.0035% with after-shower application. Some alkyl PEG ethers, such as ceteareths and oleths, have been reported to enhance the penetration of certain compounds through the skin.

Oral and Intravenous

PROPYLENE GLYCOLS

Animal studies using PPGs with average molecular weights of 425-2025 indicated that PPGs are readily absorbed from the gastro-intestinal tract and excreted in the urine and feces.

Miscellaneous Studies

PPG LANOLIN ALCOHOLS

When PPG-2, -5, -10, and -20 lanolin alcohols (0, 1, 2.5, 5, 10, 15, 20 µg/ml) were added to a petrolatum-liquid paraffin eye ointment, the antimicrobial activity of chloramphenicol and tetracycline were increased in paper disc assays.[25] The increases were greater with concentration and number of propylene oxide units.

TOXICOLOGICAL STUDIES

Acute Toxicity

Dermal – Non-Human

PEG LANOLINS

At a dose of 2.0 ml/kg, undiluted PEG-27 Lanolin caused no erythema, edema, or toxic symptoms in six rabbits, and the acute dermal LD_{50} was reported to be >2.0 ml/kg. The acute dermal LD_{50} of undiluted PEG-75 Lanolin was determined to be > 10 ml/kg.[2]

LANOLIN

The acute dermal LD_{50} of lanolin oil was > 10 ml/kg for rabbits.[26]

ALKYL PEG ETHERS

Dermally, the data available indicated the LD_{50} values for rats and rabbits were >2000 mg/kg for these families of ingredients.[23] Specifically for laureth-4, the dermal LD_{50} ranged from 0.93-1.78 ml/kg for rabbits, and the researchers observed the potential for neurotoxicity in rats (details not specified).

PROPYLENE GLYCOLS

A product formulation containing dipropylene glycol (7.2%) produced a dermal LD_{50} of >2 g/kg when tested in rabbits.[27]

Oral – Non-Human

PEG LANOLINS

PEG-20, -27, -40, -50, -75, and -85 lanolins were tested for acute oral toxicity; they were reported to be relatively nontoxic to rats and mice at concentrations higher than those used in cosmetics (Table 5).[2]

LANOLIN

The acute oral LD_{50} for lanolin for rats was reported to be >64 cc/kg, lanolin oil was 46.5 cc/kg, 50% lanolin wax in corn oil was >32 g/kg, 66% lanolin alcohol in corn oil >42.7 g/kg, and undiluted hydrogenated lanolin >64 cc/kg.[8]

ALKYL PEG ETHERS

Acute oral toxicity data were available for some of the laureths and pareth ingredients. C9-11 Pareth-8, C14-15 pareth-11, and C14-15 pareth-13 had the lowest LD_{50} values, which were 1 mg/kg in rats.[23] Many of the LD_{50} values were in the range of 2300-3300 mg/kg, with some, such as C12-13 pareth-2, having a value >10,000 mg/kg.

PROPYLENE GLYCOLS

The LD_{50} of PPG with molecular weights ranging from 300-3900, ranged from 0.5-40 g/kg for rats, while the oral LD_{50} of PPGs (molecular weights not given) ranged from 1.5-17 g/kg for guinea pigs.[28,29]

The oral LD_{50} of PPG-2 was reported to be 15.8 mg/kg for adult male and female Wistat rats.[30]

Guinea pigs, adolescent albino rats, young (30 day) rats, and adult (6-8 month) albino rats were administered a single dose of PPG-2 (3-25 g/kg).[31] The minimum lethal dose (MLD - 50% killed), for guinea pigs was 10 g/kg and for female adolescent rats was 16.5 g/kg. For male adolescent, young, and adult rats, the MLD was 12.5, 12.5, and 14.2 g/kg, respectively. Quick deaths were due to paralysis of the respiratory center while delayed deaths were from kidney injury and urine suppression.

The acute oral LD_{50} of dipropylene glycol in rats was 15 g/kg.[32] A shaving preparation containing 7.2% dipropylene glycol had an oral LD_{50} of >5 g/kg.[27]

Inhalation – Non-Human

PEG LANOLINS

Rats (n = 10) exposed for one hour to an aerosol containing PEG-27 Lanolin (200 mg/l) were observed for two weeks.[2] None exhibited toxic reactions to PEG-27 Lanolin. Necropsies revealed no abnormalities.

Peritoneal – Non-Human

PROPYLENE GLYCOL

The intraperitoneal LD_{50} of dipropylene glycol in rats and mice was 10 g/kg and 4600 mg/kg, respectively.[32] The intravenous LD_{50} in rats and dogs was 5800 mg/kg and 11,500 mg/kg, respectively.

Repeated Dose Toxicity

Dermal – Non-Human

PEG LANOLINS

In a dermal test of PEG-75 lanolin (50% in mineral oil), the rabbits (n = 4) showed no visible skin irritation or abnormalities at necropsy after 5 weeks.[2]

ALKYL PEG ETHERS

In a 2-wk dermal study, dosing with 495-1980 mg/kg/day undiluted laureth-4 under occlusion did not result in erythema or edema, and no toxicologically significant results were reported. In a 13-wk study, moderate localized erythema was observed at all dose levels of 2.5% aq. $C_{14\text{-}15}AE_7$ in rabbits.

PROPYLENE GLYCOL

In a subchronic dermal study, 1 ml/kg PPG-2 did not cause adverse effects in rabbits, but 5 and 10 ml/kg caused a slight depression in growth.[29]

Oral – Non-Human

ALKYL PEG ETHERS

In 21-day, 90-day and two 2-yr feeding studies, compounds analogous to laureth-9 had dietary NOAELs of 459-519, 50-785, and 50-162 mg/kg in rats.[23]

In a 13-day oral study with a deceth, with an unspecified number of ethylene glycol repeat units, doses of ≥25 g/kg resulted in death in rabbits. The majority of the mortality was a result of respiratory distress; signs of toxicity including post-dose inactivity, clonic convulsions, and respiratory distress, were observed occasionally in the 2 lower dose groups and frequently in the higher dose groups.

In a 14-day drinking water study, PEG-3 methyl ether was mildly to moderately toxic at 4 g/kg and severely toxic at ≥8 g/kg, while in a 91-day drinking water study, PEG-3 methyl ether had a NOAEL of 400 mg/kg/d for liver effects; testicular effects were observed, but were attributed to contamination with 2-methoxyethanol.

In a 13-wk dietary study, a dose of ≤10,000 ppm C14-15 pareth-7 produced some differences compared to controls in organ weights and clinical chemistry and hematology values, but since no microscopic lesions were observed, these were not considered toxicologically significant.

For an oleth, with an unspecified number of ethylene glycol repeat units, administered orally to rats, doses of ≥750 mg/kg resulted in either death or significant signs of toxicity, and 1 of 6 animals given 3000 mg/kg/day for 17 days was killed in moribund condition. However, at necropsy, the organs and tissues appeared normal.[23]

PROPYLENE GLYCOL

Polypropylene glycol (PPG 750) did not cause any adverse effects when given at 0.1% for 10 days, but a concentration of 1% produced slight increases in liver and kidney weight. The highest no effect level of polypropylene glycol

(PPG 1200) fed to rats and dogs for 90 days was 0.3%. No adverse effects were seen in a 90-day study in which rats or dogs fed 501 or 810 mg/kg/day, respectively, PPG 2000.[29,33]

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

PEG Lanolins

It was considered unlikely that the PEG lanolin compounds would cause reproductive or teratogenic effects based on their structural characteristics.[12] In subchronic and chronic feeding studies, PEG-6-32 (0.015, 0.059, 0.27, and 1.69 g/kg/d) and PEG-75 (0.062 g/kg/d) did not induce reproductive effects in rats.[34,35]

ALKYL PEG ETHERS

In a two-generation reproductive study, dermal administration of ≤25% C9-11 pareth-6 did not have a toxicologically significant effect on dams or offspring.[36]

In two-generation oral reproductive studies with dietary administration of compounds analogous to laureth-9, the NOAEL for reproductive toxicity was >250 mg/kg/day, and the NOAELs for maternal and developmental toxicity were 50 mg/kg/d.[23]

PROPYLENE GLYCOL

There was no maternal or developmental toxicity caused by oral administration of 800 mg/kg/day PPG-2 on days 6 – 15 of gestation to female Sprague-Dawley rats.[37] Doses of 2000 and 5000 mg/kg/day caused maternal lethality in 1/25 animals and 2/22 animals, respectively. The highest dose caused decreased maternal body weights and weight gain as well as decreased food consumption. No evidence of developmental toxicity was observed in any dose group.

Rabbits were orally administered PPG-2 (2, 200, 400, 800, or 1200 mg/kg/d) on gestation days 6-19.[38] No rabbits died at any dose. Pregnancy rates for the control to high dose groups were 95%, 83%, 91%, and 92%, respectively. PPG-2 did not affect maternal body weight, kidney or liver weights, food consumption, or clinical signs. No effect was seen on frequency of post-implantation loss, mean fetal body weight per litter, or external, visceral, or skeletal malformations. No maternal or developmental toxicity was observed at any dose level.

GENOTOXICITY

In Vitro

PEGs

In mutagenicity studies, PEG-8 was negative in the Chinese hamster ovary cell mutation test and the sister chromatid exchange test. At a concentration of 150 g/L, PEG-150 was not mutagenic in the mouse lymphoma forward mutation assay.[12]

ALKYL PEG ETHERS

A laureth, with an unspecified number of ethylene glycol repeat units, was not mutagenic or genotoxic in an Ames test, transformation assay, or mouse lymphoma assay, and it did not induce sister chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells. Compounds analogous to laureth-9 were not mutagenic in an Ames test or clastogenic in in vitro or in vivo chromosomal aberration studies. C9-11 pareth-6 were not mutagenic in Ames tests.[23,39-47]

PROPYLENE GLYCOL

Tripropylene glycol, ≤10,000 µg/plate, was not mutagenic in an Ames assay.[29,48]

CARCINOGENICITY

PEGs

PEG-8 was used as a solvent control in several carcinogenicity assays. Twenty Swiss male mice fed 0.30 ml PEG-8 weekly for 30 weeks did not have tumors.[49] PEG-8 (0.05 ml) was injected into the ventral wall of the gastric antrum of 12 guinea pigs. The animals were killed for necropsy after 8 months. No gastric lesions were found.[50] Male CB stock rats were injected intraperitoneally with 0.25 ml PEG-8 once a week for 6 months. Among the 24 animals, one case of hepatoma was reported.[51] Twenty Chester Beatty Stock mice were given weekly subcutaneous injections of PEG-8 (0.2 ml) for 1 year. No neoplasms developed in these animals.[52] Subcutaneous injections of PEG-8 (0.25 ml) were administered weekly to 20 male and 20 female Sprague-Dawley rats for 20 weeks. The mice were killed for necropsy after 106 weeks. No sarcomas or fibromas developed in the subcutaneous tissues. Mammary fibroadenomas and carcinomas were observed. However, the incidence of these neoplasms did not differ significantly from that of the untreated control rats.[53]

ALKYL PEG ETHERS

In two studies, compounds that are analogous to laureth-9 were not carcinogenic in feeding studies in which rats were given up to 1% in the diet for 2 yrs.[23]

Anti-Carcinogenicity

LANOLIN

3-Methylcholanthrene dissolved in anhydrous lanolin was less carcinogenic when painted on the skin of mice as compared to its carcinogenic effect when benzene was the vehicle.[54] There were similar results with another carcinogen, 7,12-dimethylbenz(a)anthracene.[55]

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

LANOLIN

Most lanolin ingredients are either nonirritating or at minimally irritating to the skin of guinea pigs and rabbits. The exceptions include lanolin acid which is a mild skin irritant. In the five tests conducted on undiluted lanolin acid, the Primary Irritation Index (PII) ranged from 0.78 to 2.2 (maximum of 8). Also, the PII for acetylated lanolin alcohol ws 2.3.[8]

The highest PII value obtained for each of the other undiluted lanolin ingredients were: lanolin (0.71), lanolin oil (1.0), lanolin wax (0.67), lanolin alcohol (1.5), acetylated lanolin (1.62), hydrogenated lanolin (0.6), and hydroxylated lanolin (0.0).[8]

Neither lanolin oil (5%, 15%, 50%) applied 15 times to the rabbit skin nor hydroxylated lanolin (50%) applied 65 times to the skin of rats caused any local skin irritation effects.[26,56]

PEGs

Undiluted PEGs (-6, -8, -32, -75) were nonirritating to the skin of rabbits and guinea pigs.[12]

ALKYL PEG ETHERS

Depending on the alkyl PEG ether studied, results range from non-irritating to severely irritating.[57-59] Using rabbits, the PII (max = 8) in rabbits for laneth-5 (10%) was 0.5 and undiluted laureth-9 produced moderate irritation at abraded sites, while 10% and 20% dilutions caused slight irritation at intact and abraded sites at 24 h. The dermal irritation potentials of several compounds that were analogous to laureth-9 were determined. Under semi-occlusive conditions with a 4 h application, $C_{14-15}AE_7$, 0.5 ml at 10, 25, or 100%, was not irritating to rabbit skin. Following a 4 h occlusive application to rabbit skin, undiluted $C_{12-14}AE_{10}$ and undiluted $C_{13}AE_6$ were moderately irritating, and undiluted $C_{13}AE_{6.5}$ and undiluted C12-14AE6 were severely irritating.

A contraceptive aerosol formulation containing 20% laureth-9 was mildly irritating in a Draize test. In a mixture containing an unspecified laureth, the laureth was considered to be strong irritant to rabbit skin

PROPYLENE GLYCOL

In a study using guinea pigs, 0.5 ml PG was a weak sensitizer. PPG (concentration not stated), molecular weight 425-2025, was not an irritant to rabbits.[29]

Dipropylene glycol (100%; 500 mg) caused mild irritation when administered to rabbit skin for 24 hours.[60] Dipropylene glycol (7.2%) was tested for 24 hours under occlusion on rabbit skin with no irritation.[61]

PEG LANOLIN

A dermal irritation test using rabbits (n = 3) of two samples of PEG lanolin (10% and 100% in a mixture of polysorbate 60, paraffin, and a preservative; length of PEG not provided) was conducted.[62] The test substances were applied over 2 months, however, the frequency and volume of the applications were not provided. Macroscopic and histologic examination showed that both test substances were well tolerated at 10%; one sample produced dry and cracked skin on weeks 3 – 4. However, at 100%, one sample caused vesicles or blisters at weeks 2 and 4, which resolved by week 5. The skin was dry and cracked and had a slight thickening of the skin at weeks 3 – 8.

Dermal – Human

LANOLIN

In its previous safety assessment of lanolins, the CIR Expert Panel noted that reports of adverse reactions among persons occupationally exposed during production of lanolin over a 50-year period have been reported. [8] There have been no reported adverse experiences for lanolin oil, lanolin wax, lanolin acid, lanolin alcohol, acetylated lanolin, or acetylated lanolin alcohol.

PEGS

In clinical studies, PEG-8 was a mild irritant.[12] Contact dermatitis and systemic toxicity in patients were attributed to a PEG-based topical ointment.

ALKYL PEG ETHERS

In a retrospective clinical study, 0.97% of patients had a weakly positive and 0.25% of patients had a strongly positive reaction to 0.5% laureth-9, and 1.77% and 0.34% had weakly and strongly positive allergic contact reactions, respectively, to 3% laureth-9. Undiluted and 25% aq. $C_{14-15}AE_7$ produced negligible to slight irritation in an occlusive 3-patch application test, and a 10% aq. solution of $C_{12-13}AE_{6.5}$ 1% was slightly irritating when applied under an occlusive patch for 24 h.[23,63]

PROPYLENE GLYCOLS

In HIRPT (n = 212 males, 291 females) of PPG-2 (1%, 2%, 5%, and 10%), there was one positive reaction.[64] In a patch test (n = 66; 20%), 24.9% of those tested had positive reactions to PPG-2 (20%).[65]

Mucosal

ALKYL PEG ETHERS

Laureth-9 (1% in saline) caused severe damage to the nasal mucosa of rats. Regeneration of the epithelium had

started by day 3. As a 15% aq. solution, laureth-9 was not an irritant to the vaginal mucosa of dogs.[24,66]

Ocular

PEG LANOLINS

PEG Lanolins were tested with the Draize or Modified Draize procedure for potential ocular irritancy to rabbits.[2] PEG-20, -27, and -40 lanolins (100%) were non-irritating. PEG-30, -50, -75, and 85 (100%; 50%; 50% and 100%; 50%, respectively) resulted in conjunctival irritation. The highest mean irritation score at any observation was 3.33 (maximum score = 110) indicating mild irritation. All irritation subsided by the fourth day with the exception of one case (PEG-75 Lanolin) in which the conjunctiva remained irritated throughout the test period (7 days). These results indicate that PEG Lanolins at concentrations of 50-100% are, at worst, mild eye irritants.

New Data –An ocular irritation test using rabbits (n = 3) of two samples of PEG lanolin (10% and 100% in a mixture of polysorbate 60, paraffin, and a preservative; length of PEG not provided) was conducted.[62] The low dose was not tested in the second sample. The eyes were irritated at 1 h for all doses which subsided at 5 and 48 h. The irritation was almost completely resolved in the 10% group at 48h.

LANOLIN

In three of four ocular irritation studies conducted on rabbits, undiluted lanolin acid was found to be a mild or moderately severe irritant.[8] No or only mild transient reactions were reported for lanolin, lanolin oil, lanolin wax, lanolin alcohol, acetylated lanolin, acetylated lanolin alcohol, hydrogenated lanolin, and hydroxylated lanolin.

ALKYL PEG ETHERS

A 5% aq. solution of laureth-9 was not irritating to rabbit eyes. Compounds analogous to laureth-9 were moderately to severely irritating when instilled into rabbit eyes, and a 10% solution was moderately irritating. Dilution of these compounds reduced irritancy, and 0.1-1.0% solutions were non-irritating to rabbit eyes. At varying concentrations, PEG-3 methyl ether was slightly irritating to rabbit eyes. Undiluted C9-11, C12-13, C12-15, and C14-15 pareths were moderately to extremely irritating in Draize tests using unrinsed rabbit eyes, except for C14-15 pareth-18, which was minimally to mildly irritating. Rinsing reduced irritation in some cases but not all. At concentrations of 0.1-1%, these ingredients were non- to mildly irritating, while at 10%, they were moderately to severely irritating in some cases and practically non- to mildly irritating in others. A 5% solution of Oleth-20 produced mild, transient conjunctival redness and chemosis in rabbit eyes.[23,24,39,58,67-69]

PROPYLENE GLYCOLS

Undiluted PPG, molecular weights 425-2025, were at most slight ocular irritants.[29]

Primary rabbit cornea cells from Japanese White rabbits treated with dipropylene glycol had an LD_{50} of 90 x 10^3.[70] Dipropylene glycol was not irritating to Japanese White rabbits at unspecified concentrations. This information was extrapolated to a conclusion that the concentration of PPG-2 would have to go over 100% to reach a Draize score of 20.

Undiluted dipropylene glycol is an irritant in the rabbit eye in an amount of 510 mg.[32]

Sensitization

Dermal – Non-Human

LANOLIN

A skin sensitization study with guinea pigs (n = 8) was conducted with acetylated lanolin alcohol suspended in physiological saline.[8] Ten intracutaneous injections on alternate days followed by challenge injection two weeks later showed no sensitization

Hydrogenated lanolin (2% in 1 :1:3 acetone:dioxane:corn oil) was not a sensitizer to guinea pigs when administered three times a week for seven or more applications. The challenge was applied 2 weeks after the last induction dose.[26]

Lanolin wax (in corn oil) was a mild skin sensitizer to guinea pigs (average score of 0.95; 0.1- 2.0 = mild sensitizer). The test material was injected intracutaneously three times/week for a total of 10 injections with an eleventh challenge injection two weeks later.[8]

PEGS

PEG-75 (0.1% aqueous) was not a sensitizer in guinea pigs.[12]

ALKYL PEG ETHERS

The sensitization potential of a number of alkyl PEG ethers was evaluated using guinea pigs. Laureths-5 (10%) and -9 (0.02%); compounds analogous to laureth-9 (up to 50%); C9-11 pareth-3, -5, -6, -8 (1%); C12-13 pareth-2, -3, and -7 (50%); C12-15 pareth-3, -7, and -9 (not provided); and C14-15 pareth-7, -11, -13, and -18 (not provided) were not sensitizers using guinea pigs was severely irritating to rabbit skin.[36,66,71-74]

Dermal – Human

LANOLIN

Numerous patch tests have been conducted on volunteers with lanolin and related cosmetic ingredients. Undiluted lanolin showed no evidence of primary irritation or sensitization in over 250 subjects.[8]

Lanolin oil has been skin tested in more than 300 subjects without adverse reactions.[75,76]

Undiluted lanolin wax showed extremely low irritation potential and no evidence of sensitization in over 200 subjects.[77,78]

Of the 115 subjects exposed topically to lanolin acid, three showed increased reaction not considered sensitization and one showed sensitization. There were no adverse effects noted when 50 subjects were exposed to undiluted lanolin alcohol in a human repeated insult patch test (HRIPT). Questionable evidence of fatiguing was found in 2 of 53 subjects exposed to acetylated lanolin. Acetylated lanolin alcohol caused an extremely low level of irritation in over 60 individuals.[8]

In a HRIPT on 50 subjects, undiluted hydrogenated lanolin presented no suggestions of irritation, fatiguing, or sensitization.[79]

There were no visible skin changes observed in 53 subjects exposed to hydroxylated lanolin.[8]

Lanolin has been observed to produce allergic or hypersensitivity reactions. Three large European retrospective studies of dermatology patients with lanolin alcohol hypersensitivity reported an incidence of positive patch tests of 0.70%, 2.38%, and 1.82%.[80] Using numerous assumptions, the incidence in the general population was estimated to be no more than 9.7 cases per million people[81]

Lanolin sensitivity was identified by the use of wool wax alcohol (30% in petrolatum) as the testing agent in patch testing.[82] It was noted that the addition of salicylic acid to the lanolin fraction produced false-positive reactions.[81]

Based on multiple studies, it was suggested that the greatest allergenic reaction resulted from C14-16 lanolin alcohols.[83]

A European study group noted that the incidence of hypersensitivity to topical medicaments was 14% (560/4000) in clinic patients with eczema. Positive test reactions reported for wool alcohols were 3%.[84]

The results of tests by the North American Contact Dermatitis Group showed that out of 1200 patients tested over an 18-month period ending in June 1972, wool wax alcohols (30% in petrolatum) ranked eighth in frequency of reaction with 3% of the patients reacting.[85] In the subsequent two-year testing period, wool wax alcohol ranked eleventh, again experiencing a 3% reaction rate out of 3165 patients tested.[86] The North American Contact Dermatitis Group reported positive reactions to lanolin alcohol (30% in petrolatum) at 1.8% in patch tests (n = 4451) from 2005 – 2006. This was lower than the previous 10 years.[87]

A preliminary report of testing from July 1,1975-June 30, 1976, showed wool alcohol ranking as thirteenth with a reaction incidence of 2.9% of 900-2000 patients tested.[88] An unpublished tabulation of 1976-1977 data from the groups shows a sensitivity index of 2% for wool alcohol and 1% for 100% hydrous lanolin.[8]

One study demonstrated that in lanolin-sensitive patients, the removal of free fatty lanolin alcohols and detergents reduced the incidence of detectable hypersensitivity by 96%.[89] An anonymous submission suggests that parabens, alkyl esters of p-hydroxybenzoic acid, cosmetic preservatives, may increase or be responsible for lanolin hypersensitivity.[90,91]

PEG LANOLINS

PEG-75 Lanolin at 100% concentration caused no irritation or sensitization in 53 human subjects in an HRIPT.[2] PEG-20 and PEG-50 Lanolins were also reported to be nonirritating and nonsensitizing in 261 patients at concentrations from 10 to 60 percent in prophetic patch tests.

ALKYL PEG ETHERS

In an HRIPT of formulations containing laureth-9, 12% of subjects challenged with 10 and 15% formulations and 18% of patients challenged with formulations containing 20% laureth-9 had mild reactions. Test compounds analogous to laureth-9, evaluated in HRIPTs at concentrations of 1-25%, were not sensitizers. In HRIPTs to determine the sensitization potential of 1-15% C12-13 pareth-7 and 5-25% C12-15 pareth-7, slight or mild irritation was observed, but the ingredients were not sensitizers to human subjects. The clinical effect of steareth-2, -10, and -21 was evaluated on normal and damaged skin. The steareths did not have an effect on dermal blood flow with either normal or damaged skin, but transepidermal water loss of damaged skin was decreased with steareth-2 and steareth-21. PEG-3 methyl ether was slightly irritating in a clinical study.[23,39,57,66,92]

A number of case studies, primarily with laureths, particularly laureth-9, have been reported. Reactions included, but were not limited to, eczema, contact dermatitis, and a pruritic rash.[39,93-102]

Phototoxicity

LANOLIN

Human patch tests were conducted on two product formulations, each containing lanolin acid (0.75%; n = 20), lanolin alcohol (3.0%; n = 25), and hydroxylated lanolin (0.5%; n = 20). There was no phototoxicity or photosensitivity observed.[103-105]

ALKYL PEG ETHERS

A study included exposure to ultraviolet light as a supplement to the Schwartz-Peck prophetic patch tests and Draize-Shelanski repeated insult patch tests (n = 101) on a shaving preparation containing percent dipropylene glycol (7.2%).[106] Supplemental UV exposure after the second insult did not produce any reactions.

PREVIOUS DISCUSSIONS

PPG-5 Lanolin Wax and PPG-5 Lanolin Wax Glyceride

The Panel acknowledged that there is little information available on the biologic activity and toxicity of PPG-5 lanolin wax and PPG-5 lanolin wax glyceride; however, the Panel has already reviewed such information on PG, PPG, lanolin, lanolin wax and other lanolin derivatives, and has relied extensively on these data in the review of the current cosmetic ingredients.[1] These data show little reproductive and developmental toxicity, mutagenicity, carcinogenicity, other systemic toxicity, irritation, or sensitization associated with component ingredients, which are considered chemically similar to PPG-5 lanolin wax and PPG-5 lanolin wax glyceride.

PEG Lanolins

Safety test data on the original PEGS Lanolin reviewed by the CIR Expert Panel were considered relevant to this review.[3] Likewise, the data on PEGS and on lanolin and its derivatives were considered relevant. All these data were supportive of the safety of the additional PEGS Lanolin polymers, the PEGS hydrogenated lanolin polymers, PEG-75 lanolin oil, and PEG-75 lanolin wax.

The Panel concluded that based on the structure of each PEG lanolin that was reviewed, none of these ingredients was likely to be mutagenic or carcinogenic. Additionally, based on particle size and cosmetic use concentrations, it is not likely that these ingredients, in formulation, are respirable. Thus, the Expert Panel has no concerns regarding the absence of inhalation toxicity data, and the Panel considers the PEGS lanolin safe for use in aerosolized products.

The Panel noted that comedogenic effects have resulted from the use of cosmetic products containing lanolin compounds and that data on the comedogenicity of PEGS lanolin are not available. However, it was concluded that the comedogenic potential of these compounds in cosmetics is of minor concern. The Panel was concerned about the sensitization potential of PEGS lanolin (PEG-5, -10, -20, -24, -25, -27, -30, -35, -40, -50, -55, -60, -75, -85, -100, and -150 lanolin; PEG-5, -10, -20, -24, -30, and -70 hydrogenated lanolin; PEG-75 lanolin oil; and PEG-75 lanolin wax) when applied to damaged skin. This concern arose because of positive patch tests for PEG-6 and PEG-8 in bum patients treated with a dressing that contained PEG-6, PEG-20, and PEG-75. The general corollary is that as the molecular weight of a compound decreases, expected irritancy and sensitization are increased. Consequently, product formulations should be adjusted in order to minimize any untoward effects.

It was also noted that it is unlikely that the PEGS lanolin are photoactivated ingredients, considering that product formulations containing lanolin compounds did not induce photosensitization or phototoxicity when applied to human subjects.

As discussed in this report, the possibility of reproductive and developmental effects was determined not to be of concern.

Acetylated Lanolin Alcohols and Related Ingredients

The results of tests on animals and humans with acetylated lanolin, its related cosmetic ingredients, and with numerous cosmetic formulations containing these materials attest to the safety of these ingredients as presently used.[8]

These ingredients, as a group, are used extensively in cosmetics as well as in many other consumer products, and there has been ample opportunity for a large proportion of the population to be exposed to some of these materials. The acute toxicity of these materials is low, and the animal tests for skin sensitization are negative. However, extensive clinical experience indicates that there is a low incidence of sensitivity to these materials among exposed persons. This appears to be mainly due to the lanolin alcohols. There was no evidence of photosensitization induced by these ingredients. Comedogenic effects from cosmetics incorporating lanolin and related materials have been reported.

The safety assessment of these ingredients rests on the information at hand and on the considerable usage in various concentrations in a variety of cosmetic formulations. Additional biological assessment of these ingredients might reasonably be expected to include more extended studies in the areas of percutaneous absorption, cutaneous hypersensitivity, chronic toxicity, and mutagenicity.

Alkyl PEG Ethers

The Expert Panel noted gaps in the available safety data for some of the alkyl PEG ethers in this safety assessment.[9] The available data on many of the ingredients are sufficient, however, and similar structural-activity relationships, biologic functions, and cosmetic product usage, suggest that the available data may be extrapolated to support the safety of the entire group. For example, a concern was expressed regarding the extent of dermal absorption for certain long-chain, branched alkyl PEG ethers because of a lack of information on dermal absorption and metabolism. The consensus of the Panel was, that because, dermal penetration of long chain alcohols is likely to be low, and the dermal penetration for alkyl PEG ethers is likely to be even lower, inferring toxicity characteristics from ingredients where toxicity data were available was appropriate. Additionally, the Panel has previously reviewed a number of the alkyl PEG ethers as individual groups, i.e. ceteareths, ceteths, laneths, oleths, and steareths, and in this report, the Panel has relied to a great extent on data from these past reports.

Some of the past assessments of ingredients that included a PEG moiety stated that the ingredient should not be used on damaged skin. Since an amended conclusion has been issued for the PEGs, that caveat is no longer necessary.

The potential adverse effects of inhaled aerosols depend on the specific chemical species, the concentration and the duration of the exposure and their site of deposition within the respiratory system. In practice, aerosols should have at least 99% of their particle diameters in the 10 – 110 μm range and the mean particle diameter in a typical aerosol spray has been reported as ~38 μm. Particles with an aerodynamic diameter of ≤ 10 μm are respirable. In the absences of inhalation toxicity data, the Panel determined that alkyl PEG ethers can be used safely in aerosol products, because the product size is not respirable.

Also of concern to the Expert Panel was the possible presence of 1,4-dioxane, ethylene oxide, methoxyethanol, and methoxydiglycol impurities. The Panel stressed that the cosmetics industry should continue to use the necessary procedures to remove 1,4-dioxane and ethylene oxide impurities from the ingredients before blending them into cosmetic formulations. Because methoxy PEGs are defined as having an average number of ethylene oxide units, they have the potential of containing methoxyethanol and methoxydiglycol. Cosmetic preparations should not contain these impurities. The Panel has also stated that impurities or residual by-products that may be present, such as formaldehyde, BHT, or BHA, should only be present at concentrations allowed by the Panel in past assessments.

The CIR Expert Panel considered the dangers inherent in using animal-derived ingredients, namely the transmission of infectious agents. While tallow may be used in the manufacture of some ingredients in this safety assessment and is clearly animal-derived, the Expert Panel notes that tallow is highly processed and tallow derivatives even more so. The Panel agrees with determinations by the U.S. FDA that tallow derivatives are not risk materials for transmission of infectious agents.

The Expert Panel recognized that some of these ingredients can enhance the penetration of other ingredients through the skin. The Panel cautioned 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 data, or when dermal absorption was a concern.

The Expert Panel was also concerned that the potential exists for dermal irritation with the use of products formulated using some of the alkyl PEG ethers. The Expert Panel specified that products must be formulated to be non-irritating.

Finally, this assessment is intended to address future cosmetic use of alkyl PEG ethers that vary from those in this assessment only in the number of ethylene glycol repeat units. The Expert Panel considers that the available data would extend to additional alkyl PEG ethers that could be used in cosmetics in the future.

Propylene Glycols

The CIR Expert Panel reopened the 1994 safety assessment of propylene glycol and polypropylene glycols to address the safety of current high-use-concentrations of PG, as well as to add all the PPGs currently listed in the *International Cosmetic Ingredient Dictionary and Handbook*.[11] This report is intended to also address the safety of similar PPGs that may be used as cosmetic ingredients in the future.

Since tripropylene glycol is similar to PG and the PPGs, its safety can be supported by the existing data and, therefore, the Panel included tripropylene glycol in this safety assessment.

Propylene oxide is used in the manufacture of PPGs, but should not appear in cosmetic formulations because of safety concerns. The Panel expects that PPGs contain ≤10 ppm propylene oxide, ensuring the safety of formulations in which PPGs are used.

PG and PPGs were not considered to be acute or chronic toxicants in oral or dermal studies, were not genotoxic or carcinogenic, and were not reproductive or developmental toxicants, supporting that use in cosmetics would be safe in regard to these endpoints.

At the time of the original safety assessment, a concentration limit of 50% PG and PPGs was established based on the results of existing irritation and sensitization studies.

The CIR Expert Panel, as noted earlier, considers that the available data for PPG-3 through PPG-69 would extend to any PPG-n to be used in cosmetics in the future. There are no concerns regarding residual monomers in PPGs. Were the "n" in PPG-n to be 32, for example, ample evidence suggests that its toxicity would be no different from PPG-30 or PPG-33. Were the "n" to be 120, the ingredient would be sufficiently large so that no dermal penetration would be possible.

SUMMARY

This is an amended safety assessment of 38 polyether lanolins as used in cosmetics. These include PPG- and PEG-lanolin ingredients. Since there was little data on the PPG- and PEG-lanolins, data from safety assessments on PPG, PEG, PG, and lanolins were relied on. These ingredients function mostly as hair conditioning agents, skin-conditioning agent-emollients, and surfactant-emulsifying agents.

PPG-5 lanolin wax was reported to be used in 3 lipsticks and to be used in leave-on cosmetic products at up to4% and in rinse off-products at up to 3%. PEG-20 hydrogenated lanolin was reported to be used in 17 hair products; leave-on products up to 5% and rinse-off products up to 1%. PEG-20 hydrogenated lanolin was reported to be used in 17 noncoloring hair products at up to 5%. PEG-24 hydrogenated lanolin was reported to be used in 1 hair conditioner; the Council reports use in hair dyes and colors at 0.2% and in skin care preparations at 0.3%. PEG-30 lanolin was reported to be used in 2 leave-

on products at 0.05%. PEG-40 lanolin was reported to be used in 8 leave-on hair care products and in body and hand creams at 0.25%. PEG-60 lanolin was reported to be used in 28 products, leave-on products up to 2% and rinse-off products up to 1%. PEG-75 lanolin was reported to be used in 168 products, leave-on products up to 2% and rinse-off products up to 15%. PPG-12-PEG-50 lanolin was reported to be used in 44 products, leave-on products up to 2% and rinse-off products up to 8%. PPG-12-PEG-65 lanolin oil was reported to be used in 11 products, leave-on products up to 0.1% and rinse-off products up to 0.4%.

The VCRP reported that PEG-5 lanolin was used in 3 rinse-off products. PEG-50 was reported to be used in 3 rinse-off products. PEG-85 lanolin was reported to be used in 1 rinse-off product. PEG-100 was reported to be used in 1 rinse-off product. PEG-75 lanolin oil was reported to be used in 3 leave-on and 6 rinse-off products.

There were no uses reported for PPG-5 lanolin wax glyceride, PEG-75 lanolin wax, PEG-5 hydrogenated lanolin, PEG-10 hydrogenated lanolin, PEG-15 hydrogenated lanolin, PEG-30 hydrogenated lanolin, PEG-40 hydrogenated lanolin, PEG-70 hydrogenated lanolin, PEG-5 lanolin, PEG-10 lanolin, PEG-20 lanolin, PEG-24 lanolin, PEG-27 lanolin, PEG-35 lanolin, PEG-55 lanolin, PEG-70 lanolin, PEG-100 lanolin, PEG-150 lanolin, polyglyceryl-2 lanolin alcohol ether, PPG-2 lanolin alcohol ether, PPG-5 lanolin alcohol ether, PPG-10 lanolin alcohol ether, PPG-20 lanolin alcohol ether, PPG-30 lanolin alcohol ether, PPG-20 PEG-20 hydrogenated lanolin, and PPG-40 PEG-60 lanolin oil.

Since there are almost no new data, this report summarizes previous reviews of the lanolin; PPG-5 lanolin wax and PPG-5 lanolin wax glyceride; PEG lanolin; dipropylene glycol; and alkyl PEG ethers as well as information from the special report on the reproductive and developmental toxicity of ethylene glycol. All of these cosmetic ingredients were found to be safe, but with an added proviso for the alkyl PEG ethers, which were asserted to be safe when formulated to be non-irritating.

This report also included limited new data. In one study, when PPG-2, -5, -10, and -20 lanolin alcohols (0, 1, 2.5, 5, 10, 15, 20 μg/ml) were added to a petrolatum-liquid paraffin eye ointment, the release rate and the antimicrobial activity of chloramphenicol and tetracycline were increased. In another study, PEG lanolin (length of PEG unknown) was reported to be "slightly dermally irritating" at 100% in one sample, and not irritating in another. These same samples were also reported to be slight ocular irritants.

DISCUSSION

Although there are data gaps for the polyether lanolin ingredients, the similar chemical structures, physicochemical properties, and functions and concentrations in cosmetics allow grouping these ingredients with other related ingredients and extending the available toxicological data available on any of the related ingredients to support the safety of the entire group.

In particular, data are available for acute and repeated dose toxicity, irritation, and sensitization for PEG-75 lanolin (the ingredient with the most uses in this safety assessment). For lanolin itself, toxicokinetics, acute and repeated dose toxicity, irritation, and sensitization, reproductive and developmental toxicity, genotoxicity, and phototoxicity data are available. For alkyl PEG ethers, toxicokinetics, acute and repeated dose toxicity, irritation and sensitization, reproductive and developmental toxicity, genotoxicity and carcinogenicity data are available. For dipropylene glycol (aka PPG-2), toxicokinetics, acute and repeated dose toxicity, and irritation and sensitization data are available. For PGs, data are available for toxicokinetics, acute and repeated dose toxicity, reproductive and developmental toxicity, genotoxicity, and irritation. All were safe for use in cosmetics.

The Panel did acknowledge that a safety assessment of diethylene glycol (aka PEG-2) has not been completed. In its safety assessment of the PEGs group of ingredients, however, it was noted that PEG-4 is actually a mixture that includes PEG-2, and the Panel concluded that PEG-3 and all PEGs ≥4 were safe in the present practices of use and concentration.

A wide range of alkyl ethers of polyethylene glycols have been assessed by the Panel as presenting little or no potential toxicity. The Panel concluded that the likelihood of these polyether ingredients being metabolized to reproductive or developmental toxins was very low.[6]

The Panel concluded, based on the structure of each polyether lanolin reviewed, that none of these ingredients was likely to be mutagenic or carcinogenic.

Because these ingredients was/were reported to be used in products that may be aerosolized, including colognes and toilet waters; powders; and body and hand creams, lotions, and powders, the Panel discussed the issue of incidental inhalation exposure. The limited data available from one short-term exposure study on PEG-27 lanolin suggest little potential for respiratory effects at relevant doses. Although particles appear to have reached the lungs in these animal studies, the sizes of the particles used were either clearly within the respirable range (i.e., ≤10 μm) or were not reported. The Panel believes that the sizes of a substantial majority of the particles in these ingredients, as manufactured, are larger than those in the respirable range and/or aggregate and agglomerate to form much larger particles in formulation. Thus, the adverse effects reported using high doses of respirable particles in the inhalation studies do not indicate risks posed by use in cosmetics. The Panel considered other data available to characterize the potential for polyether lanolins to cause systemic toxicity, irritation, sensitization, or other effects through the examination of the safety of the components. They noted the lack of systemic toxicity at high doses in several acute and repeated dose dermal and oral exposure studies. There was little or no irritation or sensitization in multiple tests of dermal and ocular exposure, as was the absence of genotoxicity in multiple tests. Further, these ingredients are reportedly used at concentrations a maximum concentration of ≤4% in cosmetic products that may be aerosolized. The Panel noted that 95% – 99% of droplets/particles produced in cosmetic aerosols would not be respirable to

any appreciable amount. However, the potential for inhalation toxicity is not limited to respirable droplets/particles deposited in the lungs. Inhaled droplets/particles deposited in the nasopharyngeal and thoracic regions of the respiratory tract may cause toxic effects depending on their chemical and other properties. 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.

CONCLUSION

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

- PPG-5 lanolin wax
- PPG-5 lanolin wax glyceride*
- PEG-75 lanolin wax*
- PEG-5 hydrogenated lanolin*
- PEG-10 hydrogenated lanolin*
- PEG-15 hydrogenated lanolin *
- PEG-20 hydrogenated lanolin
- PEG-24 hydrogenated lanolin
- PEG-30 hydrogenated lanolin *
- PEG-40 hydrogenated lanolin *
- PEG-70 hydrogenated lanolin *
- PEG-5 lanolin
- PEG-10 lanolin*
- PEG-20 lanolin*
- PEG-24 lanolin*
- PEG-27 lanolin*
- PEG-25 lanolin*
- PEG-30 lanolin
- PEG-35 lanolin*
- PEG-40 lanolin
- PEG-50 lanolin
- PEG-55 lanolin*
- PEG-60 lanolin
- PEG-70 lanolin*
- PEG-75 lanolin
- PEG-85 lanolin
- PEG-100 lanolin
- PEG-150 lanolin*
- PEG-75 lanolin oil
- Polyglyceryl-2 lanolin alcohol ether*
- PPG-2 lanolin alcohol ether*
- PPG-5 lanolin alcohol ether*
- PPG-10 lanolin alcohol ether*
- PPG-20 lanolin alcohol ether*
- PPG-30 lanolin alcohol ether*
- PPG-20-PEG-20 hydrogenated lanolin*
- PPG-12-PEG-50 lanolin
- PPG-12-PEG-65 lanolin oil
- PPG-40-PEG-60 lanolin oil*

*Not 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. Definition and function of the PEG- and PPG-lanolin ingredients in this safety assessment.[107]

Ingredient CAS No.	Definition	Function
PEG-75 lanolin wax 71990-24-4 (generic for PEG-lanolin waxes)	PEG-75 lanolin wax is a polyethylene glycol derivative of lanolin wax with an average of 75 moles of ethylene oxide.	Surfactant-emulsifying agent; surfactant-solubilizing agent
PEG-5 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-5 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 5 moles of ethylene oxide.	Hair conditioning agent; skin-conditioning agent-emollient; surfactant-emulsifying agent
PEG-10 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-10 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 10 moles of ethylene oxide.	Hair conditioning agent; skin-conditioning agent-emollient; surfactant-emulsifying agent
PEG-15 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-15 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 15 moles of ethylene oxide	Hair conditioning agent; surfactant-emulsifying agent
PEG-20 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-20 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 20 moles of ethylene oxide.	Hair conditioning agent; surfactant-emulsifying agent
PEG-24 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-24 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 24 moles of ethylene oxide.	Hair conditioning agent; surfactant-emulsifying agent
PEG-30 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-30 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 30 moles of ethylene oxide.	Hair conditioning agent; surfactant-cleansing agent; surfactant-solubilizing agent
PEG-40 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-40 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 40 moles of ethylene oxide.	Hair conditioning agent; surfactant-emulsifying agent
PEG-70 hydrogenated lanolin 68648-27-1 (generic for PEG-hydrogenated lanolins)	PEG-70 hydrogenated lanolin is a polyethylene glycol derivative of hydrogenated lanolin with an average of 70 moles of ethylene oxide.	Hair conditioning agent; surfactant-cleansing agent; surfactant-solubilizing agent
PEG-5 lanolin 61790-81-6 (generic)	PEG-5 lanolin is a polyethylene glycol derivative of lanolin with an average of 5 moles of ethylene oxide.	Surfactant-emulsifying agent
PEG-10 lanolin 61790-81-6 (generic)	PEG-10 lanolin is a polyethylene glycol derivative of lanolin with an average of 10 moles of ethylene oxide.	Surfactant-emulsifying agent
PEG-20 lanolin 61790-81-6 (generic)	PEG-20 lanolin is a polyethylene glycol derivative of lanolin with an average of 20 moles of ethylene oxide.	Surfactant-emulsifying agent
PEG-24 lanolin 61790-81-6 (generic)	PEG-24 lanolin is a polyethylene glycol derivative of lanolin with an average of 24 moles of ethylene oxide.	Surfactant-emulsifying agent
PEG-25 lanolin[1] 61790-81-6 (generic)	PEG-25 lanolin is a polyethylene glycol derivative of lanolin with an average of 25 moles of ethylene oxide.	
PEG-27 lanolin 8051-81-8 61790-81-6 (generic)	PEG-27 lanolin is a polyethylene glycol derivative of lanolin with an average of 27 moles of ethylene oxide.	Surfactant-emulsifying agent; surfactant-solubilizing agent
PEG-30 lanolin 61790-81-6 (generic)	PEG-30 lanolin is a polyethylene glycol derivative of lanolin with an average of 30 moles of ethylene oxide.	Surfactant-emulsifying agent; surfactant-solubilizing agent
PEG-35 lanolin 61790-81-6 (generic)	PEG-35 lanolin is the polyethylene glycol derivative of lanolin with an average of 35 moles of ethylene oxide.	Surfactant-cleansing agent; surfactant-solubilizing agent
PEG-40 lanolin 8051-82-9 61790-81-6 (generic)	PEG-40 lanolin is a polyethylene glycol derivative of lanolin with an average of 40 moles of ethylene oxide.	Surfactant-cleansing agent; surfactant-emulsifying agent; surfactant-solubilizing agent
PEG-50 lanolin 61790-81-6 (generic)	PEG-50 lanolin is a polyethylene glycol derivative of lanolin with an average of 50 moles of ethylene oxide.	Surfactant-cleansing agent; surfactant-solubilizing agent
PEG-55 lanolin 61790-81-6 (generic)	PEG-55 lanolin is the polyethylene glycol derivative of lanolin with an average of 55 moles of ethylene oxide.	Surfactant-cleansing agent; surfactant-solubilizing agent
PEG-60 lanolin 61790-81-6 (generic)	PEG-60 lanolin is a polyethylene glycol derivative of lanolin with an average of 60 moles of ethylene oxide.	Surfactant-cleansing agent
PEG-70 lanolin 61790-81-6 (generic)	PEG-70 lanolin is a polyethylene glycol derivative of lanolin with an average of 70 moles of ethylene oxide.	Surfactant-cleansing agent
PEG-75 lanolin 8039-09-6 61790-81-6 (generic)	PEG-75 lanolin is a polyethylene glycol derivative of lanolin with an average of 75 moles of ethylene oxide.	Surfactant-cleansing agent
PEG-85 lanolin 61790-81-6 (generic)	PEG-85 lanolin is a polyethylene glycol derivative of lanolin with an average of 85 moles of ethylene oxide.	Surfactant-cleansing agent
PEG-100 lanolin 61790-81-6 (generic)	PEG-100 lanolin is a polyethylene glycol derivative of lanolin with an average of 100 moles of ethylene oxide.	Surfactant-cleansing agent
PEG-150 lanolin 61790-81-6 (generic)	PEG-150 lanolin is a polyethylene glycol derivative of lanolin with an average of 150 moles of ethylene oxide.	Surfactant-cleansing agent
PEG-75 lanolin oil 68648-38-4 (generic)	PEG-75 lanolin oil is a polyethylene glycol derivative of lanolin oil with an average of 75 moles of ethylene oxide.	Surfactant-cleansing agent; surfactant-solubilizing agent
Polyglyceryl-2 lanolin alcohol	Polyglyceryl-2 lanolin alcohol ether is an ether of lanolin	Skin-conditioning agent-

Table 1. Definition and function of the PEG- and PPG-lanolin ingredients in this safety assessment.[107]

Ingredient CAS No.	Definition	Function
ether	alcohol and diglycerin.	emollient; surfactant-emulsifying agent
PPG-2 lanolin alcohol ether 68439-53-2 (generic)	PPG-2 lanolin alcohol ether is the polypropylene glycol ether of lanolin alcohol with an average propoxylation value of 2.	Hair conditioning agent; skin-conditioning agent-emollient
PPG-5 lanolin alcohol ether 68439-53-2 (generic)	PPG-5 lanolin alcohol ether is the polypropylene glycol ether of lanolin alcohol with an average propoxylation value of 5.	Hair conditioning agent; skin-conditioning agent-emollient
PPG-10 lanolin alcohol ether 68439-53-2 (generic)	PPG-10 lanolin alcohol ether is the polypropylene glycol ether of lanolin alcohol with an average propoxylation value of 10.	Hair conditioning agent; skin-conditioning agent-emollient
PPG-20 lanolin alcohol ether 68439-53-2 (generic)	PPG-20 lanolin alcohol ether is the polypropylene glycol ether of lanolin alcohol with an average propoxylation value of 20.	Hair conditioning agent; skin-conditioning agent-emollient
PPG-30 lanolin alcohol ether 68439-53-2 (generic)	PPG-30 lanolin alcohol ether is the polypropylene glycol ether of lanolin alcohol with an average propoxylation value of 30.	Hair conditioning agent; skin-conditioning agent-emollient
PPG-20-PEG-20 hydrogenated lanolin	PPG-20-PEG-20 hydrogenated lanolin is the polyoxypropylene, polyoxyethylene derivative of hydrogenated lanolin with an average propoxylation value of 20 and an average ethoxylation value of 20.	Hair conditioning agent; skin-conditioning agent-emollient; surfactants-emulsifying agent
PPG-12-PEG-50 lanolin 68458-88-8 [generic]	PPG-12-PEG-50 lanolin is the polyoxypropylene, polyoxyethylene derivative of lanolin with an average propoxylation value of 12 and an average ethoxylation value of 50.	Hair conditioning agent; surfactants-emulsifying agent
PPG-12-PEG-65 lanolin oil 156715-46-7 (generic to PPG-X-PEG-X lanolin oil)	PPG-12-PEG-65 lanolin oil is the polyoxypropylene, polyoxyethylene derivative of lanolin oil with an average propoxylation value of 12 and an average ethoxylation value of 65.	Hair conditioning agent; surfactants-emulsifying agent
PPG-40-PEG-60 lanolin oil 156715-46-7 (generic to PPG-X-PEG-X lanolin oil)	PPG-40-PEG-60 lanolin oil is the polyoxypropylene, polyoxyethylene derivative of lanolin oil with an average propoxylation value of 40 and an average ethoxylation value of 60.	Hair conditioning agent; skin-conditioning agent-emollient; surfactants-emulsifying agent
PPG-5 lanolin wax 71990-25-5 (generic to PPG-X lanolin wax)	PPG-5 lanolin wax is a polypropylene glycol derivative of lanolin wax with an average propoxylation value of 5.	Skin-conditioning agent-emollient
PPG-5 lanolin wax glyceride	PPG-5 lanolin wax glyceride is the polypropylene glycol ether of the condensation product of lanolin wax and glycerin with an average propoxylation value of 5.	Skin-conditioning agent-emollient

[1] PEG-25 lanolin was included in the 1999 report but is currently not listed in the Council's database. A survey of use is being conducted.

Table 2. Previous review status of PEG and PPG lanolins and components.

Ingredients	Conclusion	Concentration range	Year
PPG-5 Lanolin wax; PPG-5 lanolin wax glyceride	Safe as used in cosmetics	0.1%-50%	1997[1]
PEG Lanolin (PEG-20, 27, 30, 40, 50, 60, 75, 85)	Safe as presently used in cosmetic products	≤0.1%-25%	1982[2]
PEG Lanolin (PEG-20, 27, 30, 40, 50, 60, 85) adding more PEG lanolins (PEG-5, 10, 24, 25, 35, 50, 55, 60, 75, 85, 100, 150) and hydrogenated PEG lanolins (PEG-5, 10, 20, 24, 30, 70)	Safe for use in cosmetic formulation under the present practices of use	0.30%-5%	1999[3]
Special report of PEG-derived ingredients including: Ceteth-1. -2, -3, -4, -5, -6, -10, -12, -14, -15, -16, -20, -24, -25, -30, and -45 Oleth-2, -3, -4, -5, -6, -7, -8, -9, -10, -12, -15, -16, -20, -23, -25, -30, -40, -44, and -50 PEG-2, -3, -5, -10, -15, and -20 cocamine PEG-7, -3, -4, -8, -9, -12, -20, -32, -75, -120, -150, and -175 distearate PEG-7, -30, -40, -78, -80 glyceryl cocoate PEG-5, -10, -20, -24, -25, -27, -30, -35, -40, -50, -55, -60, -75, -85, and -100 lanolin; PEG-5, -10, -20, -24, -30, and -70 hydrogenated lanolin; PEG-75 lanolin oil; and PEG-75 lanolin wax PEG-5, -10, -16, -25, and -40 soy sterol	Metabolites of some ethylene glycol monoalkyl ethers are reproductive and developmental toxins. In general, these metabolites of concern are not expected to be formed in cosmetic formulations that contain polymers of ethylene glycol.	N/A	1999[3,6], 2004[5], 2010[9]
Lanolin, lanolin oil, lanolin wax, lanolin acid, lanolin alcohol, acetylated lanolin, acetylated lanolin alcohol, hydrogenated lanolin, hydroxylated lanolin	Safe for topical application in the present practices of use and concentration	≤0.1%-50% 0.5%-25%	1980, 2005[7,8]
Butylene glycol, hexylene glycol, ethoxydiglycol, dipropylene glycol	Safe for topical application in the present practices of use and concentration	≤0.01%->50% 0.004%-50%	1985, 2006[4,5]
Alkyl PEG ethers	Safe as used in cosmetics when formulated to be non-irritating	0.0002%-21%	2010[9]

Table 2. Previous review status of PEG and PPG lanolins and components.

Ingredients	Conclusion	Concentration range	Year
PPGs (PPG-3, 7, 9, 12, 13, 15, 16, 17, 20, 26, 30, 33, 34, 51, 52, 69)	PPGs ≥3 are safe as used in cosmetic formulations when formulated to be non-irritating	0.00004%-99%	2010[11]
PEG-75 Lanolin Wax, PEG 75 lanolin oil, polyglyceryl-2 lanolin alcohol ether, PPG-2 lanolin alcohol ether, PPG-5 lanolin alcohol ether, PPG-10 lanolin alcohol ether, PPG-20 lanolin alcohol ether, PPG-30 lanolin alcohol ether, PPG-20-PEG-20 hydrogenated lanolin, PPG-12-PEG-50 lanolin, PPG-12-PEG-65 lanolin oil, and PPG-40-PEG60 lanolin oil	Not reviewed	N/A	N/A

Table 3. Typical compositions of whole lanolin, lanolin wax, and lanolin oil.[14]

Group	Whole lanolin (%)	Lanolin wax (%)	Lanolin oil (%)
Esters of sterols and triterpene alcohols	35.4	28.9	44.0
Esters of aliphatic alcohols	23.7	13.9	16.0
Monohydroxyestes of sterols and of triterpene and aliphatic alcohols	20.0	16.4	15.0
Di- and polyhydroxyestrs of free diols	7.9	9.3	7.7
Free aliphatic alcohols	5.6	20.2	10.4
Free sterols	4.1	5.3	4.4
Free hydrocarbons	0.6	0.4	0.3
Free fatty acids	0.5	1.0	0.7
Unknowns	2.2	4.6	1.5
Total	100.0	100.0	100.0

Table 3. Frequency and concentration of use according to duration and exposure type of polyether lanolins.[21,22]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PPG-5 lanolin wax		PEG-20 hydrogenated lanolin		PEG-24 hydrogenated lanolin		PEG-5 lanolin	
Total/range	**3**	**2-4**	**17**	**1-5**	**1**	**0.2-0.3**	**3**	NR
Duration of use								
Leave-on	3	2-4	7	5	NR	0.3		
Rinse-off	NR	2-3	10	1	1	0.2	3	NR
Diluted for (bath) use	NR	3	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	2-4	NR	NR	NR	NR	NR	NR
Incidental ingestion	3	4	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	NR	2[1]	NR	NR	NR	NR	NR	NR
Incidental inhalation-powders	NR	4	NR	NR	NR	NR	NR	NR
Dermal contact	NR	2-4[2]	NR	NR	NR	0.3	NR	NR
Deodorant (underarm)	NR	3[3]	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	3	17	1-5	1		NR	NR
Hair-coloring	NR	NR	NR	NR	NR	0.2	3	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	3	2-4	NR	NR	NR	NR	NR	NR
Baby	NR	NR	NR	NR	NR	NR	NR	NR

Table 3. Frequency and concentration of use according to duration and exposure type of polyether lanolins.[21,22]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PEG-30 lanolin		**PEG-40 lanolin**		**PEG-50 lanolin**		**PEG-60 lanolin**	
Total/range	**2**	**0.5**	**8**	**0.25**	**3**	NR	**3**	**0.4-2**
Duration of use								
Leave-on	2	0.5	8	0.25	NR	NR	3	0.4-2
Rinse-off	NR	NR	NR	NR	NR	NR	25	0.05-1
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	NR	NR	NR	NR	NR	NR	2	0.4-2
Incidental ingestion	NR	NR	NR	NR	NR	NR	NR	0.4
Incidental Inhalation-sprays	NR	NR	NR	NR	NR	NR	NR	NR
Incidental inhalation-powders	NR	NR	NR	NR	NR	NR	NR	NR
Dermal contact	2	0.5	NR	0.25	1	NR	2	0.05-2
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	NR	NR	8	NR	2	NR	25	1
Hair-coloring	NR	NR	NR	NR	NR	NR	1	NR
Nail	NR	NR	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	NR	NR	NR	NR	NR	NR	0.4
Baby	NR	NR	NR	NR	NR	NR	NR	NR

	PEG-75 Lanolin		**PEG-85 lanolin**		**PEG-100 lanolin**		**PEG-75 lanolin oil**	
Total/range	**168**	**0.001-15**	**3**	NR	**1**		**9**	NR
Duration of use								
Leave-on	84	0.001-2	3	NR			3	NR
Rinse-off	84	0.02-15	NR	NR	1		6	NR
Diluted for (bath) use	NR	NR	NR	NR	NR	NR	NR	NR
Exposure type								
Eye area	1	0.6	NR	NR	NR	NR	NR	NR
Incidental ingestion	NR	0.8	NR	NR	NR	NR	NR	NR
Incidental Inhalation-sprays	35	0.001-0.3	NR	NR	NR	NR	1	NR
Incidental inhalation-powders	NR	0.8	NR	NR	NR	NR	NR	NR
Dermal contact	116	0.001-5	NR	NR	NR	NR	2	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR	NR	NR
Hair-noncoloring	143	0.05-15	NR	NR	1	NR	6	NR
Hair-coloring	9	0.3	NR	NR	NR	NR		NR
Nail	NR	0.1-0.3	NR	NR	NR	NR	1	NR
Mucous Membrane	8	0.001-2	3	NR	NR	NR	2	NR
Baby	NR	0.05-0.8	NR	NR	NR	NR	NR	NR

Table 3. Frequency and concentration of use according to duration and exposure type of polyether lanolins.[21,22]

Use type	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)	Uses	Maximum Concentration (%)
	PPG-12-PEG-50 lanolin		PPG-12-PEG-65 lanolin oil					
Total/range	**44**	**0.2-8**	**11**	**0.002-04**				
Duration of use								
Leave-on	25	0.3-2	7	0.1				
Rinse-off	19	0.2-8	4	0.002-0.4				
Diluted for (bath) use	NR	NR	NR	NR				
Exposure type								
Eye area	NR	NR	NR	NR				
Incidental ingestion	NR	NR	NR	NR				
Incidental Inhalation-sprays	6	NR	1	NR				
Incidental inhalation-powders	NR	NR	NR	NR				
Dermal contact	1	0.8-3	2	0.4				
Deodorant (underarm)	NR	NR	NR	NR				
Hair-noncoloring	40	0.3-8	9	0.1				
Hair-coloring	1		NR					
Nail	2	0.2	NR	0.002				
Mucous Membrane	NR	3	NR	NR				
Baby	NR	NR	NR	NR				

NR = Not Reported; 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.

[1] May or may not be a spray.

[2] Skin cleansing creams/lotions/liquids/pads and face and neck creams/lotions/powders are not sprays.

[3] Aerosol hair sprays at 0.07%-0.2%.

Table 5. Acute oral toxicity of various PEG lanolins.

Lanolin	Concentration (%)	Dosage	Animal	n	Acute oral LD_{50}	Comments	Reference
PEG-20	30	15.9 g/kg	Rat	10/sex	>15.9 g/kg	One death-no data	[108]
PEG-27	100	5.0 ml/kg	Rat	5/sex	>5.0 cc/kg	-	[109]
PEG-40	100	2.0-32 g/kg	Rat	5	18.5 g/kg	Lethargy with impaired locomotion, diarrhea, unkempt coats at 16 and 20 g/kg. Coma preceded death at 25 and 32 g/kg.	[110]
PEG-40	50	2.0-32 g/kg	Rat	5	20.6 g/kg	-	[110]
PEG-50	30	15.9 g/kg	Rat	10 f	>15.9g/kg	-	[111]
PEG-75	100	2.5-40 g/kg	Rat	2	~30 g/kg	-	[112]
PEG-75	100	0.7-21.3 g/kg	Rat	5	>21/3 g/kg	Diarrhea and unkempt coats at 10.7 and 21.3 g/kg	[113]
PEG-75	100	50 and 100 ml/kg	Mouse	5, 10	>100 cc/kg	-	[114]
PEG-75	50	8-64 ml/kg	Rat	5	54 cc/kg	Where death occurred, debility was slow. Dad animals with nasal hemorrhage and oozing urine.	[113]
PEG-75	50	0.46-10 ml/kg	Rat	5 m	>10 cc/kg	-	[115]
PEG-75	50	20 g/kg	Rat	5 m	>20 g/kg	Congested renal tubules in 11 test animals	[112]
PEG-75	25	0-16 g/kg	Rat	5/sex	>16 g/kg	Pilo-erection, lethargy, diarrhea, and matted fur in test animals	[116]
PEG-85	100	1.0-32 g/kg	Rat	5	>32 g/kg	-	[117]

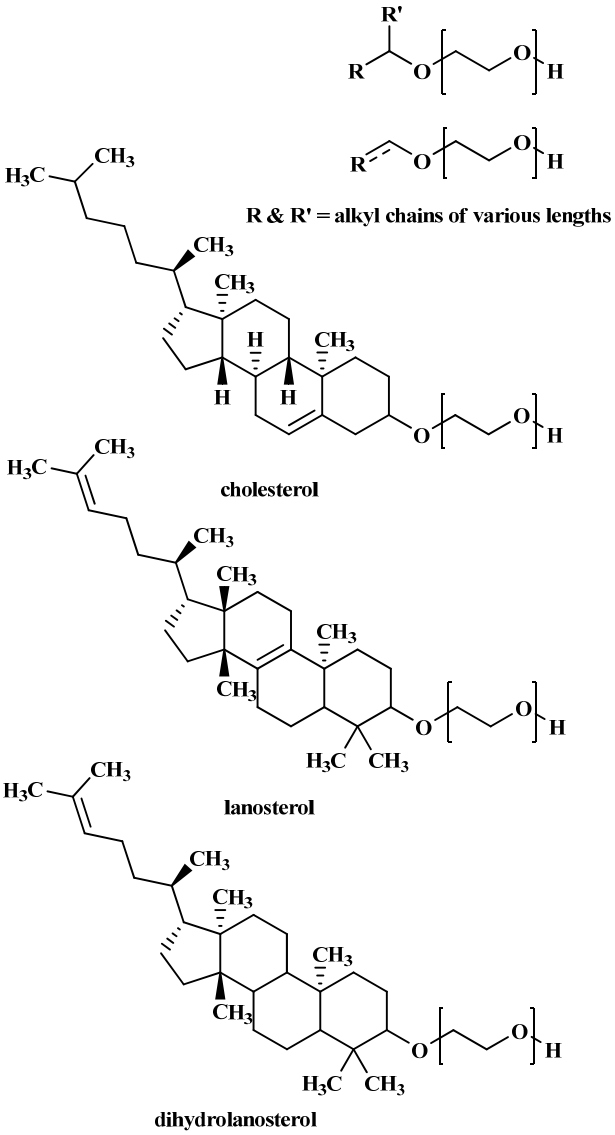

Figure 1. Some of the potential products of lanolin ethoxylation.

REFERENCES

1. Andersen FA eds. Final report on the safety assessment of PPG-5 lanolin wax and PPG-5 lanolin wax glyceride. *International Journal of Toxicology*. 1997;16(3):307-315.

2. Elder RL eds. Final report of the safety assessment for PEG-75 lanolin, PEG-20 lanolin, PEG-27 lanolin, PEG-30 lanolin, PEG-40 lanolin, PEG-50 lanolin, PEG-60 lanolin, and PEG-85 lanolin. *Journal of the American College of Toxicology*. 1982;1(4):91-102.

3. Andersen FA (ed). Addendum to the final report on the safety assessment of PEGs lanolin to include PEG-5, -10, -24, -25, -35, -55, -100, and -150 lanolin; PEG-5, -10, -20, 24, -30, and -70 hydrogenated lanolin; PEG-75 lanolin oil; and PEG-75 lanolin wax. *International Journal of Toxicology*. 1999;18(Suppl. 1):61-68.

4. Andersen FA. Assessment of butylene glycol, hexylene glycol, ethoxydiglycol, and dipropylene glycol. *Journal of the American College of Toxicology*. 1985;4(5):223-248.

5. Annual review of cosmetic ingredient safety assessments -- 2004/2005. *International Journal of Toxicology*. 2006;25(Suppl. 2):1-89.

6. Andersen FA. Special Report: Reproductive and developmental toxicity of ethylene glycol and its ethers. *International Journal of Toxicology*. 1999;18(Suppl. 2):53-67.

7. Andersen FA eds. Annual review of cosmetic ingredients safety assessments - 2002/2003. *International Journal of Toxicology*. 2005;24(Suppl. 1):1-102.

8. Elder RL ed. Final report of the safety assessment for acetylated lanolin alcohol and related compounds. *Journal of Environmental Pathology and Toxicology*. 1980;4(4):63-92.

9. Fiume MM, Bergfeld WF, Belsito DV, Klaassen CD, Liebler DC, Hill RA, Marks Jr JG, Shank RC, Slaga TJ, Snyder PW, and Andersen FA. Alkyl PEG ethers as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2010. pp. 1-99.

10. Elder RL ed. Final report on the safety assessment of laneth- 10 acetate group. *International Journal of Toxicology*. 1982;1(4):1-23.

11. Fiume MM, Bergfeld WF, Belsito DL, Hill RA, Klaassen CD, Liebler DC, Marks Jr JG, Shank RC, Slaga TJ, and Snyder PW. Safety assessment of propylene glycol, tripropylene glycol, and PPGs as used in cosmetics. Washington, DC, Cosmetic Ingredient Review. 2010. pp. 1-31.

12. Andersen FA (ed). Final report on the safety assessment of polyethylene glycols (PEGs) -6,-8, -32, -75,-150, -14M, -20M. *Journal of the American College of Toxicology*. 1993;12:429-457.

13. Schlossman ML and McCarthy JP. Lanolin and its derivatives. AOCS Meeting: Fats in Cosmetics. 1977. New York.

14. Chemtob C, Fawaz F, and Puisieux F. Analysis of ointments, oils, and waxes. XIX. Study of the chemical composition of liquid lanolin. 2. Study of alcohols. *Annales Pharmaceutiques Francaises*. 1975;33(2):109-118.

15. Fawaz F, Miet C, and Puisieux F. Analysis of ointments, oils, and waxes. XII. Study of the chemical composition of wool fat (lanolin). I. Preliminary examination and fractionation of a sample. *Annales Pharmaceutiques Francaises*. 1973;31(1):63-72.

16. Robinson JJ and Ciurczak EW. Direct gas chromatographic determination of 1,4-dioxane in ethoxylated surfactants. *Journal of the Society of Cosmetic Chemistry*. 1980;31:329-337.

17. Cosmetic, Toiletry, and Fragrance Association. 1979. Submission of data from CTFA for PEG-75 Lanolin and related compounds. CTFA cosmetic ingredient chemical descriptions.

18. Silverstein BD, Furcinitti PS, Cameron WA, Brower JE, and White Jr O. Biological effects summary report-Polyethylene glycol. *Government Reports Announcements & Index*. 1984;15(NTIS No. DE84007984).

19. hamburger R, Azaz E, and Donbrow M. Autoxidantion of polyoxyethylenic non-ionic surfactants and of polyethylene glycols. *Pharmaceutica Acta Helvetiae*. 1975;50:10-17.

20. McGinity JW, Hill JA, and La Via AL. Influence of peroxide impurites in polyethylene glycols on drug stability. *Journal of Pharmaceutical Sciences*. 1975;64:356-357.

21. US Food and Drug Administration (FDA). Frequency of use of cosmetic ingredients. *FDA Database*. 2012. Washington, DC: FDA.

22. Personal Care Products Council. 4-24-2012. Concentration of Use by FDA product category: PPG and PEG Lanolin Ingredients. Unpublished data submitted by Personal Care Products Council. 5 pages.

23. Scientific Committee on Consumer Products. Opinion on polidocanol (laureth-9). http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_113.pdf. Date Accessed 5-13-2010.

24. Zhou, M. and Donovan, M. D. Recovery of the nasal mucosa following laureth 9 induced damage. *Int.J.Pharm.* 1996;130:93-102.

25. El Sayed AA and Mohamed MS. Influence of lanoline alcohol propoxylates on the release of drugs from a lipophilic ointment base and their antimicrobial action. *Egyptian Journal of Pharmaceutical Sciences*. 1979;20(1-4):185-192.

26. Rosner Hixson Laboratories. 1964. Primary eye and skin irritation, sensitization and subacute dermal toxicity. Unpublished RITA Chemical Company data submitted by CTFA. 7 pages.

27. Cosmetic, Toiletry, and Fragrance Association. CIR safety data test summary. Product containing dipropylene glycol. 1977. Data from Dipropylene Glycol 1985 report. Report No. CTFA Code 2-17-166. Unpublished data submitted by CTFA.

28. Dow Chemical Co. Initial submission: Letter regarding an oral gavage study in rats dated 041993. 1993. Report No. DOCNO- TSCATS/424506.

29. Andersen, F. A. Final report on the safety assessment of propylene glycol and polypropylene glycols. *J Am Coll Toxicol*. 1994;13(6):437-491.

30. Dow Chemical Co. Determintatin of the acute oral toxicity of dipropylene glycol in rats with cover letter dated 032894 (sanitized). 1994. http://cfpub.epa.gov/ols/catalog/catalog_display.cfm?&FIELD1=SUBJECT&INPUT1=Dipropylene%20glycol&TYPE1=EXACT&item_count=8. Report No. EPA/OTS Doc #86940000276S.

31. Mellon Institute. Letter from Union Carbide Corp to USEPA regarding toxicity studies of various chemicals referenced in 40 CFR part 716, 58 FED REG 68311-68322 (1227/93) w/attachments dated 04294. 1994. Report No. EPA/OTS Doc #86940001887.

32. National Institute for Occupational Safety and Health (NIOSH). Toxic Substances List. Washington, DC, US Government Printing Office. 1981. From the Dipropylene Glycol 1985 report.

33. Environmental Health Research and Testing. Propylene glycol: Reproduction and fertility assessment in CD-1 mice when administered in drinking water. (Revised Sept 1985.). *NTIS No.PB86140662*. 1985.

34. Smyth Jr HF, Carpenter CP, and SHAFFER CB. The toxicity of high molecular weight polyethylene glycols; chronic oral and parenteral administration. *Journal of the American Pharmaceutical Association Science Edition*. 1947;36(5):157-160.

35. Smyth Jr HF, Carpenter CP, SHAFFER CB, and Fischer L. Some pharmacological properties of polyethylene glycols of high molecular weight ("Carbowax" compounds). *Journal of Industrial Hygiene and Toxicology*. 1942;24:281-284.

36. Gingell, R. and Lu, C. C. Acute, subchronic, and reproductive toxicity of a linear alcohol ethoxylate surfactant in the rat. *J Am Coll Toxicol*. 1991;10(4):477-486.

37. Bates HK, Price CJ, Marr MC, Myers CB, and Heindel JJ. Final report on the developmental toxicity of dipropylene glycol (CAS No. 25265-71-8) in Sprague-Dawley rats. 1992. Report No. NTIS/PB92-196179.

38. Bates HK, Price CJ, Marr MC, Myers CB, and Heindel JJ. Final report onthe developmental toxicity of dipropylene glycol in New Zealand White rabbits. 1992. Report No. NTIS/PB92-196179.

39. Organisation of Economic Co-operation and Development. SIDS Intial Assessment Report for SIAM 4. 2-(2-(2-Methoxyethoxy)-ethanol. CAS NO. 112-35-6. (PEG-3 Methyl Ether). http://www.chem.unep.ch/irptc/sids/OECDSIDS/112356.pdf. Date Accessed 10-26-2010.

40. Gingell, R. and Lu, C. C. Acute, subchronic, and reproductive toxicity of a linear alcohol ethoxylate surfactant in the rat. *J Am Coll Toxicol*. 1991;10(4):477-486.

41. Hermansky, S. J. and Leung, H. W. Cutaneous toxicity studies with methoxy polyethylene glycol-350 (MPEG-350) in rats and rabbits. *Food Chem Toxicol*. 1997;35:1031-1039.

42. Loveday, K. S., Anderson, B. E., Resnick, M. A., and Zeiger, E. Chromosome aberration and sister chromatid exchange tests in Chinese hamster ovary cells in vitro. V: Results with 46 chemicals. *Environ Mol Mutagen*. 1990;16:272-303.

43. Matthews, E. J., Spalding, J. W., and Tennant, R. W. Transformation of BALB/c-3T3 cells: V. Transformation responses of 168 chemicals compared with mutagenicity in Salmonella and carcinogenicity in rodent bioassays. *Environ Health Perspect*. 1993;101(Suppl 2):347-482.

44. Myhr, B. C. and Caspary, W. J. Chemical mutagenesis at the thymidine kinase locus in L5178Y mouse lymphoma cells: Results for 31 coded compounds in the National Toxicology Program. *Environ Mol Mutagen*. 1991;18:51-83.

45. Shelby, M. D., Erexson, G. L., Hook, G. J., and Tice, R. R. Evaluation of a three-exposure mouse bone marrow micronucleus protocol: Results with 49 chemicals. *Environ Mol Mutagen*. 1993;21:160-179.

46. Zeiger, E., Anderson, B., Haworth, S., Lawlor, T., Mortelmans, K., and Speck, W. Salmonella mutagenicity tests: III. Results from the testing of 255 chemicals. *Environ Mutagen*. 1987;9(Suppl 9):1-110.

47. Zhou, M. and Donovan, M. D. Recovery of the nasal mucosa following laureth 9 induced damage. *Int.J.Pharm.* 1996;130:93-102.

48. National Toxicology Program. Salmonella study summary. Study A04474. Tripropylene glycol. http://ntp-apps.niehs.nih.gov/ntp_tox/index.cfm?fuseaction=salmonella.salmonellaData&study_no=A04474&cas_no=24800%2D44%2D0&endpointlist=SA. Date Accessed 10-7-2009.

49. Berenblum I and Haran N. The influence of croton oil and of polyethylene glycol-400 on carcinogenesis in the forestomach of the mouse. *Cancer Research*. 1955;15:501-506.

50. Zaldivar RSD. Precancerous lesions in guinea-pigs after intramural injections of 3-methylcholanthrene. *Die Naturwissenschaften*. 1963;50(10):380-381.

51. Boyland E, Carter RL, Gorrod JW, and Roe FJC. Carcinogenic properties of certain rubber additives. *European Journal of Cancer*. 1968;9:233-239.

52. Roe FJC, Ross WCJ, and Mitchley BCV. Carcinogenicity of certain glycidyl derivatives. *Food and Cosmetics Toxicology*. 1966;4(3):365-367.

53. Carter RL. Early development of injection site sarcomas in rats: A study of tumors induced by a rubber additive. *British Journal of Cancer*. 1969;23(2):408-416.

54. Simpson WL, Carruthers C, and Cramer W. Loss of carcinogenic activity when methylcholanthrene is dissolved in anhydrous lanolin. *Cancer Research*. 1945;5:1-4.

55. Bareblum I and Schoental R. The apparent anticarcinogenic action of lanolin. *Cancer Research*. 1947;7:390-392.

56. Avon Products, Inc. Four week subacute dermal toxicity study in rabbits; Baby lotion. 1974. LB 33. Unpublished data submitted by CTFA.

57. Shell Chemical Company. Human safety of neodol products. 1981. NTIS No. OTS0513412-4. (This report is a portion of this NTIS document.).

58. Shell Oil Company. Initial submission. Toxicology of detergents: Acute mammalian toxicity, skin and eye irritancy and skin sensitizing potential of Dobanol 25-3 (Final report). W-attaqch & lttr 011792. 1-20-1978. OTS0535381.

59. Shell Oil Company. Initial submission. Toxicology of detergent intermediates: Acute mammalian toxicity, skin and eye irritancy, and skin sensitizing potential of Dobanol 23-2 (Final report). W-ltte 111291. 10-1-1979. OTS0534685.

60. Diechman WB. Toxicology of Drugs and Chemicals. New York, NY: Acedemic Press, 1969.

61. Leberco Laboratories. Primary skin irritation test of body lotion containing ethoxydiglydol. 1980. From Dipropylene Glycol 1985 report. Report No. CTFA Code 2-17-25. Unpublished data submitted by CTFA.

62. Guillot JP, Giauffret JY, Martini MC, Gonnet JF, and Soulé G. Etude toxicologique chez l'animal de différents échantillons de lanoline anhydre, de lanoline modifiée et de dérivés de lanoline. *International Journal of Cosmetic Science*. 1980;2:1-38.

63. Goossens, A., Beck, M. H., Haneke, E., Mcfadden, J. P., Nolting, S., Durupt, G., and Ries, G. Adverse cutaneous reactions to cosmetic allergens. *Contact Derm*. 1999;40:112-113.

64. Johansen JD, Jemec GBE, and Rastogi SC. Contact sensitization to diprpylene glycol in an eczema population. *Contact Dermititis*. 1995;33(3):211-212.

65. Xie Z, Hayakawa R, Sugiura M, Kato Y, and Takeuchi Y. Causative agents and prognosis of 66 patients with occupational contact dermatitis. *Environmental Dermatology*. 1999;6(2):56-63.

66. Berberian, D. A., Gorman, W. G., Drobeck, H. P., Coulston, F., and Slighter, R. G., Jr. The toxicology and biological properties of laureth 9 (a polyoxyethylene lauryl ether), a new spermicidal agent. *Toxicol Appl Pharmacol.* 1965;7:206-214.

67. Bushy Run Research Center. Tergitol nonionic surfactant 24-L-60N: Nine-day cutaneous dose toxicity study with neurotoxicity evaluation in albino rats. 1-29-1990. Submitted to EPA by Union Carbide Corporation, dated Feb 23, 1990. NTIS No. OTS0513412-8.

68. Kleyn, C. E., Bharati, A., and King, C. M. Contact dermatitis from 3 different allergens in Solaraze gel. *Contact Derm*. 2004;51:215-216.

69. Suzuki, M., Machida, M., Adachi, K., Otabe, K., Sugimoto, T., Hayashi, M., and Awazu, S. Histopathological study of the effects of a single intratracheal instillation of surface active agents on lung in rats. *J Toxicol Sci*. 2000;25(1):49-55.

70. Watanabe M, Watanabe K, Suzuki K, Nikaido O, Ishii I, Konishi H, Tanaka N, and Sugahara T. Use of primary rabbit cornea cells to replace the Draize rabbit eye irritancy test. *Toxicology in Vitro*. 1989;3(4):329-334.

71. Scientific Committee on Consumer Products. Opinion on polidocanol (laureth-9). http://ec.europa.eu/health/ph_risk/committees/04_sccp/docs/sccp_o_113.pdf. Date Accessed 5-13-2010.

72. Shell Chemical Company. Human safety of neodol products. 1981. NTIS No. OTS0513412-4. (This report is a portion of this NTIS document.).

73. Shell Oil Company. Initial submission. Toxicology of detergents: Acute mammalian toxicity, skin and eye irritancy and skin sensitizing potential of Dobanol 25-3 (Final report). W-Attach & Lttr 011792. 1-20-1978.

74. Shell Oil Company. Initial submission. Toxicology of detergent intermediates: Acute mammalian toxicity, skin and eye irritancy, and skin sensitizing potential of Dobanol 23-2 (Final report). W-lttr 111291. 10-1-1979.

75. Malmstrom Chemicals. Draize human sensitization test. 1975. Malstrom B; Lanolin Oil; LB 23. Unpublished data submitted by CTFA.

76. Bio-Toxicology Laboratories, Inc. Repeated insult patch test. 1973. Lanolin Oil, Croda B, LB 20. Unpublished data submitted by CTFA.

77. Malmstrom Chemicals. Draize human sensitization test. 1975. Malstrom Chemicals; Lanolin Wax; LB 16. Unpublished data submitted by CTFA.

78. Bio-Toxicology Laboratories, Inc. Primary irritation study: :Lanfrax (551). 1968. Malstrom Chemicals C; Lanolin Wax; LB 15. Unpublished data submitted by CTFA.

79. Bio-Toxicology Laboratories, Inc. Repeated insult patch test for Croda, Inc. 1974. Croda G; Hygrodgenated Lanolin; LB 22. Unpublished data submitted by CTFA.

80. Clark EW. Estimation of the general incidence of specific lanolin allergy. *Journal of the Society of Cosmetic Chemistry*. 1975;26(7): 335.

81. Epstein E. The detection of lanolin allergy. *Archives of Dermatology*. 1972;106(5):678-681.

82. Breit R and Bandmann HJ. Contact dermatitis. XXII. Dermatitis from lanolin. *British Journal of Dermatology*. 1973;88(4):414-416.

83. Peter C, Schropl I, and Franzwa H. Experimentelle untersuchungen über die allergene. *Wirkung von Wollwachsachsachsalkoholen Hautarzt*. 1969;20:450-455.

84. Bandmann HJ, Calnan CD, Cronin E, Fregert S, Jhorth N, Magnusson B, Maibach H, Malten KE, Meneghini CL, and Piril'a V. Dermatitis from applied medicaments. *Archives of Dermatology*. 1972;106:335.

85. North American Contact Dermatits Group. Epidemiology of contact dermatitis in North America: 1972. *Archives of Dermatology*. 1973;108(10):537-540.

86. North American Contact Dermatits Group. The frequency of contact sensitivity in North America: 1972-74. *Contact Dermititis*. 1975;1:277-280.

87. Zug KA, Warshaw EM, Fowler Jr JF, Maibach HI, Belsito DL, Pratt MD, Sasseville D, Storrs FJ, Taylor JS, Mathias CGT, DeLeo VA, and Rietschel RL. Patch-test results of the North American Contact Dermatitis Group 2005 - 2006. *Dermatitis*. 2009;20(3):149-160.

88. Rudner EJ. North American group results. *Contact Dermititis*. 1977;3(4):208-209.

89. Clark EW, Cronin E, and Wilkinson DS. Lanolin with reduced sensitizing potential. A preliminary note. *Contact Dermititis*. 1977;3(2):69-74.

90. Anonymous. Cream bases fro topical agents can cause dermatitis. *Journal of the American Medical Association*. 1971;217(7):893-896.

91. DeBeukelaar L. Allergic reactions to wool fat alcohols. *Dermatologica*. 1968;136(5):434-439.

92. Bárány E, Lindberg M, and Lodén M. Unexpected skin barrier influence from nonionic emulsifiers. *Int J Pharm*. 2000;195:189-195.

93. Abdullah, A., Walker, S., Tan, C. Y., and Foulds, I. S. Sensitization of oleth-3-phosphate and oleth-5 in a hair wax. *Contact Derm*. 1997;37:188.

94. Field, S., Hazelwood, E., Bourke, B., and Bourke, J. F. Allergic contact dermatitis from tertiary-butylhydroquinone and Laureth 12 in a hair dye. *Contact Derm*. 2007;56:116-117.

95. Frosch, P. J. and Schulze-Dirks, A. Contact allergy caused by polidocanol (thesit). *Hautarzt*. 1989;40(3):146-149.

96. Gallo, R., Basso, M., Voltolini, S., and Guarrera, M. Allergic contact dermatitis from laureth-9 and polyquaternium-7 in a skin-care product. *Contact Dermititis*. 2001;45:356-357.

97. Grills, C. E. and Cooper, S. M. Polidocanol: a potential contact allergen in shampoo. *Contact Derm*. 2007;56:178.

98. Henriquez-Santana, A., Fernandez-Guarino, M., González deOlano, D., Gonzalez-Cervera, J., Huertas-Barbudo, B., and Aldanondo, I. Urticaria induced by Etoxisclerol (polidocanol). *J Eur Acad Dermatol Venereol*. 2008;22:261-262.

99. Huber-Riffeser, G. Allergic contact dermatitis to polidocanol (Thesit). *Contact Derm*. 1978;4(4):245.

100. Kimura, M. and Kawada, A. Follicular contact dermatitis due to polyoxyethylene laurylether. *J Am Acad Dermatol.* 2000;42(5 Pt 2):879-880.

101. Svensson, A. Allergic contact dermatitis to laureth-4. *Contact Derm*. 1988;18(2):113-114.

102. Taibjee, S. M., Prais, L., and Foulds, I. S. Allergic contact dermatitis from polyethylene glycol monomethyl ether 350 in Solaraze gel. *Contact Derm*. 2003;49:170-171.

103. Amerchol. CIR Task Force - Cosmetic ingredient: Lanolin alcohol supplied by Amerchol. 2012. LB 32 Need to handle No Date. Unpublished data submitted by CTFA.

104. Amerchol. CIR Task Force - Cosmetic ingredient: Hydroxylated lanolin. Supplied by Amerchol. 2012. LB 31 How to handle no date. Unpublished data submitted by CTFA.

105. Amerchol. CIR Task Force - Cosmetic ingredient: Lanolin Acid supplied by : Amerchol. 2012. LB 30 Need to know how to handle no date. Unpublished data submitted by CTFA.

106. Cosmetic, Toiletry, and Fragrance Association. CIR safety data test summary. Prophetic and repeated insult patch tests of product containing dipropylene glycol. 1978. From Dipropylene Glycol 1985 Report. Report No. CTFA Code 20170167. Unpublished data submitted by CTFA.

107. Gottschalck TE and Breslawec HP. International Cosmetic Ingredient Dictionary and Handbook. 14 *ed*. Washington, DC: Personal Care Products Council, 2012.

108. ICI America. Submission of data in support of safety of PEG-Lanolin. PEG-20 Lanolin. Appendixy 6. Acute oral toxicity. 1976. From PEG Lanolin 1982 report. Unpublished data submitted by CTFA.

109. Bio-Toxicology Laboratories (BTL). Submission of data from CTFA for PEG-75 lanolins. PEG-27 lanolin. Appendix 5. Acute oral toxicity. 1975. From PEG Lanolin 1982 report. Unpublished data submitted by CTFA.

110. Bio-Toxicology Laboratories (BTL). Submission of data in support of safety of PEG-lanolins. PEG-40 lanolin. Appendix 5. Acute oral toxicity. 1975. From PEG Lanolins 1982 report. Unpublished data submitted by CTFA.

111. ICI America. Submission of data in support of safety of PEG Lanolins. PEG-50 lanolin. Appendix 6. Acute oral toxicity. 1976. From PEG Lanolin 1982 report. Unpublished data submitted by CTFA.

112. Food and Drug Research Laboratories. Submission of data in support of safety of PEG-Lanolins. PEG-75. Appendix 1. 1974. From PEG Lanolins 1982 report. Unpublished data submitted by CTFA.

113. Bio-Toxicology Laboratories (BTL). Submission of data in support of safety of PEG-Lanolins. PEG-75. Appendix 3. Acute oral toxicity and primary skin irritation. 1070. From PEG Lanolins 1982 report. Unpublished data submitted by CTFA.

114. Leberco Laboratories. Submission of data in support of safety of PEG-Lanolins. PEG-75 lanolin. Appendix 2. Acute oral toxicity. 1973. From PEG Lanolins 1982 report. Unpublished data submitted by CTFA.

115. Hilltop Research. Submission of data in support of safety of PEG-Lanolins. PEG-75 Lanolin. Appendix 5. Acute oral toxicity. 1971. From PEG Lanolins 1982 report. Unpublished data submitted by CTFA.

116. Westbrook Lanolin Laboratories. Submission of data in support of safety of PEG-Lanolins. PEG-75 Lanolin. Supplement. Acute oral toxicity. 1973. From PEG Lanolins 1982 report. Unpublished data submitted by CTFA.

117. Bio-Toxicology Laboratories (BTL). Submission of data in support of safety of PEG-Lanolin. PEG-85 Lanolin. Appendix 5. Acute oral toxicity. 1976. From PEG Lanolins 1983 report. Unpublished data submitted by CTFA.