Safety Assessment of Polyquaternium-6 as Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: November 13, 2020
Panel Date: December 7-8, 2020

The Expert Panel for Cosmetic Ingredient Safety members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; David E. Cohen, M.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.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 report 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: November 13, 2020

Subject: Safety Assessment of Polyquaternium-6 as Used in Cosmetics

Enclosed is a draft report of the Safety Assessment of Polyquaternium-6 (*polyqu122020rep*) as Used in Cosmetics. It should be noted that a Scientific Literature Review (SLR) Notice to Proceed (NTP) was announced on September 17, 2020. This announcement was made because an intensive search of the published information on Polyquaternium-6 resulted in insufficient information to justify preparation of a formal SLR. In response, the following unpublished data were received from the Council:

- Use concentrations (*polyqu122020data1*)
- Molecular weight (*polyqu122020data2*)
- Method of manufacture, composition, and impurities (*polyqu122020data2*)
- Brief summaries of acute oral toxicity, skin irritation (animal), and ocular irritation (animal) studies (*polyqu122020data2*)
- Dermal sensitization study summary (guinea pig) (*polyqu122020data2*)
- In vitro genotoxicity (*polyqu122020data3*)
- Composition/impurities; method of manufacture; acute dermal, oral, and inhalation toxicity; short-term oral toxicity; subchronic dermal toxicity; skin irritation (animal); skin sensitization (human); photoallergenicity (animal); and ocular irritation (*polyqu122020data4*)

These data are enclosed and summarized in the draft report, along with the limited safety test data that have been identified in the published literature.

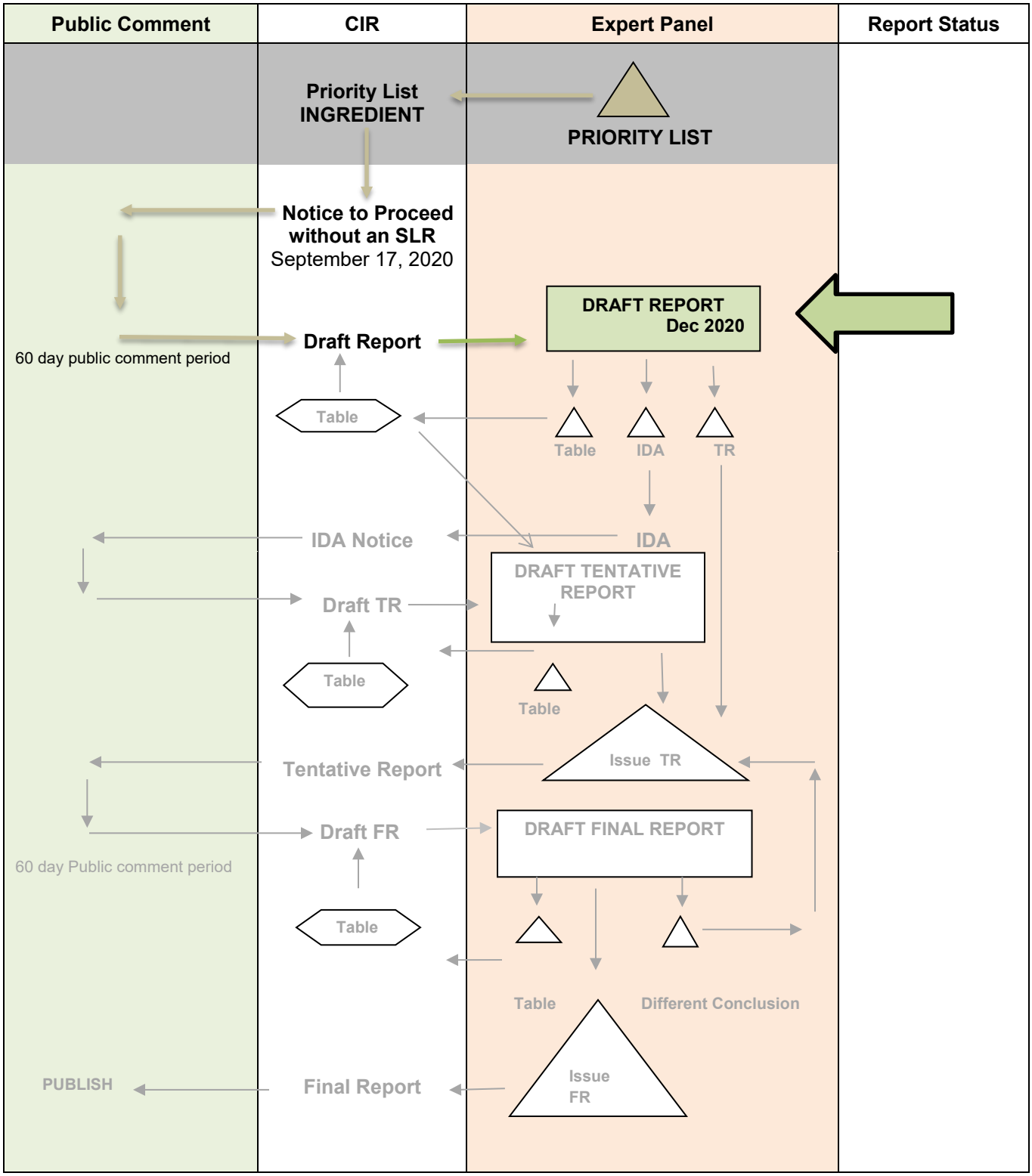
Also included in this package for your review are the report history (*polyqu122020hist*), flow chart (*polyqu122020flow*), literature search strategy (*polyqu122020strat*), ingredient data profile (*polyqu122020prof*), and 2020 FDA VCRP data (*polyqu122020FDA*).

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 insufficient, the Panel should issue an Insufficient Data Announcement (IDA), specifying the data needs therein.

SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Polyquaternium-6

MEETING December 2020



CIR History of:

Polyquaternium-6

A Scientific Literature Review (SLR) Notice to Proceed (NTP) on Polyquaternium-6 was issued on September 17, 2020.

Draft Report, Teams/Panel: December 7-8, 2020

The draft report also contains the following unpublished data that were received from the Council:

- Use concentrations
- Molecular weight
- Method of manufacture, composition, and impurities
- Acute dermal, oral, and inhalation toxicity; skin irritation (animal), and ocular irritation (animal)
- Short-term oral toxicity
- Subchronic dermal toxicity
- In vitro genotoxicity
- Skin irritation and sensitization (animal)
- Skin sensitization (human)
- Photoallergenicity (animal)
- Ocular irritation

Polyquaternium-6 Data Profile* – December 7-8, 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
Polyquaternium-6	**282**		**X**	**X**	**X**			**X**	**X**	**X**	**X**	**X**				**X**					**X**	**X**		**X**	**X**	**X**		**X**		

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

Polyquaternium-6 – 8/10-13/20; 10/20/20

Ingredient	CAS #	InfoBase	SciFinder	PubMed		FDA	EU	ECHA	IUCLID	SIDS	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	ECE-TOC	Web
Polyquaternium-6 (Quaternium-40)	26062-79-3	Yes		7/422		Yes (indirect additive)	No	No	No	No	No	No	No	No	No	No	No	Yes

*ECHA – pre-registration process

LINKS

InfoBase (self-reminder that this info has been accessed; not a public website) - http://www.personalcarecouncil.org/science-safety/line-infobase
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/

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INTRODUCTION

The safety of Polyquaternium-6 as used in cosmetics is reviewed in this safety assessment. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), Polyquaternium-6 is reported to function as an antimicrobial agent, antistatic agent, film former, and hair fixative.[1]

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing 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 provided 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 may be provided by the cosmetics industry, as well as by other interested parties. These searches yielded limited toxicity data on Polyquaternium-6

CHEMISTRY

Definition and Structure

Polyquaternium-6 (CAS No. 26062-79-3) is defined as a polymeric quaternary ammonium salt of diallyldimethyl ammonium chloride (DADMAC).[1] The idealized chemical structure is presented in Figure 1.

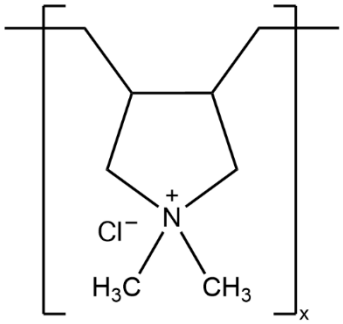

Figure 1. Polyquaternium-6 is the vinyl-type, homopolymer of DADMAC, wherein x is variable.

Chemical Properties

According to an analysis report from the cosmetics industry, Polyquaternium-6 has an average formula weight of 294,000 Da.[2] Additionally, it is soluble in water.[3] According to another source, 2 separate products identified as Polyquaternium-6 have typical molecular weights of 150,000 Da and 15,000 Da.[4] These and other properties are presented in Table 1.[2,3,5-7]

Method of Manufacture

Polyquatermium-6 is produced by the polymerization of DADMAC (21 CFR 176.170).

A cosmetics industry source indicates that the origin of the starting material for production of Polyquaternium-6 is synthetic, and that, as stated above, the production process involves polymerization of diallyl dimethylammonium chloride.[8] This process does not involve the incorporation of additives such as preservatives, antioxidants, bleaching agents, or fragrances. Furthermore, the following by-products are not expected from the Polyquaternium-6 production process: 1,4-dioxane, ethylene oxide, monochloroacetic acid, dichloroacetic acid, phthalates, pesticides, glycol ethers, and residual solvents.

According to a manufacturer of 2 other products that are identified as Polyquaternium-6, both are produced by polymerization of DADMAC in an aqueous solution.[4] Composition data on these 2 products are included at the end of the following section.

Composition/Impurities

The finished resin resulting from the polymerization of DADMAC has a nitrogen content of 8.6 6 ± 0.4% on a dry weight basis and the level of residual monomer is not to exceed 1% by weight of the polymer (dry basis) (21 CFR 176.170).

According to one supplier, Polyquaternium-6 contains 40 to 42% Polyquaternium-6 and 58% to 60% water.[8,9] The residual monomer content is up to a maximum of 0.5% dimethyldiallylamin, and data on other components are as follows: amines (maximum of 0.2%), sodium chloride (maximum of 1.5%), allyl alcohol (maximum of 250 ppm), allyl chloride (maximum of 50 ppm), and methylchlorid (< 2 ppm). Heavy metals content is up to a maximum of 10 ppm, and each of the following elements is present at concentrations of < 1 ppm: nickel, chromium, cobalt, cadmium, mercury, lead, arsenic, and antimony. The presence of nitrosamines in Polyquaernium-6 has not been determined.

Polyquaternium-6, produced by another company, contains Polyquaternium-6 (42%), water (< 58%), and free unreacted DADMAC (6.5% maximum).[4] Another product identified as Polyquaternium-6, manufactured by the same company, has the following composition: Polyquaternium-6 (33%), water (< 67%), acetic acid (0.65%), and free unreacted DADMAC (1.5% maximum). Both have the same structure, and vary by the amount of repeated monomer units to achieve the desired molecular weight.

USE

Cosmetic

The safety of the cosmetic ingredient addressed in this safety assessment is evaluated based, in part, on data received from the United States (US) Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in FDA's Voluntary Cosmetic Registration Program (VCRP) database.[10] Use concentration data are submitted by the cosmetics industry in response to surveys, conducted by the Personal Care Products Council (Council), of maximum reported use concentrations by product category.[11]

According to 2020 VCRP data, Polyquaternium-6 is reported to be used in 282 cosmetic products (16 leave-on products, 265 rinse-off products, and 1 product diluted for bath use; Table 2).[10] The results of a concentration of use survey completed in 2019 - 2020, and provided by the Council in 2020, indicate that Polyquaternium-6 is being used at maximum use concentrations up to 1.2% in leave-on products (tonics, dressings, and other hair grooming aids) and at maximum use concentrations up to 3% in rinse-off products (hair straighteners).[11] Cosmetic products containing Polyquaternium-6 may be applied to the skin/hair (at concentrations up to 3%) or, and may come in contact with mucous membranes (at concentrations up to 0.25% in bath soaps and detergents). Products containing Polyquaternium-6 are not typically applied more than once per day, and may come in contact with the skin for variable periods following application. Daily or occasional use may extend over many years.

Polyquaternium-6 is reported to be used in aerosol hair sprays (pump sprays) at maximum use concentrations up to 0.5%. 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.[12-15] 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.[12,13]

Polyquaternium-6 is not restricted from use in any way under the rules governing cosmetic products in the European Union.[16]

Non-Cosmetic

Polyquaternium-6 is an FDA-approved indirect food additive, i.e., for use as a component of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170). As a pigment dispersant and/or retention aid in the manufacture of paper, Polyquaternium-6 is used at a level not to exceed 10 pounds of active polymer per ton of finished paper and paperboard. As a pigment dispersant in coatings, it is used at a level not to exceed 3.5 pounds of active polymer per ton of finished paper and paperboard. For use only as a flocculant in the manufacture of paper and paperboard, it is used at a level not to exceed 10 mg/l (10 ppm) of influent water.

TOXICOKINETIC STUDIES

Dermal Penetration

Dermal penetration studies on Polyquaternum-6 were neither found in the published literature, nor were these data submitted.

Absorption, Distribution, Metabolism, and Excretion (ADME)

ADME studies on Polyquaternum-6 were neither found in the published literature, nor were these data submitted.

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Acute toxicity studies are presented in Table 3.

Dermal

The acute dermal toxicity of Polyquaternium-6 was evaluated in rats (number and strain not stated).[6] An LD_{50} of > 2 g/kg was reported. An acute dermal toxicity study on Polyquaternium-6 (42% aqueous) was performed using 4 groups of 4 rabbits (strain not stated).[17] The test substance was administered for 24 h (under a binder) at the following doses: 2.15 g/kg , 4.64 g/kg, 10.0 g/kg, and 21.5 g/kg. The LD_{50} was estimated to be 21.5 g/kg, and no consistent test substance-related signs of systemic toxicity were observed.

Oral

The acute oral toxicity of Polyquaternium-6 was evaluated in a study involving mice (number and strain not stated). An LD_{50} of 1.72 g/kg was reported, and respiratory depression was observed.[18] Acute oral toxicity studies on Polyquaternium-6 were performed using rats (number and strain not stated).[3,18] An LD_{50} of 3/g/kg was reported in both studies. Respiratory depression was noted in one of the studies.[18] In another acute oral toxicity test involving rats (number and strain not stated), an LD_{50} of > 2 g/kg was reported.[6] The same LD_{50} (> 2 g/kg) was reported in an acute oral toxicity study (rats) on an unidentified material that is comparable to Polyquaternium-6 (40 to 42% aqueous) that was performed using OECD Guideline 401(protocol details not included).[8] The acute oral toxicity of Polyquaternium-6 (42% aqueous) was evaluated using 6 groups of 5 male albino rats.[17] The animals received doses up to 14.7 g/kg via oral intubation. Necropsy findings were normal, and an LD_{50} of 8.71 g/kg was reported. An acute oral toxicity study on 42% aqueous Polyquaternium-6 (contained ~ 40% solids) was performed using 4 groups of albino rats (5 males and 5 females per group).[17] The animals received doses up to 9.62 ml/kg via oral intubation. An acute oral LD_{50} of 3.15 ml/kg was reported. In an acute oral toxicity study on Polyquaternium-6 involving guinea pigs (number and strain not stated), an LD_{50} of 3.25 g/kg was reported. [18] Respiratory depression was observed.

Inhalation

The acute inhalation toxicity of Polyquaternium-6 (42% aqueous) was evaluated using 10 CD rats (5 females and 5 males).[17] The aerosolized test substance (1:1, in distilled water) was introduced into the breathing zone of each animal. The animals were exposed to the test substance at an average analytical concentration of 0.2 mg/l, with a nominal exposure concentration of 28 mg/l of diluted test substance. There was no evidence of inhalation toxicity.

Short-Term Toxicity Study

Oral

The short-term oral toxicity of Polyquaternium-6 (40% aqueous) was evaluated using 5 groups of rats (strain not stated; 10 males and 10 females per group).[17] The test substance was fed in the diet at concentrations of 330, 1000, 3300 and 10,000 ppm for 28 consecutive days. Feeding with the highest concentration caused depression of body weight gain, increased water consumption, and a decrease in diet efficiency. The maximum no-effect dosage of the test substance was estimated to be 3300 ppm for both male (280 mg/kg/d) and female (295 mg/kg/d) rats.

Subchronic Toxicity Study

Dermal

The subchronic dermal toxicity of Polyquaternium-6 (40% aqueous) was evaluated using groups of rabbits (strain not stated; 10 males and 10 females per group).[17] For 89 to 92 consecutive days, the test substance was applied topically to abraded and intact skin at doses 0.25, 0.75 or 2.25 ml/kg/d. Negative control rabbits received physiological saline at a dose of 2.25 ml/kg/day. Each day the treatment area (test animals only) was cleaned with lukewarm tap water after 5 to 6 h of exposure. There was no evidence of systemic toxicity in any treatment group.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies on Polyquaternum-6 were neither found in the published literature, nor were these data submitted.

GENOTOXICITY STUDIES

In Vitro

The genotoxicity of Polyquaternium-6 (40 to 42%) was evaluated in the Ames test (OECD Guideline 471) using the following *Salmonella typhimurium* strains: TA98, TA100, TA1535, and TA1537.[19] The test substance was evaluated at doses ranging from 4 to 5000 µg/plate, with and without metabolic activation. The positive control with metabolic activation was 2-aminoanthracene, and the positive controls without metabolic activation were: sodium azide, 9-aminoacridine, and 2-nitrofluorene. Without activation, the test substance did not cause a dose-dependent increase in the number of revertants in any of the bacterial strains. With metabolic activation, the test substance did not cause relevant increases in the number of revertant colonies. It was concluded that Polyquaternium-6 (40 to 42%) was not genotoxic in this assay, with or without metabolic activation. The positive controls were genotoxic.

CARCINOGENICITY STUDIES

Carcinogenicity studies of Polyquaternium-6 were neither found in the published literature, nor were these data submitted.

DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization data summarized below are presented in detail in Table 4.

The skin irritation potential of an unidentified material that is comparable to Polyquaternium-6 (40 to 42% aqueous) was evaluated using rabbits (protocol details not included), and was classified as a non-irritant.[8] The skin irritation potential of a similar substance was evaluated using groups of rabbits (10 males and 10 females per group).[17] For 89 to 92 consecutive days, the test substance was applied topically to abraded and intact skin at a dose of 0.25, 0.75 or 2.25 ml/kg/d. Skin irritation was not observed at intact skin sites, but was observed at abraded sites. In a study involving 4 groups of 4 rabbits, Polyquaternium-6 (42% aqueous) was applied to the skin for 24 h at doses up to 21.5 g/kg. Slight to severe erythema was observed. The skin irritation potential of Polyquaternium-6 (42% aqueous) was evaluated in 6 rabbits.[17] After a 24-h application period, the test substance was not irritating to abraded or intact skin. In another study, the skin irritation potential of 42% aqueous Polyquaternium-6 (contained ~ 40% solids) was evaluated in 3 rabbits (strain not stated).[17] After 24 h of application, very slight erythema was observed at abraded sites, but not at intact sites. The Buehler test method (OECD Guideline 406) was used to evaluate the skin sensitization potential of Polyquaternium-6 (41% active in water), using 20 Pirbright-White guinea pigs [20] Repeated 6-h applications were made to the skin, and reactions were classified as negative. The skin irritation and sensitization potential of Polyquaternium-6 (42% aqueous) was evaluated in a repeated insult patch test (24-h applications) involving 50 subjects.[17] Results were classified as negative.

Photosensitization/Phototoxicity

The photoallergenicity of Polyquaternium-6 (42% aqueous) was evaluated using 29 subjects.[17] During induction, the test substance (0.3 ml) was applied for 24 h, under a patch, to 2 x 2 cm^2 areas of skin. The test site was then exposed to natural sunlight for 30 to 40 min (between 11:00 AM and 3:00 PM). Applications and sunlight exposures were repeated for a total of 9 times. At challenge, a single application of the test substance, under sets of duplicate patches, was made to new sites. One of the replicate patch test sites in each set was used in the photoallergenicity evaluation, and another was used to evaluate contact sensitization. The test substance did not induce contact irritation, sensitization or photoallergy in any of the subjects tested.

OCULAR IRRITATION STUDIES

Ocular irritation studies summarized below are presented in detail in Table 5.

The ocular irritation potential of Polyquaternium-6 was evaluated using rabbits (number and strain not stated).[6] The test substance caused slight ocular irritation. In another study, an unidentified material that is comparable to Polyquaternium-6 (40 to 42% aqueous, 0.1 ml) was evaluated for ocular irritation potential using rabbits (protocol details not included).[8] Results were negative. The ocular irritation potential of Polyquaternium-6 (42% aqueous) was evaluated in 6 New Zealand white rabbits [17] The test substance (0.1 ml) was instilled into the left conjunctival sac of each animal. Reactions were scored at 24 and 72 h. Ocular irritation was not observed. In another study, the ocular irritation potential of 42% aqueous Polyquaternium-6 (contained ~ 40% solids) was studied in 3 male and 3 female rabbits.[17] The test substance (0.1 ml) was instilled into the left conjunctival sac. Reactions were evaluated over a 14-d period. The test substance induced transient, slight ocular irritation.

SUMMARY

Polyquaternium-6, a polymeric quaternary ammonium salt of diallyldimethyl ammonium chloride, is reported to function as an antimicrobial agent, antistatic agent, film former, and hair fixative in cosmetics. A cosmetics industry source indicates that the origin of the starting material for production of Polyquaternium-6 is synthetic, and that the production process involves polymerization of diallyl dimethylammonium chloride. The residual monomer content is up to a maximum of 0.5% dimethyldiallylamin. According to the same source, Polyquaternium-6 is supplied as a solution consisting of 40 to 42% Polyquaternium-6 and 58 to 60% water.

According to a manufacturer of 2 other products (cationic homopolymers) that are each identified as Polyquaternium-6, both are produced by polymerization of diallyldimethyl ammonium chloride in an aqueous solution. One product contains Polyquaternium-6 (42%), water (< 58%), and free unreacted DADMAC (6.5% maximum). The other product has the following composition: Polyquaternium-6 (33%), water (< 67%), acetic acid (0.65%), and free unreacted DADMAC (1.5% maximum).

According to 2020 VCRP data, Polyquaternium-6 is reported to be used in 282 cosmetic products (16 leave-on products, 265 rinse-off products, and 1 product diluted for bath use). The results of a concentration of use survey provided by the Council in 2020 indicate that Polyquaternium-6 is being used at maximum use concentrations up to 1.2% in leave-on products (tonics, dressings, and other hair grooming aids) and at maximum use concentrations up to 3% in rinse-off products (hair straighteners).

Polyquaternium-6 is an FDA-approved indirect food additive, i.e., for use as a component of paper and paperboard in contact with aqueous and fatty foods.

The acute dermal toxicity of Polyquaternium-6 was evaluated in a study involving rats (protocol details not stated). An LD_{50} of > 2 g/kg was reported. An acute dermal toxicity study on Polyquaternium-6 (42% aqueous) was performed using 4

groups of 4 rabbits (strain not stated). The LD_{50} was estimated to be 21.5 g/kg, and no consistent test substance-related signs of systemic toxicity were observed.

In an acute oral toxicity study involving mice, results yielded an LD_{50} of 1.72 g/kg. An LD_{50} of 3/g/kg for Polyquaternium-6 was reported in 2 acute oral toxicity studies involving rats (protocol details not stated). An LD_{50} of > 2 g/kg was reported in an acute oral toxicity study (rats) on an unidentified material that is comparable to Polyquaternium-6 (40 to 42% aqueous). The acute oral toxicity of Polyquaternium-6 (42% aqueous) was evaluated using 6 groups of 5 male albino rats; an acute oral LD_{50} of 8.71 g/kg was reported. The acute oral toxicity of 42% aqueous Polyquaternium-6 (contained ~ 40% solids) was evaluated using 4 groups of albino rats (5 males and 5 females per group). Results indicated an acute oral LD_{50} of 3.15 ml/kg. In an acute oral toxicity study involving guinea pigs (protocol details not stated), an LD_{50} of 3.25 g/kg was reported.

The acute inhalation toxicity of Polyquaternium-6 (42% aqueous) was evaluated using 10 CD rats. The animals were exposed to the test substance at an average analytical concentration of 0.2 mg/l, with a nominal exposure concentration of 28 mg/l of diluted test substance. There was no evidence of acute inhalation toxicity.

The short-term oral toxicity of Polyquaternium-6 (40% aqueous) was evaluated using 5 groups of rats (strain not stated; 10 males and 10 females per group). The test substance was fed in the diet at concentrations of 330, 1000, 3300 and 10,000 ppm for 28 consecutive days. The maximum no-effect dosage of the test substance was estimated to be 3300 ppm for both male (280 mg/kg/d) and female (295 mg/kg/d) rats.

Subchronic dermal toxicity of Polyquaternium-6 (40% aqueous) was studied using groups of rabbits (strain not stated; 10 males and 10 females per group). The test substance was applied to abraded and intact skin at doses 0.25, 0.75 or 2.25 ml/kg/d for 89 to 92 d. There was no evidence of systemic toxicity.

The genotoxicity of Polyquaternium-6 (40 to 42%) was evaluated in the Ames test at doses up to 5000 µg/plate, using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537. Results were negative.

Skin irritation was not observed in rabbits tested with an unidentified material that is comparable to Polyquaternium-6 (40 to 42% aqueous) using OECD Guideline 404 (protocol details not included). In a study involving groups of rabbits (10 males and 10 females per group), a similar substance was applied to abraded and intact skin at doses up to 2.25 ml/kg/d for 89 to 92 consecutive days. Skin irritation was observed at abraded sites, but not at intact skin sites. In another study involving 4 groups of 4 rabbits, Polyquaternium-6 (42% aqueous) was applied to the skin for 24 h at doses up to 21.5 g/kg. Slight to severe erythema and necrosis were observed. The 24-h application of Polyquaternium-6 (42% aqueous) to the skin of 6 rabbits in another study did not cause skin irritation at intact or abraded skin sites. Skin irritation potential of 42% aqueous Polyquaternium-6 (contained ~ 40% solids) was evaluated in 3 rabbits. Very slight erythema at 2 abraded sites, but not at any intact sites, was observed at 24 h post-application and persisted for 5 d.

The Buehler test method was used to evaluate the skin sensitization potential of Polyquaternium-6 (41% active in water) using 30 guinea pigs (20 test and 10 controls). There was no evidence of skin sensitization. The skin irritation and sensitization potential of Polyquaternium-6 (42% aqueous) was evaluated in a repeated insult patch test involving 50 subjects. The dose per application was 0.1ml/cm^2, and results were negative. Polyquaternium-6 (42% aqueous) did not induce, irritation, sensitization, or photoallergy in a repeated insult patch test involving 29 subjects.

The ocular irritation potential of Polyquaternium-6 was evaluated using rabbits (protocol details not stated). The test substance caused slight ocular irritation. In another study, an unidentified material that is comparable to Polyquaternium-6 (40 to 42%) was instilled into the eyes of rabbits (protocol details not included). The material was classified as a non-irritant. The ocular irritation potential of Polyquaternium-6 (42%) was evaluated in 6 New Zealand white rabbits, and results were negative. In another study, transient ocular irritation was observed in 6 rabbits tested with 42% aqueous Polyquaternium-6 (contained ~ 40% solids).

DISCUSSION

To be developed…

CONCLUSION

To be determined…

TABLES

Table 1. Chemical Properties

Property	Value/Results	Reference
Form	Liquid; clear, light yellow liquid	3,5
Number average molecular weight (Mn) (Da)	15,100	2
Weight average molecular weight (Mw) (Da)	294,000	2
Higher average molecular weight (Mz) (Da)	1,010,000	2
Polydispersity (Mw/Mn)	19.47	2
Typical molecular weight (Da) of material that typically contains 42% Polyquaternium-6	150,000	4
Typical molecular weight (Da) of material that typically contains 33% Polyquaternium-6	15,000	4
Stability	Stable. Incompatible with strong oxidizing agents, iron and iron salts, steel, copper, copper alloys, and aluminum.	5
Water solubility	Completely soluble	3
log K_{ow}	< 10; -2.301	3,7
Density (g/ml @ 25ºC)	1.09; 1.015	3,5,6
Specific gravity (@ 25ºC)	1.04	7
Refractive index (n20/D)	1.417; 1.375	5,7
Freezing point (ºC)	100	5
Melting range (ºC)	-2.8 - 0.0	3
Boiling point (ºC @ 1,013 hPa (760 mmHg))	100	3
Flash point (ºC, closed cup)	> 100	3
Flash point (ºC, tag closed cup)	0	7
Vapor pressure (hPa @ 25ºC)	20 - 30	3

Table 2. Frequency[10] and concentration[11] of use of Polyquaternium-6 according to duration and exposure

	# of Uses	Max Conc of Use (%)
Totals*	**282**	**0.0004-3**
Duration of Use		
Leave-On	*16*	*0.0004-1.2*
Rinse-Off	*265*	*0.04-3*
Diluted for (Bath) Use	*1*	*NR*
Exposure Type		
Eye Area	NR	NR
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	9[a]	0.067-0.5; 0.41-1.2[a]
Incidental Inhalation-Powder	NR	NR
Dermal Contact	13	0.2-0.25
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	106	0.067-3
Hair-Coloring	163	0.04-0.99
Nail	NR	0.0004
Mucous Membrane	4	0.2-0.25
Baby Products	NR	0.13

*Because this ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.
[a]It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
NR – not reported (use not reported in VCRP or Council survey data)

Table 3. Acute toxicity studies

Ingredient	Animals	No./Group	Vehicle	Concentration/Dose/Protocol	LD_{50}/Results	Reference
DERMAL						
Polyquaternium-6	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not included.	LD_{50} > 2 g/kg	[3]
Polyquaternium-6 (42% aqueous)	Rabbits (strain not stated)	4 groups of 4 rabbits	Water	Test substance administered at the following doses: 2.15 g/kg , 4.64 g/kg, 10.0 g/kg, and 21.5 g/kg. After application, animals wrapped in binders for 24 h. Dosing followed by14-d observation period	LD_{50} estimated at 21.5 g/kg. No consistent test substance-related signs of systemic toxicity observed. (Dermal irritation results are presented in Table 4.)	[17]
ORAL						
Polyquaternium-6	Mice (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated	LD_{50} = 1.72 g/kg. Respiratory depression noted.	[18]
Polyquaternium-6	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not included	LD_{50} = 3 g/kg	[5]
Polyquaternium-6	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated	LD_{50} = 3 g/kg. Respiratory depression noted	[18]
Polyquaternium-6	Rats (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated	LD_{50} > 2 g/kg	[3]
Unidentified material that is comparable to Polyquaternium-6 (40 to 42%)	Wistar rats	Not stated	Water	OECD Guideline 401 used (protocol details not included)	LD_{50} > 2 g/kg	[8]
Polyquaternium-6 (42%)	Albino rats (male)	6 groups of 5	Water	Doses via oral intubation: 2.15 g/kg, 3.16 g/kg, 4.46 g/kg, 6.81 g/kg, 10.0 g/kg, and 14.7 g/kg. Dosing followed by 14-d observation period	LD_{50} = 8.71 g/kg. Necropsy findings for animals that survived to day 14 were normal.	[17]
42% Polyquaternium-6 (contained ~ 40% solids)	Albino rats	4 groups (5 males and 5 females per group)	Water	Doses via oral intubation: 1.99 ml/kg, 3.37 ml/kg, 5.69 ml/kg, and 9.62 ml/kg. Dosing followed by14-d observation period	LD_{50} = 3.15 ml/kg	[17]
Polyquaternium-6	Guinea pigs (strain not stated)	Not stated	Not stated	Details relating to test protocol not stated.	LD_{50} = 3.25 g/kg. Respiratory depression noted	[18]
INHALATION						
Polyquaternium-6 (42%)	CD rats	5 males and 5 females	Water	Aerosolized test substance (1:1, in distilled water) introduced into breathing zone of each animal. Animals exposed to test substance at average analytical concentration of 0.2 mg/l, with a nominal exposure concentration of 28 mg/l of diluted test substance.	All animals survived through 14-day post-exposure period. No evidence of inhalation toxicity	[17]

Table 4. Dermal irritation and sensitization studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Test material (unidentified) comparable to Polyquaternium-6 (40 to 42% in water)	0.5 ml/cm^2	Rabbits (number not stated)	Skin irritation potential evaluated using OECD Guideline 404 (protocol details not included)	Classified as a non-irritant.	8
Polyquaternium-6	42% in water	4 groups of 4 rabbits (strain not stated)	Test substance applied to skin (for 24 h, under binder) at the following doses: 2.15 g/kg , 4.64 g/kg, 10.0 g/kg, and 21.5 g/kg.	Signs of dermal irritation included slight to severe erythema, slight edema, blanching, and necrosis. Relationship between doses administered and reactions observed not stated	17
Polyquaternium-6	42% in water	6 rabbits (strain not stated)	Testing performed according to Federal Hazardous Substances Labeling Act specifications (16 CFR 1500). Test substance (0.5 ml) applied for 24 h to intact and abraded skin; 1 in^2 square gauze patch secured with nonabsorbent binder. Reactions evaluated after 24 h and 72 h.	Nonirritating to abraded or intact skin	17
Polyquaternium-6	42% in water (contained ~ 40% solids)	3 rabbits (strain not stated)	The test material (0.5 ml) applied for 24 h, under occlusive dressing, to intact and abraded skin sites. Reactions evaluated over 2-wk period.	Very slight erythema at 2 abraded sites observed at 24 h post-application, and persisted for 5 d. Skin irritation not observed at intact sites or at abraded sites in other animals	17
Polyquaternium-6	40% in water	Rabbits (strain not stated; 10 males and 10 females per group).	For 89 to 92 consecutive days, test substance applied topically to abraded and intact skin at doses 0.25, 0.75 or 2.25 ml/kg/d. Negative control rabbits received physiological saline at dose of 2.25 ml/kg/d. Each day, treatment area (test animals only) cleaned with lukewarm tap water after 5 to 6 h of exposure	Skin irritation was not observed at intact skin sites. At abraded sites, varying amounts of erythema and edema observed along the lines of abrasion. Doses associated these findings not identified	17
Polyquaternium-6	41% active in water	30 Pirbright-White guinea pigs (20 test and 10 controls)	Buehler test method (OECD Guideline 406) used to evaluate skin sensitization potential. Test substance applied to 20 guinea pigs on days 1, 8, and 15 of induction; challenged on day 29. Each induction and challenge exposure (0.5 ml) involved 6-h application, under 2 x 2 cm^2 occlusive patch, to clipped flank skin. Control animals treated with vehicle only during induction, and challenged test substance (41% active in water). Challenge sites evaluated at 24 h and 48h after patch removal.	No positive reactions in test or control animals. Classified as a non-sensitizer	20
			HUMAN		
Polyquaternium-6	42% in water	50 subjects	During induction, test substance (0.1ml/cm^2) applied for 24 h under occlusive dressing. Series of 12 applications made. At challenge, a series of 4 doses applied to new sites.	No evidence of skin irritation or sensitization	17

Table 5. Ocular irritation studies

Test Article	Concentration/Dose	Test Population	Procedure	Results	Reference
			ANIMAL		
Polyquaternium-6	Not stated	Rabbits (strain not stated)	Details relating to test protocol not included	Slight ocular irritation observed	[3]
Unidentified material that is comparable to Polyquaternium-6 (40 to 42%)	Not stated	Rabbits (number and strain not stated)	Ocular irritation potential evaluated using OECD Guideline 405 (protocol not included)	Classified as a non-irritant	[8]
Polyquaternium-6	42% in water	6 New Zealand white rabbits	Tested according to specifications of Federal Hazardous Substances Act (16 CFR 1500). Test substance (0.1 ml) instilled into left conjunctival sac of each animal; right eye served as control. Reactions scored at 24 h and 72 h	No evidence of ocular irritation	[17]
Polyquaternium-6	42% in water (contained ~ 40% solids)	6 rabbits (strain not stated; 3 males and 3 females)	Test substance (0.1 ml) instilled into left conjunctival sac; right eye served as untreated control. Reactions evaluated over 14-d period	Test substance induced slight ocular irritation. Slight conjunctival injection and discharge (moderate) observed in all animals. By 48 h, all reactions had cleared.	[17]

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2020 VCRP Data

Polyquaternium-6

Bubble Baths	02B	1
Hair Conditioner	05A	9
Hair Straighteners	05C	19
Shampoos (non-coloring)	05F	63
Tonics, Dressings, and Other Hair Grooming Aids	05G	9
Other Hair Preparations	05I	6
Hair Dyes and Colors (all types requiring caution statements and patch tests)	06A	159
Hair Shampoos (coloring)	06D	2
Other Hair Coloring Preparation	06H	2
Bath Soaps and Detergents	10A	3
Aftershave Lotion	11A	1
Cleansing	12A	8
Total		**282**

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: February 28, 2020

SUBJECT: Concentration of Use Information by FDA Product Category: Polyquaternium-6

Concentration of Use by FDA Product Category – Polyquaterium-6

Product Category	Maximum Concentration of Use
Baby shampoo (1B)	0.13%
Hair conditioners (5A)	0.4-0.5%
Hair sprays (5B) Pump spray	 0.067-0.5%
Hair straighteners (5C)	0.5-3%
Permanent waves (5D)	0.6-1.7%
Shampoos (noncoloring) (5F)	0.1-0.6%
Tonics, dressings and other hair grooming aids (5G)	0.41-1.2%
Hair dyes and colors (6A)	0.42-0.99%
Hair bleaches (6G)	0.04%
Other manicuring preparations (8G)	0.0004%
Bath soaps and detergents (10A)	0.2-0.25%

Information collected in 2019-2020

Table prepared: February 27, 2020

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: October 21, 2020

SUBJECT: Polyquaternium-6

Clariant. 2017. Regulatory product information Genamin PDAC (Polyquaternium-6).

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CLARIANT

Regulatory Product Information
Only Valid for Use in Cosmetics (Version 2.0)

Genamin® PDAC

1.	**General Information**	
1.1	Trade name	Genamin® PDAC
1.2	Manufacturer / Supplier *(address, phone no., fax no., contact person)*	Clariant Produkte (Deutschland) GmbH, 65926 Frankfurt Application Development Personal Care Phone: +49 (0)69 305 18172 Fax: +49 (0)69 305 38467 Corporate Product Stewardship Phone: +49 (0)6196 757 6228 Fax: +49 (0)6196 757 6244
1.3	Raw material category	Cationic polymer for the cosmetic industry
1.4	Chemical name	Poly-diallyl dimethylammonium Chloride
1.5	INCI (CTFA) name Composition	Polyquaternium-6
1.6	EC (EINECS/ELINCS) no.	Polymer
1.7	CAS no.	26062-79-3
1.8	Registration status (e.g. EU, US, Japan)	Listed on the chemical inventories of Australia, Canada, China, European Union, Japan, Korea, the Philippines, Switzerland and the USA.
1.9	Regulations for cosmetic use	In conformity with the requirements relevant to cosmetic ingredients of the Cosmetics Regulation (EC) 1223/2009.
1.10	Country of origin	Germany
2.	**Information on Production**	
2.1	Origin of starting material (plant, animal, synthetic)	synthetic Product is based on materials which do not originate from animal sources and which are not produced from genetically modified material.

CLARIANT

Regulatory Product Information
Only Valid for Use in Cosmetics (Version 2.0)

Genamin® PDAC

2.2	Does the material contain genetically modified organisms?	Product does not contain genetically modified organisms (GMOs).
2.3	Information on production process (general description)	Polymerisation of Diallyl dimethylammonium chloride
3.	**Additives**	
3.1	Preservatives	not added by recipe
3.2	Antioxidants	not added by recipe
3.3	Solvents	approx. 58 - 60 % water
3.4	Bleaching agents	not added by recipe
3.5	Fragrances (Allergens) according to the European Cosmetics Regulation (EC) 1223/2009, Annex III	not added by recipe
3.6	CMR classified ingredients	not added by recipe
3.7	Dangerous ingredients according to Annex I of Directive 67/548/EEC resp. Annex VI of Regulation (EC)1272/2008 or ingredients self-classified as dangerous	See EU safety data sheet, chapter 2 or 3 (regulatory information, hazardous components).
3.8	Others	Food allergens as of Directive 2000/13/EC (as amended), Annex IIIa and Regulation (EU) 1169/2011, Annex II are not added by recipe.
4.	**Microbiological Specification**	
4.1	Total viable count (colony-forming units/g)	< 100

CLARIANT

Regulatory Product Information
Only Valid for Use in Cosmetics (Version 2.0)

Genamin® PDAC

5.	By-products *The presence of traces of the substances listed in Annex II of Regulation (EC)1223/2009 (incl. cmr category. I-III substances marked with *) shall be allowed provided that such presence is technically unavoidable in good manufacturing practice and that it conforms with Article 3 of Regulation (EC)1223/2009.*	
5.1	1,4-Dioxane *	not expected from the process
5.2	Ethylene oxide *	not expected from the process
5.3	Residual solvents	not expected from the process
5.4	Residual monomers	max. 0.5 % Dimethyldiallylamin
5.5	Amines	max. 0.2 %
5.6	Nitrosamines	not determined
5.7	Heavy metals	max. 10 ppm typical values: Ni,Cr,Co,Cd,Hg,Pb,As,Sb, each < 1 ppm
5.8	Monochloroacetic acid	not expected from the process
5.9	Dichloroacetic acid	not expected from the process
5.10	Phthalates	not expected from the process
5.11	Pesticides	Based on information concerning raw materials, production process and equipment used, pesticides are not likely to be present.
5.12	Glycol ethers	Based on information concerning raw materials, production process and equipment used, Butyldiglycol, Ethyldiglycol and 2-Butoxyethanol are not likely to be present.
5.13	Others	max. 1.5 % NaCl max. 250 ppm Allyl alcohol max. 50 ppm Allyl chloride * Methylchlorid * < 2 ppm

CLARIANT

Regulatory Product Information
Only Valid for Use in Cosmetics (Version 2.0)

Genamin® PDAC

6.	**Toxicology**	
6.1	Information on acute toxicity	OECD 401 wistar rats LD50 > 2000 mg/kg (In analogy to similar product)
6.2	Information on skin irritation	OECD 404 rabbit non-irritant (In analogy to similar product)
6.3	Information on irritation of the mucous membrane	OECD 405 rabbit eyes non-irritant (In analogy to similar product)
6.4	Information on sensitisation potential	OECD 406 Buehler no sensitization
6.5	Information on gene toxicity	OECD 471 Ames-Test not mutagenic
6.6	Information on percutaneous permeation	no data available
6.7	Others	
7.	**Ecology**	
7.1	Degradability/Elimination	30 - 70 % (OECD 302B) (In analogy to similar product)
7.2	Acute aquatic toxicity	OECD 203 LC50 = 0,1 - 1 mg/l (96h zebra fish) (In analogy to similar product)

CLARIANT

Regulatory Product Information
Only Valid for Use in Cosmetics (Version 2.0)

Genamin® PDAC

7.3	Others	DIN 38412 T.8 EC50 = 0.8 mg/l (Pseudomonas Putida) (In analogy to similar product)
8.	**Additional Information** *(For details on specification see enclosed instruction sheet; for details on labelling and classification see enclosed safety data sheet.)*	
8.1	Nanomaterial	Product is not considered as a nanomaterial according (EC) No.1223/2009 definition art.2 (1k).

Date 06.12.2017

Regulatory Affairs Manager
(Dr. Lämmermann)

CLARIANT

Clariant Produkte (Deutschland) GmbH

CERTIFICATE OF COMPOSITION

Trade Name or Proposed Name:	Genamin PDAC

INCI Name	Concentration	CAS number	EINECS number	Function
Polyquaternium-6	40-42 %	26062-79-3	230-993-8	Active
Water	58-60 %	7732-18-5	215-185-5	Solvent

Company representative : Dr. Dieter Lämmermann Date: 06.12.2017

Function : Manager of Product Stewardship Signature:

Geschäftsführer:
Oliver Kinkel (Vorsitz)
Lars Jansson

Aufsichtsratsvorsitzender:
Patrick Jany

Handelsregister:
Frankfurt am Main
HRB 103782

Sitz der Gesellschaft:
Frankfurt am Main

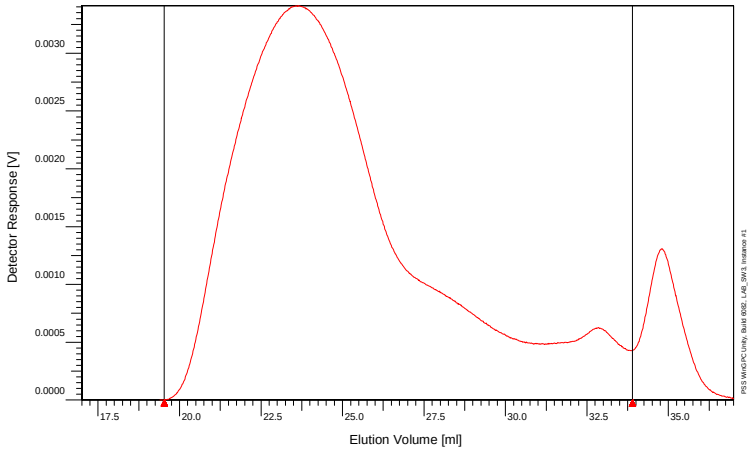
Bankverbindung:
Deutsche Bank AG
IBAN: DE41500700100092415900 EUR
IBAN: DE84500700100092415902 USD
SWIFT: DEUTDEFFXXX

WINGPC Analysis Report

Polyquaternium-6

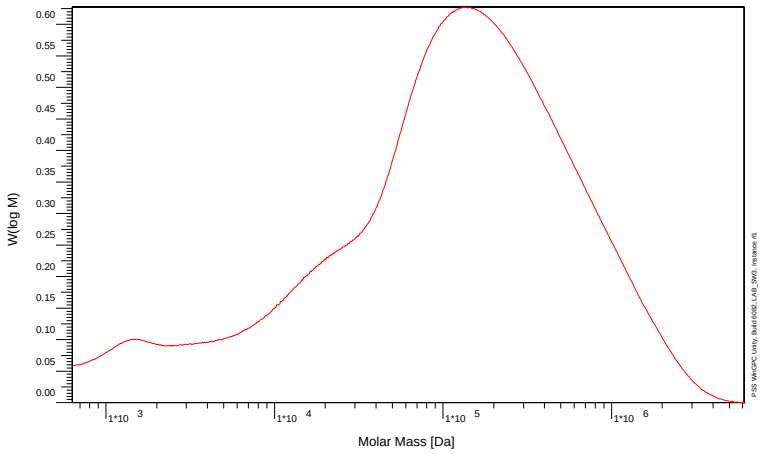
Sample name Genamin PDAC 091910

Elugram



Baseline from: 19,41 ml to: 38,27 ml
Integration from: 19,53 ml to: 33,89 ml

Molecular Weight Distribution



Detector	Mn (D)	Mw (D)	Mz (D)	D (Mw/Mn)	Vp (ml)	Mp (D)	Area (ml*V)
RID	15100	294000	1010000	19,47	23,63	199000	0,0202

Methodinformation

Project:	W:\GPC_DAT\serv10_1.LDX	Injection:	Tuesday 05/01/10 21:47:02
Calibration:	pull_0105.CAL	Calibration fit:	Polynomial 3
Int. Standard:	none		
Int. Standard - C:	0,00 ml	Int. Standard - M:	0,00 ml
Sample concentration:	3,00 g/l	Injectvolume:	100 µl
Eluent:	0.1M NaCl /0,1% TFAc	Flowrate:	1,00 ml/min
Columns:	Novema 10µm G, 30,3000,10000Å	Temperature:	23,0 °C
GPC-Instrument:	PG13	Operator:	HB

Genamin PDAC

Assessment of sensitizing properties

with Pirbright-White guinea pigs

according to Buehler (OECD 406)

27.03.1995

Summary

Genamin PDAC was tested for skin sensitizing property in Pirbright-White guinea pigs according to the Buehler test method.

In the preliminary irritation test Genamin PDAC (41% active in water) was not irritating up to the concentration of 100%. Therefore, 100% was determined as the induction and challenge concentrations.

In the main study, the induction was conducted by treatment of animals on day 1, 8 and 15 and the challenge on day 29.

For the animals of the treatment group, 0.5 ml Genamin PDAC was applied to clipped flank skin by use of occlusive patch of 2 x 2 cm2 for 6 hours for both induction and challenge. The animals of the control group were treated with vehicle only for the induction and treated with 100% Genamin for the challenge.

After challenge treatment the skin responses were recorded at 24 and 48h after patch removal.

None of the 20 treated animals and 10 control animals showed a positive response.

Therefore, the test substance was found to be not skin sensitizing.

Hoechst

Empfänger
Dr. Mandre
Entw. THTVS
C655

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Pharma Entwicklung Zentrale Toxikologie - Gewerbetoxikologie -			15.02.1995

Versuchskostenmitteilung

Versuch: **94.0699V**
Bericht: **95.0018** vom **09.02.1995**
Versuchsart: **07.1 GENMUTATION / PUNKTMUTATION**

Substanz:
Genamin PDAC
Polyquaternium-6 h.u.

Versuchskosten: **6,987.00 DM**

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KA: **81359**
Arbeitsauftrag: **R 263096**
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Study Title

Genamin PDAC

STUDY OF THE MUTAGENIC POTENTIAL

IN STRAINS OF SALMONELLA TYPHIMURIUM (AMES TEST)

Author

Dr. W. Müller

Report completion date

February 09th, 1995

Performing laboratory

HOECHST AKTIENGESELLSCHAFT
Pharma Development Corporate Toxicology
D-65926 Frankfurt am Main

Laboratory Project ID:

Study No. 94.0699

STATEMENT OF COMPLIANCE

To the best of my knowledge and belief, this study was conducted in compliance with Good Laboratory Practice regulations. No unforeseen circumstances were observed which might have affected the quality or integrity of the study.

Study Director:

Dr. W. Müller — February 9, 1995

Testing facility management:

Dr. D. Mayer — Febr. 10, 1995

Quality Assurance Statement

Title: Genamin PDAC

STUDY OF THE MUTAGENIC POTENTIAL

IN STAINS OF SALMONELLA TYPHIMURIUM (AMES TEST)

Study: 94.0699

This study was periodically inspected and properly signed records of these inspections were submitted to testing facility management and the study director as shown below:

Inspection	Report
12.12.1994	12.12.1994
03.01.1995	03.01.1995
02.02.1995	02.02.1995
09.02.1995	09.02.1995

M. Michel 09.02.1995

M. Michel

Quality Assurance (GLP)

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1. SUMMARY

Genamin PDAC was tested for mutagenicity with the strains TA 100, TA 1535, TA 1537 and TA 98 of Salmonella typhimurium.

The mutagenicity studies were conducted in the absence and in the presence of a metabolizing system derived from rat liver homogenate. The test substance was dissolved in Aqua bidest. and a dose range of 6 different doses from 4 microgram/plate to 5000 microgram/plate was used.

Control plates without mutagen showed that the number of spontaneous revertant colonies was similiar to that described in the literature. All the positive control compounds gave the expected increase in the number of revertant colonies.

Toxicity: The test compound proved to be toxic to all of the bacterial strains at a dose of 2500 microgram/plate and above.

5000 microgram/plate was chosen as top dose level for the mutagenicity study.

Mutagenicity: In the absence of the metabolic activation system the test compound did not show a dose dependent increase in the number of revertants in any of the bacterial strains. Also in the presence of a metabolic activation system, treatment of the cells with **Genamin PDAC** did not result in relevant increases in the number of revertant colonies.

Summarizing, it can be stated that **Genamin PDAC** is not mutagenic in these bacterial test systems either with or without exogenous metabolic activation at the dose levels investigated.

2. INTRODUCTION

This report describes experiments performed in a short term test using the procedure of the Salmonella / mammalian-microsome-mutagenicity test (Ames Test) (1.2) to assess the mutagenic potential of the test-material in amino acid-dependent strains of Salmonella typhimurium. The use of liver compound allows the mammalian metabolism of the test compound to be taken into account. To fulfil the requirement for metabolic activation, the test included an activation system using nicotinamide-adenin dinucleotide phosphate ($NADP^+$)-cytochrome P_{450} dependent mixed function oxidase enzymes of the liver. The 9000 g supernatant of rat liver homogenate has been shown to be very useful for the metabolic activation of foreign compounds. The animals were pretreated with Aroclor 1254, which is an inducer of several drug metabolizing enzymes (3).

The Ames test with Salmonella typhimurium strains investigates the effect of the test compound on the number of back mutations to histidine prototrophy using histidine auxotrophic mutants. The strains TA 100 and TA 1535 were originally obtained by a substitution mutation, the strains TA 1537 and TA 98 by frame shift mutations from histidine prototrophic bacteria. All four Salmonella strains are deficient in the complete structure of their lipopolysaccharide layer and in DNA excision repair system (2). TA 98 and TA 100 possess a modified postreplication DNA repair system which frequently causes an increase in the rate of mutations (4).

3. GENERAL

Study No.	:	94.0699
Artemis No.	:	ZR0122
Test compound	:	**Genamin PDAC**
Sponsor	:	01 Hoechst, E TH - TVS, Dr. Mandre
Test system	:	Point mutation assay with bacteria
Test organism Salmonella typhimurium	:	TA 100, TA 1535, TA 1537 and TA 98
Initiation of the study	:	December 14th, 1994
Termination of the study	:	January 05th, 1995

Responsibility

Head of Genetic Toxicology	:	Dr. W. MÜLLER
Head of Toxicology	:	Dr. D. MAYER
Quality assurance unit	:	S. J. HARSTON (Pharmacist)
Testing Facility and Archive	:	HOECHST AKTIENGESELLSCHAFT Pharma Development Corporate Toxicology D-65926 Frankfurt am Main

4. MATERIAL AND METHODS

4.1. Test compound

Name	:	**Genamin PDAC**
Code	:	06 FHER 145
Other names	:	Poly-diallyl-dimethyl-ammonium-chlorid
CAS No.	:	26062-79-3
Batch No.	:	E06 187883
Purity	:	41.0 % (v/v)
Certificate of analysis	:	dated October 21st, 1994 Hoechst AG, Werk Gendorf, EQG/Qualitätssicherung, Hr. Stiefel
Stability and homogeneity in solvent	:	stable for 4 hours, dated November 04th, 1994 Marketing Tenside und Hilfsmittel, ETH-TVS, Dr. Turowski
Storage stability	:	stable until July 1996, guaranteed by the sponsor
Storage conditions	:	dark at approximately 20 °C
Appearance	:	yellowish clear liquid
pH - value in water	:	4.1
Concentration of stock solution	:	5 % (w/v)

On the day of the experiment the test substance was dissolved in Aqua bidest. at appropriate concentrations.

4.2 Methods

The "Genetic Toxicology Laboratory" has a set of standard operating procedures (SOPs).
These instructions were issued to the scientists and technicians performing the experiments.

4.3 Preparation and storage of a liver homogenate fraction (S9)

Male Sprague Dawley rats (200-300 g) received a single intraperitoneal injection of Aroclor 1254 (500 mg/kg body weight) 5 days before sacrifice. Preparation was performed at approx. 0 to 4 °C using cold sterile solutions and glassware. The livers from at least 5-6 animals were removed, pooled and washed in approx. 150 mM KCl (approximately 1 ml/g wet liver). The washed livers were cut into small pieces and homogenized in three volumes of KCl. The homogenate was centrifuged at approx. 9000 *g* for 10 minutes. The supernatant is the S9 fraction. This was divided into small portions, rapidly frozen and stored at approx. -80 °C for not longer than six months.

4.4 Preparation of S9-mix

Sufficient S9 fraction was thawed immediately before each test at room temperature. One volume of S9 fraction was mixed with 9 volumes of the S9 cofactor solution, which was kept on ice until used. This preparation is termed S9-mix. The concentrations of the different compounds in the S9-mix were:

8 mM $MgCl_2$
33 mM KCl
5 mM glucose-6-phosphate
4 mM $NADP^+$
100 mM phosphate buffer pH 7.4

4.5 Bacteria

Bacteria were grown overnight in nutrient broth (25 g Oxoid Nutrient Broth No. 2 /liter) at approx. 37 °C. The amount of bacteria in the cell suspension was checked by nephelometry. Inoculation was performed with stock cultures which had been stored at approx. -80 °C. The compound was tested with the strains Salmonella typhimurium TA 98, TA 100, TA 1535 and TA 1537. Identification of the different bacterial strains is performed periodically and all criteria for a valid assay were fulfilled as described (2).

4.6 Toxicity experiments and dose range finding

The first experiment was performed with all tester strains using three plates per dose to get information on mutagenicity and toxicity for calculating an appropriate dose range. A reduced rate of spontaneously occuring colonies and visible thinning of the bacterial lawn were used as toxicity indicators. Thinning of the bacterial lawn was evaluated microscopically.

In combination with the second experiment, toxicity testing was performed as follows:
0.1 ml of the different dilutions of the test compound were thoroughly mixed with 0.1 ml of 10^6 dilution of the overnight culture of TA 100 and plated with histidine and biotin rich top agar (3 plates per dose). The solvent control is compared with the number of colonies per plate in the presence of the test compound. Results are given as a ratio of these values (= surviving fraction).

4.7 Mutagenicity test

Top agar was prepared for the Salmonella strains by mixing 100 ml agar (0.6 % (w/v) agar, 0.5 % (w/v) NaCl) with 10 ml of a 0.5 mM histidine-biotin solution.
The following ingredients were added (in the following order) to 2 ml of molten top agar at approx. 45 °C:

0.1 ml of an overnight nutrient broth culture of the bacterial tester strain
0.1 ml test compound solution
0.5 ml S-9 Mix (if required) or buffer

After mixing, the liquid was poured into a petridish with minimal agar (1.5 % (w/v) agar, Vogel-Bonner E medium with 2 % (w/v) glucose). After incubation for approximately 48 hours at approx. 37 °C in the dark, colonies (his^+ revertants) were counted.

Two independent experiments were performed.

4.8 Positive controls

Positive control plates were included for each strain. The following substances were used as positive controls.

a) without metabolic activation:

Sodium-azide: TA 100, TA 1535
9-Aminoacridine: TA 1537
2-Nitrofluorene: TA 98

b) with metabolic activation:

2-Aminoanthracene: TA 98, TA 100, TA 1535, TA 1537

4.9 Negative controls

a) solvent controls (0 microgram/plate)

b) untreated controls

4.10 Criteria for a positive response

A test article is classified as mutagenic if it has either of the following effects:

a) a test article produces at least a 2-fold increase in the mean number of revertants per plate of at least one of the tester strains over the mean number of revertants per plate of the appropriate vehicle control at complete bacterial background lawn
b) a test article induces a dose-related increase in the mean number of revertants per plate of at least one of the tester strains over the mean number of revertants per plate of the appropriate vehicle control in at least two to three concentrations of the test article at complete bacterial background lawn.

The test results must be reproducible.

5. RESULTS

Genamin PDAC was tested for mutagenicity with Salmonella typhimurium strains TA 98, TA 100, TA 1535 and TA 1537 in the absence and presence of a metabolic activation system. The results obtained with the test material and positive control compounds are presented on page 14 to 25. The number of colonies per plate with each strain as well as mean values of 3 plates are given.

5.1 Sterility checks and control plates

Sterility of S-9 Mix and the test compound were indicated by the absence of contamination on the test material and S-9 Mix sterility check plates. Control plates (background control and positive controls) gave the expected number of colonies.

5.2 Solubility

The test compound did not precipitate on the plates up to the highest investigated dose of 5000 microgram/plate.

5.3 Toxicity

The test compound was tested at doses of 4 to 5000 microgram/plate and proved to be toxic to all of the bacterial strains at a dose of 2500 microgram/plate and above.
Thinning of the bacterial lawn and a reduction in the number of colonies were observed at this dose.

Therefore 5000 microgram/plate was chosen as the highest dose in the second experiment.

5.4 Mutagenicity test

The test compound did not cause a significant increase in the number of revertant colonies with any of the tester strains either in the absence or in the presence of S-9 Mix. No dose dependent effect was obtained.

The test was performed in two independent experiments.

It is concluded that the test substance is not mutagenic in these bacterial test systems either in the absence or in the presence of an exogenous metabolizing system.

Dr. WM/Ze

Quality assurance unit
Li. 09.02.1995

HOECHST AKTIENGESELLSCHAFT

Pharma Development Corporate Toxicology

W. Müller February 9, 1995

Dr. W. Müller
Study Director

W Febr. 10, 1995

Dr. D. Mayer
Head of Toxicology

TCC900-05/00 TCC900P/2 RUN DATE: 07/02/95

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T PAGE: 1

CONTROLS

STUDY ZR0122 TEST 00 SPONSOR DIVISION E DATE TESTED 14/12/94
DATE COUNTED 16/12/94

POSITIVE CONTROLS: QR0017/84 SOLVENT CONTROLS: QN0024/14 NEGATIVE CONTROLS: QR0018/77

SOLVENT CONTROL COMMENTS:
NONE

NEGATIVE CONTROL COMMENTS:
NONE

POSITIVE CONTROL COMMENTS:
NONE

STRAIN	DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 100 +S9	SOLVENT CONTROLS	176.0	9.8			168	187	173
	NEGATIVE CONTROLS	177.3	11.9	1.0		164	187	181
	POSITIVE CONTROLS	P00001/001/001			2-AMINOANTHRACENE			
	0.5	882.3	30.4	5.0		874	916	857
TA 100 -S9	SOLVENT CONTROLS	162.0	7.5			170	155	161
	NEGATIVE CONTROLS	155.0	5.3	1.0		159	149	157
	POSITIVE CONTROLS	P00002/001/001			SODIUM-AZIDE			
	1.	519.7	62.6	3.2		483	484	592

CONTROLS

STUDY ZR0122 TEST 00 SPONSOR DIVISION E DATE TESTED 14/12/94
DATE COUNTED 16/12/94

POSITIVE CONTROLS: QR0017/84 SOLVENT CONTROLS: QN0024/14 NEGATIVE CONTROLS: QR0018/77

STRAIN	DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 1535 +S9	SOLVENT CONTROLS							
		9.7	1.2			9	11	9
	NEGATIVE CONTROLS							
		10.7	1.5	1.1		9	11	12
	POSITIVE CONTROLS		P00001/001/001		2-AMINOANTHRACENE			
	1.	137.7	12.9	14.2		134	127	152
TA 1535 -S9	SOLVENT CONTROLS							
		9.0	1.0			10	8	9
	NEGATIVE CONTROLS							
		11.0	3.0	1.2		11	8	14
	POSITIVE CONTROLS		P00002/001/001		SODIUM-AZIDE			
	1.	430.7	10.2	47.9		438	435	419
TA 1537 +S9	SOLVENT CONTROLS							
		11.0	2.0			13	9	11
	NEGATIVE CONTROLS							
		10.3	1.2	0.9		9	11	11
	POSITIVE CONTROLS		P00001/001/001		2-AMINOANTHRACENE			
	1.	137.0	2.6	12.5		138	139	134

CONTROLS

STUDY ZR0122 TEST 00 SPONSOR DIVISION E DATE TESTED 14/12/94
DATE COUNTED 16/12/94

POSITIVE CONTROLS: QR0017/84 SOLVENT CONTROLS: QN0024/14 NEGATIVE CONTROLS: QR0018/77

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 1537	-S9	SOLVENT CONTROLS	10.3	1.5			10	12	9
		NEGATIVE CONTROLS	10.7	2.1	1.0		10	9	13
		POSITIVE CONTROLS	P00003/001/001			9-AMINOACRIDINE			
		50.	91.0	6.0	8.8		97	91	85
TA 98	+S9	SOLVENT CONTROLS	29.0	1.7			28	31	28
		NEGATIVE CONTROLS	27.0	2.6	0.9		29	28	24
		POSITIVE CONTROLS	P00001/001/001			2-AMINOANTHRACENE			
		0.5	889.0	72.3	30.7		970	866	831
TA 98	-S9	SOLVENT CONTROLS	21.7	1.2			23	21	21
		NEGATIVE CONTROLS	22.3	2.1	1.0		20	23	24
		POSITIVE CONTROLS	P00004/001/001			2-NITROFLUORENE			
		2.5	668.0	108.7	30.8		545	751	708

TEST

STUDY ZR0122 TEST 00 SPONSOR DIVISION E DATE TESTED 14/12/94
DATE COUNTED 16/12/94

COMPOUND E00244/001/001 Genamin PDAC

Ch.B. E06187883

COMMENTS: VOTOX.94.0699
ALL STERILITY CONTROL PLATES WERE STERILE

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 100	+S9	0.	176.0	9.8			168	187	173
		4.	168.7	4.5	1.0		173	164	169
		20.	173.7	5.7	1.0		180	169	172
		100.	178.0	14.8	1.0		171	168	195
		500.	181.3	7.6	1.0		173	188	183
		2500.	79.3	14.0	0.5	INCOMPLETE	80	93	65
		5000.	30.0	6.2	0.2	INCOMPLETE	32	35	23
TA 100	-S9	0.	162.0	7.5			170	155	161
		4.	166.0	5.6	1.0		172	161	165
		20.	161.0	3.0	1.0		161	164	158
		100.	149.7	8.7	0.9		152	140	157
		500.	164.3	4.7	1.0		166	159	168
		2500.	89.3	15.9	0.6	INCOMPLETE	107	85	76
		5000.	26.3	3.8	0.2	INCOMPLETE	29	28	22
TA 1535	+S9	0.	9.7	1.2			9	11	9
		4.	10.3	2.1	1.1		11	12	8
		20.	10.7	2.1	1.1		10	13	9
		100.	10.7	0.6	1.1		11	10	11
		500.	8.3	1.5	0.9		8	7	10
		2500.	7.0	1.0	0.7	INCOMPLETE	7	8	6
		5000.	4.3	1.5	0.4	INCOMPLETE	4	6	3
TA 1535	-S9	0.	9.0	1.0			10	8	9
		4.	12.3	2.1	1.4		10	14	13
		20.	10.7	1.5	1.2		11	9	12
		100.	10.0	1.0	1.1		9	11	10
		500.	10.0	2.0	1.1		10	12	8
		2500.	8.0	2.6	0.9	INCOMPLETE	5	9	10
		5000.	6.3	1.5	0.7	INCOMPLETE	5	6	8

TEST

STUDY ZR0122 TEST 00 SPONSOR DIVISION E DATE TESTED 14/12/94
DATE COUNTED 16/12/94

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 1537	+S9	0.	11.0	2.0			13	9	11
		4.	10.0	1.0	0.9		9	11	10
		20.	11.3	2.1	1.0		12	9	13
		100.	9.0	1.0	0.8		8	9	10
		500.	10.3	0.6	0.9		11	10	10
		2500.	6.7	2.1	0.6	INCOMPLETE	5	9	6
		5000.	2.7	0.6	0.2	INCOMPLETE	3	2	3
TA 1537	-S9	0.	10.3	1.5			10	12	9
		4.	11.3	1.2	1.1		10	12	12
		20.	11.7	2.1	1.1		14	10	11
		100.	11.0	2.0	1.1		11	9	13
		500.	9.7	2.3	0.9		11	7	11
		2500.	8.0	3.0	0.8	INCOMPLETE	11	8	5
		5000.	2.0	2.6	0.2	INCOMPLETE	0	1	5
TA 98	+S9	0.	29.0	1.7			28	31	28
		4.	30.0	6.0	1.0		30	24	36
		20.	29.7	2.1	1.0		29	28	32
		100.	30.0	3.6	1.0		31	26	33
		500.	22.7	3.1	0.8		20	22	26
		2500.	17.7	5.0	0.6	INCOMPLETE	13	23	17
		5000.	7.3	3.8	0.3	INCOMPLETE	9	10	3
TA 98	-S9	0.	21.7	1.2			23	21	21
		4.	23.3	2.5	1.1		23	21	26
		20.	26.7	2.5	1.2		27	24	29
		100.	23.3	2.5	1.1		26	23	21
		500.	22.0	3.0	1.0		22	19	25
		2500.	18.7	2.5	0.9	INCOMPLETE	19	21	16
		5000.	7.0	1.0	0.3	INCOMPLETE	7	8	6

TCC900-05/00 TCC900P/2 RUN DATE: 07/02/95

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T PAGE: 1

CONTROLS

STUDY ZR0122 TEST 01 SPONSOR DIVISION E DATE TESTED 03/01/95
DATE COUNTED 05/01/95

POSITIVE CONTROLS: QR0017/88 SOLVENT CONTROLS: QN0024/16 NEGATIVE CONTROLS: QR0018/81

SOLVENT CONTROL COMMENTS:
NONE

NEGATIVE CONTROL COMMENTS:
NONE

POSITIVE CONTROL COMMENTS:
NONE

STRAIN	DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 100 +S9	SOLVENT CONTROLS	182.3	22.5			159	184	204
	NEGATIVE CONTROLS	159.0	37.0	0.9		128	200	149
	POSITIVE CONTROLS	P00001/001/001			2-AMINOANTHRACENE			
	0.5	958.7	109.4	5.3		898	893	1085
TA 100 -S9	SOLVENT CONTROLS	139.3	7.4			145	131	142
	NEGATIVE CONTROLS	152.7	28.0	1.1		136	185	137
	POSITIVE CONTROLS	P00002/001/001			SODIUM-AZIDE			
	1.	660.3	24.0	4.7		684	636	661

TCC900-05/00 TCC900P/2 RUN DATE: 07/02/95

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T

CONTROLS

STUDY ZR0122 TEST 01 SPONSOR DIVISION E DATE TESTED 03/01/95
DATE COUNTED 05/01/95

POSITIVE CONTROLS: QR0017/88 SOLVENT CONTROLS: QN0024/16 NEGATIVE CONTROLS: QR0018/81

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 1535	+S9	SOLVENT CONTROLS	12.7	4.7			9	11	18
		NEGATIVE CONTROLS	13.0	2.6	1.0		15	10	14
		POSITIVE CONTROLS	P00001/001/001			2-AMINOANTHRACENE			
		1.	115.3	7.8	9.1		124	109	113
TA 1535	-S9	SOLVENT CONTROLS	10.7	2.1			9	13	10
		NEGATIVE CONTROLS	10.7	2.3	1.0		12	8	12
		POSITIVE CONTROLS	P00002/001/001			SODIUM-AZIDE			
		1.	290.3	21.1	27.1		296	308	267
TA 1537	+S9	SOLVENT CONTROLS	9.0	2.6			11	10	6
		NEGATIVE CONTROLS	9.7	1.5	1.1		8	10	11
		POSITIVE CONTROLS	P00001/001/001			2-AMINOANTHRACENE			
		1.	122.0	16.7	13.6		137	104	125

TCC900-05/00 TCC900P/2 RUN DATE: 07/02/95

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T

CONTROLS

STUDY ZR0122 TEST 01 SPONSOR DIVISION E DATE TESTED 03/01/95
DATE COUNTED 05/01/95

POSITIVE CONTROLS: QR0017/88 SOLVENT CONTROLS: QN0024/16 NEGATIVE CONTROLS: QR0018/81

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 1537	-S9	SOLVENT CONTROLS	11.3	1.5			13	11	10
		NEGATIVE CONTROLS	13.0	2.6	1.2		10	15	14
		POSITIVE CONTROLS	P00003/001/001			9-AMINOACRIDINE			
		50.	129.7	27.5	11.5		98	143	148
TA 98	+S9	SOLVENT CONTROLS	29.7	3.5			26	33	30
		NEGATIVE CONTROLS	34.0	4.6	1.1		30	33	39
		POSITIVE CONTROLS	P00001/001/001			2-AMINOANTHRACENE			
		0.5	577.3	42.9	19.4		545	626	561
TA 98	-S9	SOLVENT CONTROLS	29.3	7.1			23	37	28
		NEGATIVE CONTROLS	34.7	4.9	1.2		37	38	29
		POSITIVE CONTROLS	P00004/001/001			2-NITROFLUORENE			
		2.5	625.3	6.1	21.3		620	624	632

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T

TEST

STUDY ZR0122 TEST 01 SPONSOR DIVISION E

DATE TESTED 03/01/95
DATE COUNTED 05/01/95

COMPOUND E00244/001/001 Genamin PDAC

Ch.B. E06187883

COMMENTS: VOTOX.94.0699
ALL STERILITY CONTROL PLATES WERE STERILE

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 100	+S9	0.	182.3	22.5			159	184	204
		4.	165.7	37.9	0.9		125	172	200
		20.	141.7	17.8	0.8		129	162	134
		100.	129.0	30.4	0.7		102	162	123
		500.	145.7	16.2	0.8		127	154	156
		2500.	98.3	5.0	0.5	INCOMPLETE	99	103	93
		5000.	65.7	17.2	0.4	INCOMPLETE	52	60	85
TA 100	-S9	0.	139.3	7.4			145	131	142
		4.	139.0	26.1	1.0		109	156	152
		20.	137.0	30.0	1.0		114	126	171
		100.	155.0	29.5	1.1		125	184	156
		500.	172.7	47.4	1.2		120	212	186
		2500.	129.3	7.4	0.9	INCOMPLETE	135	121	132
		5000.	51.7	11.0	0.4	INCOMPLETE	43	64	48
TA 1535	+S9	0.	12.7	4.7			9	11	18
		4.	9.7	1.5	0.8		11	8	10
		20.	13.3	1.5	1.0		15	13	12
		100.	10.3	1.2	0.8		11	9	11
		500.	13.0	4.4	1.0		11	10	18
		2500.	9.7	3.1	0.8	INCOMPLETE	13	7	9
		5000.	12.0	2.0	0.9	INCOMPLETE	12	14	10
TA 1535	-S9	0.	10.7	2.1			9	13	10
		4.	8.3	1.5	0.8		8	10	7
		20.	9.3	1.5	0.9		11	8	9
		100.	11.7	2.3	1.1		9	13	13
		500.	7.7	1.5	0.7		8	6	9
		2500.	8.3	0.6	0.8	INCOMPLETE	8	9	8
		5000.	6.7	1.2	0.6	INCOMPLETE	6	8	6

TEST

STUDY ZR0122 TEST 01 SPONSOR DIVISION E DATE TESTED 03/01/95
DATE COUNTED 05/01/95

STRAIN		DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 1537	+S9	0.	9.0	2.6			11	10	6
		4.	8.0	2.6	0.9		7	6	11
		20.	8.7	3.8	1.0		13	7	6
		100.	9.0	1.0	1.0		9	10	8
		500.	9.0	2.0	1.0		7	11	9
		2500.	8.0	1.0	0.9	INCOMPLETE	7	9	8
		5000.	6.0	3.5	0.7	INCOMPLETE	4	4	10
TA 1537	-S9	0.	11.3	1.5			13	11	10
		4.	8.3	2.1	0.7		9	6	10
		20.	8.3	2.3	0.7		7	7	11
		100.	12.7	4.0	1.1		17	9	12
		500.	12.0	2.6	1.1		10	15	11
		2500.	8.7	2.1	0.8	INCOMPLETE	11	7	8
		5000.	3.0	1.7	0.3	INCOMPLETE	2	2	5
TA 98	+S9	0.	29.7	3.5			26	33	30
		4.	32.7	3.1	1.1		36	32	30
		20.	39.0	9.5	1.3		38	49	30
		100.	39.0	4.0	1.3		43	39	35
		500.	37.7	9.5	1.3		45	41	27
		2500.	32.3	9.0	1.1	INCOMPLETE	37	38	22
		5000.	16.7	5.5	0.6	INCOMPLETE	22	17	11
TA 98	-S9	0.	29.3	7.1			23	37	28
		4.	22.0	1.7	0.8		23	23	20
		20.	21.7	3.2	0.7		18	24	23
		100.	28.0	3.6	1.0		25	32	27
		500.	31.7	6.4	1.1		29	39	27
		2500.	24.7	2.3	0.8	INCOMPLETE	26	26	22
		5000.	13.3	8.1	0.5	INCOMPLETE	12	6	22

TCC900-05/00 TCC900P/2 RUN DATE: 07/02/95

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T PAGE: 1

CONTROLS

STUDY ZR0122 TEST 02 SPONSOR DIVISION E DATE TESTED 03/01/95
DATE COUNTED 05/01/95

POSITIVE CONTROLS: QN0021/19 SOLVENT CONTROLS: QN0025/08 NEGATIVE CONTROLS: QR0014/89

SOLVENT CONTROL COMMENTS:
NONE

NEGATIVE CONTROL COMMENTS:
NONE

POSITIVE CONTROL COMMENTS:
NONE

STRAIN	DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 100 D +S9	SOLVENT CONTROLS	210.3	4.2			209	215	207
	NEGATIVE CONTROLS	211.0	4.0	1.0		211	207	215
	POSITIVE CONTROLS	N00002/001/001		NOT TESTED				
	*** NO RESULTS FOR THIS STRAIN ***							
TA 100 D -S9	SOLVENT CONTROLS	174.3	10.0			178	182	163
	NEGATIVE CONTROLS	176.7	7.1	1.0		169	183	178
	POSITIVE CONTROLS	N00002/001/001		NOT TESTED				
	*** NO RESULTS FOR THIS STRAIN ***							

TCC900-05/00 TCC900P/3 RUN DATE: 07/02/95

HOECHST AKTIENGESELLSCHAFT SECTION: GENETIC TOXICOLOGY

A M E S T E S T R E S U L T S P R I N T PAGE: 2

TEST

STUDY ZR0122 TEST 02 SPONSOR DIVISION E DATE TESTED 03/01/95
DATE COUNTED 05/01/95

COMPOUND E00244/001/001 Genamin PDAC

Ch.B. E06187883

COMMENTS: VOTOX.94.0699

STRAIN	DOSE LEVELS (MICROGRAMS/PLATE)	MEAN	STANDARD DEVIATION	RATIO: TEST/ CONTROL	BACTERIAL LAWN	NO REVERTANTS/PLATE PLATE 1	PLATE 2	PLATE 3
TA 100 D +S9	0.	210.3	4.2			209	215	207
	4.	213.7	22.4	1.0		209	194	238
	20.	216.0	15.9	1.0		234	210	204
	100.	217.7	6.4	1.0		214	214	225
	500.	207.0	13.7	1.0		222	204	195
	2500.	88.0	32.9	0.4		77	62	125
	5000.	13.7	9.0	0.1		9	8	24
TA 100 D -S9	0.	174.3	10.0			178	182	163
	4.	175.0	8.0	1.0		183	167	175
	20.	163.3	8.3	0.9		170	154	166
	100.	171.3	12.5	1.0		159	184	171
	500.	187.0	4.6	1.1		182	188	191
	2500.	76.3	1.5	0.4		75	76	78
	5000.	19.3	6.8	0.1		27	17	14

6.2 References and guidelines

A. REFERENCES

1) B.N. Ames, W.W. Durston, E. Yamasaki and F.D. Lee, Carcinogens are mutagens. A simple test system combining liver homogenate for activation and bacteria for detection, Proc. Nat. Acad. Sci. USA 70 (1973) 2281 - 2285.

2) B.N. Ames, J. McCann and E. Yamasaki: Methods for detecting carcinogens and mutagens with the Salmonella / mammalian-microsome mutagenicity test, Mutation Res. 31 (1975) 347 -364.

3) A.P. Alvares, D.R. Bickers and A. Kappas: Polychlorinated biphenyls: a new type of inducer of cytochrome P 448 in the liver. Proc. Nat. Acad. Sci. USA 70 (1973) 1321 - 1325.

4) J. McCann, N.E. Springarn, J. Kobory and B.N. Ames: Detection of carcinogens as mutagens: bacterial tester strains with R factor plasmids, Proc. Nat. Acad. Sci. USA 72 (1975) 979 - 983.

B. GUIDELINES

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

- OECD Guideline for testing of chemicals 471
  Genetic Toxicology : Salmonella typhimurium, Reverse Mutation Assay,
  Adopted : May 26th, 1983

- U.S. EPA: 798.5265
  The Salmonella typhimurium reverse mutation assay
  Fed. Reg. 50, Subpart F, September 1985

- EEC Directive 92/69, L 383 A, Annex B 14

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: October 23, 2020

SUBJECT: Polyquaternium-6

Lubrizol Advanced Materials, Inc. 2020. Polyquaternium-6 Support Information for CIR.

Lubrizol Advanced Materials, Inc. 2020. Merquat™ 100 and Merquat™ 106 (Polyquaternium-6) Toxicology Studies.

Lubrizol Advanced Materials, Inc.
9911 Brecksville Road
Cleveland, Ohio 44141-3247
216.447.5000

22 October 2020

Ms. Carol Eisenmann
The Personal Care Products Council
1620 L Street, NW, Suite 1200
Washington, D.C. 20036
Via Email: eisenmannc@personalcarecouncil.org

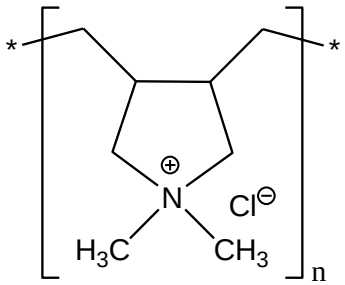
SUBJECT: Polyquaternium-6 Support information for CIR

Dear Carol,

Per your request, enclosed is information about Lubrizol Advanced Materials, Inc. products, Merquat™ 100 polymer and Merquat™ 106 polymer in support of CIR's review of Polyquaternium-6.

Lubrizol Advanced Materials, Inc. manufactures two products which have the INCI name of Polyquaternium-6. They have the trade names of Merquat™ 100 and Merquat™ 106.
Both of these products are considered cationic homopolymers. They are made via polymerization of Diallyldimethyl Ammonium Chloride (DADMAC) in an aqueous solution. Both are typically used at 1- 3% in hair care and bath/shower applications.

Both are the same structure that just vary by the amount of repeated monomer units to achieve the desired molecular weight. Structure of the Polyquaternium-6 where n is repeat units of the same structure:



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9911 Brecksville Road
Cleveland, Ohio 44141-3247
216.447.5000

Merquat 100 Composition information

Ingredient/INCI name	CAS #	Function	% typical
Polyquaternium-6	26062-79-3	Key ingredient	42
Water	7732-18-5	Diluent	<58

Typical molecular weight: 150,000 Da
Typical Impurities: Free unreacted monomer: DADMAC at 6.5% max

Merquat 106 Composition information

Ingredient/INCI name	CAS #	Function	% typical
Polyquaternium-6	26062-79-3	Key ingredient	33
Water	7732-18-5	Diluent	<67
Acetic acid	64-19-7	Buffer	0.65

Typical molecular weight: 15,000 Da
Typical Impurities: Free unreacted monomer: DADMAC at 1.5% max

I have also enclosed a toxicology summary for these two products.

Should you or CIR need additional information, please contact me.

Sincerely,

Cynthia S. Sullivan
Chief Product Steward

Enc/

Original Issue: June 2020

Merquat™ 100 and Merquat™ 106 Toxicology Studies

Toxicity studies were conducted on Merquat™ 100 that is chemically and structurally similar to Merquat™ 106. It is believed that the following results for the test material represent the toxicity potential for both Merquat™ 100 and Merquat™ 106.

Acute Oral Toxicity (Test 1)

The acute oral toxicity of the *Merquat™* 100 was evaluated on six groups of five male albino rats each. Each rat received doses through oral intubation and all animals were fasted prior to dosing. The dose levels were 2.15, 3.16, 4.46, 6.81, 10.0 and 14.7 g/kg bodyweight. The animals were observed for mortality and toxic effects immediately after dosing, at one hour, four hours, twenty-four hours and once daily for fourteen days. Animals receiving the test material surviving to day 14 appeared normal at necropsy. The acute oral median lethal dose (LD_{50}) of the test material was found to be 8.71 g/kg bodyweight.

Acute Oral Toxicity (Test 2)

The acute oral toxicity of the *Merquat™* 100 which contained approximately 40% solids was evaluated on four groups of five male and five female albino rats each. Each rat received doses through oral intubation at the dose levels of 1.99, 3.37, 5.69 and 9.62 ml/kg bodyweight. The animals were observed for mortality and toxic effects on the day of administration and once daily for fourteen days except on weekends. The acute oral median lethal dose (LD_{50}) of the test material was found to be 3.15 ml/kg bodyweight.

Acute Dermal Toxicity

The acute dermal toxicity of *Merquat™* 100 was evaluated using four groups of four rabbits. The dosage level of the test material was 2.15, 4.64, 10.0 and 21.5 g/kg bodyweight. The rabbits were wrapped in binders and after 24 hours was removed. Signs of dermal toxicity and systemic toxicity was observed in the rabbits daily for 14 consecutive days. The LD_{50} of the test material was estimated to be greater than 21.5 g/kg bodyweight. It was determined that no consistent compound-related signs of systemic toxicity were present. Signs of dermal irritation included slight to serve erythema, slight edema, blanching and necrosis.

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Acute Inhalation Toxicity

The acute inhalation toxicity potential of *Merquat™* 100 was evaluated in ten CD® rats (5 females and 5 males). The test substance was administered, using distilled water (1:1) as a vehicle, into the breathing zone of the animals as an aerosol. Test animals received an average analytical concentration of 0.2 mg/l of *Merquat™* 100**,** with a nominal exposure concentration of 28 mg/l of diluted *Merquat™* 100 . All animals survived the exposure and through the 14-day post exposure period. It was determined that the test material did not have any acute inhalation toxicity.

Eye Irritation (Test 1)

The irritation potential of *Merquat™* 100 was conducted in rabbits according to the specifications of the Federal Hazardous Substances Act. 0.1 mL of the test material was introduced into the left conjunctival sac of the six New Zealand White Rabbits. The right eye served as a control. At 24 and 72 hours, 2.0% sodium fluorescent stain was used to examine the treated eyes. It was concluded that the test material was not an eye irritant.

Eye Irritation (Test 2)

The irritation potential of *Merquat™ 100* which contained approximately 40% solids was conducted in three male and three female rabbits. 0.1 mL of the test material was placed into the left conjunctival sac, the right eye served as an untreated control. Ocular reactions were recorded for up to day 14. The test substance was slightly irritating to the rabbit eye. It produced a slight conjunctival injection and a moderate clear color-less discharge in all six eyes at 15min and 2 hours. Two of the six eyes still had a very slight injection at 24 hours but disappeared at 48 hours; the other four eyes appeared normal at 24 hours.

Skin Irritation (Test 1)

The skin irritation potential of *Merquat™* 100 was evaluated in rabbits according to the specifications of the Federal Hazardous Substances Labeling Act (16 CFR, Part 1500). A single application of 0.5 mL of the test material was placed on six intact and six abraded animals using a one-inch square gauze patch for 24 hours. During this period, the animals were restrained, and a nonabsorbent binder wrapped around the trunk. After 24- and 72-hours observations were made. It was determined that the test material was not a dermal irritant.

Skin Irritation (Test 2)

The skin irritation potential of *Merquat™ 100* which contained approximately 40% solids was conducted in three rabbits. A single application of 0.5 mL of the test material was placed on intact and abraded sites. The occlusive dressing was removed after 24 hours and the sites examined. The sites were also examined daily thereafter for two weeks. Two abraded test sites showed a very slight erythema when the dressings were removed 24 hours after treatment and lasted for five days. The other four abraded sites and all intact sites showed no irritation at 24 hours or during the two-week observation period.

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Photoallergy Test

Photoallergy of *Merquat™ 100* was conducted on 29 participants. During the induction phase, the test material was applied to individuals on 2 X 2 cm^2 areas of skin at a dose of 0.3ml and covered with a patch. The contact time the test material was 24 hours. Following this, the patch site was exposed to natural sunlight for 30 to 40 minutes between 11:00 am and 3:00 pm. This was repeated for a total of 9 times. During the challenge phase, a single application of sets of duplicate contact patches of the test material was made to naive sites. One of the replicate patches sites in each set was used to test for induced photoallergy and one was used to evaluate induced contact sensitization. It was determined that under the conditions of the test, the test material showed no evidence of contact irritation, sensitization or photoallergy.

Human Repeated Insult Patch Test

Potential hazard by dermal contact *Merquat™ 100* was evaluated on fifty individuals. During the induction phase, test material was applied to individuals at a dose of 0.1ml/cm^2 and covered by an occlusive dressing. At the end of 24 hours, the covers and test material were removed, and the sites examined for visible irritation. A series of twelve applications were administered. During the challenge phase, a series of four doses was applied to virgin sites. *Merquat™* 100 was not capable of acting as an irritant or eliciting sensitization response.

28-day Repeated Dose Study via Oral Route

The objective of this study was to evaluate the potential toxic effects of the test substance, when administered to rats for 28 consecutive days. *Merquat™ 100*, 40% solution was mixed in the diet at dosage levels of 0, 330, 1000, 3300 and 10000 ppm, and was given to five groups of ten male and ten female rats. The male and female 10000 ppm dosage groups showed a depression of the body weight gain, increase of water consumption, and decrease of diet efficiency. The maximum no-effect dosage of the test substance was estimated to be 3300 ppm for both male (280 mg/kg/day) and female (295 mg/kg/day).

90-day Repeated Dose Study via Dermal Route

The objective of this study was to evaluate the dermal irritation and systemic toxicity following repeated topical application to intact and abraded skin. *Merquat™ 100*, 40% solution was applied topically to groups of ten male and ten female rabbits at dosage levels of 0.25, 0.75 or 2.25 ml/kg/day for 89 to 92 consecutive days. The negative control rabbits received physiological saline at a dose of 2.25 ml/kg/day. Each day the treatment area was cleaned with lukewarm tap water after five to six hours exposure. The control rabbits were not subjected to a similar handling procedure.

The intact skin treated with the test substance did not show irritation during the study, the abraded skin showed varying amounts of erythema and edema observed along the lines of abrasion. No evidence of systemic toxicity was observed in all groups.

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For further information, please visit: www.lubrizol.com/beauty