Safety Assessment of Saccharide Humectants as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 21, 2020
Panel Meeting Date:	September 14-15, 2020

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The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D.; Lisa A. Peterson, Ph.D.; Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The Cosmetic Ingredient Review (CIR) Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Wilbur Johnson, Jr., M.S., Senior Scientific Analyst, CIR.

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Memorandum

To: Expert Panel for Cosmetic Ingredient Safety Members and Liaisons

From: Wilbur Johnson, Jr.
Senior Scientific Analyst, CIR

Date: August 21, 2020

Subject: Safety Assessment of Saccharide Humectants as Used in Cosmetics

Enclosed is the draft report on the Safety Assessment of Saccharide Humectants as Used in Cosmetics (*saccha092020rep*). This is the first time the Panel is seeing a safety assessment of these 7 cosmetic ingredients. Comments on the Scientific Literature Review (SLR) that was announced on January 24, 2020 were received from the Council, and the draft report has been revised to address these comments (*saccha092020pcpc*). The comments received are also enclosed.

The following unpublished data were also received from the Council, and are included in the draft report:

- Use concentration data (*saccha092020data1*)
- Human ocular irritation data on an eye cream containing 2.75% Saccharide Isomerate (*saccha092020data2*)
- Human repeated insult patch test on an eye cream containing 2.75% Saccharide Isomerate (*saccha092020data2*)

Also included in this package for your review are the report history (*saccha092020hist*), flow chart (*saccha092020flow*), literature search strategy (*saccha092020strat*), ingredient data profile (*saccha092020prof*), and 2020 FDA VCRP data (*saccha092020FDA*).

After reviewing these documents, if the available data are deemed sufficient to make a determination of safety, the Panel should issue a Tentative Report with a safe as used, safe with qualifications, or unsafe conclusion, and Discussion items should be identified. If the available data are deemed insufficient, an Insufficient Data Announcement should be issued, specifying the data needs therein.

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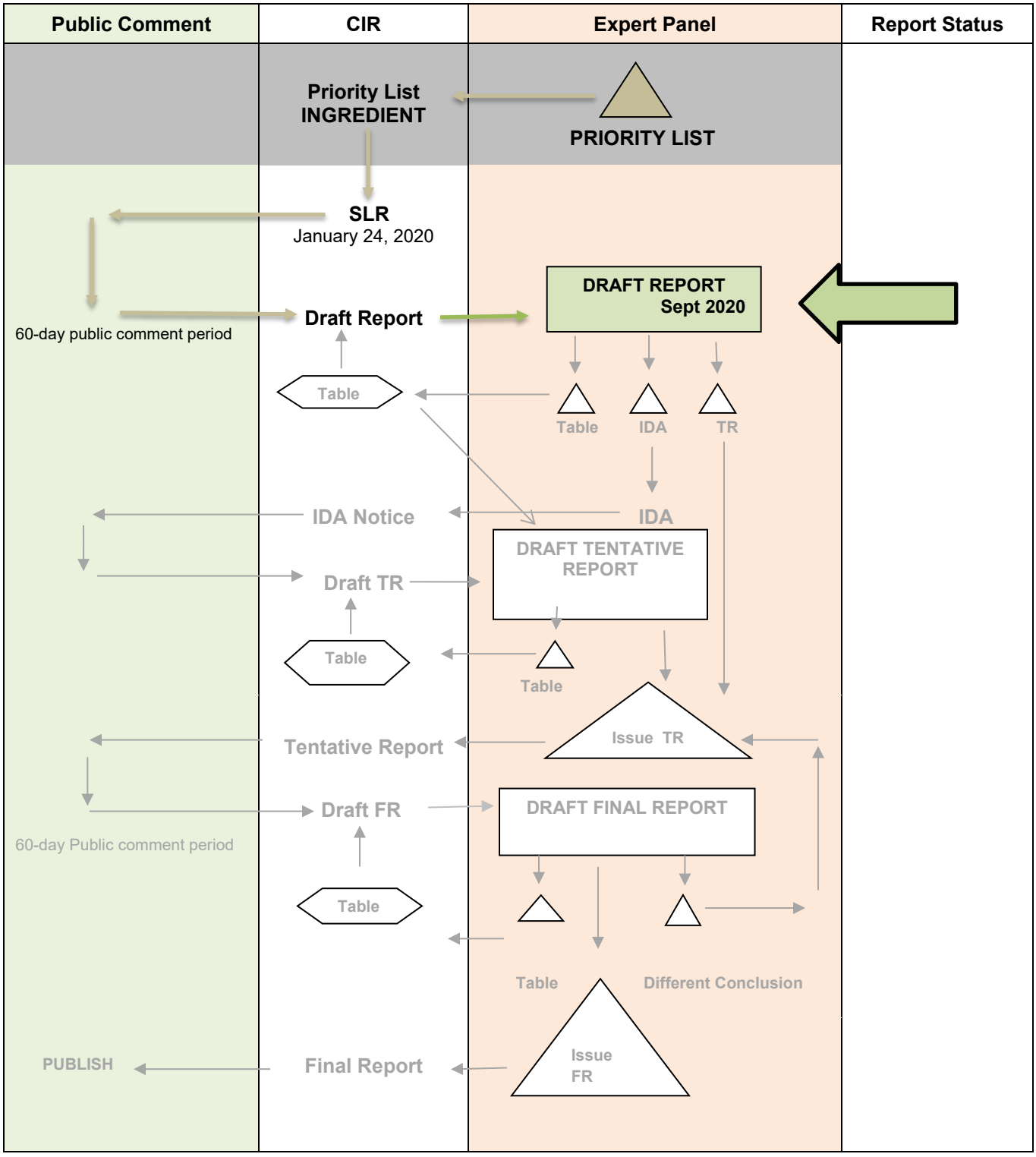
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Saccharide Humectants

MEETING September 2020



CIR History of:

Saccharide Humectants

A Scientific Literature Review (SLR) on Saccharide Humectants was issued on January 24, 2020.

Draft Report, Teams/Panel: September 14-15, 2020

The draft report has been revised to include the Council's comments, and also includes the following unpublished data that were received from the Council:

- Use concentration data
- Human ocular irritation data on an eye cream containing 2.75% Saccharide Isomerate
- Human repeated insult patch test on an eye cream containing 2.75% Saccharide Isomerate

Saccharide Humectants Data Profile* – September 14-15, 2020 – Wilbur Johnson, Jr.

						Toxico-kinetics		Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	GRAS	Method of Mfg	Constituents	Impurities	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
Saccharide Isomerate	**455**																					**X**			**X**			**X**		
Saccharide Hydrolysate	**30**	**Yes**		**X**	**X**																									**X**
Anhydrogalactose (is L-Anhydrogalactose)	**0**																													
Anhydroglucitol (is D-Anhydroglucitol)	**0**						**X**					**X**																		
Anhydroxylitol (is D-Anhydroxylitol)	**151**					**X**		**X**	**X**			**X**				**X**	**X**				**X**			**X**				**X**		
Arabinose (is D-Arabinose)	**0**						**X**		**X**			**X**						**X**												**X**
Psicose (also allulose; Dictionary does not state whether D, L, or DL)	**0**						**X**		**X**			**X**																		**X**

* "X" indicates that data were available in a category for the ingredient

Saccharide Humectants – 8/21-22/2019; 9/20/2019;8/7/2020]

Ingredient	CAS #	InfoBase	SciFinder	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Saccharide Isomerate	100843-69-4	Yes		0/0	Yes	No	No	No	No	No	No	No	No	No	No	No	No	
Saccharide Hydrolysate	8013-17-0	Yes		89/8	Yes	Yes	No	Yes	No	No	No	No	No	No	Yes	No	No	
Anhydrogalactose (is L-Anhydrogalactose)	28251-55-0	Yes		86/5	Yes	Yes	No	No	No	No	No	No	No	No	No	No	No	
Anhydroglucitol (is D-Anhydroglucitol)	154-58-5	Yes		487/16	1/0	No	No	Yes	No	No	No	No	No	No	No	No	No	
Anhydroxylitol (is D-Anhydroxylitol)	53448-53-6	Yes		5/2	1/0	No	No	Yes	No	No	No	Yes	No	No	No	No	No	
Arabinose (is D-Arabinose)	10323-20-3	Yes		510/6	12/0	Yes	No	Yes	Yes	No	No	No	No	No	No	No	No	
Psicose (also allulose; Dictionary does not state whether D, L, or DL)	23140-52-5	Yes		260/11	7/0	No	No	Yes	No	No	No	No	No	No	No	No	No	

Search Strategy

[*document search strategy used for SciFinder, PubMed, and Toxnet*]

[*identify total # of hits /# hits that were useful or examined for usefulness*]

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
ScfFinder (usually a combined search for all ingredients in report; list # of this/# useful) - https://scifinder.cas.org/scifinder
PubMed (usually a combined search for all ingredients in report; list # of this/# useful) - http://www.ncbi.nlm.nih.gov/pubmed
Toxnet databases (usually a combined search for all ingredients in report; list # of this/# useful) – https://toxnet.nlm.nih.gov/ (includes Toxline; HSDB; ChemIDPlus; DAR; IRIS; CCRIS; CPDB; GENE-TOX)

FDA databases – http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm (CFR); then,
list of all databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm; then,
http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true (EAFUS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm (GRAS);
http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm (SCOGS database);
http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives (indirect food additives list);
http://www.fda.gov/Drugs/InformationOnDrugs/default.htm (drug approvals and database);
http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf (OTC ingredient list);
http://www.accessdata.fda.gov/scripts/cder/iig/ (inactive ingredients approved for drugs)

EU (European Union); check CosIng (cosmetic ingredient database) for restrictions and SCCS (Scientific Committee for Consumer Safety) opinions - http://ec.europa.eu/growth/tools-databases/cosing/
ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
OECD SIDS documents (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/
NTIS (National Technical Information Service) - http://www.ntis.gov/
NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/
FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/ (FAO);
FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/
Web – perform general search; may find technical data sheets, published reports, etc
ECETOC (European Center for Ecotoxicology and Toxicology Database) - http://www.ecetoc.org/

Botanical Websites, if applicable
Dr. Duke's https://phytochem.nal.usda.gov/phytochem/search
Taxonomy database - http://www.ncbi.nlm.nih.gov/taxonomy
GRIN (U.S. National Plant Germplasm System) - https://npgsweb.ars-grin.gov/gringlobal/taxon/taxonomysimple.aspx
Sigma Aldrich plant profiler http://www.sigmaaldrich.com/life-science/nutrition-research/learning-center/plant-profiler.html

Fragrance Websites, if applicable
IFRA (International Fragrance Association) – http://www.ifraorg.org/
RIFM (the Research Institute for Fragrance Materials) should be contacted

Qualifiers

Absorption	Genotoxic	Sensitization
Acute	Irritation	Skin
Allergy	Metabolism	Subchronic
Allergic	Mutagen	Teratogen
Allergenic	Mutagenic	Teratogenic
Cancer	Penetration	Toxic
Carcinogen	Percutaneous	Toxicity
Chronic	Pharmacokinetic	Toxicokinetic
Development	Repeated dose	Toxicology
Developmental	Reproduction	Tumor
Excretion	Reproductive	

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INTRODUCTION

The safety of the following 7 saccharide humectants, as used in cosmetics, is reviewed in this safety assessment:

Anhydrogalactose	Anhydroxylitol	Psicose	Saccharide Isomerate
Anhydroglucitol	Arabinose	Saccharide Hydrolysate	

According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), all 7 saccharide humectants are reported to function as skin-conditioning agents – humectant in cosmetics (See Table 1).[1] Anhydrogalactose is also reported to function as an antioxidant, and Anhydroglucitol also functions as an oral care agent.

Because Saccharide Hydrolysate contains glucose and fructose, and saccharides/saccharide mixtures are being reviewed in this report, it is important to note that the Expert Panel for Cosmetic Ingredient Safety (Panel) has evaluated the safety of glucose and fructose (monosaccharides), as well as other monosaccharides and disaccharides. In 2019, the Panel published a report with a conclusion stating that the monosaccharides, disaccharides, and related ingredients are safe in the present practices of use and concentration in cosmetics described in the safety assessment.[2] This report is available on the Cosmetic Ingredient Review (CIR) website (https://www.cir-safety.org/ingredients).

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

Of the 5 discrete saccharides that are reviewed in this safety assessment, Anhydrogalactose is supplied as the L-stereoisomer; while the other 4 (Anhydroglucitol, Anhydroxylitol, Arabinose, and Psicose) are each defined as the D-stereoisomers. For any one of the monosaccharides reviewed in this report, available relevant data on a different stereoisomer may be included, as these data may have some value in the safety assessment of isomer(s) under review. In such instances, the *Dictionary* name (including capitalization) will not be used (e.g., L-arabinose). Since Saccharide Hydrolysate and Saccharide Isomerate are defined as products by various processes, various stereochemistries are possible.

A National Industrial Chemicals Notification and Assessment Scheme (NICNAS) public report on Anhydroxylitol is available.[3] Data summaries from that report are included in this safety assessment.

CHEMISTRY

Definition and Structure

All of the ingredients in this report are hygroscopic, saccharides or saccharide derivatives. Such ingredients are commonly used for their moisturizing (humectant) properties. For example, Anhydroglucitol (CAS No. 154-58-5), a pyranoid polyol, is similar in structure to that of glucose, except for a methylene group at the C1 position (Figure 1).[1,4,5] Psicose (CAS No. 23140-52-5) has been defined as a C-3 epimer of D-fructose (Figure 2).[1,6]

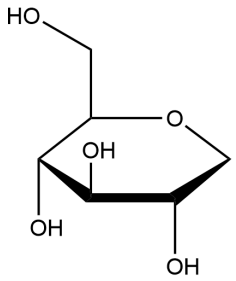


Figure 1. Anhydroglucitol

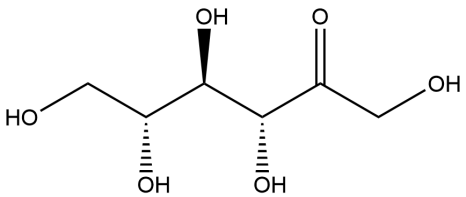


Figure 2. Psicose

The definitions, structures, and CAS Nos. of all the saccharide humectants included in this safety assessment are presented in Table 1.[1]

Chemical Properties

Chemical properties of saccharide humectants are presented in Table 2.[3,7-12] Anhydrogalactose, Anhydroxylitol, Psicose, and Saccharide Hydrolysate are water-soluble.

Method of Manufacture

Methods of manufacture specific to cosmetics were neither found in the publicly available literature, nor were such methods submitted as unpublished data. However, these ingredients are chemical entities known and utilized in other industries, and, general methods, not specific to the cosmetics industry, are thus know. Such are described below.

Anhydrogalactose

Anhydrogalactose may be prepared by enzymatic saccharification of agar, using a combination of agarolytic enzymes.[13] According to another source, the following 3 steps are required for production of high purity Anhydrogalactose from agarose: acid pre-hydrolysis of agarose; enzymatic saccharification; and purification of Anhydrogalactose.[14]

Anhydroglucitol

A single-enzyme process for the production of Anhydroglucitol has been designed.[15] The process involves the acid pre-hydrolysis of agarose into agarobiose and the enzymatic hydrolysis of agarobiose into Anhydroglucitol and galactose.

Psicose

It has been reported that Psicose is easily generated by heating sugar preparations.[16] Details relating to this process were not provided. According to another source, Psicose has been produced from fructose using the enzyme tagatose 3-epimerase.[17]

Composition and Impurities

Composition and impurities data specific to cosmetics were neither found in the publicly available literature, nor were such methods submitted as unpublished data. However, these ingredients are chemical entities known and utilized in other industries, and, general composition/impurities profiles, not specific to the cosmetics industry, are thus know. Such are described below.

Saccharide Hydrolysate

According to the *Food Chemicals Codex* description*,* invert sugar is marketed as invert sugar syrup and contains dextrose (glucose), fructose, and sucrose in various amounts, as represented by the manufacturer.[9] In accordance with the *Food Chemicals Codex,* the acceptance criteria for invert sugar are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of invert sugar. Other acceptance criteria for invert sugar in the *Food Chemicals Codex* relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

USE

Cosmetic

The safety of the cosmetic ingredients addressed in this assessment is evaluated based on data received from the US Food and Drug Administration (FDA) and the cosmetics industry on the expected use of these ingredients in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in the FDA Voluntary Cosmetic Registration Program (VCRP) database. Use concentration data are submitted by the cosmetic industry in response to a survey, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.

According to 2020 VCRP data, Saccharide Isomerate is reported to be used in 494 cosmetic products (438 leave-on products and 56 rinse-off products).[18] Of the saccharide humectants reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2018 indicate that Saccharide Hydrolysate is used at maximum use concentrations up to 4.6% in rinse off products (skin cleansing products), and that Saccharide Isomerate is used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not spray).[19] These are the highest use concentrations in rinse-off and leave-on products reported for the saccharide humectants that are reviewed in this safety assessment. Further use data are presented in Table 3.

According to VCRP and Council survey data, the following 3 ingredients are not currently in use in cosmetic products: Anhydrogalactose, Arabinose, and Psicose.

Cosmetic products containing saccharide humectants may be applied to the skin, or, incidentally, may come in contact with the eyes (e.g., Saccharide Isomerate at concentrations up to 1% in eye shadows). Anhydroglucitol (at concentrations up to 0.17% in bubble baths) is used in products that come in contact with mucous membranes. Anhydroxylitol and Saccharide Isomerate are also used in products that come in contact with mucous membranes; however, there are no reported uses of these 2 ingredients in products of this type in the Council's use concentration survey. Products containing saccharide humectants may be applied as frequently as several times per day, and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Anhydroxylitol is reported to be used in products (other fragrance preparations) that are sprayed; however, there are no reported uses of this ingredient in products of this type in the Council's use concentration survey.[20] 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.[21-24] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and bronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount.[21,22]

The saccharide humectants reviewed in this safety assessment are not restricted from use in any way under the rules governing cosmetic products in the European Union.[25]

Risk Assessment

Dermal

Anhydroxylitol

A risk assessment was performed by NICNAS.[3] Data on typical use patterns of cosmetic product categories in which Anhydroxylitol may be used were obtained from a 2010 Scientific Committee on Cosmetic Safety (SCCS) Notes of Guidance, 7th revision.[26] The use patterns involved the following 8 product types: body lotion, face cream, eyeliner, lipstick, makeup remover, shower gel, shampoo, and hair conditioner. Systemic exposure was based on a trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol) in each product. In the absence of dermal absorption data, the default dermal absorption of 100% was assumed for calculation purposes.[27,28] An adult body weight of 60 kg was also assumed for calculation purposes. The worst-case scenario estimation using these assumptions is for a person who is a simultaneous user of all 8 products, each containing 1.5% Anhydroxylitol (from trade mixture at concentration of 5%). This would result in a systemic dose of 8.550 mg/kg/d of the trade mixture.

The repeated dose toxicity potential was estimated by calculation of the margin of exposure (MoE) of the trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol) using the worst-case exposure scenario (from the use of multiple products) of 8.550 mg/kg/d and the NOAEL of 1000 mg/kg/d for xylitol (from 2-yr dietary studies). An MoE value of ≥ 100 was considered acceptable to account for intra- and inter-species differences. Using the NOAEL of 1000 mg/kg/d, an MoE of 117 was estimated for cosmetic products containing up to 5% of the trade mixture (equivalent to 1.5% Anhydroxylitol). Thus, based on the available information, it was concluded that the risk to the public associated with use of Anhydroxylitol up to a concentration of 1.5% in cosmetic products is not considered to be unreasonable.

Non-Cosmetic

Anhydroglucitol

The use of Anhydroglucitol to monitor new classes of therapies for managing post-meal glucose in patients with diabetes has been reported.[29] The use of Anhydroglucitol is included in the International Diabetes Federation guideline for management of post-meal glucose as an emerging technology to measure postprandial glucose levels.

Arabinose

The stereoisomer, L-arabinose, is used in the bacterial mutagenesis test system that is known as the *Salmonella*/arabinose-resistant (Ara^r) assay system.[30] In the Ara^r assay system, L-arabinose is added to molten soft agar.

Psicose

Psicose (rarely found in nature) is a sugar substitute that has 70% of the sweetness of sucrose, but almost zero calories.[6]

Saccharide Hydrolysate

Saccharide Hydrolysate is a direct food substance affirmed generally recognized as safe (GRAS) by the US FDA [21 CFR 184.1859]. This ingredient is used in food with no limitation other than current good manufacturing practice.

According to one source, the indications for use of invert sugar in an obstetrics and gynecology center in the US have been limited to diabetic women during the intrapartum period.[31]

TOXICOKINETIC STUDIES

Dermal Penetration

Anhydroxylitol

According to NICNAS, based on the low molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract.[3] However, this may be limited by its high water-solubility (674 g/l), and low partition coefficient (log P_{ow} = -2).

Absorption, Distribution, Metabolism, and Excretion

Animal

Oral

Anhydroglucitol

The fate of anhydroglucitol (stereochemistry not stated) in white laboratory rats after dosing was studied.[32] Anhydroglucitol (2 to 7 mg, in saline) was administered orally as a single dose to 5 rats as follows: 2 mg (1 rat), 5 mg (3 rats), and 7 mg (1 rat). The concentration of anhydroglucitol in the serum of 11 untreated rats was 47 ± 24 (standard deviation) µmol/l, and no anhydroglucitol was found in the urine. These control data suggest that anhydroglucitol is efficiently reabsorbed by rat kidney tubuli. In the 5 test rats, the serum anhydroglucitol concentration increased rapidly after oral dosing. The peak concentration in the serum was observed at 1 h post-dosing, suggesting that anhydroglucitol was readily absorbed by the gut. Of the 5 mg dose that was administered, 1.4 to 1.6 mg was recovered in the urine in 48 h. There was no urinary excretion of anhydroglucitol after 48 h.

In another experiment involving 12 white laboratory rats, Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 wk.[32] Six rats served as controls. Blood and urine samples were collected (schedule for collection of samples not stated). In test animals, a high serum Anhydroglucitol concentration (62 to 126 µmol/l) was maintained in the 12 rats. The concentration of Anhydroglucitol in the serum of the 6 control rats (not dosed with Anhydroglucitol) ranged from 24 to 62 µmol/l. Data from this study relating to toxicity are included in the Short-Term Oral Toxicity section of this report.

Psicose

U-[^{14}C]Psicose (2 µCi) was administered by stomach tube to rats (number and strain not stated).[33] Of the exhaled [^{14}C]carbon dioxide, 26% was exhaled within 7 h and 80% was inhaled within 24 h. Much of the radioactivity was rapidly excreted in the urine, whereby 95% of the excreted radioactivity was recovered within the first 7 h. Of the excreted radioactivity recovered, at least 70% was U-[^{14}C]Psicose. The remaining 30% of the radioactivity in the urine was associated with unidentified products of metabolism. The authors noted that rapid excretion of orally administered U-[^{14}C]Psicose is suggestive of easy passage though the wall of the small intestine. It then enters the blood and is eliminated through the kidneys. The authors also stated that the increased metabolism to [^{14}C]carbon dioxide and the finding that 39% of the radioactivity is retained by the carcass for 72 h after oral feeding suggests that a large portion of the U-[^{14}C]Psicose is metabolized by intestinal microorganisms. It was noted that some of these metabolites are absorbed into the metabolic system of the rat.

The intestinal absorption, organ distribution, and urinary excretion of [^{14}C]Psicose was studied using 30 male Wistar rats.[34] All of the rats were fasted for 24 h. Approximately 0.6 ml of [^{14}C]Psicose solution (30 mg, 120 kilobecquerels (kBq)) was administered at an oral dose of 100 mg/kg. The rats were killed at 10, 30, 60, and 120 min post-administration. [^{14}C]Psicose entered the blood after oral dosing, and the maximum blood concentration (48.5 ± 15.6 µg/g) was observed at 1 h. Urinary excretion was 20% within 1 h and 33% within 2 h. [^{14}C]Psicose levels in the liver were 41.4 ± 28.7, 126.3 ± 45.0, 200 ± 86.3, and 127.5 ± 32.6 µg/g liver tissue at 10, 30, 60, and 120 min, respectively. Other organs (lung, thymus, spleen, heart, brain, skin, and muscle) showed lower radioactivity, whereas the kidney showed higher radioactivity. At 7 days after oral dosing, the remaining amounts of the test substance in the whole body were < 1%. After reviewing the results of this experiment, the authors concluded that [^{14}C]Psicose was absorbed well after oral dosing and eliminated rapidly.

Parenteral

Anhydroglucitol

The distribution of Anhydroglucitol was evaluated using normal and diabetic rats, and perfused rat bodies.[4] The 3 non-diabetic male Sprague-Dawley used were identified as having very low, very high, and medium concentrations of plasma Anhydroglucitol. The variable plasma concentrations were, perhaps, due to less controlled feeding conditions. Another group of 3 rats was rendered diabetic by intravenous (i.v.) streptozocin injection. Animals of both groups were thoroughly depleted of blood, after which various organs and tissues were immediately removed. The perfusion experiment involved 2 male Sprague-Dawley rats (controls). An isotonic solution containing heparin was used as the perfusion solution, which was infused through a cannula inserted into the pulmonary trunk through the right ventricle. At the end of perfusion, several organs were removed. The plasma of control rats contained 3 to 12 µg/ml of Anhydroglucitol. In the 3 normal rats, Anhydroglucitol was distributed throughout the rat bodies. Low, but highly variable, concentrations were present in lipid-rich tissues, such as adipose tissue and the testis. The liver and kidney contained much higher concentrations, though they were less than the corresponding plasma concentrations. The authors noted that these observations are indicative of Anhydroglucitol distribution that was dependent on the concentration equilibrium between the circulation and the intra- and inter-cellular water spaces. The concentration of Anhydroglucitol in the brain appeared to have been less dependent on the concentration in the plasma. Other results are summarized below.

In all 3 diabetic rats, the Anhydroglucitol concentration in plasma was < 0.5 µg/ml. The diabetic kidney, liver, and some other organs and tissues contained little Anhydroglucitol, and the same was true for the brain. Anhydroglucitol depletion during perfusion was demonstrated in several organs, except for the spleen. The plasma of the 2 rats perfused for 100 min and 300 min contained 8.8 µg/ml and 9.0 µg/ml of Anhydroglucitol, respectively. Anhydroglucitol was almost completely depleted from the lung, liver, and kidney of the rat perfused for 300 min. In the other rat (100-min perfusion), it was completely depleted only from the lung. Also, in this rat (100-min perfusion), the concentrations of Anhydroglucitol in the liver and kidney were considerably

lower than what would have been expected based on its concentration in the plasma. The spleens of both perfused rats contained 5.1 µg/g and 4.4 µg/g of Anhydroglucitol . The authors noted that these 2 values were as high as could have been expected for the spleen of an untreated rat with a plasma Anhydroglucitol concentration similar to that of the 2 perfused rats. The authors noted that the observations made in this study indicated that Anhydroglucitol from the circulation readily diffused into the inter- and intra-cellular water spaces. They also suggested that the plasma membranes of cells in the organs were permeable to Anhydroglucitol.

Psicose

The intestinal absorption, organ distribution, and urinary excretion of [^{14}C]Psicose was studied using 30 male Wistar rats.[34] All of the rats were fasted for 24 h. Approximately 0.6 ml of [^{14}C]Psicose solution (30 mg, 120 kBq) was administered i.v. at a dose of 100 mg/kg. The rats were killed at 10, 30, 60, and 120 min post-administration. After i.v. dosing, the concentration of [^{14}C]Psicose in the blood decreased (half-life = 57 min). Also, excretion in the urine was up to ~ 50% within 1 h. High counts of radioactivity were detected in the liver and kidney. An experiment involving mice, summarized below, is also included in this study.

After fasting for 24 h, 10 male C3H mice were injected i.v. with [^{14}C]Psicose (20 KBq in saline, dose of 100 mg/kg).[34] At 30 min post-injection, the animals were perfused and whole-body frozen sections from the sagittal plane were prepared. Autoradiography results indicated high signals of [^{14}C]Psicose in the liver, kidney, and bladder, but no accumulation in the brain. After reviewing the results of rat and mouse i.v. dosing experiments in this study, the authors concluded that [^{14}C]Psicose was absorbed and eliminated rapidly.

U-[^{14}C]Psicose (15 mg; 1.5 µCi in 0.5 ml of saline) was injected i.v. in a series of fasted rats (number and strain not stated).[33] Urine and exhaled [^{14}C]carbon dioxide were collected for 6 h. During this period, 97% to 98% of the radioactivity was excreted in the urine, where it was associated with U-[^{14}C]Psicose. Liver glycogen contained 1% of the radioactivity, and only 0.6% of the radioactivity was exhaled as [^{14}C]carbon dioxide. The authors noted that these results indicate that i.v.-administered U-[^{14}C]Psicose is rapidly removed by the kidney and is metabolized to only a small degree.

Human

Anhydroglucitol

Anhydroglucitol is present in human blood, and the average plasma concentration is in the vicinity of 20 µg/ml.[5] A remarkable decrease in plasma Anhydroglucitol is observed in diabetes mellitus.

The origin and disposal of Anhydroglucitol , a major polyol in the human body, was studied using 36 normal subjects (20 mem and 16 women).[35] The amount of urinary Anhydroglucitol was measured 3 times in each subject. The mean Anhydroglucitol supplement through foods was estimated to be ~ 4.38 mg per day. The mean Anhydroglucitol excretion in the urine was ~ 4.76 mg per day. An Anhydroglucitol balance study was performed using a subgroup (6 men and 2 women) of the 36 normal subjects. Total dietary calorie intake was fixed to 35 kcal/real body weight (kg) of individual subjects. Fasting plasma Anhydroglucitol and 24-h urinary Anhydroglucitol were monitored over 3 consecutive days, and their mean values were calculated. In another subgroup (6 men and 3 women), the subjects were observed for urinary Anhydroglucitol excretion after a breakfast meal. The subjects fasted for 14 h before urination. The study results implied that urinary excretion of Anhydroglucitol occurred soon after food ingestion, and that the amount excreted in the urine was closely correlated with daily supplement through foods. The fundamental kinetics of Anhydroglucitol were recognized as follows: Anhydroglucitol in the body originates mainly from foods, is well absorbed in the intestine, and is little degraded and metabolized in the body.

Psicose

In a study involving 26 human subjects (16 males and 10 females) on a normal diet (composition not stated), 24-h urine samples were collected.[36] All subjects were healthy and undergoing normal physical activity. Individual sugars (psicose; stereochemistry not stated) included in the urine were determined using gas chromatography, accounting for over 90% of the total neutral sugars. Psicose was the most common neutral sugar that was found in human urine. The excretion of total neutral sugars in the urine ranged from 0.1 to 4.1 mmol/24 h, based on 28 urine samples from 26 subjects. The excretion of psicose in the urine ranged from 0.1 to 2.7 mmol/24 h. The authors stated that there is uncertainty regarding the source of psicose in the urine. They noted that psicose was absent from the urine of 6 patients who were maintained on total parenteral nutrition (method of feeding that bypasses the gastrointestinal tract), suggesting an exogenous origin of the sugar.

Psicose is present in human urine in amounts of 15 to 30 mg/l, presumably from a dietary source because it disappears from the urine of subjects who have fasted for 48 h.[33]

Oral

Arabinose

After an overnight fast, 40 normal volunteers drank an isosmotic solution containing raffinose (8 g), lactose (20 g), and L-arabinose (2 g) in 250 ml of water.[37] The median 5-h urinary sugar excretion was 0.26% of ingested raffinose, 0.05% of ingested lactose, and 17.5% of ingested L-arabinose.

Parenteral

Arabinose

The metabolic stability of L-arabinose was investigated using 5 normal subjects.[37] A sterile, pyrogen-free solution containing 500 mg of L-arabinose in 5 ml of water was injected intravenously into each subject. Within 5 h, 63.3 ± 4.1% (mean + standard deviation) of administered L-arabinose was excreted in the urine. Within 12 h, 73.1 ± 4.5% was excreted in the urine.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Dermal

Anhydroxylitol

The dried extract of a trade name mixture containing 25% to 35% Anhydroxylitol was evaluated for acute dermal toxicity in rats (number not stated), according to Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 402.[3] Doses up to 2 g/kg were tested. No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes were observed in this study. The LD_{50} was > 2 g/kg.

Oral

Anhydroxylitol

The acute oral toxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in rats (number not stated), according to OECD TG 401.[3] Doses up to 2 g/kg were tested. No mortalities, abnormal clinical signs, body weight changes, or gross pathological changes were observed in this study. The LD_{50} was > 2 g/kg.

Arabinose

In an acute oral toxicity study on Arabinose, the LD_{50} was calculated to be 12.1 g/kg in male rats and 11.6 g/kg in female rats.[38] This data summary is from an English language translation of a publication abstract written in Japanese. Details relating to the number of animals used, test protocol, and study results are not included in the abstract.

Psicose

The acute oral toxicity of 50% aqueous Psicose was evaluated using 5 groups of 8 male Wistar rats.[39] The groups received single oral doses ranging from 8 g/kg to 20 g/kg. A stainless feeding tube attached to a 20 ml syringe was used for dosing. A 14-d observation period was initiated after test substance administration. Necropsy was performed on animals that died. Animal deaths were reported as follows: 3 rats (14 g/kg dose group), 3 rats (17 g/kg dose group), and 8 rats (20 g/kg dose group). The animals died within 2 days after dosing. The calculated LD_{50} values were 16.3 g/kg (using the Behrens-Karber method) and 15.8 g/kg (using the Litchfield-Wilcoxon method). All of the rats experienced diarrhea at 1 h to 24 h after dosing. The condition of high-dose animals (17 g/kg and 20 g/kg doses) was described as quite weak. There was no evidence of abnormalities in surviving rats after 3 days. At necropsy, bleeding was observed in the mucous layers of the stomach or small intestine in rats of the 17 g/kg or 20 g/kg dose groups.

Each of 6 beagle dogs received a single oral dose (by plastic syringe) of Psicose (1 g/kg and 4 g/kg) or a placebo (water, 100 ml).[40] The test substance was administered in 100 ml of water. The control, 1 g/kg of Psicose, and 4 g/kg of Psicose were administered on 3 different study days. Thus, each animal received the control on day 1, the 1 g/kg dose on day 2, and the 4 g/kg dose on day 3. The mean values in the data presented were representative of 6 dogs (for control and 1 g/kg dose) and 5 dogs (for 4 g/kg dose). All dogs were active and had a good appetite throughout the study. The 4 g/kg dose caused vomiting in 1 dog and transient diarrhea in the remaining 5 dogs. Two dogs had transient nausea within 1 h after receiving the 1 g/kg dose. The blood glucose was slightly decreased, without an increase in the plasma insulin concentration, at 2 h after dosing with the test substance. A mild, dose-dependent increase ($P < 0.05$) in plasma alkaline phosphatase activities was also observed between 12 h and 48 h after dosing. Histological examination of the liver or other tissues was not performed in this study. Furthermore, the plasma inorganic phosphorus concentration in dogs dosed with 4 g/kg was slightly higher ($P < 0.05$) at 8-h post-dosing when compared to control dogs. Though no possible causes of inorganic phosphorus alteration were observed in this study, the authors stated that dosing with Psicose may mildly exaggerate the diurnal pattern of plasma inorganic phosphorus concentration in dogs. The authors concluded that these data indicate that Psicose did not induce severe toxicity in dogs.

Short-Term Toxicity Studies

Oral

Anhydroglucitol

In an experiment involving 12 white laboratory rats, anhydroglucitol (stereochemistry not stated; 7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) daily for 7 wk.[32] Six rats served as controls. No apparent toxic signs were observed in test animals after dosing. Body weight gain (5.2 g/rat/wk) in test animals was similar to that reported for control rats (4.6 g/rat/wk). (Results relating to the distribution and excretion of anhydroglucitol after oral dosing are included in the section on Toxicokinetic Studies.)

Anhydroxylitol

A 28-day oral toxicity study on a tradename mixture comprising ~ 25% Anhydroxylitol (and unstated quantities of xylitol and xylitylglucoside) was performed using groups of at least 10 rats (5 males and 5 females per group), according to OECD TG 407.[3] The test substance was administered at doses of 0 (vehicle was negative control (water)), 15, 150, and 1000 mg/kg/day. Study results indicated no treatment-related changes in the following: mortality, clinical observations, behavioral assessment, functional performance, sensory reactivity, body weight, food consumption, hematology, blood chemistry, organ weights. Additionally, no treatment-related changes were observed at necropsy of animals in the highest dose group. However, minimal focal myocarditis was observed in 2 males and 1 female of the highest dose group. Histopathological examination was not performed on animals of the other 2 dose groups. NICNAS noted that the lesions observed in this study are typical of findings that are expected in animals of this type, strain, and age. They also noted that the incidence of these lesions is typical of that observed in rats in this type of study. However, no historical data supporting this statement were provided. Given the uncertainty relating to the cause of myocarditis in animals of the highest dose group and the limited histopathology data, NICNAS noted that it was not possible to clearly establish a no-observed-adverse-effect-level (NOAEL) for the test substance in this study.

Arabinose

In a short-term toxicity test, rats were given feed containing 5% Arabinose.[38] The rats developed diarrhea. This data summary is from an English translation of an abstract from a publication that is written in Japanese. Details relating to the number of animals used, test protocol, study duration, and study results are not included in the abstract.

Psicose

Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 days.[41] A control group (6 rats) was fed a normal diet and consumed water without Psicose. At the end of the experiment, the animals were killed and body, testes, and liver weights were determined. There was no difference in mean testes weight (2.0 ± 0.2 g) between treated and control rats. The mean body weight of treated rats (232 ± 12 g) was higher when compared to the control group (214 ± 14 g). Mean liver weight values were 12 .7 ± 0.7 g (treated rats) and 12.7 ± 0.7 g (controls). These 2 groups (treated and controls) were among the groups included in a study evaluating the protective effect of Psicose on di-(2-ethylhexyl) phthalate-induced testicular injury in the rat.

Groups of 7 male Wistar rats were fed diets containing 10%, 20%, 30%, and 40% Psicose for 34 d.[39] Butylated hydroxytoluene (0.01 g/kg diet) was added to all diets as an antioxidant. The control group was fed the diet without Psicose. After day 34, the rats were fasted for 3 h and then killed. One rat fed 30% and 5 rats fed 40% Psicose died during the experimental period. Body weight gain, food intake, and food efficiency were more extensively suppressed after feeding with the higher % Psicose diets (i.e., 30% and 40% diets). A statistically significant difference in body weight gain was observed between the 0, 10%, 20%, and 30% dietary groups ($P < 0.05$). The rats fed the 20%, 30%, and 40% diets experienced diarrhea during the first 8 days. The weights of the heart and spleen were smaller ($P < 0.05$) in rats fed the higher Psicose concentration diets. Liver and kidney weights were heavier ($P < 0.05$) in rats fed the 10% diet than in rats fed the 0 and 30% diets. Cecal enlargement was observed in rats fed 10% to 40% diets. Epididymal, perirenal, and mesenteric adipose tissue weights were statistically significantly smaller ($P < 0.05$) in rats fed the higher Psicose concentration diets. Other results indicated that serum glucose and triacylglycerol concentrations were significantly lower ($P < 0.05$) in the 30% dietary group than in the other groups. Furthermore, liver triacylglycerol content was higher in the 10% dietary group than in the 0% group. Many of the effects observed were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. It was also noted that it is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen disposition. The authors concluded that the feeding of diets extremely high in Psicose appears to be harmful to the intestinal tract.

In another study, Psicose (0.2 g/kg) was fed to 5 beagle dogs daily for 12 wk.[42] The control group (5 dogs) was fed a placebo (not stated) according to the same procedure. During the course of the experiment, plasma triglyceride concentrations increased in the control group, whereas they remained low in the group fed Psicose. At week 2 and thereafter, plasma total cholesterol concentrations in the test group were statistically significantly lower ($P < 0.05$) when compared to the control group. Platelet count levels in the test group were statistically significantly lower at both week 0 and week 12 ($P < 0.05$). Dosing with the test substance had no influence on body weight. With the exception of a change in lipid levels (lipid lowering effect), dosing with Psicose did not cause clinical signs or changes in biochemical parameters (plasma alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total bilirubin, urea nitrogen, creatinine, total protein, albumin, total cholesterol, triglyceride, total calcium, inorganic phosphorus, sodium, potassium, and chlorine concentrations). Also, there was no cumulative effect of test substance dosing on glucose metabolism, and there were not statistically significant differences in the following between test and control groups: liver enzymes, renal function markers, and electrolytes. The mild increase in plasma alkaline phosphatase was not considered suggestive of Psicose toxicity. The authors concluded that dosing with Psicose did not cause any harmful effects in dogs.

Chronic Toxicity Studies

Oral

Psicose

The chronic oral toxicity of Psicose was evaluated using groups of 18 male Wistar rats.[43] The test group had free access to a commercial rodent diet containing 3% Psicose, and the control group to diet containing 3% sucrose, for 12 or 18 mo. The rats

actually ingested 1.28 g/kg/d Psicose and 1.22 g/kg/d sucrose. After 12 mo of feeding, 8 rats from each group were fasted prior to collection of blood for hematological analysis. The remaining rats (10 per group) were killed at the end of 18 months, and various organs were weighed. Parts of the liver and kidney were preserved for histopathological examination. At 12 mo, final body weights and weight gains in the 3% Psicose dietary group were comparable to those in the 3% sucrose control group. At 18 mo, final body weights and weight gains in the 3% Psicose dietary group were significantly lower when compared to the 3% sucrose control group. Liver and kidney weights were found to be statistically significantly heavier in the 3% Psicose group at 12 mo, when compared to the control group. However, there were no differences in weight when this comparison involved other tissues. At 18 mo, liver and kidney weights were also statistically significantly heavier in the test group when compared to the control group. Higher weights were also reported for the brains, lungs, and pancreas in test animals. On the other hand, relative intraabdominal adipose tissue weights at 18 mo were statistically significantly lighter in the 3% Psicose group, when compared to the control group.

At 12 mo, mean corpuscular hemoglobin was statistically significantly lower in the test group when compared to the control group. Hemoglobin and mean corpuscular volume at 18 mo were statistically significantly greater in the test group than in the control group. Serum chemistry analysis results for rats fed 3% Psicose in the diet for 12 mo did not indicate any differences between test and control animals. Age-related, naturally-occurring lesions were observed in the liver and kidneys at 12 mo; however, no abnormalities due to test substance ingestion were observed. Histopathological examination of the liver at 18 mo revealed fatty degeneration and hepatocellular fibrosis in the group fed 3% Psicose in the diet, but not in the control group. These findings appeared to be slight and local. The mean value for pathological lesions (liver) in the test group was statistically significantly higher ($p < 0.0498$; i.e., slight difference) when compared to the control group. At 12 mo, there was no difference in histopathological observations (in liver and kidneys) between test and control groups. In the kidneys at 18 mo, the total value for pathological lesions did not differ between test and control groups. The authors concluded that this study found the effects of long-term dietary administration of 3% Psicose to rats to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy. They also concluded that the hematological and chemical values were not suggestive of overt Psicose toxicity, and that, overall, no adverse effects were seen after feeding with 3% Psicose in the diet.[43]

Subcutaneous

Arabinose

Chronic subcutaneous toxicity data are presented in a carcinogenicity study on L-arabinose involving 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females).[44] Details relating to the experimental procedure and results relating to tumor formation are summarized in the section on Carcinogenicity Studies. A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck for periods up to 2 yr. The rats tolerated the test substance injections without any untoward effects. However, the mice developed symptoms of shock, and some died (number not stated). Also, in mice, white necrotic masses were identified in the subcutaneous tissue of the nape of the neck. There was no histologic evidence of an injurious effect of the injected test substance on any internal organ, especially the liver and kidneys, in mice or rats. However, nephrotic changes of varying degrees were observed in many animals (number not stated), including controls. Rather extensive amyloidosis of the liver, spleen, and kidneys occurred frequently in mice.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies of saccharide humectants were neither found in the published literature, nor were these data submitted.

GENOTOXICITY

In Vitro

Anhydroxylitol

The genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in a bacterial reverse mutation assay, according to OECD TG 471.[3] The test substance was classified as non-mutagenic in this assay. The same test substance was evaluated for genotoxicity in a chromosome aberration assay using human peripheral blood lymphocytes, according to OECD TG 473. Results were also classified as negative in this assay. (Further details were not provided for these studies.)

In Vivo

Anhydroxylitol

The micronucleus test was used to evaluate the genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol, according to OECD TG 474.[3] Mice received a dose of ≤ 2000 mg/kg/d for 2 d. (Further details, including route of administration, were not provided.) The test substance was classified as non-genotoxic in this assay. However, NICNAS stated that it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay.

CARCINOGENICITY STUDIES

Subcutaneous

Arabinose

The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females).[44] (Results relating to chronic subcutaneous toxicity are included in that section of this report.) A 25% aqueous solution of L-arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck twice per week for periods up to 2 yr. Control animals (60 rats and 60 mice) were injected with water. In rats, a total of 11 tumors was observed after dosing with the test substance. The tumor types observed (mostly at 22 to 24 months) in rats included urinary bladder papilloma, lymphangiosarcoma of the subcutis, adenofibroma of the breast, and carcinoma of the uterus. In mice, no tumors were observed. Injection site tumors were not observed in rats. The great majority of the benign and malignant tumors found in test and control rats were at sites remote from the nape of the neck. Furthermore, the numbers and sites of these neoplasms were found to be similar when results for test and control rats were compared. Therefore, the authors noted that it is unlikely that the development of most of the tumors was related to test substance administration.

ANTI-CARCINOGENICITY STUDIES

Psicose

The effect of Psicose on cell proliferation was evaluated in the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, using the following cancer cell lines: human cervical cancer (HeLa), human hepatocarcinoma (HepG2), human hepatocarcinoma (HuH-7), and immortalized human skin keratinocytes (HaCaT).[45] The assay was initiated when the cells were in the logarithmic growth phase. The following concentrations of Psicose were added to the medium: 1 mM, 5 mM, 10 mM, 20 mM, and 50 mM. After exposure to the test substance for 24 h, 48 h, and 72 h, MTT was added and the plates were incubated for 4 h. Psicose did not have an antiproliferative effect on the cell lines at any of the concentrations tested.

OTHER RELEVANT STUDIES

Cytotoxicity

Anhydrogalactose

In the MTT assay, Anhydrogalactose was not cytotoxic to melanin-producing murine B16 melanoma cells or human epidermal melanocytes at concentrations of 12.5, 25, and 50 µg/ml during the 2-h incubation period.[7] The MTT assay was also used to evaluate the cytotoxicity of Anhydrogalactose and D-anhydrogalactose using B16F10 mouse melanoma cells and RAW264.7 cells (mouse macrophages).[14] The cells were treated for 24 h with concentrations up to 100 µg/ml (B16F10 cells) and up to 200 µg/ml (RAW264.7 cells). There was no statistically significant inhibition of growth of either cell type at the concentrations of Anhydrogalactose and D-anhydrogalactose tested.

Anti-Melanogenic Activity

Anhydrogalactose

A study was performed to determine whether Anhydrogalactose exerts anti-melanogenic activity in murine B16F10 melanoma cells and human epidermal melanocytes.[7] The effect on melanogenesis at non-cytotoxic concentrations was determined by measuring α-melanocyte stimulating hormone (α-MSH)-induced intracellular and extracellular melanin levels in the 2 cell types. The cells were pretreated with Anhydrogalactose (50 µg/ml) for 1 h prior to exposure to α-MSH (100 nM). Melanin content was assayed 3 d later. Anhydrogalactose markedly inhibited melanin secretion.

The skin-whitening activity of L-Anhydrogalactose (95.6% pure) was evaluated using B16F10 mouse melanoma cells.[14] The melanoma cells were induced for melanin production by treatment with α-MSH, and were cultured for 1 h with L-Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/ml. Arbutin (up to 100 µg/ml) served as the positive control. The extracellular melanin concentration of melanoma cells treated with 100 µg/ml L-Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin or D-anhydrogalactose. Particularly, the extracellular melanin concentration of melanoma cells treated with 100 µg/ml Anhydrogalactose was only 23.9% of melanoma cells treated with 100 nM α-MSH. The authors noted that these study results suggested that treatment with Anhydrogalactose strongly suppressed melanin production in B1610 melanoma cells.

Anti-Inflammatory Activity

Anhydrogalactose

Nitrite levels in the culture media of RAW264.7 mouse macrophages (stimulated by lipopolysaccharide (LPS) to produce nitrite) were measured in an experiment investigating the possible anti-inflammatory activity of Anhydrogalactose (95.6% pure).[14] Cellular nitrite levels increase considerably under inflammatory conditions. The macrophages were incubated for 24 h with Anhydrogalactose and D-anhydrogalactose at concentrations up to 200 µg/ml. Statistically significant ($P < 0.05$) suppression of nitrite production was observed at concentrations of 100 µg/ml and 200 µg/ml Anhydrogalactose. Nitrite levels in the culture media of cells treated with 100 µg/ml and 200 µg/ml Anhydrogalactose were 64.5% and 38.8% of those in LPS-treated controls. Anhydrogalactose also had a nitrite-suppressing effect, only at a concentration of 200 µg/ml. However, the effect of the

D-anhydrogalactose was statistically significantly lower when compared to the Anhydrogalactose. The authors noted that Anhydrogalactose had statistically significant anti-inflammatory activity.

Antimicrobial Activity

Anhydrogalactose

The inhibitory activity of Anhydrogalactose against *Streptococcus mutans* ATCC 25175 growth was evaluated in the spot assay by monitoring the bacterial cell mass concentration and counting the colonies formed on the growth medium.[46] Bacterial cells were diluted to 10, 10^2, 10^3, 10^4, and 10^5-fold, and each diluted cell suspension was spotted on the growth medium. The bacteria were cultured for 30 h on growth medium supplemented with 10 g/l (w/v) Anhydrogalactose. Growth inhibitory activity of Anhydrogalactose was compared to that of xylitol (10 g/l). Spot assay results indicated that the numbers of *S. mutans* colonies were lower in the presence of Anhydrogalactose than in the presence of xylitol or in growth medium without sugar. When Anhydrogalactose (10 g/l) was present in the growth medium, *S. mutans* colonies were not formed; that is, when plates were seeded with bacterial inocula of either 10^4 or 10^5 dilution. In contrast, *S. mutans* colonies were formed on a minimal agar plate inoculated with bacterial dilutions of either 10^4 or 10^5, when 10 g/l xylitol was supplied as the sole carbon source.

Effect of Epidermal Barrier Recovery

Psicose

The effect of topical application of aqueous Psicose on epidermal permeability barrier recovery rate after barrier disruption (by tape stripping) was evaluated using male hairless mice of the HR-1 strain (number not stated).[47] Permeability barrier function was evaluated by measurement of transepidermal water loss. Skin on both flanks was treated by repeated tape stripping until the transepidermal water loss reached 7 to 10 mg/cm^2/h. Immediately after tape stripping, 100 µm of a 0.1 M aqueous solution of Psicose was applied to the skin. Transepidermal water loss was then measured at the same sites at 1 h, 2 h, 6 h, and 24 h later. Barrier recovery results were expressed as % recovery because of the day-to-day variations in the extent of barrier disruption. Psicose accelerated barrier recovery of tape-stripped skin. This effect on barrier recovery rate appeared within 1 h. The authors stated that Psicose may influence phase transition of the lipid bilayers of lamellar bodies and cell membrane, which is a crucial step in epidermal permeability barrier homeostasis.

DERMAL IRRITATION AND SENSITIZATION

Irritation

Animal

Anhydroxylitol

The skin irritation potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in 3 New Zealand White albino rabbits, according to OECD TG 404.[3] Test substance application to the skin for 4 h, using a semi-occlusive patch, was followed by a 72-h observation period. The dose per cm^2 was not stated. There was no evidence of erythema or edema in any animal during the observation period. The test substance was classified as non-irritating to the skin of rabbits.

Sensitization

Animal

Anhydroxylitol

The skin sensitization potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in the maximization test, according to OECD TG 406.[3] The number of guinea pigs used was not stated; however, a minimum of 10 test animals and 5 controls is in keeping with this protocol. The undiluted test substance was applied during induction. However, the challenge concentration was 50% (actual concentration = 17.5%). The test substance was classified as a non-sensitizer in guinea pigs.

Human

Saccharide Isomerate

A human repeated insult patch test (HRIPT) involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate.[48] The product, under an occlusive patch, was applied to the upper back (between the scapulae and waist, lateral to midline). The dose per area was not stated. Applications were made 3 times per week (Mondays, Wednesdays, and Fridays) for a total of 9 applications. Reactions were scored 48 h after patch application on Mondays and Wednesdays, and at 72 h post-application on Fridays. After a 2-wk non-treatment period, challenge patches were applied to original and new sites on the back. Challenge reactions were scored at 48 h, 72 h, and 96 h. The product did not demonstrate dermal irritation or sensitization potential in this study.

OCULAR IRRITATION STUDIES

Animal

Anhydroxylitol

The ocular irritation potential of the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was evaluated in 3 New Zealand White albino rabbits, according to OECD TG 405.[3] Instillation of the test substance was followed by a 72-h observation period. Slight conjunctival irritation (redness and chemosis) was observed, but had fully resolved by the end of the observation period. The conjunctival irritation was first observed at 1 h post-instillation. The test substance was classified as slightly irritating to the eyes of rabbits.

Human

Saccharide Isomerate

The ocular irritation potential of an eye cream containing 2.75% Saccharide Isomerate was evaluated using the following 56 female subjects: 19 contact lens wearers, 19 non-contact lens wearers, and 18 sensitive eye, non-contact lens wearers.[49] A total of 53 subjects completed the study. The protocol for product use in the study was not stated. Trace increases in palpebral conjunctival irritation observed in 3 subjects were said to have been unrelated to use of the eye cream. There were no reports of subjective irritation in the group of subjects tested. Increases in lacrimation, eyelid inflammation, or bulbar conjunctival inflammation were not observed. The absence of changes in visual acuity, and corneal tissue integrity was also noted. The authors concluded that the eye cream did not have the potential for causing ocular irritation.

CLINICAL STUDIES

Case Reports

Arabinose (L-arabinose)

A pediatric patient presented with large amounts of L-arabinose and L-arabitol (Arabinose metabolite) in the urine.[27] The sugar L-arabinose mainly originated from the fruit formula in the child's diet. Highly elevated levels of L-arabitol were also found in the plasma and cerebrospinal fluid. The authors stated that the accumulation of L-arabinose and L-arabitol suggested a disturbance in L-arabinose metabolism at the level of L-arabitol degradation. Therefore, they presumed that the enzyme L-arabitol dehydrogenase was deficient in the pediatric patient.

Psicose and Saccharide Hydrolysate

A male patient had urticarial attacks over a period of 6 months after eating foods such as hamburgers, spaghetti, and cakes, and after consuming certain drinks.[16,50] When the patient was given a refreshing drink (type not stated), urticarial lesions developed within 2 h. The ingredients of the drink were then given separately, with a week between each test. Two ingredients of the drink, invert sugar (also known as Saccharide Hydrolysate) and high-fructose corn syrup (containing mostly glucose and 0.07% Psicose), induced urticarial lesions. High-fructose corn syrup caused the stronger reaction, and a skin test on this ingredient (3 mg) yielded a positive reaction. Psicose was partly purified using thin layer chromatography, and yielded a positive skin reaction when applied at a dose of 21.8 µg. The authors concluded that Psicose was responsible for the urticarial attacks in the male patient.

Other Clinical Reports

Psicose

The safety of long-term ingestion of Psicose was studied using 17 normal subjects (males and females).[51] A randomized, double-blind, placebo-controlled crossover experiment was performed. The subjects consumed Psicose (5 g) with meals 3 times per day for 12 continuous weeks. Physical examinations, blood examinations, and urine analyses were performed. There was no evidence of abnormal effects or clinical problems.

SUMMARY

The safety of 7 saccharide humectants as used in cosmetics is reviewed in this safety assessment. According to the *Dictionary*, all 7 saccharide humectants are reported to function as skin-conditioning agents – humectant in cosmetics. Anhydrogalactose is also reported to function as an antioxidant, and Anhydroglucitol functions as an oral care agent.

In the *Food Chemicals Codex* description, invert sugar (Saccharide Hydrolysate) is marketed as invert sugar syrup and contains dextrose (glucose), fructose, and sucrose in various amounts, as represented by the manufacturer. In accordance with the *Food Chemicals Codex*, the acceptance criteria for invert sugar are that it contains not less than 90% and not more than 110% of the labeled amount of sucrose and of invert sugar. Other acceptance criteria for invert sugar in the Food Chemicals Codex relate to lead content (not more 0.1 mg/kg) and sulfated ash content (not more than 0.2%).

According to 2020 VCRP data, Saccharide Isomerate is reported to be used in 494 cosmetic products (438 leave-on products and 56 rinse-off products). Of the saccharide humectants reviewed in this safety assessment, this is the greatest reported use frequency. The results of a concentration of use survey conducted by the Council in 2018 indicate that Saccharide Hydrolysate is being used at maximum use concentrations up to 4.6% in rinse off products (skin cleansing products), and that Saccharide Isomerate is being used at maximum use concentrations up to 2.8% in leave-on products (face and neck skin care preparations, not

spray). These are the highest use concentrations in rinse-off and leave-on products reported for the saccharide humectants that are reviewed in this safety assessment.

In a risk assessment for dermal exposure to 8 product types that was performed by NICNAS, the repeated dose toxicity potential was estimated by calculation of the MoE of the trade mixture containing 30% Anhydroxylitol at a use concentration of 5% (equivalent to 1.5% Anhydroxylitol). An MoE of 117 was estimated.

Psicose is a sugar substitute that has 70% of the sweetness of sucrose, but almost zero calories. The cosmetic ingredient Saccharide Hydrolysate contains fructose and glucose, and Saccharide Hydrolysate is also a direct food substance affirmed as GRAS by the US FDA.

Anhydroglucitol (2 to 7 mg, in saline) was administered orally to 5 rats as follows: 2 mg (1 rat), 5 mg (3 rats), and 7 mg (1 rat). Anhydroglucitol was readily absorbed by the gut, and there was no urinary excretion of anhydroglucitol after 48 h. In another study, Anhydroglucitol (7 mg, 0.14 mmol/kg body weight) was administered orally (in drinking water) to rats daily for 7 wk. A high serum Anhydroglucitol concentration (62 to 126 µmol/l) was maintained in the animals tested.

The intestinal absorption, organ distribution, and urinary excretion of [^{14}C]Psicose was studied using male rats and male mice. [^{14}C]Psicose was absorbed well after oral dosing, and eliminated rapidly after both oral and i.v. administration. In another oral dosing study, U-[^{14}C]Psicose (2 µCi) was administered by stomach tube to rats. Much of the radioactivity was rapidly excreted in the urine, whereby 95% of the excreted radioactivity was recovered within the first 7 h.

Anhydroglucitol is present in human blood, and the normal average plasma concentration is in the vicinity of 20 µg/ml. The origin and disposal of Anhydroglucitol, was studied using normal subjects. It was concluded that Anhydroglucitol in the body originates mainly from foods, is well absorbed in the intestine, and is little degraded and metabolized in the body. According to NICNAS, based on the low molecular weight of Anhydroxylitol (134 Da), there is potential for dermal absorption and passage across the gastrointestinal tract. However, this may be limited by its high water-solubility (674 g/l), and low partition coefficient (log P_{ow} = -2).

After an overnight fast, normal volunteers drank an isosmotic solution containing raffinose (8 g), lactose (20 g), and L-arabinose (2 g) in 250 ml of water. The median 5-h urinary excretion was 17.5% of ingested L-arabinose. In a study involving human subjects on a normal diet, 24-h urine samples were collected. The excretion of Psicose (most common neutral sugar found in human urine) ranged from 0.1 to 2.7 mmol/24 h. Results from another study involving human subjects indicate that Psicose is present in human urine in amounts of 15 to 30 mg/l. The diet is presumed to be the source of Psicose because it disappears from the urine of subjects who have fasted for 48 h.

In an acute dermal toxicity study involving rats (number not stated), an LD_{50} of > 2 g/kg was reported for a trade name mixture containing 25% to 35% Anhydroxylitol. No mortalities or gross pathological changes were observed.

An oral LD_{50} of > 2 g/kg was also reported for the same trade name mixture containing 25% to 35% Anhydroxylitol in a study involving rats (number not stated). No mortalities or gross pathological changes were observed. LD_{50} values of 12.1 g/kg and 11.6 g/kg were reported for male and female rats (number not stated), respectively, in an acute oral toxicity study on Arabinose. In an acute oral toxicity study on 50% aqueous Psicose involving groups of 8 male Wistar rats, calculated LD_{50} values (2 different methods used) of 15.8 g/kg and 16.3 g/kg were reported. Bleeding in the mucous layers of the stomach or small intestine (17 g/kg or 20 g/kg dose groups) was observed at necropsy. Single oral doses of 1 g/kg and 4 g/kg administered to 6 Beagle dogs did not induce severe toxicity in dogs. A dose-dependent increase ($P < 0.05$) in plasma alkaline phosphatase activity was reported. However, histological examination of the liver or other tissues was not performed.

A 28-day oral toxicity study on a tradename mixture comprising ~25% Anhydroxylitol (and unstated quantities of xylitol and xylitylglucoside) was performed using groups of least 10 rats. Doses up to 1000 mg/kg/day were tested. Minimal focal myocarditis was observed in 3 animals of the highest dose group; due to uncertainty relating to the cause of myocarditis and limited histopathology data, the authors noted that it was not possible to clearly establish NOAEL for the test substance in this study. No apparent toxicity signs were observed after anhydroglucitol (stereochemistry not stated) was administered orally (in drinking water) to 12 white rats daily for 7 weeks. Rats (number not stated) given feed containing 5% Arabinose in a short-term oral toxicity test developed diarrhea.

Six Sprague-Dawley rats were fed a normal diet and consumed 2% Psicose-supplemented water for 14 days. There was no difference in mean testes weight (2.0 ± 0.2 g) between treated and control rats. The short-term oral toxicity of Psicose was evaluated using groups of 7 male Wistar rats. The groups were fed diets containing 10%, 20%, 30%, and 40% Psicose for 34 days. Liver and kidney weights were heavier ($P < 0.05$) in rats fed the 10% diet than in rats fed the 0 and 30% diets. It was also noted that it is not clear whether or not the cause of Psicose-induced liver enlargement was due to liver glycogen disposition. Many of the effects observed were assumed to be secondary to a decrease in food consumption or the consumption of large amounts of a non-nutritive, poorly absorbed, osmotically active substance. However, it was noted that Psicose appears to be harmful to the intestinal tract. In another short-term study, Psicose (0.2 g/kg) was fed to 5 beagle dogs daily for 12 weeks. Dosing with Psicose did not cause any harmful effects in dogs. The mild increase in plasma alkaline phosphatase was not considered suggestive of Psicose toxicity.

A group of 18 male Wistar rats had free access to a commercial rodent diet containing 3% Psicose for 12 or 18 months. The hematological and chemical values were not suggestive of overt Psicose toxicity and, overall, no adverse effects were seen after feeding with 3% Psicose in the diet. The effects of long-term 3% Psicose administration in the diet to rats were found to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy. In a carcinogenicity study on L-arabinose involving 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females), there was no histologic evidence of an injurious effect of the injected test substance on any internal organ, especially the liver and kidneys, in mice or rats. However, extensive amyloidosis of the liver, spleen, and kidneys occurred frequently in mice.

The genotoxicity of the dried extract of a trade mixture containing 25% to 35% Anhydroxylitol was evaluated in a bacterial reverse mutation assay. Results were classified as negative in this assay. The same test material was non-genotoxic in a chromosome aberration assay using human peripheral blood lymphocytes. The micronucleus test was used to evaluate the genotoxicity of the same test substance. Mice received a dose of ≤ 2000 mg/kg/d (route of administration not specified) for 2 d, and results were negative. However, it is not clear that the test substance was systemically absorbed and reached the bone marrow in this in vivo assay.

The carcinogenicity of L-arabinose was evaluated using 60 rats of the Bethesda black strain (30 males, 30 females) and 60 C57BL mice (30 males, 30 females). A 25% aqueous solution of Arabinose (2 ml [in rats] and 0.5 ml [in mice]) was injected subcutaneously into the nape of the neck twice per week for periods up to 2 years. In rats, a total of 11 tumors was observed. Tumors were not observed in mice. The great majority of the benign and malignant tumors found in test and control rats and mice were at sites remote from the nape of the neck. It was concluded that it is unlikely that development of most of the tumors was related to test substance administration.

In the in vitro MTT cell proliferation assay involving various cancer cell lines, Psicose did not have an antiproliferative effect over the range of concentrations tested (1 mM to 50 mM). The following results relate to use of the MTT assay to evaluate the cytotoxicity of Anhydrogalactose and D-anhydrogalactose in various cell types. Anhydrogalactose was not cytotoxic to melanin-producing murine B16 melanoma cells or human epidermal melanocytes at concentrations of 12.5, 25, and 50 µg/ml. Anhydrogalactose and D-anhydrogalactose at concentrations up to 100 µg/ml (B16F10 cells) and up to 200 µg/ml (RAW264.7 cells) did not cause statistically significant growth inhibition.

Anhydrogalactose markedly inhibited melanin secretion at a concentration of 50 µg/ml in murine B16F10 melanoma cells and human epidermal melanocytes. The cells were pretreated with the test substance for 1 h prior to exposure to α-MSH. In a similar assay, Anhydrogalactose strongly suppressed melanin production in B1610 mouse melanoma cells. The extracellular melanin concentration of melanoma cells treated with 100 µg/ml Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin (positive control) or D-anhydrogalactose.

The anti-inflammatory activity of Anhydrogalactose and D-anhydrogalactose was evaluated at concentrations of 100 µg/ml and 200 µg/ml using RAW264.7 mouse macrophages. Cellular nitrite levels, which increase considerably under inflammatory conditions, were monitored. Anhydrogalactose had statistically significant anti-inflammatory activity at both concentrations. The stereoisomer D-anhydrogalactose had a nitrite-suppressing effect, only at a concentration of 200 µg/ml; however, the effect of D-anhydrogalactose was statistically significantly lower when compared to Anhydrogalactose.

In an antimicrobial assay, *S. mutans* colonies were not formed when Anhydrogalactose (10 g/l) was present in the growth medium.

The effect of topical application of aqueous Psicose (0.1 M aqueous solution) on epidermal permeability barrier recovery rate after barrier disruption (by tape stripping) was evaluated using male hairless mice of the HR-1 strain (number not stated). The test substance accelerated barrier recovery.

The dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside) was classified as non-irritating to the skin of 3 New Zealand White albino rabbits, when applied for 4 h using a semi-occlusive patch. The same test substance was evaluated in the maximization test using a minimum of 10 guinea pigs in the test group. At a challenge concentration of 50% (actual concentration = 17.5%), the test substance did not induce skin sensitization. An HRIPT involving 213 subjects was used to evaluate the skin irritation and sensitization potential of an eye cream containing 2.75% Saccharide Isomerate. The product did not have dermal irritation or sensitization potential in this study.

In an ocular irritation test (3 New Zealand White albino rabbits) on the dried extract of a trade mixture containing ~35% Anhydroxylitol (and undeclared percentages of xylitol and xylitylglucoside), slight ocular irritation was observed. The ocular irritation potential of an eye cream containing 2.75% Saccharide Isomerate was evaluated using 53 female subjects. The eye cream did not have the potential for causing ocular irritation.

In a case report, a pediatric patient presented with large amounts of L-arabinose and L-arabitol (an Arabinose metabolite) in the urine. The stereoisomer L-arabinose mainly originated from the fruit formula in the child's diet. It was presumed that the enzyme L-arabitol dehydrogenase was deficient in the child patient. A male patient had urticarial attacks over a period of 6 months after consuming certain drinks. Two ingredients of the drink, Saccharide Hydrolysate and high-fructose corn syrup (containing mostly glucose and 0.07% Psicose), induced urticarial lesions. Psicose yielded a positive skin reaction when applied at a dose of 21.8 µg.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions, structures, and reported functions[1,CIR Staff]

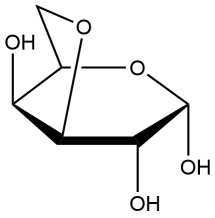
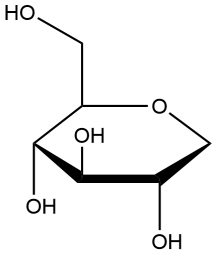
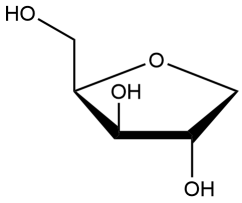
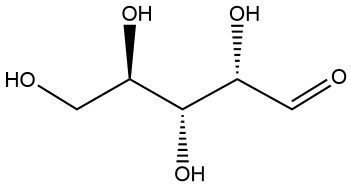
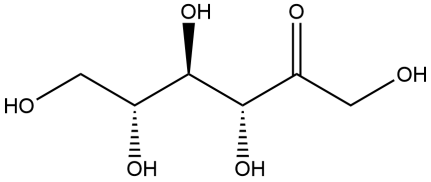
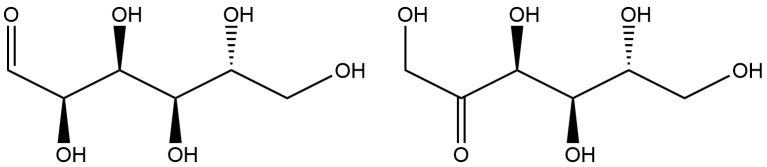
Ingredient CAS No.	Definition	Function(s)
Anhydrogalactose 28251-55-0	Anhydrogalactose is the organic compound that conforms to the structure: 	Antioxidants; Humectants; Skin-Conditioning Agents - Humectant
Anhydroglucitol 154-58-5	Anhydroglucitol is the organic compound that conforms to the structure: 	Humectants; Oral Care Agents; Skin-Conditioning Agents - Humectant
Anhydroxylitol 53448-53-6	Anhydroxylitol is the organic compound that conforms to the structure: 	Skin-Conditioning Agents - Humectant
Arabinose 10323-20-3	Arabinose is the organic compound that conforms to the structure: 	Skin-Conditioning Agents - Humectant
Psicose 23140-52-5	Psicose is the monosaccharide that conforms to the structure: 	Skin-Conditioning Agents - Humectant
Saccharide Hydrolysate 8013-17-0	Saccharide Hydrolysate is an invert sugar derived by the hydrolysis of sucrose by acid, enzyme, or other method of hydrolysis. It is characterized by a content of fructose and glucose. 	Skin Protectants; Skin-Conditioning Agents - Humectant
Saccharide Isomerate 100843-69-4	Saccharide Isomerate is a carbohydrate complex formed from a base catalyzed rearrangement of a mixture of saccharides.	Skin-Conditioning Agents - Humectant

Table 2. Chemical Properties

Property	Value/Results	Reference
Anhydrogalactose		
Molecular weight (Da)	162.14	10
log K_{ow}	-2.01 (estimated)	12
Anhydroglucitol		
Molecular weight (Da)	164.16	10
log K_{ow}	-2.17 (estimated)	12
Anhydroxylitol		
Molecular weight (Da)	134.13	10
log K_{ow}	-1.72 (estimated)	12
Anhydroxylitol ~35% in dried extract of tradename mixture (comprising in part, xylitol and xylitylglucoside)		
Form (of tradename mixture)	Clear, light yellow liquid	3
Density (g/ml at 20ºC)	1.435	3
Melting point (ºC)	< 50	3
Boiling point (ºC at 760 mmHg)	315	3
Vapor pressure (mmHg at 25ºC)	2.7×10^{-6}	3
Water solubility (g/l at 20ºC)	674	3
Partition coefficient (log P_{ow})	-2	3
Arabinose		
Molecular weight (Da)	150.13	10
log K_{ow}	-1.98 (estimated)	12
Psicose		
Form	White crystalline solid	8
Molecular weight (Da)	180.156	8
Melting point (ºC)	96	8
Solubility (% w/w at 25ºC; 50 ºC)	74; 83	8
log K_{ow}	-1.46 (estimated)	12
Saccharide Hydrolysate		
Form	Hygroscopic liquid	9
Molecular weight (average; Da)	180.16	11
Solubility	Very soluble in water, glycerin, and in glycols; very sparingly soluble in acetone and in ethanol	9
log K_{ow}	-1.46; -2.43 (estimated)	12

Table 3. Frequency (2020) and Concentration (2018) of Use According to Duration and Type of Exposure.[18,19]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Anhydroglucitol		**Anhydroxylitol**		**Saccharide Hydrolysate**	
Totals*/Conc. Range	**NR**	**0.17-1**	**180**	**0.0028-0.88**	**30**	**0.002-4.6**
Duration of Use						
Leave-On	*NR*	*0.33-1*	*150*	*0.28-0.88*	*28*	*0.002*
Rinse off	*NR*	*0.28*	*30*	*0.0028*	*2*	*4.6*
Diluted for (bath) Use	*NR*	*0.17*	*NR*	*NR*	*NR*	*NR*
Exposure Type						
Eye Area	NR	0.28-0.83	7	NR	3	NR
Incidental Ingestion	NR	NR	NR	NR	NR	NR
Incidental Inhalation- Sprays	NR	NR	1;58[a];65[b]	0.88[a]	10[a]; 4[b]	NR
Incidental Inhalation- Powders	NR	0.9[c]	65[b];1[c]	0.88[c]	4[b];7[c]	0.002[c]
Dermal Contact	NR	0.17-1	172	0.0028-0.88	30	0.002-4.6
Deodorant (underarm)	NR	NR	1[a]	NR	NR	NR
Hair - Non-Coloring	NR	NR	7	NR	NR	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	NR	NR
Mucous Membrane	NR	0.17	18	NR	NR	NR
Baby Products	NR	NR	1	NR	5	NR

	Saccharide Isomerate	
	# of Uses	Conc. (%)
Totals/Conc. Range	**494**	**0.001-2.8**
Duration of Use		
Leave-On	*438*	*0.001-2.8*
Rinse off	*56*	*0.01-0.7*
Diluted for (bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	32	1
Incidental Ingestion	NR	NR
Incidental Inhalation- Sprays	172[a];149[b]	0.01[a]
Incidental Inhalation- Powders	149[b];2[c]	0.02-2.8[c]
Dermal Contact	466	0.001-2.8
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	12	0.27
Hair-Coloring	NR	NR
Nail	13	0.03
Mucous Membrane	8	NR
Baby Products	2	NR

NR = Not Reported

* Because each ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

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

[b] Not specified these products are sprays or powders, but it is possible the use can be as a spray or powder, therefore the information is captured in both categories

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

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2020 VCRP Data

Anhydrogalactose - No FDA Data

Anhydroglucitol - No FDA Data

Anhydroxylitol

Baby Lotions, Oils, Powders, and Creams	01B	1
Eye Lotion	03D	3
Mascara	03F	1
Other Eye Makeup Preparations	03G	3
Other Fragrance Preparation	04E	1
Hair Straighteners	05C	2
Shampoos (non-coloring)	05F	3
Tonics, Dressings, and Other Hair Grooming Aids	05G	2
Foundations	07C	5
Other Makeup Preparations	07I	2
Bath Soaps and Detergents	10A	4
Deodorants (underarm)	10B	1
Other Personal Cleanliness Products	10E	7
Aftershave Lotion	11A	1
Cleansing	12A	11
Face and Neck (exc shave)	12C	52
Body and Hand (exc shave)	12D	13
Moisturizing	12F	52
Night	12G	4
Paste Masks (mud packs)	12H	3
Other Skin Care Preps	12J	9
Total		**180**

Arabinose - No FDA Data

Psicose - No FDA Data

Saccharide Hydrolysate

Baby Lotions, Oils, Powders, and Creams	01B	2
Other Baby Products	01C	3
Eye Lotion	03D	3
Makeup Bases	07F	1
Cleansing	12A	1
Depilatories	12B	1
Face and Neck (exc shave)	12C	8
Body and Hand (exc shave)	12D	6
Moisturizing	12F	6
Night	12G	1
Other Skin Care Preps	12J	3
Total		**35**

Saccharide Isomerate

Baby Lotions, Oils, Powders, and Creams	01B	2
Eye Lotion	03D	20
Other Eye Makeup Preparations	03G	12
Hair Conditioner	05A	5
Shampoos (non-coloring)	05F	4
Tonics, Dressings, and Other Hair Grooming Aids	05G	3
Other Hair Preparations	05I	2
Foundations	07C	11
Makeup Bases	07F	2
Makeup Fixatives	07H	1
Other Makeup Preparations	07I	2
Basecoats and Undercoats	08A	1
Cuticle Softeners	08B	1
Nail Polish and Enamel	08E	4
Other Manicuring Preparations	08G	7
Bath Soaps and Detergents	10A	4
Other Personal Cleanliness Products	10E	4
Aftershave Lotion	11A	2
Shaving Cream	11E	1
Other Shaving Preparation Products	11G	1
Cleansing	12A	18
Face and Neck (exc shave)	12C	123
Body and Hand (exc shave)	12D	23
Foot Powders and Sprays	12E	3
Moisturizing	12F	117
Night	12G	27
Paste Masks (mud packs)	12H	19
Skin Fresheners	12I	7
Other Skin Care Preps	12J	50
Indoor Tanning Preparations	13B	18
Total		**494**

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: January 31, 2019

SUBJECT: Concentration of Use Information: Saccharide Isomerate and Related Ingredients

Concentration of Use by FDA Product Category*

Saccharide Isomerate
Saccharide Hydrolysate
Anhydrogalactose
Anhydroglucitol
Anhydroxylitol
Arabinose
Psicose

Ingredient	Product Category	Maximum Concentration of Use
Saccharide Isomerate	Eye shadows	1%
Saccharide Isomerate	Other hair preparations (noncoloring)	0.27%
Saccharide Isomerate	Foundations	0.001-1.25%
Saccharide Isomerate	Basecoats and undercoats	0.03%
Saccharide Isomerate	Aftershave lotions	0.49%
Saccharide Isomerate	Shaving cream	0.055%
Saccharide Isomerate	Skin cleansing (cold creams, cleansing lotions liquids and pads)	0.01-0.54%
Saccharide Isomerate	Face and neck products Not spray	0.02-2.8%
Saccharide Isomerate	Body and hand products Not spray	0.5-1.3%
Saccharide Isomerate	Moisturizing products Not spray	0.6-1.7%
Saccharide Isomerate	Paste masks and mud packs	0.01-0.7%
Saccharide Isomerate	Skin fresheners	0.01%
Saccharide Isomerate	Suntan products Not spray	0.41%
Saccharide Hydrolysate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	4.6%
Saccharide Hydrolysate	Face and neck products Not spray	0.002%
Anhydroglucitol	Bubble baths	0.17%
Anhydroglucitol	Eye shadows	0.83%
Anhydroglucitol	Eye makeup removers	0.28%
Anhydroglucitol	Foundations	0.33%
Anhydroglucitol	Face and neck products Not spray	0.9%
Anhydroglucitol	Moisturizing products Not spray	0.9-1%
Anhydroxylitol	Skin cleansing (cold creams cleansing lotions, liquids and pads)	0.0028%
Anhydroxylitol	Body and hand products Not spray	0.88%
Anhydroxylitol	Moisturizing products Not spray	0.28%
Anhydroxylitol	Other suntan preparations	0.88%

*Ingredients included in the title of the table but not found in the table were included in the concentration of use survey, but no uses were reported.

Information collected in 2018

Table prepared January 31, 2019

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Carol Eisenmann, Ph.D.
Personal Care Products Council

DATE: February 10, 2020

SUBJECT: Saccharide Isomerate

Clinical Research Laboratories, Inc. 2011. An evaluation of the ophthalmic safety and efficacy of an eye cream containing 2.75% Saccharide Isomerate.

Clinical Research Laboratories, Inc. 2011. Repeated insult patch test (Marzulli and Maibach method) of an eye cream containing 2.75% Saccharide Isomerate.

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Clinical
Research
Laboratories, Inc.

Final Report

An Evaluation of the Ophthalmic Safety and Efficacy of an Eye Cream Containing 2.75% Saccharide Isomerate

CLIENT: [redacted]

ATTENTION: [redacted]

TEST MATERIAL: [redacted]

CRL STUDY NUMBER: CRL79410

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
Ophthalmic Investigator
Diplomate American Board of Ophthalmology
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

Yang Gao, M.D.
Senior Medical Research
Scientist/Ophthalmologist

Marc J. Shaffer
Senior Vice President

REPORT DATE: January 13, 2011
REVISION DATE: June 7, 2011

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Clinical Research Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL79410

Start Date: October 4, 2010

Completion Date: December 7, 2010

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Signature of QA Auditor

06-07-2011
Date

Clinical Research Laboratories, Inc.

FINAL REPORT

An Evaluation of the Ophthalmic Safety and Efficacy of an Eye Cream

OBJECTIVE

The objectives of this study were:

a) to evaluate the ocular irritation potential of an eye cream, when used for eight weeks by self-assessed sensitive eye non-contact lens wearers, contact lens wearers and non-contact lens wearers;

b) to assess the potential of the test material to improve skin surface topography and reduce the appearance of wrinkles, as well as increase skin surface hydration.

INVESTIGATORS/INVESTIGATIVE SITE

Bruce E. Kanengiser, M.D.
Diplomate American Board of Ophthalmology

Yang Gao, M.D.
Medical Research Scientist/Ophthalmologist

Marc J. Shaffer
Senior Vice President

Clinical Research Laboratories, Inc.
371 Hoes Lane, Suite 100
Piscataway, New Jersey 08854
(732) 981-1616

SPONSOR

[redacted]

TEST MATERIAL

The following test material was provided by [redacted] and received by Clinical Research Laboratories, Inc. on September 16, 2010:

Test Material	CRL Identification
[redacted]	CRL79410

STUDY DATES

This study was initiated on October 4, 2010 and was completed on December 7, 2010.

STUDY POPULATION

A total of 56 female subjects, ranging in age from 35 to 61years, were selected for the study (Subject Demographics – Appendix 1.) Nineteen subjects were contact lens wearers, 19 subjects were non-contact lens wearers, and 18 subjects were self-assessed sensitive eye non-contact lens wearers. Subjects who met all of the inclusion criteria and none of the exclusion criteria listed in the study protocol were enrolled for participation.

TEST METHOD

This study was conducted according to the study protocol, CRL79410 BI 3.0 (Attachment I).

STUDY RELATED COMMENTS

One subject (#5) exceeded the upper limit of the age inclusion range by one year. This subject met all other criteria and was allowed to participate. In the opinion of the Investigator, inclusion of this subject did not affect the integrity of the study.

Four subjects (#3, #5, #39, and #54) were identified as outliers (raw data lies more than 3 times the IQR (Inter Quartile Range) above the 3rd quartile or less than 3 times the IQR below the 1st quartile) and were excluded from PRIMOS data analysis.

TEST RESULTS

Completed and Discontinued Subjects

A total of 53 subjects completed the study. Three subjects (#21, #23, and #49) discontinued study participation for reasons unrelated to test material use.

Ophthalmic Examinations

Individual ophthalmic examination scores appear in Table I.

Trace increases in palpebral conjunctival irritation were observed in only three subjects. In the opinion of the Investigator, these findings were not related to test material use and were probably caused by external factors such as hair products, mechanical factors, contact lens wear, sensitive eye status, environmental and/or seasonal factors. There were no reports of subjective irritation. There were no increases in lacrimation, eyelid inflammation, or bulbar conjunctival inflammation, and no changes in visual acuity, corneal tissue integrity or contact lenses were observed.

TEST RESULTS (Continued)

Evaluation of Skin Surface Hydration

Table II lists the average Corneometer® measurements and calculated percentage changes from baseline for each subject at the Week 4 and Week 8 evaluations. A statistical summary of Corneometer® measurements appears below:

Mean Corneometer® Measurements				Mean of Percent Change from Baseline	
Baseline	Week 4	Week 8		Week 4	Week 8
38	65	49		**75% (p<0.0001)**	**31% (p<0.0001)**

Shading/bold indicates statistical significance.

Evaluation of Skin Surface Topography

Tables IIIA-IIIC list the individual PRIMOS 3D parameters (Ra, Rz and Rmax) and calculated percentage changes from baseline for each subject at the Week 4 and Week 8 evaluations. A statistical summary of PRIMOS 3D measurements appears below:

Parameter	Mean PRIMOS Measurements				Mean of Percent Change from Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
Ra	95.095	99.059	99.873		5% (p 0.1858)	6% (p 0.0946)
Rz	588.70	590.68	611.21		2% (p 0.9809)	4% (p 0.1217)
Rmax	1510	1475	1562		3% (p 0.8866)	10% (p 0.7763)

Ra = the average roughness
Rz = the average of the greatest differences from peak to valley across the profile
Rmax = the maximum difference between the highest measured peak and the lowest valley in the skin profile

Daily Diaries

There were no comments recorded on the Daily Diary that were related to reactions or symptoms perceived during test material use.

Adverse Events

There were no adverse events reported during the study.

CONCLUSION

Based on the test results of the subjective and objective ophthalmic evaluations following the eight-week use period, it was determined that the test material, [redacted], did not demonstrate a potential for eliciting ocular irritation. In this test population and under the conditions of the study, the test material was determined to be clinically safe for use by normal eye contact lens wearers, normal eye non-contact lens wearers, and self-assessed sensitive eye non-contact lens wearers.

Following four and eight weeks of test material use, statistically significant increases in Corneometer® measurements were observed, indicating improved skin surface hydration. No statistically significant changes in skin surface topography were observed during the study period.

REVISION HISTORY

Questionnaire data from the report issued on January 13, 2011 was removed.

Clinical Research Laboratories, Inc.

Table I

Ophthalmic Examination Results

Maximum Increase from Baseline Examination at Week 8														
Subject Number	Subjective Irritation		Lacrimation		Eyelid Irritation (Upper/Lower)		Palpebral Conjunctival Irritation (Upper/Lower)		Bulbar Conjunctival Irritation		Cornea		Contact Lens Changes	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L
1	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
2	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
3	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
4	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
5	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
6	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
7	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
8	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
9	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
10	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
11	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
12	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
13	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
14	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
15	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
16	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
17	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
18	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
19	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
20	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
22	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
24	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
25	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
26	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
27	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
28	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
29	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
30	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA

NA Not Applicable. Subject is not a contact lens wearer. Scoring scales appear in the attached study protocol.
R Right Eye
L Left Eye

Clinical Research Laboratories, Inc.

Table I
(Continued)

Ophthalmic Examination Results

Maximum Increase from Baseline Examination at Week 8														
Subject Number	Subjective Irritation		Lacrimation		Eyelid Irritation (Upper/Lower)		Palpebral Conjunctival Irritation (Upper/Lower)		Bulbar Conjunctival Irritation		Cornea		Contact Lens Changes	
	R	L	R	L	R	L	R	L	R	L	R	L	R	L
31	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
32	0	0	0	0	0/0	0/0	0/1	0/1	0	0	0	0	0	0
33	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
34	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
35	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
36	0	0	0	0	0/0	0/0	1/1	1/1	0	0	0	0	0	0
37	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
38	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
39	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
40	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
41	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
42	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
43	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
44	0	0	0	0	0/0	0/0	1/1	1/1	0	0	0	0	0	0
45	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
46	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
47	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
48	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
50	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
51	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
52	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	0	0
53	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
54	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
55	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA
56	0	0	0	0	0/0	0/0	0/0	0/0	0	0	0	0	NA	NA

NA = Not Applicable. Subject is not a contact lens wearer. Scoring scales appear in the attached study protocol.
R = Right Eye
L = Left Eye

Table II

Corneometer® Measurements

Subject Number	Corneometer Measurements			% Change From Baseline	
	Baseline	Week 4	Week 8	Week 4	Week 8
1	41	62	52	51%	27%
2	34	46	40	35%	18%
3	35	52	44	49%	26%
4	34	89	62	162%	82%
5	40	62	51	55%	28%
6	41	74	46	80%	12%
7	38	69	45	82%	18%
8	40	53	47	33%	18%
9	42	53	24	26%	-43%
10	33	54	54	64%	64%
11	38	78	58	105%	53%
12	32	62	48	94%	50%
13	38	65	53	71%	39%
14	37	81	59	119%	59%
15	36	60	62	67%	72%
16	37	91	64	146%	73%
17	34	65	49	91%	44%
18	43	84	58	95%	35%
19	32	65	34	103%	6%
20	39	84	37	115%	-5%
21	42	71	55	69%	31%
24	42	56	49	33%	17%
25	33	64	49	94%	48%
26	43	61	52	42%	21%
27	41	77	43	88%	5%
28	34	41	32	21%	-6%
29	38	47	42	24%	11%
30	35	57	46	63%	31%
31	44	87	66	98%	50%
32	35	71	37	103%	6%
33	35	88	62	151%	77%
34	38	57	47	50%	24%
35	35	45	69	29%	97%

Clinical Research Laboratories, Inc.

Table II
(Continued)

Corneometer® Measurements

Subject Number	Corneometer Measurements				% Change From Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
36	32	55	43		72%	34%
37	33	63	49		91%	48%
38	43	66	54		53%	26%
39	36	65	45		81%	25%
40	38	86	62		126%	63%
41	42	66	54		57%	29%
42	32	70	51		119%	59%
43	35	69	52		97%	49%
44	43	64	55		49%	28%
45	40	57	58		43%	45%
46	36	62	41		72%	14%
47	39	51	47		31%	21%
48	37	53	47		43%	27%
50	35	73	48		109%	37%
51	43	63	30		47%	-30%
52	39	62	31		59%	-21%
53	40	63	48		58%	20%
54	36	81	58		125%	61%
55	43	63	46		47%	7%
56	33	54	45		64%	36%
Mean	**38**	**65**	**49**	**Mean**	**75%**	**31%**
Std.Dev.	**4**	**12**	**10**	**Std.Dev.**	**35%**	**27%**

Clinical Research Laboratories, Inc.

Table IIIA

PRIMOS 3D Measurements

Subject Number	Ra			%Change From Baseline	
	Baseline	Week 4	Week 8	Week 4	Week 8
1	120.230	114.230	113.740	-5%	-5%
2	88.427	62.943	105.450	-29%	19%
4	93.479	99.530	94.358	6%	1%
6	97.867	110.700	99.720	13%	2%
7	66.791	68.620	93.595	3%	40%
8	108.940	111.240	110.470	2%	1%
9	85.629	83.799	84.938	-2%	-1%
10	95.650	115.480	96.502	21%	1%
11	101.080	169.470	118.590	68%	17%
12	92.331	75.425	118.590	-18%	28%
13	93.390	92.055	92.153	-1%	-1%
14	78.093	78.048	78.936	0%	1%
15	99.960	81.017	87.738	-19%	-12%
16	149.450	150.630	149.740	1%	0%
17	115.650	114.780	117.310	-1%	1%
18	97.468	122.490	100.420	26%	3%
19	147.760	143.200	147.850	-3%	0%
20	70.714	138.260	71.059	96%	0%
22	73.604	73.902	74.489	0%	1%
24	73.942	125.420	132.410	70%	79%
25	68.420	68.512	67.800	0%	-1%
26	149.940	152.410	164.710	2%	10%
27	117.200	119.070	117.690	2%	0%
28	117.150	82.706	101.970	-29%	-13%
29	73.171	83.484	90.579	14%	24%
30	74.065	79.127	81.575	7%	10%

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Table IIIA (Continued)

PRIMOS 3D Measurements

Subject Number	Ra				%Change From Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
31	92.331	86.214	92.202		-7%	0%
32	103.890	102.230	111.780		-2%	8%
33	106.920	103.570	113.840		-3%	6%
34	80.281	115.480	79.316		44%	-1%
35	98.061	100.010	97.786		2%	0%
36	91.097	93.043	100.710		2%	11%
37	82.116	82.214	82.769		0%	1%
38	93.033	94.932	93.655		2%	1%
40	77.906	79.121	73.006		2%	-6%
41	66.328	65.346	84.269		-1%	27%
42	96.231	100.480	84.269		4%	-12%
43	93.961	89.256	131.590		-5%	40%
44	92.773	93.768	106.510		1%	15%
45	103.490	106.790	109.630		3%	6%
46	102.360	99.610	102.220		-3%	0%
47	98.964	108.880	99.320		10%	0%
48	101.080	98.904	94.555		-2%	-6%
50	95.070	95.938	95.519		1%	0%
51	61.364	59.041	59.992		-4%	-2%
52	99.130	90.607	96.199		-9%	-3%
53	101.840	102.570	101.760		1%	0%
55	69.704	71.055	69.938		2%	0%
56	101.320	98.261	100.570		-3%	-1%
Mean	**95.095**	**99.059**	**99.873**	**Mean**	**5%**	**6%**
Std.Dev.	**20.019**	**24.168**	**21.239**	**Std.Dev.**	**22%**	**16%**

Clinical Research Laboratories, Inc.

Table IIIB

PRIMOS 3D Measurements

Subject Number	Rz				%Change From Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
1	625.40	537.32	616.08		-14%	-1%
2	527.72	512.48	495.56		-3%	-6%
4	424.92	483.16	462.12		14%	9%
6	585.80	798.84	673.52		36%	15%
7	658.68	860.72	743.08		31%	13%
8	622.60	615.20	611.52		-1%	-2%
9	549.80	521.56	573.00		-5%	4%
10	672.08	657.60	664.40		-2%	-1%
11	532.56	780.36	760.12		47%	43%
12	618.16	513.12	760.12		-17%	23%
13	518.24	489.88	478.28		-5%	-8%
14	418.72	431.56	432.28		3%	3%
15	444.52	558.88	493.92		26%	11%
16	743.56	789.96	815.60		6%	10%
17	706.44	640.48	701.64		-9%	-1%
18	585.44	652.80	614.72		12%	5%
19	623.92	669.88	606.52		7%	-3%
20	475.92	665.84	487.92		40%	3%
22	510.68	520.84	486.12		2%	-5%
24	969.72	853.48	840.28		-12%	-13%
25	434.48	400.52	405.04		-8%	-7%
26	758.12	733.96	900.24		-3%	19%
27	650.72	646.48	613.12		-1%	-6%
28	550.52	589.76	574.52		7%	4%
29	578.12	593.40	556.96		3%	-4%
30	445.44	516.08	552.40		16%	24%

Clinical Research Laboratories, Inc.

Table IIIB
(Continued)

PRIMOS 3D Measurements

Subject Number	Rz				%Change From Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
31	618.16	534.84	670.04		-13%	8%
32	596.84	605.56	697.88		1%	17%
33	620.96	554.20	693.96		-11%	12%
34	514.28	657.60	579.84		28%	13%
35	687.20	511.32	670.64		-26%	-2%
36	543.32	559.40	510.20		3%	-6%
37	433.44	432.96	433.64		0%	0%
38	556.20	565.68	555.24		2%	0%
40	637.68	595.08	509.16		-7%	-20%
41	671.48	530.04	655.60		-21%	-2%
42	533.04	504.72	655.60		-5%	23%
43	688.92	569.76	754.12		-17%	9%
44	522.96	505.56	595.08		-3%	14%
45	708.68	791.44	939.80		12%	33%
46	610.40	647.36	617.16		6%	1%
47	975.32	780.24	918.76		-20%	-6%
48	532.56	512.24	527.36		-4%	-1%
50	479.64	511.60	491.80		7%	3%
51	407.96	369.24	342.92		-9%	-16%
52	632.92	524.00	597.88		-17%	-6%
53	509.60	519.48	497.84		2%	-2%
55	507.16	515.28	498.60		2%	-2%
56	625.28	611.40	617.08		-2%	-1%
Mean	**588.70**	**590.68**	**611.21**	**Mean**	**2%**	**4%**
Std.Dev.	**119.55**	**115.44**	**133.85**	**Std.Dev.**	**16%**	**12%**

Clinical Research Laboratories, Inc.

Table IIIC

PRIMOS 3D Measurements

Subject Number	Rmax				%Change From Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
1	1374	1220	1301		-11%	-5%
2	1305	1119	1067		-14%	-18%
4	965	1114	1002		15%	4%
6	1771	1951	1837		10%	4%
7	1338	3428	3105		156%	132%
8	1433	1469	1493		3%	4%
9	963	950	1011		-1%	5%
10	1642	1414	1643		-14%	0%
11	1109	2556	3162		130%	185%
12	1124	1281	3162		14%	181%
13	1274	1238	1249		-3%	-2%
14	711	711	711		0%	0%
15	1217	1068	1782		-12%	46%
16	1875	1915	1875		2%	0%
17	1536	1536	1521		0%	-1%
18	1449	1373	1467		-5%	1%
19	1742	1592	1710		-9%	-2%
20	1119	1481	1142		32%	2%
22	964	960	943		0%	-2%
24	3570	2903	1736		-19%	-51%
25	904	847	883		-6%	-2%
26	2007	1978	1785		-1%	-11%
27	1458	1447	1428		-1%	-2%
28	1372	1855	1453		35%	6%
29	2663	1404	2246		-47%	-16%
30	940	1165	952		24%	1%

Clinical Research Laboratories, Inc.

Table IIIC (Continued)

PRIMOS 3D Measurements

Subject Number	Rmax				%Change From Baseline	
	Baseline	Week 4	Week 8		Week 4	Week 8
31	1124	1121	1636		0%	46%
32	1375	1373	1315		0%	-4%
33	1149	1180	1533		3%	33%
34	1079	1414	1949		31%	81%
35	1348	1054	1340		-22%	-1%
36	1526	1526	1100		0%	-28%
37	947	988	979		4%	3%
38	1139	1154	1144		1%	0%
40	2562	2351	1200		-8%	-53%
41	3003	3002	1376		0%	-54%
42	1094	990	1376		-10%	26%
43	2037	1090	2555		-46%	25%
44	1099	1074	1274		-2%	16%
45	3169	3269	3184		3%	0%
46	2036	1351	2038		-34%	0%
47	3653	1788	3546		-51%	-3%
48	1109	1107	886		0%	-20%
50	1016	1064	1016		5%	0%
51	822	794	658		-3%	-20%
52	1468	1169	1467		-20%	0%
53	1230	1255	1213		2%	-1%
55	914	876	858		-4%	-6%
56	1279	1297	1238		1%	-3%
Mean	**1510**	**1475**	**1562**	**Mean**	**3%**	**10%**
Std.Dev.	**691**	**631**	**690**	**Std.Dev.**	**34%**	**46%**

Clinical Research Laboratories, Inc.

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Eye Type	Age	Sex
1	PD	05799	SASE	57	F
2	JJ	21891	SASE	53	F
3	LL	05112	SASE	50	F
4	DM	22995	NCLW	44	F
5	MS	27450	NCLW	61	F
6	LZ	26623	DISP	48	F
7	MR	21928	SASE	35	F
8	MG	12004	NCLW	40	F
9	CM	24368	NCLW	45	F
10	PE	26776	DISP	47	F
11	JD	18532	SASE	46	F
12	LD	18531	NCLW	49	F
13	CC	05998	DSCL	55	F
14	JM	27231	DISP	40	F
15	RH	21877	NCLW	49	F
16	AN	26348	NCLW	59	F
17	PG	26622	NCLW	47	F
18	GO	22764	NCLW	60	F
19	JM	27582	NCLW	39	F
20	JM	27581	NCLW	38	F
21	SD	27633	NCLW	57	F
22	MD	26978	NCLW	40	F
23	NG	27309	SASE	60	F
24	SM	24425	NCLW	52	F
25	RA	23557	SASE	39	F
26	LC	26456	SASE	55	F
27	AP	24717	NCLW	52	F
28	LD	20032	DISP	41	F

Subject Number	Subject Initials	CRL ID#	Eye Type	Age	Sex
29	AR	27178	SASE	40	F
30	PH	01487	SASE	45	F
31	TR	24421	SASE	36	F
32	TA	11100	DISP	49	F
33	LM	25200	SASE	52	F
34	NK	16367	DISP	52	F
35	MC	25920	DISP	43	F
36	LW	24914	DISP	47	F
37	RL	09017	DISP	48	F
38	LG	26018	DISP	46	F
39	JG	27625	DSCL	59	F
40	NT	12586	DISP	51	F
41	DK	19073	SASE	45	F
42	VP	09263	RGP	55	F
43	MZ	07414	SASE	52	F
44	RM	16184	DISP	46	F
45	BB	04876	SASE	60	F
46	CM	16725	DISP	44	F
47	LD	08929	DSCL	53	F
48	EH	20600	SASE	59	F
49	CR	26517	CL*	51	F
50	MH	27486	SASE	43	F
51	SC	17212	NCLW	53	F
52	MT	15520	DSCL	51	F
53	NP	06660	NCLW	51	F
54	WS	23637	NCLW	51	F
55	SS	23756	NCLW	55	F
56	JG	17522	SASE	39	F

*CL = Contact Lens Wearer – Type Not Reported

EyeType: NCLW = Non Contact Lens Wearer
DISP = Disposable Soft Contact Lens Wearer
DSCL = Daily Soft Contact Lens Wearer
RGP = Rigid Gas Permeable Contact Lens Wearer
SASE = Self-Assessed Sensitive Eyes (Non Contact Lens Wearer)

Clinical
Research
Laboratories, Inc.

Final Report

Repeated Insult Patch Test
(Marzulli and Maibach Method)

CLIENT: [redacted]

ATTENTION: [redacted]

TEST MATERIAL: [redacted]
Excrean containing
2.75% Saccharide
Isomerate

CRL STUDY NUMBER: CRL83510

AUTHORIZED SIGNATURES:

Bruce E. Kanengiser, M.D.
President/Medical Director

Michael J. Muscatiello, Ph.D.
Executive Vice President/COO

Anita Lee Cham, M.D.
Dermatologist

REPORT DATE: January 19, 2011

371 Hoes Lane • Piscataway, NJ 08854 • (732) 981-1616 • FAX (732) 981-0520

Clinical
Research
Laboratories, Inc.

Good Clinical Practice
Quality Assurance Audit Statement

Clinical Study Number: CRL83510

Start Date: October 4, 2010

Completion Date: January 10, 2011

The clinical study listed above was conducted in accordance with Clinical Research Laboratories, Inc. Standard Operating Procedures, which incorporate the principles of Good Clinical Practice defined by applicable guidelines and regulations established by U.S. Regulatory Agencies. The conduct of the study was monitored for compliance, and the associated records, including source documents or raw data, were reviewed for documentation practices and accuracy by a Project Manager/Study Director and/or a Quality Assurance Representative. Standard Quality Assurance audit procedures for this final report and study related documents were conducted.

Karen Hayley
Signature of QA Auditor

January 19, 2011
Date

Clinical Research Laboratories, Inc.

FINAL REPORT

REPEATED INSULT PATCH TEST (MARZULLI AND MAIBACH METHOD)

PURPOSE

The purpose of this study was to determine the dermal irritation and sensitization potential of a test material and to support the product claim of "non-irritating" and "Dermatologist Tested".

INVESTIGATIVE SITE

Clinical Research Laboratories, Inc.
371 Hoes Lane, Suite 100
Piscataway, New Jersey 08854
732-981-1616

TEST MATERIAL

The following test material was provided by [redacted] and received by Clinical Research Laboratories, Inc. on September 16, 2010:

Test Material	Test Condition	Patch Type
[redacted]	Test as Received	Occlusive*

The test material was coded with the following CRL identification number:

CRL83510

STUDY DATES

This study was initiated on October 4, 2010 and was completed on January 10, 2011.

* Occlusive Strip with Flexcon® (Brady Medical, Mesquite,TX)

PANEL SELECTION

Each subject was assigned a permanent CRL identification number. All subjects signed an Informed Consent Form in compliance with 21 CFR Part 50: "Protection of Human Subjects" and a HIPAA Authorization Form in compliance with 45 CFR Parts 160 and 164. All subjects completed a Panelist Profile/Medical History Form provided by Clinical Research Laboratories, Inc. prior to the study (Subject Demographics - Appendix I). Subjects who met the following Inclusion Criteria and none of the Exclusion Criteria were impaneled:

Inclusion Criteria

a. Male and female subjects between the ages of 18 and 70 years;

b. Subjects who do not exhibit any skin diseases which might be confused with a skin reaction from the test material;

c. Subjects who agree to avoid exposure of the test sites to the sun and to refrain from visits to tanning salons during the course of this study;

d. Subjects willing to sign an Informed Consent in conformance with 21CFR Part 50: "Protection of Human Subjects;"

e. Subjects who have completed a HIPAA Authorization Form in conformance with 45CFR Parts 160 and 164;

f. Subjects in generally good health who have a current Subject Profile/Medical History on file;

g. Subjects who are dependable and able to follow directions as outlined in the protocol.

Exclusion Criteria

a. Female subjects who are pregnant or nursing;

b. Subjects who are currently using any systemic or topical corticosteroids, anti-inflammatory drugs, or antihistamines on a regular basis;

c. Subjects exhibiting any skin disorder, sunburn, scars, excessive tattoos, etc. in the test area.

TEST METHOD

Prior to the application of the patch, the test area was wiped with 70% isopropyl alcohol and allowed to dry. The test material, which was prepared as described in the Test Material section of the report, was applied to the upper back, between the scapulae and the waist, lateral to the midline.

The test material was applied to the same site three times per week (Monday, Wednesday, and Friday) for a total of nine applications. However, the schedule may have been modified to accommodate inclement weather, holidays, or missed applications. At the discretion of the Study Director, the test material may have been applied on two consecutive days during the Induction Phase or a makeup day may have been added at the end of the Induction Phase.

The sites were graded by a CRL technician for dermal irritation and sensitization 48 hours after application of the patches on Monday and Wednesday and 24 hours after removal of the patches on Sunday, unless the patching schedule was altered as described above.

The sites were graded according to the following scoring system:

Dermal Scores

-	= No reaction
?	= Minimal or doubtful response, slightly different from surrounding normal skin
+	= Definite erythema No edema
++	= Definite erythema Definite edema
+++	= Definite erythema Definite edema and vesiculation

If a "++" reaction or greater occurred, the test site did not receive any further Induction Phase patches, and the test material was instead applied to an adjacent virgin site. If a "++" reaction or greater occurred on the new site, the subject was not patched again during the Induction Phase but was challenged on the appropriate day of the study. At the discretion of the Study Director, patch sites with scores less than "++" may have been changed.

TEST METHOD (Continued)

Following a 2-week rest period, the challenge patches were applied to the previously treated test sites on the back (original) and to newly defined sites, previously unexposed (virgin). After 48 hours, the patches were removed by a CRL technician, and the test sites were evaluated for dermal reactions. The test sites were re-evaluated at 72 and 96 hours.

STUDY RELATED COMMENT

Due to inclement weather on Friday, January 7, 2011, Clinical Research Laboratories, Inc. was closed early. Some subjects on Panel B (second 100 subjects) were unable to return for the 96 hour Challenge examination and were instructed to return on Monday, January 10, 2011, for a final examination.

RESULTS

This study was initiated with 224 subjects. Eleven subjects discontinued study participation for reasons unrelated to the test material. A total of 213 subjects completed the study.

Individual dermal scores recorded during the Induction and Challenge Phases appear in Table I.

CONCLUSION

Based on the test population of 213 subjects and under the conditions of this study, the sample identified as [redacted] Formula: [redacted] did not demonstrate a potential for eliciting dermal irritation or sensitization.

RETENTION

Test materials and all original forms of this study will be retained by Clinical Research Laboratories, Inc. as specified in CRL Standard Operating Procedures 30.6 and 30.6C, unless designated otherwise by the Sponsor.

Clinical Research Laboratories, Inc.

TABLE I

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
1A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7A	-	-	?	-	-	-	-	-	?	-	-	-	-	-	-
8A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
15A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19A	-	-	-	-	-	-	-	-	-	Discontinued					
20A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
22A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
24A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores 48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
26A	-	-	-	-	-	-	-	-	-	-	-	-	-	Discontinued	
27A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
28A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
29A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
31A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
38A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
47A	-	-	Discontinued												
48A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
49A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
51A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
56A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
57A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
58A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
59A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
61A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
63A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
64A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
66A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
67A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69A	-	-	Discontinued												
70A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
74A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
76A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
79A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
80A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
81A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
82A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
84A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
85A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
87A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
88A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
89A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
90A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
92A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
93A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
94A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
95A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
96A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
97A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
98A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
99A	Discontinued														
100A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
101A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
103A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
104A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
105A	-	-	-	-	-	-	-	Discontinued							
106A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
108A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
109A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
110A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
111A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
112A	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
1B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
4B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
5B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
6B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
7B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
10B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
11B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
12B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
13B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
14B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X*
15B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
16B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
17B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
18B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
19B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
20B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
21B	-	-	Discontinued												
22B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
23B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
24B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
25B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent
*Subject could not return on Monday, January 10, 2011.
**No reaction was observed at the 96 hour reading.

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
26B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
27B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
28B	Discontinued														
29B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
30B	-	-	Discontinued												
31B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
32B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
33B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
34B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
35B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
36B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
37B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
38B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
39B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
40B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
41B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
42B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
43B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
44B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
45B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
46B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
47B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
48B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
49B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
50B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent
**No reaction was observed on Monday, January 10, 2011.

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
51B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
52B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
53B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
54B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
55B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
56B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
57B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
58B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
59B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
60B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
61B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
62B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
63B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
64B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
65B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
66B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
67B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
68B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
69B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
70B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
71B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
72B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
73B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
74B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
75B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent
**No reaction was observed on Monday, January 10, 2011.

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
Subject Number	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
76B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
77B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
78B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
79B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
80B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
81B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
82B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
83B	Discontinued														
84B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
85B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
86B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
87B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
88B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
89B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
90B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
91B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
92B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
93B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
94B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
95B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
96B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
97B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X**
98B	-	-	-	Discontinued											
99B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
100B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent
**No reaction was observed on Monday, January 10, 2011.

Clinical Research Laboratories, Inc.

TABLE I
(Continued)

Tabulation of Individual Scores

Test Material: [redacted]

Subject Number	Induction Scores									Challenge Scores					
										48 Hours		72 Hours		96 Hours	
	1	2	3	4	5	6	7	8	9	O	V	O	V	O	V
101B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
102B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
103B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
104B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
105B	-	-	-	-	-	-	-	-	-	-	-	-	-	X	X*
106B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
107B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
108B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
109B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
110B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
111B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
112B	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

O = Original Site
V = Virgin Site
X = Subject Absent
*Subject could not return on Monday, January 10, 2011.

Clinical Research Laboratories, Inc.

Appendix I

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1A	PS	17113	67	F
2A	JA	27496	41	F
3A	MS	18675	70	F
4A	MS	17112	31	F
5A	SH	25349	61	F
6A	DD	19959	49	F
7A	GE	26227	54	M
8A	EN	26847	58	F
9A	RF	27326	21	F
10A	JG	26548	68	F
11A	AL	24030	52	F
12A	AC	03970	60	F
13A	MS	26602	60	F
14A	RB	25573	51	M
15A	DL	19589	59	F
16A	MJ	24157	42	F
17A	EL	26069	49	F
18A	VB	25771	65	F
19A	TB	22676	34	F
20A	MB	25677	38	M
21A	AC	19922	19	F
22A	JH	19225	46	M
23A	BL	20206	61	F
24A	DL	23982	56	M
25A	RR	26591	23	F
26A	DB	08725	40	M
27A	SG	23926	48	F
28A	RR	10112	52	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
29A	FR	24101	39	M
30A	DL	21338	39	F
31A	AJ	23767	61	M
32A	JP	24490	49	F
33A	WV	17705	46	M
34A	KM	00302	57	F
35A	RB	23882	38	M
36A	VR	27497	23	F
37A	JP	25901	39	F
38A	AR	17119	39	F
39A	PG	13984	49	F
40A	SB	14645	66	M
41A	NM	25732	30	F
42A	KO	23725	51	F
43A	CL	14668	66	F
44A	MI	14669	66	F
45A	MR	17214	67	F
46A	KV	25297	41	F
47A	DZ	20352	24	F
48A	WJ	27415	50	F
49A	CM	19646	52	F
50A	BM	18748	62	F
51A	RK	25864	56	F
52A	DB	12144	30	F
53A	EV	21621	31	F
54A	SS	25766	41	F
55A	BS	25765	64	F
56A	PS	25822	37	F

Clinical Research Laboratories, Inc.

Appendix I (Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
57A	CC	05998	55	F
58A	AA	25921	20	F
59A	BA	23376	62	F
60A	AO	26167	64	F
61A	JC	27453	62	M
62A	TH	17294	48	F
63A	DH	23605	47	F
64A	SM	10885	47	F
65A	NK	26532	65	F
66A	NF	18858	42	F
67A	TO	22359	33	F
68A	TS	23518	44	F
69A	CP	19567	46	F
70A	SC	23058	47	F
71A	HS	07067	55	F
72A	PP	15763	58	F
73A	DH	12327	52	F
74A	LP	27319	52	F
75A	CC	18896	30	F
76A	MJ	17644	57	F
77A	RR	24439	54	F
78A	SB	22825	49	F
79A	MB	22824	46	M
80A	MH	24503	58	F
81A	CH	18972	59	F
82A	MD	15442	58	F
83A	TR	27308	45	F
84A	JC	17375	42	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
85A	KE	21519	38	M
86A	DM	20610	41	M
87A	VJ	20455	53	F
88A	WS	25037	60	M
89A	SS	02364	26	M
90A	CP	26218	47	F
91A	EJ	24955	49	M
92A	EB	24168	48	M
93A	AS	25415	52	M
94A	RG	06155	59	M
95A	UP	26008	53	F
96A	SP	26003	32	F
97A	HP	26009	60	M
98A	GD	27374	35	F
99A	SP	25063	30	F
100A	AS	26758	33	F
101A	LL	21886	65	F
102A	KL	25144	53	F
103A	AD	16718	35	M
104A	CR	26517	51	F
105A	AP	27277	49	M
106A	MS	13309	31	F
107A	AD	20034	51	F
108A	ND	20506	23	F
109A	AS	02343	61	F
110A	FM	12729	48	F
111A	MA	24169	54	M
112A	KT	16885	20	M

Clinical Research Laboratories, Inc.

Appendix I
(Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
1B	DG	16950	52	F
2B	AT	14294	69	F
3B	JB	14759	59	F
4B	SG	23926	48	F
5B	DD	19959	49	F
6B	MJ	24157	42	F
7B	JA	15332	37	F
8B	KE	21519	38	M
9B	FR	24101	39	M
10B	BW	27548	64	F
11B	MC	20467	43	M
12B	KO	23725	51	F
13B	DJ	27153	49	F
14B	LL	21886	65	F
15B	CM	19646	52	F
16B	TH	17294	48	F
17B	SJ	27561	35	F
18B	PG	13984	49	F
19B	MB	18220	63	F
20B	TR	24421	37	F
21B	LM	22551	33	F
22B	AB	20778	50	M
23B	MS	18675	70	F
24B	JC	17375	42	F
25B	RS	27334	70	M
26B	LP	27319	52	F
27B	MJ	17644	58	F
28B	BG	21058	46	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
29B	LD	18531	49	F
30B	TP	27193	29	F
31B	MI	14669	66	F
32B	CL	14668	66	F
33B	JG	26548	68	F
34B	EN	26847	58	F
35B	GJ	01177	60	F
36B	AS	02343	61	F
37B	WJ	27415	50	F
38B	NK	26532	66	F
39B	SC	23058	47	F
40B	DL	19589	59	F
41B	CD	25061	42	F
42B	PO	01532	46	F
43B	CT	25861	25	F
44B	LT	26553	51	F
45B	RK	25864	56	F
46B	DL	21338	39	F
47B	PP	24006	55	M
48B	AJ	23767	61	M
49B	KS	26718	24	F
50B	CD	22327	57	F
51B	MD	15442	58	F
52B	EJ	24955	49	M
53B	AN	23619	43	M
54B	MB	15153	61	M
55B	AK	21288	64	F
56B	TL	27348	44	F

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Appendix I (Continued)

Subject Demographics

Subject Number	Subject Initials	CRL ID #	Age	Sex
57B	EL	25343	62	F
58B	CC	05998	55	F
59B	BM	18748	62	F
60B	JM	08354	60	M
61B	BC	19526	63	F
62B	LH	19614	46	F
63B	TW	27494	62	F
64B	WW	16548	41	F
65B	JA	27496	41	F
66B	DP	12717	48	F
67B	AK	06659	54	F
68B	RR	10112	52	F
69B	SB	14645	66	M
70B	MO	19978	52	F
71B	JJ	24466	24	F
72B	RB	01250	66	F
73B	LT	19586	34	F
74B	JP	25058	33	F
75B	MA	24427	37	F
76B	AD	20034	51	F
77B	ND	20506	23	F
78B	AD	16718	35	M
79B	EL	26069	49	F
80B	SM	27559	20	M
81B	NJ	27273	29	F
82B	GD	27374	35	F
83B	CN	18537	29	F
84B	CP	26218	47	F

Subject Number	Subject Initials	CRL ID #	Age	Sex
85B	CL	26977	42	F
86B	FM	12729	48	F
87B	GE	26227	54	M
88B	MA	20580	46	F
89B	SB	22825	49	F
90B	SB	09997	50	F
91B	RM	27622	29	M
92B	DL	23982	56	M
93B	JH	19225	46	M
94B	CG	20357	68	F
95B	AS	25836	32	F
96B	RS	21197	28	F
97B	AC	27383	26	M
98B	KT	16885	21	M
99B	WM	22781	60	M
100B	MA	18802	49	F
101B	CP	26975	23	F
102B	CA	00159	61	F
103B	AF	21927	49	F
104B	CG	24297	30	F
105B	AR	19479	27	F
106B	SE	20804	52	F
107B	DB	14921	32	F
108B	AO	16224	64	F
109B	BA	22252	64	F
110B	AR	25676	35	F
111B	WS	25037	60	M
112B	MA	24169	55	M

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

TO: Bart Heldreth, Ph.D.
Executive Director - Cosmetic Ingredient Review (CIR)

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: February 11, 2020

SUBJECT: Scientific Literature Review: Safety Assessment of Saccharide Humectants as Used in Cosmetics (release date: January 24, 2020)

The Personal Care Products Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Saccharide Humectants as Used in Cosmetics.

ADME, Oral, Psicose - It is not clear that it is appropriate to call the presence of Psicose in the liver "Accumulation". This study only lasted 120 minutes post-dosing and it also stated that Psicose was "eliminated rapidly".

Acute, Oral, Psicose - It is not clear if each dog received each treatment as the first sentence (reference 36) states: "(1 g/kg and 4 g/kg) and a placebo". If each dog received one treatment it should state "(1 g/kg or 4 g/kg) or a placebo".

Short-Term, Anhydroxylitol; Summary - As the 28-day oral study in rats is cited to NICNAS (reference 6), the identity of "the authors" is not clear. Does this refer to the investigators that completed the study, or NICNAS?

Chronic, Oral, Psicose - Please delete the first "lighter" in the following statement from the SLR: "relative intraabdominal adipose tissue weights lighter at 18 months were statistically significantly lighter in the 3% Psicose group, when compared to the control group."

Please revise the second paragraph as it currently states that there were no treatment-related effects in the kidneys and liver twice.

Risk Assessment - Rather than calling the SCCS reference (reference 41) a "published document", it would be clearer to call it the "Notes of Guidance, 7th revision".

Genotoxicity, In Vivo - As this study is cited to NICNAS, please clarify if "the authors" refers to NICNAS or the study investigators.

Anti-Melanogenic Activity - What concentration of arbutin was used as a control (reference 14)? As they were looking at melanin levels, perhaps the first word of the following sentence should be "Melanin". "Anhydrogalactose was statistically significantly lower than that of cells treated with the same concentration of arbutin or D-anhydrogalactose."

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Other Clinical Reports - If the "subjects consumed Psicose (5 g) with meals 3 times per day for 12 continuous weeks." This study should not be described as "single ingestion" (in the first sentence).

Summary - Please revise this sentence into at least two sentences as it describes two different studies (one is an oral study, the second is a subcutaneous study). "The effects of long-term 3% Psicose administration in the diet to rats were found to be increased liver and kidney weights, with no gross pathological findings correlated with this hypertrophy in a carcinogenicity study on L-arabinose involving 60 rats of the Bethesda black strain (30 males and 30 females) and 60 C57BL mice (30 males, 30 females), there was no histologic evidence of an injurious effect of the injected test substance on any internal organ, especially the liver and kidneys, in mice or rats."