Safety Assessment of Glycerin as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 18, 2014
Panel Meeting Date:	September 8-9, 2014

The 2014 Cosmetic Ingredient Review Expert Panel members are: Chairman, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Director is Lillian J. Gill, D.P.A. This report was prepared by Lillian C. Becker, Scientific Analyst/Writer.

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MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: August 18, 2014

Subject: Glycerin as Used in Cosmetics

Attached is the Draft Report of Glycerin as used in cosmetics. The SLR was issued in June, 2014. Comments from the Personal Care Products Council have been addressed. No other comments were received.

Glycerin (also referred to as glycerol in the literature) was the third most frequently reported ingredient in the Voluntary Cosmetic Registration Program VCRP database (after water and fragrance). Most of the data available for this ingredient are decades old; very little recent research has been conducted.

The Panel is to examine the report and decide if there is sufficient data to come to a conclusion. If not, the Panel is to issue an Insufficient Data Announcement with a list of data needs. If there is enough data for a conclusion, the Panel is to develop the Abstract, Discussion, and Conclusion and issue a Tentative Report.

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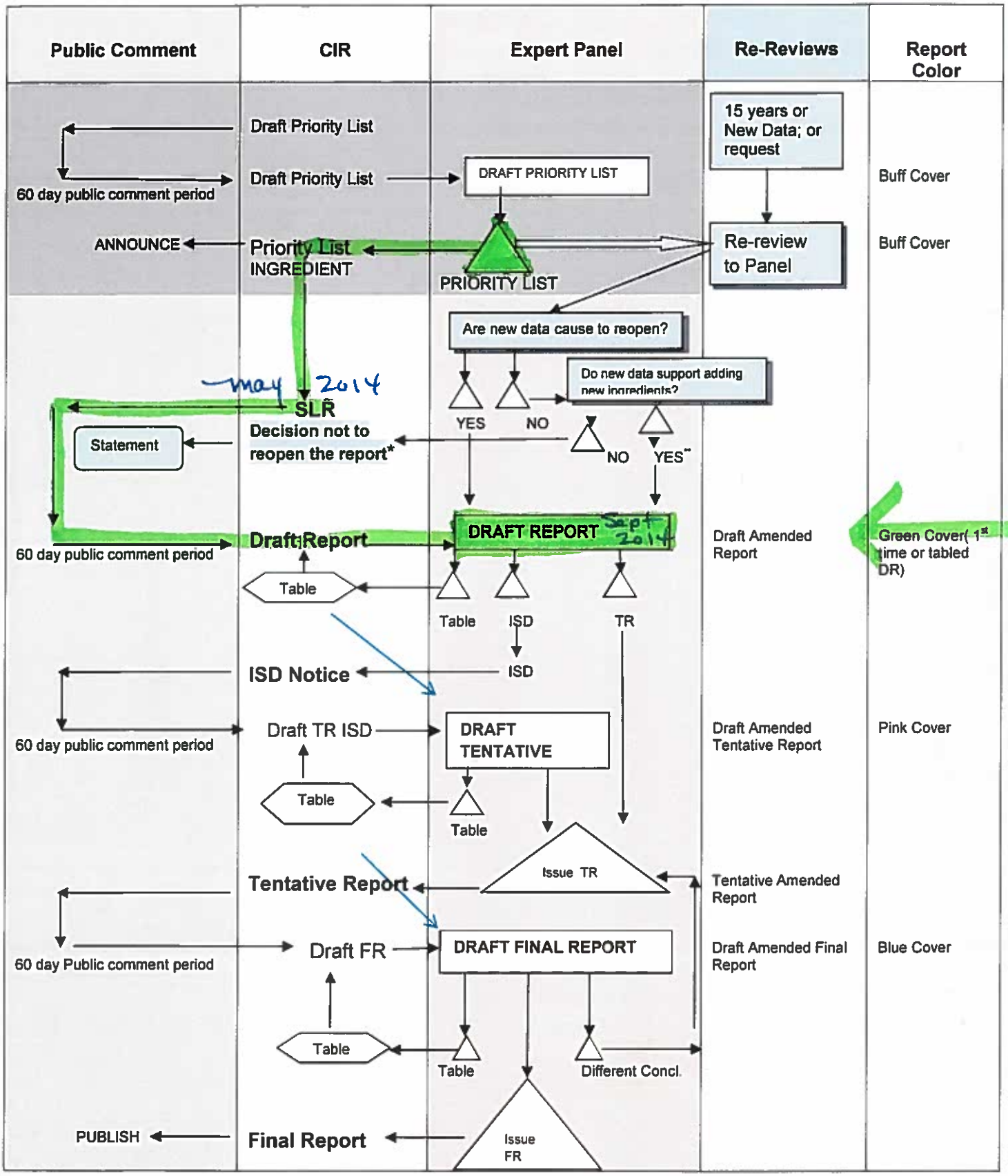
Glycerin

SAFETY ASSESSMENT FLOW CHART

Sept 2014



*The CIR Staff notifies of the public of the decision not to re-open the report and prepares a draft statement for review by the Panel. After Panel review, the statement is issued to the Public.

**If Draft Amended Report (DAR) is available, the Panel may choose to review; if not, CIR staff prepares DAR for Panel Review.

History – Glycerin

June, 2014 - SLR issued.

September, 2014 - Panel examines the Draft Report

Glycerin Data Profile for September, 2014. Writer - Lillian Becker																		
	ADME			Acute toxicity			Repeated dose toxicity			Irritation			Sensitization					
	Dermal Penetration	Log K_{ow}	Use	Oral	Dermal	Inhale	Oral	Dermal	Inhale	Ocular Irritation	Dermal Irr. Animal	Dermal Irr Human	Sensitization Animal	Sensitization Human	Repro/Devel toxicity	Genotoxicity	Carcinogenicity	Phototoxicity
Glycerin			X	X	X		X	X	X	X	X	X	X	X	X	X	X	

Search Strategy – Glycerin

SciFinder – Substance search "glycerin" and CAS No. 137489 hits. Culled by document type to 10,814. Culled with "toxicity", "dermal", and 1960+

Google – "glycerin", "glycerol", "FDA + glycerin"

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INTRODUCTION

This is a review of the available scientific literature and unpublished data provided by industry relevant to assessing the safety of glycerin as used in cosmetics. Glycerin is reported to function in cosmetics as a denaturant; fragrance ingredient; hair conditioning agent; humectant; oral care agent; oral health care drug; skin protectant; skin-conditioning agent - humectant; and viscosity decreasing agent.[1]

CHEMISTRY

Definition and Structure

Glycerin (CAS No. 56-81-5) is the polyhydric alcohol that conforms generally to the structure in Figure 1.[1] The molecular formula is $C_3H_8O_3$. Glycerin (also referred to as glycerol in the literature) is a simple polyol compound that has three hydroxyl groups.

Glycerin is naturally occurring in all animals and plant matter in combined form as glycerides in fats and oils, or, intracellular spaces as the backbone of lipids.[2]

Natural glycerin is obtained as a byproduct in the conversion of fats and oils to fatty acids or fatty acid methyl esters.[3] Synthetic glycerin refers to material obtained from non-triglyceride sources.

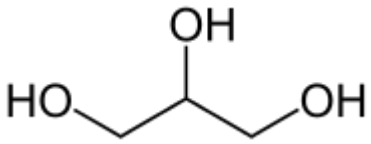

Figure 1. Glycerin

Physical and Chemical Properties

Glycerin is a clear, syrupy liquid (Table 1).[4,5]

Glycerin can be in a crystallized state, but seldom is because of its tendency to supercool, and the pronounced effect of small amounts of water depressing the freezing point.[2]

Glycerin has solvent properties, similar to those of water and simple aliphatic alcohols, because of its three hydroxyl groups.[3] It is completely miscible with water, methanol, ethanol, and the isomers of propanol, butanol, and pentanol. Glycerin is also fully miscible with phenol, glycol, propanediols, amines, and heterocyclic compounds containing a nitrogen atom in the ring (e.g., pyridine, quinoline). It has less solubility in acetone, diethyl ether, and dioxane. Glycerin is almost insoluble in hydrocarbons, long-chain aliphatic alcohols, fatty oils, and halogenated solvents such as chloroform.

Method of Manufacture

The starting material for synthetic glycerin may be allyl chloride, acrolein, propylene oxide, sugar, polyalcohols, fats, or epichlorohydrin.[3] Natural or native glycerin is obtained as a byproduct in the conversion of fats and oils to fatty acids or fatty acid methyl esters.

Multiple methods exist for the manufacture of glycerin. One method includes the oxidation of allyl chloride with hypochlorite to produce dichlorohydrin, which is then converted, without isolation, to epichlorohydrin by ring closure with calcium hydroxide or sodium hydroxide.[3] Epichlorohydrin is hydrolyzed to yield glycerin by heating to 80-200˚C with a 10%-15% aqueous solution of sodium hydroxide or sodium carbonate at atmospheric pressure or overpressure. The yield of dilute (10%-25%) glycerin solution is >98%, and it contains 5%-10% sodium chloride and <2% other impurities. The aqueous glycerin solution is evaporated in a multistage evaporation plant under vacuum to produce a glycerin concentration of >75%, after separating precipitated sodium chloride. The glycerin solution is then distilled under high vacuum; and the co-distilled water is separated by fractional condensation. The glycerin is treated further to remove color impurities and odorous material; this can be performed, for example, using activated carbon.

A second method involves the oxidation of propene to acrolein, which is then reduced under Meerwein-Ponndorf-Verley conditions to yield allyl alcohol.[3] The allyl alcohol is then epoxidized with hydrogen peroxide, and the resulting glycidol is hydrolyzed to produce glycerin.

Impurities

The U.S. Pharmacopeial (USP) Convention recommended that glycerin intended for use in pharmaceuticals be analyzed for diethylene glycol (safety limit 0.1%).[6]

The U.S. Food and Drug Administration (FDA) notes that glycerin is a byproduct of biodiesel fuel produced from the *Jatropha curcas* plant.[7] There is a possibility that toxic compounds, including phorbol esters, may be present in glycerin produced this way. Conventional impurity tests may not detect these toxins and glycerin from this source should not be used

in human and animal food, medical products, cosmetics, and other FDA-regulated products. The FDA advises industry to be aware of the potential for substitution or use of oils, glycerin, and proteins derived from the *J. curas* plant.

Glycerin is reported to be 95%-99.5% pure.[4] Impurities are water and trace levels of polyglycerol.

USE

Cosmetic

Glycerin is reported to function in cosmetics as a denaturant; fragrance ingredient; hair conditioning agent; humectant; oral care agent; oral health care drug; skin protectant; skin-conditioning agent - humectant; and viscosity decreasing agent.[1]

The FDA collects information from manufacturers on the use of individual ingredients in cosmetics as a function of cosmetic product category in its Voluntary Cosmetic Registration Program (VCRP). In 2014, glycerin was the third most frequently reported ingredient in the VCRP database (after water and fragrance). Glycerin was reported to be used in 15,654 cosmetic products; 10,046 are leave-on products, 5441 are rinse-off products, and 167 products are diluted for the bath. These uses include 862 products for use near the eye, 160 lipsticks, 369 hair dyes and colors, 1259 bath soaps and detergents, 7756 skin care products, and 244 suntan preparations (Table 2).[8] Glycerin is reported to be used in 125 baby products. Two uses for anhydrous glycerin were reported in the VCRP; these uses were incorporated with the glycerin uses.

A survey was conducted by the Personal Care Products Council (Council) of the maximum use concentrations for ingredients in this group. Glycerin is reported to be used up to 78.5% in leave-on products, 68.6% in rinse-off products, and 47% in products diluted for the bath. It is used up to 21% in baby products, 40.6% in eye lotion, 25% in perfumes, 47.3% in hair grooming aids, 68.6% in oral hygiene products, 78.5% in body and hand skin care products, and 17.9% in suntan preparations.[9]

Glycerin was reported to be used in aerosol/spray products that include: hair sprays (in propellant spray products up to 10% and in pump spray products up to 30%), deodorants up to 2%, face and neck products up to 10%, body and hand products up to 5%, moisturizing products up to 3.3%, and suntan products (in propellant spray products up to 6% and in pump spray products up to 10%). These propellant/pump spray products could possibly be inhaled. In practice, 95% to 99% of the droplets/particles released from cosmetic sprays have aerodynamic equivalent diameters >10 µm, with propellant sprays yielding a greater fraction of droplets/particles below 10 µm compared with pump sprays.[10-13] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (ie, they would not enter the lungs) to any appreciable amount.[10,12] There is some evidence indicating that deodorant spray products can release substantially larger fractions of particulates having aerodynamic equivalent diameters in the range considered to be respirable.[10] However, the information is not sufficient to determine whether significantly greater lung exposures result from the use of deodorant sprays, compared to other cosmetic sprays.

Non-Cosmetic

Glycerin is considered generally recognized as safe (GRAS) by the FDA for food packaging and as a multiple purpose food substance (Table 3).[21CFR182.90; 21CFR182.132] Glycerin functions as a humectant, solvent, cake icing component, confectionary component, bodying agent, and plasticizer for foods.[2]

Glycerin is also used as an active ingredient in over-the-counter drugs, such as external analgesic, dermal protectant (up to 45%), and in ophthalmic drug products (up to 1%).

Glycerin has been administered orally and/or intravenously to reduce intracranial pressure caused by various medical conditions.[14] Glycerin has been used to reduce brain volume for neurosurgical procedures. It is also used as the active ingredient in laxative products (ie, glycerin suppositories).

Glycerin is used in paints, lacquers, and varnishes; polymers; tobacco; absorbents and adsorbents; adhesives and binding agents; anti-freezing agents; cleaning agents and disinfectants; explosives; heat transferring agents; pesticides; and softeners.[2] It is an intermediate and monomer in resins, polyols, and polyurethanes.[4]

TOXICOKINETICS

Absorption, Distribution, Metabolism, and Excretion

Glycerin is rapidly absorbed in the intestine and the stomach, distributed over the extracellular space and excreted.[4,15,16] Glycerin is phosphorylated to α-glycerophosphate by glycerol kinase, predominantly in the liver (80%-90%) and kidneys (10%-20%), and incorporated in the standard metabolic pathways to form glucose and glycogen.[15,17] Glycerin kinase is also found in intestinal mucosa, brown adipose tissue, lymphatic tissue, lung and pancreas. Glycerin may also combine with free fatty acids in the liver to form triglycerides (lipogenesis) that can be distributed to adipose tissues. The glycerin turnover rate is directly proportional to plasma glycerin levels.[18]

Free glycerin is naturally present in human plasma.[4,15] Normal serum levels in adult humans range from 0.05-0.1 mmol/L. Its excretion in the urine stops if levels fall below 1 mg/mL plasma.

Dermal/Percutaneous

Data on dermal absorption, distribution, metabolism, and excretion of glycerin were not found in the published literature nor were unpublished data provided.

Oral

Orally administered glycerin is rapidly absorbed from the gastrointestinal tract, and peak serum concentrations occur within 60-90 min.[14] Glycerin is distributed throughout the blood. Glycerin generally does not appear in ocular fluids; however, it may enter the orbital sac when the eye is inflamed. It is not known if glycerin is distributed into milk.

The elimination half-life of glycerin is approximately 30-45 min. Most orally administered glycerin is incorporated into body fat, metabolized by glycerokinase, principally in the liver to carbon dioxide and water, or is utilized in glucose or glycogen synthesis. Glycerin can also combine with free fatty acids to form triglycerides. Approximately 80% of glycerin metabolism takes place in the liver and approximately 10%-20% in the kidney. The metabolism of glycerin to carbohydrate produces 4.3 calories/g glycerin. Most of an oral dose of glycerin is metabolized within 2.5 h. Approximately 7%-14% of an oral dose of glycerin is excreted unchanged in urine during this time.

Orally administered glycerin elevates the osmotic pressure of the plasma to such an extent that water from the extravascular spaces is drawn into the blood. The osmotic effect of glycerin produces a decrease in intraocular pressure (IOP) by reducing the volume of intraocular fluids in a manner completely independent of the normal ocular fluid inflow and outflow mechanisms. The extent of IOP reduction varies with the dose of glycerin and the etiology and degree of the increased pressure. Reduction in IOP reaches its maximum within 30 min to 2 h and may persist for 4-8 h. In general, reduction in IOP is greatest when the pretreatment intraocular pressure is high. The osmotic effect of glycerin may also produce tissue dehydration and a decrease in cerebrospinal fluid pressure. Glycerin produces only very slight diuresis in healthy individuals receiving a single oral dose of 1.5 g/kg or less.[14]

Acute ingestion of glycerin (1 mL/kg in water) in male subjects led to an increase in plasma glycerides. In female subjects, the oral administration of glycerin (1 mL/kg in water) resulted in no change in plasma glyceride concentration. When glycerin (1 mL/kg/d in 3 doses) was orally administered for 42 days, increased serum glyceride concentrations were observed in both sexes, however, the increase was greater in men.[19]

TOXICOLOGICAL STUDIES

Acute Toxicity

Non-Human

The reported oral LD_{50} of glycerin ranged from 2530-58 400 mg/kg in rats; there were no deaths at 24 000 mg/kg in one study (Table 4).[2,17,20-24] The reported oral LD_{50} of glycerin ranged from 4090->38 000 mg/kg in mice, 27 000 mg/kg in rabbits, and 77 500 mg/kg in guinea pigs.[2,17,20,21,23-26] The dermal LD_{50} of glycerin in rats was reported to be >21 900 mg/kg and >18 700 mg/kg in rabbits.[2,23] The intraperitoneal LD_{50} of glycerin in rats ranged from 4420-10 100 mg/kg and 8600-9500 mg/kg in mice.[2] The subcutaneous LD_{50} of glycerin was 100 mg/kg in rats and ranged from 91-10 000 mg/kg in mice.[2,26] The intravenous LD_{50} of glycerin ranged from 5200-6600 mg/kg in rats, 4250-6700 mg/kg in mice, and was 53 000 mg/kg in rabbits.[2]

Oral – Human

The LD_{LO} of glycerin was reported to be 1428 mg/kg for humans.[2]

There were no signs of toxicity when subjects (n=10 men, 4 women) were administered glycerin (30 mL; 95% in orange juice) after each of 3 daily meals in 1 day.[4]

Adverse effects following the oral administration of glycerin include mild headache, dizziness, nausea, vomiting, thirst, and diarrhea.[14] Headache may result from cerebral dehydration, which may be prevented or relieved by having the subject lie down during and after treatment. Hypotonic fluids will relieve thirst and headache caused by the dehydrating action of glycerin.

Repeated Dose Toxicity

Oral – Non-Human

Undiluted glycerin caused a dose-dependent increase in the number of animals showing hyperemia, petechial hemorrhage, and erosions in the gastro-intestinal tract (Table 5). In short-term feeding experiments, glycerin at 20% for 4 weeks in feed produced no adverse effects, but at 53.4%, increased the kidney weights and increased liver enzyme activity were observed.[27-29] The no observed adverse effect level (NOAEL) was between 115 and 2300 mg/kg when administered in water for 44 days.[30] Calcified masses were observed in kidney tubules between the cortex and medulla in 3 of 5 rats administered either natural and synthetic glycerin (3335 mg/kg/d) in drinking water for 6 months.[25] When glycerin was administered in the diet for 2 years, feed consumption was increased in males at 5% and 10% natural glycerin. There were no treatment related effects in organ weights and gross pathology.[23]

The no observed effect level (NOEL) in mongrel dogs was 950 mg/kg/d when orally administered for 3 days (Table 5). At 3800 mg/kg/d, the mucosa of the stomach was severely hyperemic with petechial hemorrhages.[31] Mongrel dogs experienced weight loss after 36 weeks when glycerin (35%) was incorporated into their feed. The weight loss continued when the glycerin content was reduced by 50%-80% for the remainder of a 50-week study.[27]

There were no pathological changes in guinea pigs (n=10) orally administered glycerin (6300 mg/kg/d) for 30-40 days (Table 5).[32]

Oral – Human

There were no signs of toxicity or effects on blood or urine production when subjects (n = 10 male, 4 female) were orally administered glycerin (~1.3 - ~2.2 g/kg/d; glycerin in orange juice with meals) for 50 days.[2] The NOAEL was ≥2200 mg/kg/d. No further information was provided.

There were no adverse effects observed in subjects (n=14) administered glycerin (30 mL, neat) 3 times daily with each meal for 50 days.[15]

Dermal – Non-Human

There were no treatment effects when glycerin (100%; 0.5-4 mL) was administered to 30% of the body surfaces of rabbits for 45 weeks (Table 5).[23]

Inhalation – Non-Human

The inhalation LOAEL was 1000 mg/L for glycerin administered nose only 6 h/day, 5 days/week for 2 weeks in Crl:DCD Sprague-Dawley rats, based on local effects on the epithelium of the upper respiratory tract (Table 5).[33]

The inhalation NOAEL was 0.167 mg/L for glycerin administered nose only for 5 h/day, 5 days/week for 13 weeks in Crl:DCD Sprague-Dawley rats (Table 5).[33] There was minimal squamous metaplasia of the epiglottis in 2/25, 1/19, 4/20 and 10/21 rats at 0, 33, 167 and 662 mg/L, respectively; 1 male in the high-dose group showed mild squamous metaplasia.

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

In a two-generation reproductive study in rats, (n=10/sex), the administration of glycerin (0, 20%; ~ 2000 mg/kg/d in drinking water) for 8 weeks before mating until weaning of pups produced no adverse effects on the reproductive efficiency of the parents (F_0 generation), or the growth, fertility, or reproductive performance of the untreated F_1 generation.[4] No histological changes occurred in the tissues of either the F_1 or F_2 generations. The onset of estrus cycles, weight gain, and microscopic observations of the endocrine organs were comparable to those of the controls in both the F_1 and the F_2 generation. In the F_0 generation, all 10 females became pregnant with similar litter size as controls (9.0 vs. 8.1). In the F_1 generation, 9 of 10 females became pregnant.

When glycerin (13.1, 60.8, 282 and 1310 mg/kg/d) was administered by gavage to Wistar rats (n=25-28) on days 6 through 15 of gestation, there were no adverse effects observed in the dams.[34] The NOAEL for maternal toxicity and teratogenicity was 1310 mg/kg/d. The number of pregnancies was: 23 of 25, 24 of 25, 22 of 28, 22 of 25 for 13.1, 60.8, 282 and 1310 mg/kg/d, respectively, and 21 of 25 for controls. The number of implantations, resorptions, litter sizes, weights, and sex ratio were similar among groups, as were the incidences of external, visceral, and skeletal abnormalities.

When glycerin (12.8, 59.4, 276 and 1280 mg/kg/d) was administered by gavage to CD-1 mice (n=25) on days 6 through 15 of gestation, there were no adverse effects observed in the dams.[34] The NOAEL for maternal toxicity and teratogenicity was 1280 mg/kg/d. The number of pregnancies was: 14 of 15, 12 of 15, 10 of 18, 13 of 20 and 13 of 15 for controls, 12.8, 59.4, 276 and 1280 mg/kg, respectively. The number of implantations, resorptions, litter sizes, weights, and sex ratio were similar among groups as were external, visceral, and skeletal abnormalities.

When glycerin (11.8, 54.8, 254.5 and 1180 mg/kg/d) was administered by gavage to Dutch-belted rabbits (n=25) on days 6 through 18 of gestation, there were no adverse effects found in the dams.[34] The NOAEL for maternal toxicity and teratogenicity was 1180 mg/kg/d. The number of pregnancies was: 22 of 25, 23 of 25, 20 of 25, 22 of 25 and 21 of 25 for controls, 11.8, 54.8, 254.5 and 1180 mg/kg/d, respectively. The number of implantations, resorptions, litter sizes, weights, and sex ratio were similar among groups, as were external, visceral, and skeletal abnormalities.

Male Fertility – Non-Human

Glycerin injected into the testes of rats (50-200 µL and 862 mg/kg body weight) and monkeys (119 mg/kg body weight) suppressed spermatogenesis (Table 6).[35-37]

Male Fertility – Human

In a fertility study of male employees (n=64) who manufacture glycerin, there were no differences observed in sperm counts and percent normal forms compared with a control group (n=63) who did not work with glycerin (Table 6).[38]

GENOTOXICITY

In Vitro

Glycerin was not genotoxic in multiple Ames tests using multiple strains of *Salmonella typhimurium* up to 50 mg/plate (Table 7).[22,39-43] It was not genotoxic in a cytogenetic assay, X-linked hypoxanthine-guanine phosphoribosyl transferase (HGPRT) assay, sister chromatid exchange assay using Chinese hamster ovary (CHO) cells, unscheduled DNA synthesis assay using rat hepatocytes, or chromosome aberration test using CHO cells; up to 1.0 mg/mL was tested in these studies.[39,41]

In Vivo

In two chromosome aberration assays, glycerin was not genotoxic when administered orally to rats at 1 mg/kg or by injection into the abdomen at 1000 mg/kg (Table 7).[44] In a dominant lethal gene assay, there were ambiguous results when

glycerin was injected into the abdomen of rats.

CARCINOGENICITY

Glycerin administered in the feed of rats at doses up to 20% for 1 year or up to 10 g/kg for 2 years did not increase the incidence of tumors (Table 8).[23] Glycerin administered in drinking water, up to 5%, had a synergistic effect with 4-nitroquinoline 1-oxide (4NQO) in mice.[45-47] There was an increased number of pulmonary tumor-bearing mice in the treated mice compared to controls.

IRRITATION AND SENSITIZATION

Irritation

Dermal – Non-Human

Glycerin was not dermally irritating in rabbits at concentrations up to 100% (Table 9).[22,23,48] Glycerin was a mild dermal irritant at 100% in guinea pigs.[26]

Dermal – Human

Glycerin (50% in water) was not irritating to subjects with dermatitis (n = 420) when administered for 20-24 h under occlusion.[49] One subject had a positive reaction. She reported using a mixture of glycerin (1 part) and 70% ethanol (9 parts) applied on the hands after washing with soap and water. She was tested with glycerin (1%, 5%, 10% in water) and her glycerin-ethanol mixture (100%), resulting in +++ reactions for both test substances 48 and 72 h after exposure.

Glycerin (10%; 0.05 ml) was slightly irritating in a 48-h occlusive patch test.[2] The irritation score was 4 out of 9 on day 14 of observation. No further information was provided.

Ocular -- Non-Human

Glycerin was not irritating to the eyes of rabbits at concentrations up to 100% (Table 10).[22,23,26,48]

Ocular -- Human

Topical administration of anhydrous glycerin to the eyes of human subjects with edema of the superficial layers of the cornea resulted in reduced edema and improved visualization.[14] Pain and/or irritation have occurred following administration of glycerin to the eye.

Glycerin (100%) was not irritating when administered to the eyes of human subjects (n not specified).[2] There was a strong burning and stinging sensation, with tear production, but no injury was observed.

Sensitization

Dermal – Non-Human

Natural and synthetic glycerin were not sensitizing to white male guinea pigs (n=12).[23] The induction phase consisted of 10 injections of 0.1 mL of a 0.1% solution every other day. The challenge phase consisted of an injection of 0.05 mL of the 0.1% solution after a 2 week resting phase.

Dermal – Human

A moisturizer containing glycerin (65.9%) was not sensitizing in a modified Draize test (n=48).[50] There were no reactions during either the induction phase or the challenge phase. The test substance was administered 10 times under occlusion for 48 or 72 h (over the weekend). The challenge patch was in place for 48 h. The test site was observed at removal and 48 h after removal.

Subjects (n=15) who worked in a foam rubber factory and were regularly exposed to glycerin were not sensitized to glycerin (concentration not specified; in water) when patched tested at 100% for 48 h.[51]

SUMMARY

This is a safety assessment of glycerin, a polyhydric alcohol. Glycerin is reported to function in cosmetics as a denaturant; fragrance ingredient; hair conditioning agent; humectant; oral care agent; oral health care drug; skin protectant; skin-conditioning agent - humectant; viscosity decreasing agent.

Impurities were reported to be water, polyglycerol, and diethylene glycol. Biotoxins may be present if the source material is the *Jatropha curcas* plant.

Glycerin is reported to be used in 15 654 cosmetic products; 10 046 are leave-on products, 5441 are rinse-off products, and 167 are products that are diluted for the bath. Glycerin is reported to be used at concentrations up to 78.5% in leave-on products, 68.6% in rinse-off products, and 47% in products diluted for the bath.

Glycerin is considered to be GRAS by the FDA for food packaging and as a multiple-purpose food substance. Glycerin is also used as an active ingredient in over-the-counter drugs.

Glycerin is rapidly absorbed in the intestine and the stomach, distributed over the extracellular space and excreted in urine. Free glycerin is naturally present in human plasma.

The reported oral LD_{50} of glycerin ranged from 2530-58 400 mg/kg in rats, 4090->38 000 mg/kg in mice, 27 000 mg/kg in rabbits, and 77 500 mg/kg in guinea pigs. The dermal LD_{50} of glycerin in rats was reported to be >21 900 mg/kg and >18 700 mg/kg in rabbits. The intraperitoneal LD_{50} of glycerin in rats ranged from 4420-10 100 mg/kg and 8600-9500 mg/kg in mice. The subcutaneous LD_{50} of glycerin was 100 mg/kg in rats and ranged from 91- 10 000 mg/kg in mice. The intravenous LD_{50} of glycerin ranged from 5200-6600 mg/kg in rats, 4250-6700 mg/kg in mice, and 53 000 mg/kg in rabbits.

The LD_{LO} of glycerin was reported to be 1428 mg/kg for humans. There were no signs of toxicity when human subjects were orally administered 30 mL glycerin. Adverse effects in human subjects following the oral administration of glycerin include mild headache, dizziness, nausea, vomiting, thirst, and diarrhea.

In short-term feeding experiments using rats, 20% glycerin for 4 weeks in feed had no adverse effects, but at 53.4% the kidneys exhibited increased weights and livers increased enzyme activity. When glycerin was administered in the diet for 2 years, feed consumption was increased in males at 5% and 10% natural glycerin. There were no treatment related effects in organ weights and gross pathology. The NOEL in mongrel dogs was 950 mg/kg/d when orally administered for 3 days. At 3800 mg/kg/d, the mucosa of the stomach was severely hyperemic with petechial hemorrhages. Mongrel dogs experienced weight loss after 36 weeks when 35% glycerin was incorporated into their feed. There were no pathological changes in guinea pigs orally administered 6300 mg/kg/d glycerin for 30-40 days.

There were no signs of toxicity or effects on blood or on urine production when human subjects were orally administered approximately 1300-2200 g/kg/d glycerin for 50 days. The NOAEL was ≥2200 mg/kg/d.

There were no treatment effects when 100% glycerin was topically applied daily to 30% of the body surfaces of rabbits for 45 weeks.

The inhalation LOAEL was 1000 mg/m^3 for glycerin administered 6 h/day, 5 days/week for 2 weeks in rats. The inhalation NOAEL was 0.167 mg/L for glycerin administered for 5 h/day, 5 days/week for 13 weeks in rats.

No adverse effects were observed in rats administered 20% glycerin in drinking water throughout gestation and nursing of pups. The F_1 generation reproduced normally. The oral NOAEL for maternal toxicity and teratogenicity for rats was 1310 mg/kg/d. The NOAEL for maternal toxicity and teratogenicity in mice was 1280 mg/kg/d. The NOAEL for maternal toxicity and teratogenicity in rabbits was 1180 mg/kg/d.

Glycerin injected into the testes of rats (50-200 µL and 862 mg/kg body weight) and monkeys (119 mg/kg body weight) suppressed spermatogenesis.

Glycerin was not genotoxic in multiple Ames tests using multiple strains of *S. typhimurium* at concentrations up to 50 mg/plate. It was not genotoxic in a cytogenetic assay, X-linked HGPRT, sister chromatid exchange assay, unscheduled DNA synthesis assay, and chromosome aberration test at concentrations up to 1.0 mg/mL.

In two chromosome aberration assays, glycerin was not genotoxic when administered orally to rats at 1 mg/kg or by injection into the abdomen at 1 g/kg. In a dominant lethal gene assay, the results were ambiguous.

Glycerin administered in the feed of rats at doses up to 20% in feed for 1 year or up to 10 g/kg for 2 years did not increase the incidence of tumors. Orally administered glycerin, in concentrations up to 5%, had a synergistic effect on the carcinogenicity of 4NQO in mice.

Glycerin was not dermally irritating to rabbits when applied at concentrations up to 100% to up to 30% of the body surface 8 h/day, 5 days/week for 45 weeks. Glycerin was a mild dermal irritant at 100% in guinea pigs.

Glycerin at 50% was not irritating to subjects with dermatitis.

Undiluted glycerin was not irritating when administered to the eyes of human subjects. There was a strong burning and stinging sensation, with tear production but no injury was observed.

Natural and synthetic glycerin were not sensitizing to white male guinea pigs at 0.1%.

A moisturizer containing 65.9% glycerin was not sensitizing to human subjects.

DISCUSSION

The Discussion will be developed at the September, 2014 Panel meeting.

CONCLUSION

The Conclusion will be developed at the September, 2014 Panel meeting.

TABLES

Table 1. Chemical and physical properties of glycerin.

Property	Value	Reference
Physical Form	Liquid, syrupy	[4,5]
Color	Clear	[5]
Odor	Odorless, mild	[3]
Molecular Weight g/mol	92.09	[52]
Density/Specific Gravity @ 20°C	1.26	[4]
Viscosity kg/(s m)@ °C	1.41	[4]
Vapor pressure mmHg@ 50°C	0.0025	[5]
Vapor Density mmHg	3.17	[5]
Melting Point °C	18 17.9	[4] [5]
Boiling Point °C	290	[4]
Water Solubility	Miscible	[4]
log K_{ow}	1.76	[4]
Disassociation constants (pKa, pKb) @°C	$0.07E^{-13}$	[4]

Table 2. Frequency of use according to duration and exposure of glycerin.[8,9]

Use type	Uses	Maximum Concentration (%)
Total/range	**15 654**	**0.0001-78.5**
Duration of use		
Leave-on	10 046	0.0001-78.5
Rinse-off	5441	0.0007-68.6
Diluted for (bath) use	167	0.66-47
Exposure type[a]		
Eye area	862	0.025-40.6
Incidental ingestion	353	2-68.6
Incidental Inhalation-sprays	4341[b]; 2643[d]	0.075-77.3[b]; spray: 0.006-10, pump: 0.11-30; 1.1-2.6[d]
Incidental inhalation-powders	3216[c]; 2643[d]	1-77.3[c]; powder: 0.024-15; 1.1-2.6[d]
Dermal contact	12 710	0.006-78.5
Deodorant (underarm)	136	Not spray: 0.1-10.4; pump: 2
Hair-noncoloring	1911	0.015-47.3
Hair-coloring	490	0.0007-20
Nail	5[7]	0.0001-45
Mucous Membrane	2597	0.66-68.6
Baby	125	2-21

Totals = Rinse-off + Leave-on + Diluted for Bath Product Uses.

[a] 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.

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

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

[d] Not specified whether a powder or a spray, so this information is captured for both categories of incidental inhalation.

Table 3. FDA regulations on glycerin.

Citation	Regulation
	Food additive
21CFR172.866	FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Synthetic glycerin produced by the hydrogenolysis of carbohydrates may be safely used in food, subject to the provisions of this section: (a) It shall contain not in excess of 0.2 percent by weight of a mixture of butanetriols. (b) It is used or intended for use in an amount not to exceed that reasonably required to produce its intended effect.
	Indirect food additive
21CFR175.300	INDIRECT FOOD ADDITIVES: ADHESIVES AND COMPONENTS OF COATINGS Resinous and polymeric coatings may be safely used as the food-contact surface of articles intended for use in producing, manufacturing, packing, processing, preparing, treating, packaging, transporting, or holding food, in accordance with the following prescribed conditions: (a) The coating is applied as a continuous film or enamel over a metal substrate, or the coating is intended for repeated food-contact use and is applied to any suitable substrate as a continuous film or enamel that serves as a functional barrier between the food and the substrate. The coating is characterized by one or more of the following descriptions: (1) Coatings cured by oxidation. (2) Coatings cured by polymerization, condensation, and/or cross-linking without oxidation. (3) Coatings prepared from prepolymerized substances. (b) The coatings are formulated from optional substances that may include: (1) Substances generally recognized as safe in food. (3) Any substance employed in the production of resinous and polymeric coatings that is the subject of a regulation in subchapter B of this chapter and conforms with any specification in such regulation. Substances named in this paragraph (b)(3) and further identified as required: (*b*) Rosin esters formed by reacting rosin (paragraph (b)(3)(v)(*a*) of this section) with: Glycerol (*c*) Polyhydric alcohols: Glycerol Trimellitic anhydride adducts of ethylene glycol and glycerol, prepared by the reaction of 1 mole of trimellitic anhydride with 0.4-0.6 mole of ethylene glycol and 0.04-0.12 mole of glycerol, for use only as a cross-linking agent at a level not to exceed 10 percent by weight of the cured coating, provided that the cured coating only contacts food containing not more than 8 percent alcohol. Glycerol (ii) Reconstituted oils from triglycerides or fatty acids derived from the oils listed in paragraph (b)(3)(i) of this section to form esters with: (iv) Natural fossil resins, as the basic resin: Glycerol ester of damar, copal, elemi, and sandarac. (v) Rosins and rosin derivatives, with or without modification by polymerization, isomerization, incidental decarboxylation, and/or hydrogenation, as follows: (*b*) Rosin esters formed by reacting rosin (paragraph (b)(3)(v)(*a*) of this section) with: Glycerol. (*c*) Polyhydric alcohols: Glycerol.
21CFR178.3500	INDIRECT FOOD ADDITIVES: ADJUVANTS, PRODUCTION AIDS, AND SANITIZERS Synthetic glycerin may be safely used as a component of articles intended for use in packaging materials for food, subject to the provisions of this section: (a) It is produced by the hydrogenolysis of carbohydrates, and shall contain not in excess of 0.2 percent by weight of a mixture of butanetriols. (b) It is used in a quantity not to exceed that amount reasonably required to produce its intended physical or technical effect, and in accordance with any limitations prescribed by applicable regulations in parts 174, 175, 176, 177, 178 and 179 of this chapter. It shall not be intended to, nor in fact accomplish, any direct physical or technical effect in the food itself.
21CFR182.90	SUBSTANCES GENERALLY RECOGNIZED AS SAFE Substances migrating to food from paper and paperboard products. Substances migrating to food from paper and paperboard products used in food packaging that are generally recognized as safe for their intended use, within the meaning of section 409 of the Act, are as follows: Glycerin
21CFR182.1320	SUBSTANCES GENERALLY RECOGNIZED AS SAFE Subpart B--Multiple Purpose GRAS Food Substances (a)*Product.* Glycerin. (b)*Conditions of use.* This substance is generally recognized as safe when used in accordance with good manufacturing practice.
	Drug
21CFR346.14	ANORECTAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE Active Ingredients Protectant active ingredients. (a) The following active ingredients may be used as the sole protectant active ingredient in a product if the ingredient as identified constitutes 50 percent or more by weight of the final product. In addition, the following active ingredients may be used in concentrations of less than 50 percent by weight only when used in combinations in accordance with 346.22 (a), (b), or (n). (3) Glycerin in a 20- to 45-percent (weight/weight) aqueous solution so that the final product contains not less than 10 and not more than 45 percent glycerin (weight/weight). Any combination product containing glycerin must contain at least this minimum amount of glycerin.
21CFR347.10	SKIN PROTECTANT DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE Active Ingredients Skin protectant active ingredients. The active ingredients of the product consist of any of the following, within the concentration specified for each ingredient: (h) Glycerin, 20 to 45 percent.

21CFR349.12	OPHTHALMIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE Active Ingredients The active ingredients of the product consist of any of the following, within the established concentrations for each ingredient: (d) Polyols, liquid: (1) Glycerin, 0.2 to 1 percent. demulcents.
	Agriculture
21CFR582.1320	SUBCHAPTER E--ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS SUBSTANCES GENERALLY RECOGNIZED AS SAFE General Purpose Food Additives (a)Product. Glycerin. (b)Conditions of use. This substance is generally recognized as safe when used in accordance with good manufacturing or feeding practice.
27CFR21.151	Title 27 - Alcohol, Tobacco Products and Firearms. CHAPTER I - ALCOHOL AND TOBACCO TAX AND TRADE BUREAU, DEPARTMENT OF THE TREASURY. SUBCHAPTER A - ALCOHOL. PART 21 - FORMULAS FOR DENATURED ALCOHOL AND RUM. Subpart G - Denaturants Authorized for Denatured Spirits. List of denaturants authorized for denatured spirits. Context: Glycerin (Glycerol), U.S.P; Specially Denatured Alcohol. 31-A.
40CFR180.1250 40CFR180.910 40CFR180.920 40CFR180.930 40CFR180.950	Glycerin is used in several pesticide applications, including those applied to food and feed crops. Glycerin is exempted from the requirement of a tolerance when used in accordance with good agricultural practice as inert (or occasionally active) ingredients in pesticide formulations applied to growing crops only.
	Other
27CFR21.58	Alcohol, Tobacco Products and Firearms. CHAPTER I - ALCOHOL AND TOBACCO TAX AND TRADE BUREAU, DEPARTMENT OF THE TREASURY ALCOHOL. PART 21 - FORMULAS FOR DENATURED ALCOHOL AND RUM. Subpart D - Specially Denatured Spirits Formulas and Authorized Uses (a) Formula. To every 100 gallons of alcohol add: One hundred pounds of glycerin (glycerol), U.S.P., and 20 pounds of hard soap, N.F. XI. (b) Authorized uses. (1) As a solvent: 113.Lotions and creams (hands, face, and body). 131.Tooth paste and tooth powder. 141.Shampoos.

Table 4. Acute toxicity studies of glycerin

Animal (n, if provided)	Results and notes	Reference
	Oral	
Rat	LD_{50} >10000 mg/kg	2
Rat	LD_{50}=12600 mg/kg	2
Long-Evans, rat, female (12)	LD_{50}=27200 mg/kg for both natural and synthetic glycerin. Purity of both test materials = 99.5% administered neat. Clinical signs included muscle spasms and convulsions. Survivors appeared normal within 2.5 h of dosing. Number of deaths was not reported. Macroscopic examination of decedents and survivors showed hyperemia of the pylorus, small intestine and cerebral meninges (3 rats), and congestion of the lungs and pale spleen.	23
Sprague-Dawley rat (10)	LD_{50}>2530 mg/kg	20
Fischer 344 rat, female (5)	LD_{50}>24000 mg/kg Glycerin/water mixture of unknown composition. No deaths at 48 h.	22
Wistar rat, male (10)	LD_{50}=27500 mg/kg	24
Rat	LD_{50}>25000 mg/kg	17
Rat	LD_{50}=58400 mg/kg	21
NMRI mouse, male and female (10)	LD_{50}=37950 mg/kg	20
Mouse	LD_{50}=4090 mg/kg	2
Mouse	LD_{50}~26000 mg/kg. LD_{50} for natural glycerin = 20.65 cc/kg; LD_{50} for synthetic glycerin = 20.81 cc/kg. Purity of the synthetic glycerin = 99.8%.	25
Mouse	LD_{50} = 38000 mg/kg	20
Swiss mouse, male	LD_{50}=23000 for both natural and synthetic glycerin. Purity of both test materials = 99.5% administered neat. Body tremors, erection of the tail, and generalized clonic convulsions preceded all observed deaths of mice.	23
Mouse	LD_{50}=4250 mg/kg	2
Mouse	LD_{50}>38000 mg/kg	17
Mouse	LD_{50}=37763 mg/kg	21
Mouse	LD_{50}=25888 mg/kg	21
Mouse	LD_{50}=12500 mg/kg	26
Mouse	LD_{50}=25000 mg/kg	26

Table 4. Acute toxicity studies of glycerin

Animal (n, if provided)	Results and notes	Reference
Rabbit	LD_{50}=27000 mg/kg	2
Guinea pig (9-10)	LD_{50}=10000 ± 130 mg/kg for natural glycerin and 11500 ± 2800 mg/kg for synthetic glycerin.. Purity of both test materials = 99.5%; administered neat. Tremors of the head and body, initiated by auditory stimuli, occurred immediately after injection. Death was usually preceded by tremors, but not all guinea pigs with tremors died.	23
Guinea pigs (10)	LD_{50}=77500 mg/kg	24
Dermal		
Rat	LD_{50}>21900 mg/kg. 2.52g of the neat liquid (21900 mg/kg) for more than 20 min produced excretion of hemoglobin in the urine of male rats, indicating red blood cell damage. No deaths.	2
Rabbit (6)	LD_{50}>18700 mg/kg for both natural and synthetic glycerin. Purity for both natural and synthetic glycerin=99.5%. Glycerin under occlusion for 8 h. No clinical signs were observed for either synthetic or natural glycerin.	23
Intraperitoneal		
Rat	LD_{50}=7500 – 10100 mg/kg	2
Rat	LD_{50}=4420 mg/kg	2
Mouse	LD_{50}=8600 – 9500 mg/kg	2
Mouse	LD_{50}=8700 mg/kg	2
Subcutaneous		
Rat	LD_{50}=100 mg/kg	2
Mouse	LD_{50}=91 mg/kg	2
Mouse	LD_{50}=10000 mg/kg	26
Intravenous		
Rat	LD_{50}=5200–6600 mg/kg	2
Rat	LD_{50}=5566 mg/kg	2
Mouse	LD_{50}=5700–6700 mg/kg	2
Mouse	LD_{50}=4250–4370 mg/kg. LD_{50} for natural glycerin=4.37 g/kg; LD_{50} for synthetic glycerin=4.25 g/kg. Purity of the synthetic glycerin = 99.8%.	2
Mouse	LD_{50}=4250 mg/kg	2
Mouse	LD_{50}=6000 mg/kg	26
Rabbit	LD_{50}=53000 mg/kg	2

Table 5. Repeated dose toxicity studies.

Animal	n		Results and notes	References
		Oral		
Charles River rat, female	10, 20 control	0, 0.75, 1.5, or 3.0 mg/kg glycerin; 100% by stomach tube; 3 times/day for 3 days.	Undiluted glycerin caused a dose-dependent increase in the number of animals showing hyperemia, petechial hemorrhage and erosions. Dilution of glycerin reduced the effects.	27
Wistar rats, male	24, 18 controls. 3 control and 4 treatment rats were killed and necropsied at 6 times	Glycerin replaced the 53.4% carbohydrate in feed for 20 d. Controls had stock carbohydrate or were fed a stock diet calculated to deliver the same calories as the glycerin diet. A rat was necropsied each day at the same time. Several enzymes, including glycerol kinase, were assayed.	Controls gained weight at 6%/d, glycerin fed and pair-fed controls gained 3%/d. Livers were 6% bw in the glycerin-fed rats and 4.6% in the other two groups. Kidneys of the glycerin-fed rats were 45% heavier than normal; the fat pad was normal. Enzymes increased and remained high in activity in the kidneys and livers of the glycerin-fed rats. At the end of the experiment, 95% of the ingested glycerin was being retained and blood glucose and liver glycogen were above normal. Water intake and urine production in the glycerin-fed rats were ~ 5 times higher than the normal.	28
Carworth rat, male	Not specified	Diet containing 20% glycerin (8824 mg/kg bw/d) for 4 weeks. At the end of 4 weeks, 5 rats were killed and necropsied. Both epididymus fat pads were excised, dried, and weighed. Liver total lipids and cholesterol were determined.	No adverse effects.	29
Rat, male	20	0, 1%, 5%, 10%, 20% (115, 575, 1150 and 2300 mg/kg	No adverse effects were observed for growth curves, lethality, and histological examination of the kidneys, livers, and bladders. Mortality	30

		aqueous); 1 mL; for 44 days	was 15% in all groups.	
Rat, female	5	5% natural and synthetic glycerin in drinking water (3335 mg/kg/day) for 6 months.	No effects on growth, red blood cells and hemoglobin. Macroscopic incidental findings were a small thymus in 2 rats and slight interstitial pneumonia in one on natural glycerin and small spleen (with small lymph nodes and moderate hemosiderin deposits) and thymus atrophia in one animal that died on synthetic glycerol. Calcified masses in kidney tubules between cortex and medulla in 3/5 rats on natural glycerin and 3/5 rats on synthetic glycerin.	[25]
Long-Evans rat, male and female (22/sex; 26 controls)	6-7	Diet containing 0, 5%, 10%, or 20% natural or synthetic glycerin for 2 years. Purity 99.5%.	Feed consumption was increased in males at 5% and 10% natural glycerin. No treatment related effects in hematology, urinalysis, albumin, organ weights, gross pathology, and liver glycogen and lipids. Incidental bronchiectasis, pneumonia, pulmonary abscesses, *taenia* infestation of the liver, hydronephrosis and pyelonephritis (27 rats total).	[23]
Rabbit	4	0 or 50%, 10 mL in saline or saline by stomach tube or from a drinking cup daily for 30-40 d.	No adverse effects. Well tolerated. Necropsy at the end of the experiment showed no gross pathological changes. Neither the plasma nor the red blood cell cholesterol levels showed any consistent changes which could be attributed to glycerin.	[32]
Mongrel dog, male and female	Not specified	950, 1900 and 3800 mg/kg 3 times/d for 3 days	NOEL=950 mg/kg.. At 950 mg/kg bw: no abnormalities. At 1900 mg/kg: stomach mucosa was severely hyperemic with petechial hemorrhages. At 3800 mg/kg: stomach mucosa was (slightly to) severely hyperemic with areas with petechial hemorrhages or erosions; duodenum appeared normal or with hyperemic areas.	[27]
Dog	Not specified	0, 35% in feed for 50 weeks, then reduced to 50%-80% of previous dose.	Body weight similar between groups until week 36 then after week 36 weight loss (16%, 1.8 kg) in dogs on glycerin rich diet but not in controls. Erythrocyte counts were similar between groups.	[31]
Guinea pig	10	0 or 50% in saline (= 6300 mg/kg/day) by stomach tube or from a drinking cup daily for 30–40 d.	Guinea pigs administered > 5 mL of the 50% glycerin solution by stomach tube died with acute symptoms. Necropsies revealed no pathological changes. Plasma cholesterol levels had no changes attributable to glycerin. Red blood count of 3 guinea pigs (2 stomach tube, 1 drinking water) indicated a probable anemic effect.	[32]
			Dermal	
Rabbit	12	90 days of administration of 0.5-4 mL of both natural and synthetic glycerin administered to 30% of the body surface for 8 h/d 5 d/wk, 45 weeks. Purity of both = 99.5%.	No treatment related effects at 100%	[23]
			Inhalation	
Sprague-Dawley Crl:CD Rat,, male/female	10/sex	0, 1000, 2000, 4000 mg/L for 6 h/d, 5 d/wk for 2 weeks. Nose only exposure. Particle size=<1.5µm.	LOAEL=1000 mg/m^3 based on local effects on the epithelium of the upper respiratory tract. 2 males at 1000 mg/m^3 and 1 male and 1 female at 2000 mg/m^3 died. No clinical signs observed. Body weight gains were decreased in males and females at all concentrations (28%-58% in females). Glucose decreased in females at all concentrations (19%-28%). No treatment related effects for hematology, organ weights, and gross pathology. Histopathology: minimal to mild squamous metaplasia of the epiglottis in males and females (1/10, 13/18, 16/19, and 13/14, respectively). No dose-related increase in the frequency, but the incidence of mild metaplasia was greatest in the high-dose (7 animals with minimal and 6 with mild).	[33]
Sprague-Dawley Crl:DCD rat, male/female	15/sex	0, 0.033, 0.167, 0.662 mg/L for 5 h/d, 5 d/week, 13 weeks. purity >99.8%, particle size <2.0 µm Nose–only study.	NOAEL = 0.167 mg/L. Minimal to mild squamous metaplasia of the epithelium lining the base of the epiglottis at the high dose. 3/sex necropsied at 10 and 13 weeks to examine lungs with electron microscope. No clinical signs or mortalities. No treatment related effects for body weights, clinical chemistry, hematology, organ weights, and gross pathology. Histopathology at 13 weeks: minimal squamous metaplasia of the epiglottis in 2/25, 1/19, 4/20 and 10/21 rats, respectively; 1 male at 662 mg/L showed mild squamous metaplasia. No differences in morphology of the Clara cells in control and high dose rats and histopathology.	[33]

Table 6. Fertility studies of glycerin in males.

Test animal (n)	Concentration; route	Results; notes	Reference
Sprague-Dawley rat; age 48, 69, 90-95 days old (12)	0, 50-200 µL; 2 intratesticular injections 7 days apart into right testes; left was control	Testis treated with 50 µL decreased in weight (45%-60% within 2 weeks) compared to control side for all ages and complete loss of spermatogenic cells. Testis treated with 200 µL had decreased weights of prostate and seminal vesicles over 73 d. Number of sperm/epididymis declined rapidly, reduced by 99.99% (of controls) after the 3rd mating. Females were added in weeks 2, 3, 4, 5 and 6. Treated males mated with virgin females at same frequency as controls but all were infertile after 3rd mating and remained infertile for the duration of the tests (21 weeks after treatment). No resumption of spermatogenesis	37
Rat (not provided)	862 mg/kg; Intratesticular injection 1 day prior to mating	Suppressed spermatogenesis (meiosis). No evidence of toxic or endocrine effects.	35
Monkey	119 mg/kg; Intratesticular injection 1 day prior to mating	Suppressed spermatogenesis (meiosis). No evidence of toxic or endocrine effects.	36
Human (64; control, 63)	Exposure through working in a factory manufacturing glycerin; manufacturing process not provided.	No differences observed sperm counts and percent normal forms compared with a control group.	38

Table 7. Genotoxicity assays of glycerin.

Assay	Concentration	Result; comments	Reference
		In Vitro	
Ames test using *S. typhimurium* (strain TA100)	0.1 and 1 mmol/plate	Negative with and without metabolic activation	42
Ames test using .*S typhimurium* (strains TA98, TA100, TA1535, TA1537, and TA1538)	0.2, 0.4, 0.6, 0.8, and 1.0 mg/plate	Negative with and without metabolic activation	39
Ames test using .*S typhimurium* (strains TA98, TA100, TA1535, and TA1537)	10 mg/plate	Negative with and without metabolic activation; tested in 3 laboratories. One lab had ambiguous results.	40
Ames test using .*S typhimurium* (strains TA98, TA100, TA1537, and TA1538)	10 mg/plate	Negative with and without metabolic activation	22
Ames test using *S. typhimurium* (strain TA100)	0.5 mg/plate	Negative with and without metabolic activation	43
Ames test using *S. typhimurium* (strains TA94, TA98, TA100, TA1535, and TA1537)	50 mg/plate	Negative with and without metabolic activation	41
Ames test using .*S typhimurium* (strains TA98, TA100, TA1535, and TA1537)	1 -10 µg/plate; Glycerin/water mixture of unknown composition	Negative with and without metabolic activation	22
Cytogenetic Assay using CHO cell line WBL	0.1, 0.2, 0.3, 0.6, 0.8, and 1.0 mg/mL	Negative with and without metabolic activation	39
HGPRT assay using CHO (K1 and BH4 cell lines)	0.1, 0.2, 0.4, 0.6, 0.8, and 1.0 mg/mL	Negative with and without metabolic activation	39
Sister chromatid exchange assay using CHO (cell line WBL)	0.2, 0.4, 0.6, 0.8, and 1.0 mg/mL	Negative with and without metabolic activation; purity >99.5%.	39
Unscheduled DNA synthesis using rat hepatocytes	0.1, 0.25, 0.5, 0.75, and 1.0 mg/mL	Negative without metabolic activation; purity >99.5%.	39
Chromosomal aberration test using CHO cells	1 mg/mL	Negative 100 metaphases analyzed.	41
		In Vivo	
Chromosome aberration assay using male rats (species and number not specified)	1 mg/kg; orally in water or saline administration	Number of cells with aberrations 2.2% vs. 0% in concurrent controls; cells with gaps 1.6% vs. 0%; polyploid cells 3.2% vs. 0%. Purity of the test substance is not specified.	44
Chromosome aberration assay using male rats	1000 mg/kg by injection into abdomen	Negative Cytogenic analysis was performed in 50 metaphases	44
Dominant lethal gene using male rats	0, 10, 100 and 1000 mg/kg	Male rats (number not specified) were probably injected in the abdomen then 2 weeks after mating females were killed and necropsied. Trend for potential mutagenic effect on gender cells, resulting in post-implantation deaths but did not reach statistical significance. Implantation sites: 116, 101, 104, respectively. Fetal loss: 8%, 11%, 20%, and 59%, respectively. Live fetuses: 107, 90, 83 and 37, respectively. No anomalies observed in treatment and control groups.	44

Table 8. Carcinogenicity studies of glycerin.

Test animal (n)	Concentration and administration route	Result; comments	Reference
Male and female rats (strain not specified; 24)	5 or 10 g/kg in feed for 2 yr	No increase in the incidence of tumors	[23]
Male and female Long-Evans rats (22/sex)	0, 5%, 10%, in diet for 2 yr; 20% in diet for 1 yr; natural and synthetic glycerin	No increased incidence of tumors following treatment with glycerin. Body weight gain: no differences between treatment and control groups. Histopathology: malignant neoplasms in 5/26 rats in the control group and 1/22, 5/22, 0/22, rats for natural glycerin and 0/21, 5/22 and 0/22 for synthetic glycerin, for 5%, 10%, and 20%, respectively. Benign neoplasms in 0/26 rats in the control group and 2/22, 1/22, 0/22, rats for natural glycerin and 4/21, 4/22 and 1/22, respectively. Among the benign tumors 3 rats were found with pheochromocytomas, 2 with granulosa cell tumors.	[23]
Synergistic effects			
ddy Mouse (18-20)	0 or 5% in drinking water for 1–4 weeks	Increased number of pulmonary tumor–bearing mice and mean number of induced tumors/mouse in mice administered glycerin for 4–25 weeks after 4NQO treatment, compared with mice given 4NQO alone. No. of mice with tumors: controls (no 4NQO)-1/20; controls (4NQO)-8/20; 1 week glycerin-11/20; 2 weeks glycerin-11/19; 3 weeks glycerin-7/18; 4 weeks glycerin-15/19	[47]
Male ddy mice (n = 20)	0, 5% (~8350 mg/kg/d) in drinking water for 25 weeks with and without a single injection of 4NQO	Glycerin alone did not result in an increase in number of mice with tumors compared to untreated controls. Glycerin did have a synergistic effect with 4NQO. 2 rats in the treatment group died (weeks 25-28) with only fibrosarcomas at injection site, only these had these tumors. Body weight: no treatment related effects. Pulmonary tumors: No. of mice with tumors: controls-2/20; controls (glycerin)-2/20; treatment (4NQO)-5/20; treatment (4NQO + glycerin) -17/20. Mean number of tumors/mouse: increased after 4NQO + glycerin-2.9/mouse vs. 0.1-0.45/mouse in the other groups. Histopathology: 4NQO treated mice all tumors were identified as type II adenomas. In 4NQO + glycerin treated mice 52 tumors were identified as type II adenomas and 6 as Clara cell adenomas.	[45]
Male ddy mice (n = 10)	0, 5% (~8350 mg/kg/d) in drinking water for 25 weeks with and without a single injection of 4NQO	Glycerin promoted tumorigenesis when administered after 4NOQ. No. of mice with tumors: controls 0/10; controls (glycerin)-0/10; controls (4NQO)-1/10; treatment (4 weeks glycerin)-8/10; treatment (25 weeks glycerin)-8/9; treatment (glycerin week 4-25)- 7/10. - Mean number of tumors/mouse: controls-0; controls (glycerin 25 weeks)-0; controls (4NQO)-0.1; treatment (4 weeks glycerin)-3.5; treatment (25 weeks glycerin)-2.3; treatment (glycerin week 4-25)-1.9. Histopathology: All tumors were adenomas.	[46]

4NQO – 4-Nitroquinoline 1-oxide

Table 9. Dermal irritation studies.

Animal (n, if provided)	Results and notes	Reference
Rabbit (12)	Not irritation at 100% after 90 days of administration. Draize test of 0.5-4 mL of both natural and synthetic glycerin administered to 30% of the body surface for 8 h/d 5 d/wk, 45 weeks. Purity of both = 99.5%.	[23]
Rabbit, New Zealand female (6)	Not irritating 0.5 mL glycerin/water mixture of unknown composition. Draize scale score 0.1 for intact and abraded skin.	[22]
Rabbit, albino male (8)	Not irritating 0.5 mL administered to 6.25 cm^2 of skin for 24 hours. No signs of irritation at 24 and 72 h. Draize scale scores 0-0.4 compared to a maximum score of 30.	[48]
Guinea pig (~45)	Mildly irritating; + 0.1 cc administered to the shaved abdominal skin and observed at 4 and 24 h.	[26]

Table 10. Ocular irritation studies.

Animal (n)	Results and notes	Reference
Rabbit (6)	Not irritating 0.1 mL at 100%. No irritation at 1, 24 and 72 h and 7 days. Overall Draize score 0-2 on a scale of 110.	48
Rabbit (4)	Not irritating for both natural and synthetic glycerin with purity of 99.5%. The conjunctiva was irritated in all rabbits 1 h after treatment. Resolved at 24 h after treatment.	23
Rabbit, New Zealand White, female (6)	Not irritating 0.1 mL at 100% glycerin/water mixture of unknown composition. Overall Draize score 0.4 at 1h, 0 at 24-96 h.	22
Rabbit (5)	Mildly irritating; + for both edema and hyperemia. ~0.5 cc at 100%	26

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Cosmetic Ingredient Review

Commitment & Credibility since 1976

MEMORANDUM

To: CIR Expert Panel and Liaisons

From: Lillian C. Becker, M.S.
Scientific Analyst and Writer

Date: August 18, 2014

Subject: Glycerin as Used in Cosmetics

Unpublished data were submitted for the glycerin safety assessment by the Personal Care Products Council. Frequency of use data from the Food and Drug Administration were collected. The data in this packet include:

Data1&2: Concentration of use data

Data3: VCRP data

Data4: Sensitization test of a moisturizer that contains 65.9% glycerin

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Personal Care Products Council
Committed to Safety, Quality & Innovation

TO: Lillian Gill, Ph.D.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Halyna Breslawec, Ph.D.
Industry Liaison to the CIR Expert Panel

DATE: February 4, 2014

SUBJECT: Concentration of Use by FDA Product Category: Glycerin

Concentration of Use by FDA Product Category
Glycerin

Product Category	Maximum Concentration of Use
Baby lotions, oils and creams not powder	 3-21%
Other baby products	2-11%
Bath oils, tablets and salts	24.9-30%
Bubble baths	0.66-3%
Bath capsules	26%
Other bath preparations	2.8-47.9%
Eyebrow pencil	3-6.6%
Eye liner	0.5-21.3%
Eye shadow	2.6-21.3%
Eye lotion	4-40.6%
Eye makeup remover	1.1-7.8%
Mascara	0.025-9.7%
Other eye makeup preparations	1-14.8%
Colognes and toilet waters	5-6%
Perfumes	2-25%
Sachets	5%
Other fragrance preparations	5.1-12.8%
Hair conditioners	0.015-38%
Hair sprays aerosol pump	 0.11-10% 0.11-30%
Hair straighteners	2-3%
Permanent waves	18.8%
Rinses (noncoloring)	1-13%
Shampoos (noncoloring)	0.015-20%
Tonics, dressings and other hair grooming aids	0.65-47.3%
Wave sets	27%
Other hair preparations (noncoloring)	0.5-40%

Hair dyes and colors	0.014-5%
Hair tints	20%
Hair rinses (coloring)	10%
Hair shampoos (coloring)	0.39%
Hair color sprays	0.035%
Hair lighteners with color	0.74%
Hair bleaches	0.007-6.1%
Other hair coloring preparations	0.0007-2%
Blushers	0.5-42%
Face powders	0.024-15%
Foundations	1.9-24.4%
Leg and body paints	0.03%
Lipstick	2-28.8%
Makeup bases	0.75-13%
Makeup fixatives	4-10.8%
Other makeup preparations	0.94-11.4%
Basecoats and undercoats	4%
Cuticle softeners	2-23.6%
Nail creams and lotions	6.1-45%
Nail polish and enamel	0.0001-0.025%
Nail polish and enamel removers	0.2-5%
Other manicuring preparations	10%
Dentifrices	4.8-58.8%
Mouthwashes and breath fresheners	10%
Other oral hygiene products	5-68.6%
Bath soaps and detergents	1-60%
Deodorants not spray pump spray	 0.1-10.4% 2%
Feminine hygiene deodorants	1.1-2.6%
Other personal cleanliness products	1.1-46%
Aftershave lotions	1.5-10.5%

Shaving cream	0.09-12.2%
Shaving soap	5-9%
Other shaving preparations	3.5-10%
Skin cleansing	1-65.7%
Depilatories	0.84-8.7%
Face and neck products not spray spray	 6-54% 0.5-10%
Body and hand products not spray spray	 4.5-78.5% 0.006-5%
Foot powders and sprays	12.1-77.3%
Moisturizing products not spray spray	 0.14-66% 3.3%
Night products not spray	 2-21%
Paste masks and mud packs	2.6-58.3%
Skin fresheners	1-15%
Other skin care preparations	0.12-45.1%
Suntan products not spray aerosol pump spray	 3-17.9% 6% 10%
Indoor tanning preparations	1.1-14%
Other suntan preparations	0.075-10%

Information collected 2013-2014
Table prepared February 4, 2014

2014 VCRP for Glycerin

01A - Baby Shampoos	GLYCERIN	17
01B - Baby Lotions, Oils, Powders, and Creams	GLYCERIN	53
01C - Other Baby Products	GLYCERIN	55
02A - Bath Oils, Tablets, and Salts	GLYCERIN	23
02B - Bubble Baths	GLYCERIN	91
02C - Bath Capsules	GLYCERIN	1
02D - Other Bath Preparations	GLYCERIN	52
03A - Eyebrow Pencil	GLYCERIN	4
03B - Eyeliner	GLYCERIN	41
03C - Eye Shadow	GLYCERIN	84
03D - Eye Lotion	GLYCERIN	293
03E - Eye Makeup Remover	GLYCERIN	46
03F - Mascara	GLYCERIN	130
03G - Other Eye Makeup Preparations	GLYCERIN	263
04A - Cologne and Toilet waters	GLYCERIN	233
04B - Perfumes	GLYCERIN	16
04C - Powders (dusting and talcum, excluding aftershave talc)	GLYCERIN	1
04D - Sachets	GLYCERIN	1
04E - Other Fragrance Preparation	GLYCERIN	192
05A - Hair Conditioner	GLYCERIN	567
05B - Hair Spray (aerosol fixatives)	GLYCERIN	90
05C - Hair Straighteners	GLYCERIN	9
05D - Permanent Waves	GLYCERIN	18
05E - Rinses (non-coloring)	GLYCERIN	13
05F - Shampoos (non-coloring)	GLYCERIN	490
05G - Tonics, Dressings, and Other Hair Grooming Aids	GLYCERIN	414
05H - Wave Sets	GLYCERIN	19
05I - Other Hair Preparations	GLYCERIN	274
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	GLYCERIN	369
06B - Hair Tints	GLYCERIN	32
06C - Hair Rinses (coloring)	GLYCERIN	8
06D - Hair Shampoos (coloring)	GLYCERIN	7
06F - Hair Lighteners with Color	GLYCERIN	2
06G - Hair Bleaches	GLYCERIN	9
06H - Other Hair Coloring Preparation	GLYCERIN	63
07A - Blushers (all types)	GLYCERIN	36
07B - Face Powders	GLYCERIN	68
07C - Foundations	GLYCERIN	273
07D - Leg and Body Paints	GLYCERIN	27
07E - Lipstick	GLYCERIN	160
07F - Makeup Bases	GLYCERIN	71
07G - Rouges	GLYCERIN	29
07H - Makeup Fixatives	GLYCERIN	6
07I - Other Makeup Preparations	GLYCERIN	145

08A - Basecoats and Undercoats	GLYCERIN	1
08B - Cuticle Softeners	GLYCERIN	15
08C - Nail Creams and Lotions	GLYCERIN	9
08E - Nail Polish and Enamel	GLYCERIN	2
08F - Nail Polish and Enamel Removers	GLYCERIN	18
08G - Other Manicuring Preparations	GLYCERIN	12
09A - Dentifrices	GLYCERIN	60
09B - Mouthwashes and Breath Fresheners	GLYCERIN	58
09C - Other Oral Hygiene Products	GLYCERIN	75
10A - Bath Soaps and Detergents	GLYCERIN	1295
10B - Deodorants (underarm)	GLYCERIN	136
10C - Douches	GLYCERIN	3
10E - Other Personal Cleanliness Products	GLYCERIN	779
11A - Aftershave Lotion	GLYCERIN	213
11D - Preshave Lotions (all types)	GLYCERIN	5
11E - Shaving Cream	GLYCERIN	91
11F - Shaving Soap	GLYCERIN	18
11G - Other Shaving Preparation Products	GLYCERIN	68
12A - Cleansing	GLYCERIN	1028
12B - Depilatories	GLYCERIN	5
12C - Face and Neck (exc shave)	GLYCERIN	1368
12D - Body and Hand (exc shave)	GLYCERIN	1260
12E - Foot Powders and Sprays	GLYCERIN	15
12F - Moisturizing	GLYCERIN	2611
12G - Night	GLYCERIN	351
12H - Paste Masks (mud packs)	GLYCERIN	269
12I - Skin Fresheners	GLYCERIN	131
12J - Other Skin Care Preps	GLYCERIN	717
13A - Suntan Gels, Creams, and Liquids	GLYCERIN	40
13B - Indoor Tanning Preparations	GLYCERIN	181
13C - Other Suntan Preparations	GLYCERIN	23
03G - Other Eye Makeup Preparations	GLYCERIN, ANHYDROUS	1
12F - Moisturizing	GLYCERIN, ANHYDROUS	1
		15654

Personal Care Products Council
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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: July 8, 2014

SUBJECT: Information on a Product Containing Glycerin

International Research Services Inc. 2006. A study to assess the skin sensitization potential of one test product (moisturizer containing 65.9% Glycerin) when applied to the skin of 50 healthy human subjects in a shared panel assay.

1620 L Street, N.W., Suite 1200 | Washington, D.C. 20036 | 202.331.1770 | 202.331.1969 (fax) | www.personalcarecouncil.org

INTERNATIONAL RESEARCH SERVICES INC.

A STUDY TO ASSESS THE SKIN SENSITIZATION POTENTIAL OF ONE (1) TEST PRODUCT WHEN APPLIED TO THE SKIN OF 50 HEALTHY HUMAN SUBJECTS IN A SHARED PANEL ASSAY

Moisturizer containing 65.9% Glycerin

FINAL REPORT

PROTOCOL NO. 31401105KN
Version 1.0

Submitted to:

January 10, 2006

STUDY SITE:
International Research Services, Inc.
222 Grace Church Street
Port Chester, NY 10573
(914) 937-6500

INVESTIGATOR:
Gerald Davis, M.D.

STUDY COORDINATOR:
Sandra P. Haney, B.S., M.T. (ASCP)

222 Grace Church Street • Port Chester, NY 10573 • (914) 937-9483 • 1-800-548-0158 • Fax (914) 937-8067

January, 2006

Re: A Study To Assess The Skin Sensitization Potential Of One (1) Test Product When Applied To The Skin Of 50 Healthy Human Subjects In A Shared Panel Assay; IRSI 31401105KN

This report accurately reflects the data derived from the procedures and materials tested in this study. The conclusions are based on an interpretation of the data and have been reviewed by the Principal Investigator and by personnel from International Research Services, Inc. responsible for assuring its accuracy.

01.11.06

Edward K. Boisits, Ph.D.
Vice President, Clinical Research

1/12/06

Stephen R. Schwartz, MS
President

TABLE OF CONTENTS

SUMMARY / RESULTS & DISCUSSION

The objective of the present study was to assess the skin sensitization potential of

when applied to the skin of human subjects in accordance with a modified Draize Assay. The study was initiated on November 28, 2005 and completed on January 6, 2006. Fifty-eight (58) subjects were enrolled and 48 subjects completed the study. Three (3) subjects discontinued for schedule conflicts and seven (7) subjects discontinued for personal reasons. There were no adverse experiences recorded during the study.

In conclusion, under the conditions employed in this study, there were no challenge reactions or induction responses and as such, no evidence of irritation or sensitization was observed.

Gerald Davis, M.D.

1.0 INVESTIGATOR/STUDY LOCATION/STATUS

The study was initiated on November 28, 2005 and was conducted in the facilities of International Research Services, Inc. in Port Chester, New York. Gerald Davis, M.D., was the Principal Investigator. The study concluded on January 6, 2006. Fifty-eight (58) subjects were enrolled and 48 subjects completed the study.

2.0 TEST PRODUCTS

The following product was supplied in sufficient quantity by

#	PRODUCT NAME & DESCRIPTION	PRODUCT NUMBER	TEST AS
1			Occlusive, as received

3.0 STUDY PROCEDURE

This study was conducted as per the protocol found in Appendix III.

4.0 STUDY DEMOGRAPHICS

4.1 DEMOGRAPHICS

Age Mean (years)	Sex	Race
50.85±2.16	Male - 16 (33.3%) Female - 32 (66.7%)	Caucasian - 27 (56.3%) Afro-American - 11 (22.9%) Hispanic - 10 (20.8%)

4.2 STATUS

Enrolled	Discontinued	Completed
58	3 – Discontinued for schedule conflicts. 7 – Discontinued for personal reasons.	48

4.0 STUDY DEMOGRAPHICS (Continued)

4.3 ADVERSE EXPERIENCES

There were no adverse experiences recorded during this study.

5.0 PROTOCOL DEVIATIONS

None.

6.0 Q.A. STATEMENT

One hundred percent of the data generated by the statistician was checked against the source documentation by a member of the staff who has not participated in the study conduct. The report then went through internal Q.A. and validation.

7.0 DEFINITION OF DATA ANALYSIS TERMS

"Insult"	=	Induction (ten applications). Usually conducted after 48 hours or 72 hours on weekends/holidays.
"CHLG"	=	Challenge readings at 48 hours (patch removed). Challenge reading at 96 hours (no patch applied between 48 hour and 72 hour reading). Patches applied for challenge 10-14 days after last induction reading.
"Total"	=	Total (right column) induction results. Does not include challenge results. Total (left margin) number of subjects present at each induction or challenge visit.
"Not Applied"	=	Number of subjects to whom patches were not applied at a given time point.
"Absent"	=	Number of subjects not present at a given induction or challenge visit. Subjects who make up a visit with 24 hours are not listed as absent. All such instances are recorded on the examination CRF.
"Mean Induction Value"	=	Cumulative scores for a given time point --- Total number of subjects present at the same time point
"Mean Reaction Value"	=	Cumulative scores for a given time point --- Total number of subjects with reactions at the same time point

APPENDIX I

REACTION DATA:

INTERNATIONAL RESEARCH SERVICES, INC.

RIPT STUDY #31401105KN 01/23/06

	INSULT -1-	-2-	-3-	-4-	-5-	-6-	-7-	-8-	-9-	-10-	CHLG 48HR	CHLG 96HR	TOTAL
NEGATIVE	48	48	48	48	48	48	48	48	48	48	48	48	480
1.0													
2.0													
3.0													
4.0													
NOT APPLIED													
ABSENT													
TOTAL	48	48	48	48	48	48	48	48	48	48	48	48	480
MIV													
MRV													

MIV = MEAN INDUCTION VALUE
MRV = MEAN REACTION VALUE

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Memorandum

TO: Lillian Gill, D.P.A.
Director - COSMETIC INGREDIENT REVIEW (CIR)

FROM: Jay Ansell, Ph.D., D.A.B.T.
Industry Liaison to the CIR Expert Panel

DATE: June 26, 2014

SUBJECT: Comments on the Scientific Literature Review: Safety Assessment of Glycerin as Used in Cosmetics

Key Issue

Glycerin used in cosmetic products is not different than Glycerin used in other products. Currently, there is no standard setting body for cosmetic ingredients. In the past, CTFA developed standards for a few cosmetic ingredients, including Glycerin (available on the On-Line from Ingredient Composition Information, Cosmetic Ingredient Specification). The CTFA standard, which has not been updated, relies on the USP standard for Glycerin at the time the CTFA standard was developed. The CIR report should present specification information from the USP and Food Chemical Codex as these standards will be representative of the Glycerin that is available on the market.

The method of manufacture section should note that FDA recommends that industry monitor the source of Glycerin as some sources such as *Jatropha* plants may contain toxins (*Jatropha* contains phorbol esters). The FDA notification from 2012 and the 2014 update can be found at:
http://www.fda.gov/ForIndustry/IndustryNoticesandGuidanceDocuments/ucm391133.htm

Additional Comments

Physical and Chemical Properties - As the CIR Expert Panel does not assess environmental safety, the information about biodegradation should be deleted from the report.

Cosmetic Use - To put the use of Glycerin in cosmetic products into perspective, it would be helpful to state that after water and the term fragrance, Glycerin is the ingredient with the most uses reported to the FDA VCRP. Because of the large number of uses of Glycerin reported to the VCRP, the following paragraph should be deleted from this report.

"Industry is not required to register products with the VCRP. It is understood that the data in the database are a sampling of what cosmetics are available on the

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market and are not comprehensive. Not all cosmetic manufacturers are members of the Council and not all members respond to the survey request. It is understood that the information collected are also not comprehensive but do represent a large sampling of cosmetic products."

As Glycerin has a relatively high use in baby products, this use should be mentioned in the Cosmetic Use section.

Non-Cosmetic Use, Summary - In which OTC drug categories is Glycerin considered an active ingredient? What is the maximum concentration of Glycerin permitted in these products?

Toxicokinetics - At what concentration is Glycerin naturally present in human plasma? What is the route of exposure in the study in which Glycerin produced "slight diuresis in healthy individuals receiving a single dose of 1.5 g/kg or less."

Acute Exposure, Summary - The units should be consistent throughout this paragraph (it starts with g/kg then switches to mg/kg).

Repeated Dose Exposure - What was the effect observed at 950 mg/kg in rats dosed for 3 days?

Inhalation - Non-Human - Please use consistent concentration units in this section - it switches from mg/L to mg/m^3.

Reproductive and Developmental Toxicity - The description of the two-generation study does not state whether or not male rats were treated. It states "(n=10 females)", and that "no effects were observed on the reproductive efficiency of the parents" - the first statement suggests only females were treated, the second statement suggests both sexes were treated. Both sexes are generally treated in a two-generation study.

Male Fertility - Human, Table 6 - As indicated in the method of manufacture section, there is more than one method for producing Glycerin. What was the method of manufacture used in the plant of the male employees in which sperm counts were determined?

Genotoxicity, In Vitro - Please indicate the cell types used in the *in vitro* assays in mammalian cells.

Genotoxicity, In Vivo - Please state that species, dose and route of exposure used in the dominant lethal study.

Table 3 - The details unrelated to Glycerin should be deleted from 21CFR175.300. Please delete 21CFR310.545 as this section is for drugs for which there are inadequate data. These are not approved uses of Glycerin as suggested in Table 3.

The meaning of the "Agriculture" subheading is not clear. The entries 21CFR582.1320 and 27CFR21.58 do not have anything to do with agriculture. The EPA regulations (40CFR) could be combined into one row. For the purpose of this report it would be sufficient to say that when used in a number of pesticide applications, Glycerin is exempt from the requirement of a tolerance.

Table 4 - The use of the equal sign with the LD_{50} values is confusing, especially when the LD_{50} could not be determined, e.g., >1000 mg/kg.

Table 5 - An additional column in this table for study methods (duration and dose) would be helpful.

Reference 24 - The meaning of the two sets of doses ("0, 0.75, 1.5, or 3.0 mg/kg glycerin (950, 1900 and 3800 mg/kg bw)") is not clear.

Reference 25 - At what time points were the rats sacrificed? What enzymes were assessed in this study?

Reference 27 - Was this a drinking water or gavage study?

Table 7, Dominant lethal study - As only male rats are treated in dominant lethal studies, it is misleading to include "male/female" in the assay column.

Reference 37 - Please correct "in vetro"