Safety Assessment of Adenosine Ingredients as Used in Cosmetics

Status:	Draft Report for Panel Review
Release Date:	August 22, 2019
Panel Meeting Date:	September 16-17, 2019

The 2019 Cosmetic Ingredient Review Expert Panel 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., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.

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Memorandum

To: CIR Expert Panel Members and Liaisons

From: Priya Cherian, Scientific Analyst/Writer

Date: August 22, 2019

Subject: Draft Report on Adenosine ingredients

A Scientific Literature Review (SLR) on Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate was issued on May 31, 2019. Enclosed is the draft report on these ingredients. This is the first time the Panel is reviewing the safety of these 5 ingredients.

The attached report (*adenos092019rep*) includes the following unpublished data that were received from the Council:

1) Use concentration data (*adenos092019data1*)
2) A summary of a Magnusson Kligman assay using a trade name mixture containing 15% mannitol and 15% Disodium Adenosine Triphosphate; 0.5% (intracutaneous induction) and 10% (epicutaneous induction and challenge) aqueous dilutions of the trade name mixture were used (*adenos092019data2*)
3) A summary of a phototoxicity assay using a 10% aqueous dilution of a mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate (*adenos092019data2*)
4) A summary of a photosensitization test using a 2% aqueous dilution of a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate (*adenos092019data2*)
5) A summary of a 48-hour patch test performed on 10 subjects using a test substance containing 0.2% Adenosine (*adenos092019data3*)
6) A summary of an HRIPT performed on 205 subjects using a test substance containing 0.2% Adenosine (*adenos092019data3*)

Also included in this package for your review are the CIR report history (*adenos092019hist*), flow chart (*adenos092019flow*), literature search strategy (*adenos092019strat*), ingredient data profile (*adenos092019prof*), and 2019 FDA VCRP data (*adenos092019fda*). Comments on the Scientific Literature Review provided by Council were received, and addressed (*adenos092019pcpc*).

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.

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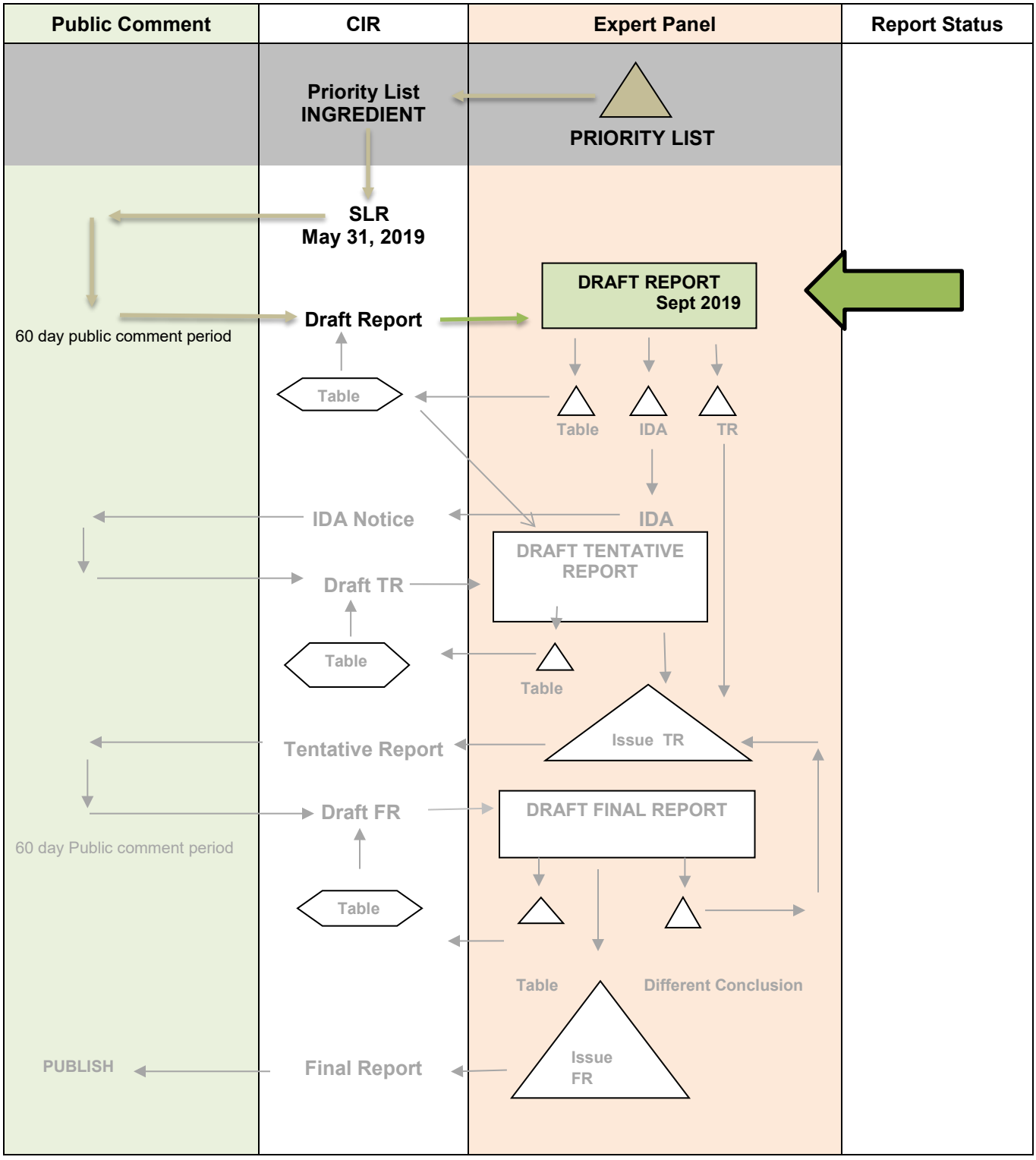
SAFETY ASSESSMENT FLOW CHART

INGREDIENT/FAMILY Adenosine Ingredients

MEETING September 2019



Adenosine Ingredients History

May 2019

-SLR posted

June 2019

-Summary sensitization, phototoxicity, and photosensitization information received from Council

-Comments received on SLR

August 2019

-summary 48-hour patch test and HRIPT data on Adenosine received from Council

September 2019

-Draft report reviewed by Panel

Adenosine ingredients Data Profile* – September 2019 – Writer, Priya Cherian

				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Impurities	log P	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
Adenosine		X			X			X			X				X				X	X	X	X		X		X	X	X	
Adenosine Phosphate						X																							
Adenosine Triphosphate		**X**				X		X			X																	X	
Disodium Adenosine Phosphate																													
Disodium Adenosine Triphosphate								X															X	X	X				

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

[September 2019 Meeting - Adenosine – Writer: Priya Cherian]

Ingredient	CAS #	InfoB	PubMed	TOXNET	FDA	EU	ECHA	IUCLID	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	FEMA	Web
Adenosine	58-61-7	yes	yes	yes	yes	yes	yes	no	no	no	no	no	no	no	no	no	no	no	yes
Adenosine Phosphate	61-19-8	yes	yes	yes	yes	yes	yes	no	no	No	No	No	No	No	No	No	No	No	No
Adenosine Triphosphate	56-65-5	yes	yes	yes	yes	yes	yes	No	No	No	No	No	No	No	No	No	No	No	No
Disodium Adenosine Phosphate	4578-31-8	yes	yes	yes	no	yes	no	no	no	no	no	no	no	no	no	No	No	No	No
Disodium Adenosine Triphosphate	987-65-5	yes	no	yes	no	Yes	No	No	No	No	No	No	No	No	No	No	No	No	no

Typical Search Terms

- Adenosine
- Adenosine Phosphate
- Adenosine Triphosphate
- ATP
- Disodium Adenosine Phosphate
- Disodium Adenosine Triphosphate
- 58-61-7
- 61-19-8
- 56-65-5
- 4578-31-8
- 987-65-5
- cosmetic, irritation, dermal, sensitization, toxicity
- medicine
- skin irritation
- genotoxicity
- carcinogenicity
- metabolism

LINKS

Search Engines

- Pubmed (- http://www.ncbi.nlm.nih.gov/pubmed)
- Toxnet (https://toxnet.nlm.nih.gov/); (includes Toxline; HSDB; ChemIDPlus; DART; IRIS; CCRIS; CPDB; GENE-TOX)
- Scifinder (https://scifinder.cas.org/scifinder)

appropriate qualifiers are used as necessary
search results are reviewed to identify relevant documents

Pertinent Websites

- wINCI - http://webdictionary.personalcarecouncil.org

- FDA databases http://www.ecfr.gov/cgi-bin/ECFR?page=browse
- FDA search databases: http://www.fda.gov/ForIndustry/FDABasicsforIndustry/ucm234631.htm;,
- EAFUS: http://www.accessdata.fda.gov/scripts/fcn/fcnnavigation.cfm?rpt=eafuslisting&displayall=true
- GRAS listing: http://www.fda.gov/food/ingredientspackaginglabeling/gras/default.htm
- SCOGS database: http://www.fda.gov/food/ingredientspackaginglabeling/gras/scogs/ucm2006852.htm
- Indirect Food Additives: http://www.accessdata.fda.gov/scripts/fdcc/?set=IndirectAdditives
- Drug Approvals and Database: http://www.fda.gov/Drugs/InformationOnDrugs/default.htm

- http://www.fda.gov/downloads/AboutFDA/CentersOffices/CDER/UCM135688.pdf
- FDA Orange Book: https://www.fda.gov/Drugs/InformationOnDrugs/ucm129662.htm
- OTC ingredient list: https://www.fda.gov/downloads/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm135688.pdf
- (inactive ingredients approved for drugs: http://www.accessdata.fda.gov/scripts/cder/iig/

- HPVIS (EPA High-Production Volume Info Systems) - https://ofmext.epa.gov/hpvis/HPVISlogon
- NIOSH (National Institute for Occupational Safety and Health) - http://www.cdc.gov/niosh/
- NTIS (National Technical Information Service) - http://www.ntis.gov/
- NTP (National Toxicology Program) - http://ntp.niehs.nih.gov/
- Office of Dietary Supplements https://ods.od.nih.gov/
- FEMA (Flavor & Extract Manufacturers Association) - http://www.femaflavor.org/search/apachesolr_search/

- EU CosIng database: http://ec.europa.eu/growth/tools-databases/cosing/
- ECHA (European Chemicals Agency – REACH dossiers) – http://echa.europa.eu/information-on-chemicals;jsessionid=A978100B4E4CC39C78C93A851EB3E3C7.live1
- ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals) - http://www.ecetoc.org
- European Medicines Agency (EMA) - http://www.ema.europa.eu/ema/
- IUCLID (International Uniform Chemical Information Database) - https://iuclid6.echa.europa.eu/search
- OECD SIDS (Organisation for Economic Co-operation and Development Screening Info Data Sets)- http://webnet.oecd.org/hpv/ui/Search.aspx
- SCCS (Scientific Committee for Consumer Safety) opinions: http://ec.europa.eu/health/scientific_committees/consumer_safety/opinions/index_en.htm
- NICNAS (Australian National Industrial Chemical Notification and Assessment Scheme)- https://www.nicnas.gov.au/

- International Programme on Chemical Safety http://www.inchem.org/
- FAO (Food and Agriculture Organization of the United Nations) - http://www.fao.org/food/food-safety-quality/scientific-advice/jecfa/jecfa-additives/en/
- WHO (World Health Organization) technical reports - http://www.who.int/biologicals/technical_report_series/en/

- www.google.com - a general Google search should be performed for additional background information, to identify references that are available, and for other general information

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INTRODUCTION

This is a safety assessment of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI; *Dictionary*), these ingredients function as skin-conditioning agents – miscellaneous.[1] (Table 1)

These adenosine ingredients are structurally similar to one another, naturally-occurring in the human body, and are involved in biological processes including neurotransmission, muscle contraction, cardiac function, platelet function, vasodilation, signal transduction, and secretion in various cell types.[2] Because these ingredients are present in living organisms and their general biology is well characterized, this safety assessment focuses predominantly on the chemistry and on effects due to topical exposure.

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 CIR 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 are provided by the cosmetics industry, as well as by other interested parties.

Some of the data included in this safety assessment were found on the European Chemicals Agency (ECHA) website.[3] These summaries are available on the ECHA website, and when deemed appropriate, information from these summaries have been included in this report.

CHEMISTRY

Definition and Structure

The definitions and structures of the ingredients included in this review are provided in Table 1. All of these ingredients share Adenosine as the core structure.

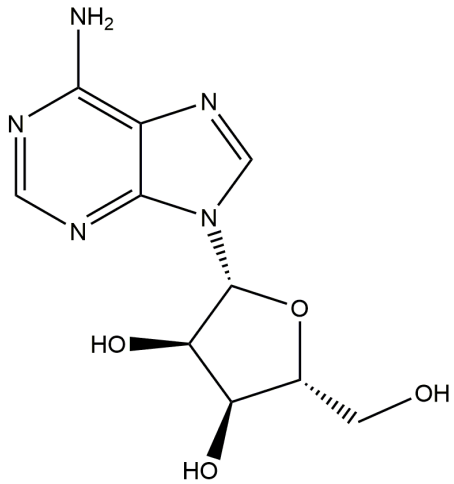


Figure 1. Adenosine

Adenosine Triphosphate (ATP) is composed of a purine nucleoside esterified with three phosphate groups.[4] ATP is a ubiquitous organophosphate that connects anabolism and catabolism, but also fuels processes such as motile contraction, phosphorylations, and active transport.[5] Both Adenosine and Adenosine Phosphate (AMP) are formed when ATP is consumed in metabolic processes. Adenosine, a ribonucleoside comprising adenine and ribose, exerts pleiotropic functions throughout the body.[6] AMP is an ester of phosphoric acid and Adenosine. Like ATP, AMP plays an important role in many cellular metabolic processes, and is a component in the synthesis of RNA.

Physical and Chemical Properties

The ingredients named in this report (with reported properties) are solids at room temperature and are soluble in water. Available information on the physical and chemical properties are presented in Table 2.

Method of Manufacture

These methods are general to the production of Adenosine and Adenosine Triphosphate; no methods specific to cosmetic ingredient manufacture were found in the literature or submitted as unpublished data.

Adenosine

The main methods of manufacturing Adenosine include chemical synthesis, RNA degradation, and microbial fermentation.[7] *Bacillus subtilis* is commonly used as it is a safe and stable producer of purine nucleosides.

Adenosine Triphosphate

Adenosine Triphosphate may be produced by microbial phosphorylation of Adenosine Phosphate.[8]

Impurities

Impurities data were not found in the published literature, and unpublished data were not submitted.

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 2019 VCRP survey data, Adenosine has the highest frequency of use, with a total of 737 formulations (Table 3).[9] Adenosine is most commonly used in face and neck products (259 formulations) and moisturizing products (186 formulations). Disodium Adenosine Triphosphate is reported to be used in 111 formulations, 95 of which are leave-on formulations. The remaining ingredients are reported to be used at 98 formulations or less. The results of the concentration of use survey conducted by the Council indicate that Adenosine has the highest concentration of use in a leave-on formulation; it is used at up to 1% in body and hand products.[10] Disodium Adenosine Phosphate is not reported to be in use.

These ingredients have been reported to be used around the eyes (e.g., at up to 0.041% Adenosine in eye lotions and at up to 0.5% Adenosine Phosphate in mascara). In addition, Adenosine could result in incidental ingestion as it is used in lipstick and dentifrices (concentrations not reported). Some of the adenosine ingredients are used in cosmetic sprays and could possibly be inhaled; for example, Adenosine is reported to be used at 0.041% in spray moisturizing formulations, and Adenosine Phosphate is used in aerosol hair spray formulations at up to 0.04%. 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 < 10 μm compared with pump sprays.[11,12] Therefore, most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and thoracic regions of the respiratory tract and would not be respirable (i.e., would not enter the lungs) to any appreciable amount.[13,14] Adenosine was also reportedly used in face powders at concentrations up to 0.1% and could be incidentally inhaled. Conservative estimates of inhalation exposures to respirable particles during the use of loose powder cosmetic products are 400-fold to 1000-fold less than protective regulatory and guidance limits for inert airborne respirable particles in the workplace.[15-17]

All of the adenosine ingredients named in this report are listed in the European Union inventory of cosmetic ingredients with no restrictions.[18]

Non-Cosmetic

Adenosine

According to the US FDA, Adenosine is used for the treatment of paroxysmal supraventricular tachycardia and approved for use in nuclear stress testing in patients who cannot exercise adequately.[19] Adenosine is typically given intravenously at a dose of 3 mg/mL.[20] In 2013, the FDA issued a warning informing health care professionals of the rare but serious risk of heart attack with the use of Adenosine-containing drugs in nuclear stress testing. Health care professionals are advised to avoid using this ingredient in patients with signs or symptoms of unstable angina or cardiovascular instability. In addition, Adenosine is used to treat surgical and nerve pain, and pulmonary hypertension.[21,22]

Adenosine Phosphate and Adenosine Triphosphate

According to 21 CFR 216.24, all drug products containing Adenosine Phosphate or Adenosine Triphosphate were withdrawn or removed from the market because the product or product components were found to be neither safe nor effective for its intended use as a vasodilator and anti-inflammatory. Adenosine Phosphate is used in the therapeutic treatment of herpes, post-herpetic neuralgia, photosensitivity, and porphyria cutanea tarda.[23-25] Adenosine Triphosphate is given orally and intravenously to treat acute kidney failure, high blood pressure, cystic fibrosis, and lung cancer.[26,27]

TOXICOKINETIC STUDIES

Dermal Penetration

In Vitro

Adenosine

In a dermal penetration study, human skin samples (500 µm thick) were mounted in stainless steel doubly jacketed diffusion cells.[28] The acceptor solution consisted of phosphate buffered saline and the test substance consisted of Adenosine (1.5 or 3%) in propionic acid, (0.5%) in hexanoic acid, or (1.5%) in a binary vehicle of propionic and hexanoic acid. A volume of 450 µL of the test substance was pipetted into the donor reservoir. Perfusate samples were collected after 25 or 30 minutes, and analyzed. The observed optimal permeability coefficients (K_p) of Adenosine from the binary vehicle, propionic acid solution, and hexanoic acid solution were 0.0004, 0.00012, and 0.00016 cm/min, respectively.

Human

According to a risk profile from the Norwegian Food Safety Authority (NFSA), it is believed that application of a cream containing Adenosine at low concentrations to skin (thickness of 2 mg/cm^2) would result in absorption of up to 2%.[29]

Absorption, Distribution, Metabolism, and Excretion (ADME)

Animal

Oral

Adenosine Phosphate

Male and female Wistar rats (number of animals not stated) were given a single dose of 10 mg/kg [^{14}C]-Adenosine Phosphate dissolved in 9% aqueous sodium chloride via gavage.[30] The specific activity of the [^{14}C]-Adenosine Phosphate was reported to be 46 mCi/mmol. Within 72 hours of administration, 28% of the injected activity was excreted in the urine and 6% was recovered in the feces. Plasma levels of Adenosine Phosphate were maximal approximately 30 minutes after oral administration. Adenosine Phosphate was considered to be rapidly absorbed by the intestinal mucosa and quickly distributed two hours after absorption; only 20% of the maximal concentration remained in the plasma.

Human

Oral

Adenosine Triphosphate

Eight volunteers were given singles doses of 5000 mg Adenosine Triphosphate or placebo via an ingested pellet targeted at release in the proximal or distal small intestine, or via a naso-duodenal tube.[31] Blood Adenosine Triphosphate and metabolite concentrations were monitored by high performance liquid chromatography (HPLC) 4.5 hours (naso-duodenal tube) or 7 hours (pellets) post-administration. Adenosine Triphosphate concentrations in the blood did not increase after supplementation of Adenosine Triphosphate via pellets or naso-duodenal tube. Concentrations of uric acid were significantly increased compared to placebo by approximately 50% after administration via proximal-release pellets and naso-duodenal tube but not after administration via distal-release pellets. The mean time to peak uric acid concentration was shorter for naso-duodenal tube administration (75 to 195 minutes) as compared to the pellet administration (150 - 390 minutes).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Adenosine

An LD_{50} of greater than 2000 mg/kg bw was in a study involving mice given Adenosine orally.[29] No other details regarding this study were provided.

An acute oral toxicity study on Adenosine was performed on 3 female Wistar rats (3 rats/group) according to Organization for Economic Cooperation and Development (OECD) Test Guideline (TG) 423.[3] In both groups, the test substance (Adenosine in methylcellulose) was given at a dose of 2000 mg/kg bw. Animals were observed for 14 days following treatment and killed on day 15. All rats survived treatment and no treatment-related clinical symptoms were observed. Necropsy revealed pale kidneys in two animals of group 1 and all animals of group 2. The LD_{50} was reported to be greater than 2000 mg/kg bw.

Adenosine Triphosphate

The oral LD_{50} of Adenosine Triphosphate was reported to be > 2000 mg/kg in rats.[32] No other details regarding this study were provided. In a different study, groups of 5 male anesthetized New Zealand White rabbits were given 2 or 20 mg/kg

Adenosine Triphosphate via a gastric cannula.[33] The test substance did not have an effect on diastolic aortic pressure, heart rate, central venous pressure, iliac venous blood flow, lung resistance, or the arterial partial pressure of oxygen (Pa_{O2}).

Disodium Adenosine Triphosphate

An oral LD_{50} of > 2000 g/kg was reported for both mice and rats treated with Disodium Adenosine Triphosphate.[34] No other details regarding these studies were provided.

Short-Term Toxicity Studies

Oral

Adenosine and Adenosine Triphosphate

New Zealand White rabbits were given doses of either 3 mg/kg/d (n = 4) or 20 mg/kg/d Adenosine Triphosphate mixed with cellulose (n = 12), or 20 mg/kg/d adenosine hemisulfate salt (n = 4) for 14 days.[33] Adenosine Triphosphate and adenosine hemisulfate, dissolved in saline, were administered daily via gastric cannula. Control rabbits received a corresponding amount of saline. No modification of electrocardiogram morphology or heart rate was detected in treated animals compared to controls. Central venous and arterial pressures were comparable in all groups. After treatment with 3 and 20 mg/kg/d, increases of 30 and 50% in the intervillous vein blood flow (IVBF) were observed, respectively. The left ventricular work index (LVWI) was significantly increased by 10% in animals given 20 mg/kg/d Adenosine Triphosphate. In addition, treatment with the higher dose level led to a 12.5% decrease of the spontaneous respiratory frequency. A 26% reduction of lung resistance was noted in all Adenosine Triphosphate -treated groups. Increases of 22 and 23% of Pa_{O2} were observed in rabbits treated with 3 mg/kg/d and 20 mg/kg/d Adenosine Triphosphate, respectively. Similar results were noticed in rabbits treated with adenosine hemisulfate; however, lung resistance and Pa_{O2} levels remained unchanged.

DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Intraperitoneal

Adenosine

Adenosine (50, 100, and 150 mg/kg) was administered intraperitoneally to mice and rats once a day for 5 days.[29] Decreased spermatogenesis and increased numbers of abnormal sperm were noted. No other details regarding this study were provided.

GENOTOXICITY

In Vitro

The genotoxicity studies summarized below are detailed in Table 4.

Adenosine

Adenosine was non-mutagenic in several Ames tests using *Salmonella typhimurium* or *Escherichia coli* at concentrations up to 5000 µg/plate, with and without metabolic activation.[3,35] Adenosine was also non-genotoxic in a Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase (CHO/HGPRT) assay at up to 2000 µg/mL, with and without metabolic activation.[36]

CARCINOGENICITY STUDIES

No data regarding the carcinogenicity of these ingredients were found in the published literature, and unpublished data were not submitted.

OTHER RELEVANT STUDIES

Cytotoxicity

Adenosine

The cytotoxic effect of Adenosine in Swiss albino mouse embryo fibroblasts (3T3 and 3T6) and immortalized cervical cancer (HeLa) cells, cultured with and without adenosine deaminase, was studied.[36] [^{14}C]-Adenosine (0.2 - 2.5 µCi) was diluted with unlabeled Adenosine (to 10^{-5} - 10^{-3} M) in 0.3 mL of a solution containing serum-free medium, 50 mM phosphate buffer, and 10% serum. Both calf and horse serum were used; however, horse serum did not contain adenosine deaminase. Cells were exposed to Adenosine at concentrations of 0, 0.002, 0.005, 0.01, 0.02, 0.20, 1.0, and 2.0 mM, and cultures were observed over a period of 1 week. When Adenosine was added to cell cultures in a medium containing horse serum, it was found to be toxic at low concentrations. In 10% calf serum, there was no effect on cell growth at low or moderate Adenosine concentrations, while in medium containing 10% horse serum, there was definite inhibition of growth at a concentration of 0.005 mM and a killing of cells at 0.02 mM. Cell inhibition in calf serum was observed when Adenosine was used at concentrations of 1.0 mM and higher. When the same experiment was performed with horse serum with the addition of 1mM uridine to the cell culture medium, toxic effects were not observed at any concentration up to 0.2 mM.

Tumor Cell Proliferation

Adenosine

The effects of Adenosine on DNA synthesis and cell growth in human (HT-29, T84, HRT-18, Colo320HSR) and mouse (MCA-38) colorectal carcinoma cell lines were studied.[37] Cells were seeded in 24-well plates at 20,000 cells/well. Adenosine was added at final concentrations of 1 µCi/mL, 1 µM, with [methyl-[^{3}H]-thymidine. Plates were incubated for 36 - 48 hours. DNA synthesis and cell proliferation were stimulated in all cell lines tested, with a half maximal effective concentration (EC_{50}) of 2.8 - 30 µM, and a maximum stimulation being reached at 10 -100 µM.

Effect on Histamine Release

Adenosine Phosphate and Adenosine Triphosphate

Thirty-nine patients with various dermatoses were used in a study evaluating histamine release from human cutaneous mast cells following intracutaneous injection with the polycondensation product of *N*-methyl-*p*-methoxyphenethylamine with formaldehyde (compound 48/80; causes histamine degranulation from mast cells), Adenosine Triphosphate, Adenosine Diphosphate, or Adenosine Phosphate.[38] Solutions of Adenosine Triphosphate (60 mg/mL), Adenosine Diphosphate (30 mg/mL), Adenosine Phosphate (37 mg/mL), and compound 48/80 (1 mg/mL) in distilled water were prepared. The pH of these solutions was adjusted to 7.0 with sodium hydroxide. Subjects were injected with 0.02 mL of each solution. In addition, histamine dihydrochloride was also injected (1, 3, and 10 µg/mL), and used to compare the responses elicited from the test substance. Injections of approximately 6 mg/mL Adenosine Triphosphate caused a flare response similar to that of histamine at less than 10 µg/mL. Adenosine Triphosphate released histamine at concentrations > 1 mg/mL, while compound 48/80 stimulated histamine release in skin at concentrations > 1 µg/mL. Adenosine Diphosphate had a weaker releasing effect, and Adenosine Phosphate did not induce histamine release. In order to determine that the skin reaction was due to released histamine, the study was repeated in 17 subjects with the addition of the antihistamine chlorcyclizine. After administration of the antihistamine and Adenosine Triphosphate, the area of the flare decreased significantly.

Adenosine Phosphate and Adenosine Triphosphate

The effects of intradermal injections of Adenosine Phosphate and Adenosine Triphosphate compared to intradermal injections of histamine were evaluated.[39] The backs of subjects were injected with 50 µL isosmotic phosphate buffered saline containing Adenosine Triphosphate, Adenosine Phosphate, histamine, compound 48/80, or phosphate-buffered saline alone. Injections were carried out in 2.5-minute intervals. The area of erythema induced by the injection was delineated at 30 seconds and after 4.5 minutes. Solutions that were extremely acidic were neutralized with sodium hydroxide prior to injection. Injection of Adenosine Triphosphate resulted in immediate erythematous reaction of the surrounding skin. This reaction faded after one minute, and was replaced by slightly darker erythema that lasted for up to two hours. The extent of these reactions was dose-dependent. No wheals were formed after injection with Adenosine Phosphate or phosphate-buffered saline; however, at doses greater than 30 nmol of Adenosine Triphosphate, wheals were formed. Adenosine Triphosphate produced wheals in 5 out of 7 subjects injected with 10 nmol, and in all subjects at higher doses, in a dose-dependent manner. Wheals that resulted from 1080 nmol Adenosine Triphosphate were approximately equal to wheals due to histamine (1.63 nmol). Injections of Adenosine Triphosphate at high doses produced sensations of persistent pain which was not observed with injection of saline or histamine. In order to evaluate the role of histamine and prostaglandins in the inflammatory response to Adenosine Triphosphate, the study was also performed with the addition of pre-treatment with an antihistamine (diphenhydramine, cimetidine, indomethacin, or doxantrazole). Erythema and wheal responses were significantly suppressed with the addition of diphenhydramine pre-treatment. Indomethacin, doxantrazole, and cimetidine did not alter the Adenosine Triphosphate reaction.

DERMAL IRRITATION AND SENSITIZATION

Irritation

In Vitro

Adenosine

An in vitro skin irritation study was performed using reconstructed human epidermis according to OECD TG 439.[3] Ten mg of Adenosine (in powder form; concentration not provided) were applied to the epidermal surface. (The epidermal surface was first moistened with 5 µL deionized water to improve further contact between powder and epidermis.) Phosphate buffered saline and sodium dodecyl sulfate (5%) were used as the negative and positive controls, respectively. The test substance did not significantly reduce cell viability compared to the negative control. The test substance was predicted to be non-irritating to the skin.

Animal

Adenosine

According to a risk profile from the NFSA, Adenosine was non-irritating to animal skin in multiple conventional tests.[29] No other details regarding these studies were provided.

Human

Adenosine

A 48-hour patch test was performed on 10 subjects.[40] Each subject received an occlusive patch with 15 µL of a cosmetic ingredient containing 0.2% Adenosine on the inside upper arm. Skin reactions were evaluated 1, 24, and 48 hours after patch removal. One hour after patch removal, slight erythema was observed on one volunteer. However, after 24 and 48 hours, no skin reaction was observed in any subject.

Sensitization

Animal

Adenosine

According to a risk profile from the NFSA, Adenosine was non-sensitizing in a Magnusson and Kligman maximization study.[29] No other details regarding this study were provided.

Disodium Adenosine Triphosphate

A Magnusson-Kligman test was performed on Pirbright white guinea pigs (number of animals not stated).[41] The test substance was a trade name mixture containing 15% mannitol and 15% Disodium Adenosine Triphosphate. A 0.5% aqueous dilution of the test substance (i.e., 0.075% mannitol and 0.075% Disodium Adenosine Triphosphate) was used for the intracutaneous induction, and a 10% aqueous dilution of the test substance (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate) was used for the epicutaneous induction and challenge. No signs of irritation or skin reactions indicative of an immune response were observed.

Human

Adenosine

A human repeated insult patch test (HRIPT) was completed in 205 subjects using a test material containing 0.2% Adenosine.[40] Each of the subjects received 0.2 mL of the test substance on the upper back area under a semi-occlusive patch. After a 24-hour exposure period, the patches were removed and sites were evaluated. A series of 9 test patches were applied followed by a two-week non-treatment period. Challenge patches were applied to previously unexposed sites and allowed to remain in skin contact for 24 hours. Challenge sites were scored at 24 and 72 hours post patching. No signs of sensitization were observed.

Disodium Adenosine Triphosphate

An HRIPT was completed on 50 volunteers using a trade name material consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate.[41] A 10% aqueous dilution of the trade name material (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate) was applied to the backs of subjects under an occlusive patch for a total of 9 applications within a 3-week period. A challenge patch was applied two weeks later to the previously exposed area, as well as an unexposed area. Readings were taken 24, 48, and 96 hours after patch removal. No skin reactions were noted in any volunteers.

OCULAR IRRITATION STUDIES

In Vitro

Adenosine

According to a risk profile from the NFSA, Adenosine was slightly irritating to the eyes in an in vitro hen's egg test-chorioallantoic membrane (HET-CAM) assay.[29] No other details were provided for this study.

Animal

Adenosine

A Draize assay was performed on 3 Japanese White rabbits according to OECD TG 405.[3] The test substance, 100 mg undiluted Adenosine, was instilled into the left eye of each animal. The eyes, which were not rinsed, were observed for 21 days. The test substance was considered to be non-irritating to the eye.

PHOTOTOXICITY/PHOTOSENSITIZATION

Human

Disodium Adenosine Triphosphate

A phototoxicity study was conducted with a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate in 10 volunteers.[41] A 10% aqueous solution of the trade name mixture (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate; 0.2 mL) was applied under an occlusive patch to two different areas of the forearm, one irradiated and one non-irradiated. After a 24-hour exposure, one site was irradiated with long-wave ultraviolet (UVA) light (320 - 400 nm) for 15 minutes; the other test site served as a non-irradiated control. Skin reactions were scored immediately after light exposure as well as 24 and 48 hours later. No reactions were noted on either the irradiated or non-irradiated test site in any subject.

A photosensitization test was completed on 34 subjects with a trade name mixture consisting of 15% Mannitol and 15% disodium adenosine triphosphate (i.e., 0.3% mannitol, 0.3% Disodium Adenosine Triphosphate).[41] For three weeks, six 24-hour induction patches were applied containing a 2% aqueous solution of the trade name mixture. Applications were performed in duplicate; one site was subsequently irradiated with UV light (260 - 400 nm) for 15 minutes each session. After 2 weeks, a challenge patch was applied at virgin sites with and without irradiation. At the challenge phase, no skin reactions were exhibited at either the irradiated site or the non-irradiated site.

CLINICAL STUDIES

Effects of Inhalation

Adenosine

The effect of inhaled Adenosine was studied in 8 asthmatic subjects.[42] Before administration of Adenosine, two baseline blood samples were taken, and five baseline measurements of specific airway conductance (SG_{aw}) were made. Volunteers then inhaled a single concentration of Adenosine, ranging from 0.6 to 6.7 mg/mL. The test material was nebulized from a volume of 4 mL in disposable nebulizers driven by compressed air at 8 L/min. Approximately 0.5 mL of the test solution left the nebulizer as an aerosol each minute; 12.5% of this entered the lungs with a mass median particle diameter of 4.5 microns. After inhalation, SG_{aw} and blood sample measurements were taken at 1, 3, 5, 10, 15, 20, 25, and 30 minutes. Significant falls in SG_{aw} from a mean baseline of 0.124 ± 0.024 to 0.046 ± 0.008 and 0.066 ± 0.012 s/cm/H_2O, were observed at 3 and 30 minutes, respectively. Inhalation did not produce significant changes in levels of histamine, neutrophil chemotactic factor, or cyclic adenosine phosphate in the blood.

Adenosine Phosphate and Adenosine Triphosphate

The effects of aerosolized Adenosine Triphosphate and Adenosine Phosphate on dyspnea and airway caliber were studied.[43] The perception of dyspnea quantified by a modified Borg Scale of Perceived Exertion and other symptoms was determined in 10 nonsmokers and 10 patients with asthma. Each subject attended the laboratory on three occasions. The first visit included a screening, recording of medical history, lung function assessment, and skin-prick testing of common aeroallergens. On the second and third visit, subjects were administered either Adenosine Triphosphate or Adenosine Phosphate, in aerosolized form. Before, immediately after, and 30 minutes after the challenge, spirometry was performed, the Borg score was determined, and symptoms other than dyspnea were recorded. In order to determine the Borg scale, subjects were asked to determine the degree of breathlessness they were experiencing on a scale of 0 - 10. For the inhalation challenge tests, Adenosine Triphosphate (0.125 - 512 mg/mL) and Adenosine Phosphate (0.048 - 400 mg/mL) were dissolved in a normal saline solution and administered via a breath-activated dosimeter with an output of 10 µL per inhalation. Participants wore a nose clip and inhaled 5 breaths of the normal saline solution, followed by sequential doubling concentrations of either Adenosine Triphosphate or Adenosine Phosphate. Subjects who were healthy nonsmokers did experience dyspnea when given Adenosine Triphosphate or Adenosine Phosphate. All patients with asthma experienced dyspnea when given Adenosine Triphosphate, and 90% of patients with asthma experienced dyspnea when given Adenosine Phosphate. The geometric mean provocative dose (PD_{20}) in responsive subjects was 26.9 mg/mL and 39.6 mg/mL for Adenosine Triphosphate and Adenosine Phosphate, respectively. In patients with asthma, the perception of dyspnea assessed by the Borg score increased from 0.1 to 3.3 and 0.2 to 2.5 after Adenosine Triphosphate and Adenosine Phosphate, respectively. Eighty percent of subjects coughed after the Adenosine Triphosphate challenge, whereas 40% of subjects coughed after the Adenosine Phosphate challenge. Throat irritation was noted after the Adenosine Triphosphate and Adenosine Phosphate challenge in 70% and 35% of subjects, respectively.

A different study was performed to evaluate whether inhaled Adenosine Triphosphate or Adenosine Phosphate produces a tussive response, and whether chronic cough patients are hypersensitive to these ingredients compared to healthy volunteers.[44] All participants received two cumulative cough challenges, one with Adenosine Triphosphate and one with Adenosine Phosphate. Saline (0.9%) was used as the solvent for both Adenosine Phosphate and Adenosine Triphosphate. The two challenges were administered on two different days, at least 48 hours apart. Each volunteer started with a saline inhalation, followed by Adenosine Triphosphate or Adenosine Phosphate delivered in increasing concentrations on a half-log scale from 0.1 to 300 mM. The number of coughs produced in the first 15 seconds after inhalation were counted. The

challenge was terminated once the volunteer coughed at least five times (C5), or the maximum concentration was inhaled. Two out of 19 healthy patients coughed with Adenosine Phosphate, none reaching C5. Eighteen out of 20 volunteers coughed after administration of Adenosine Triphosphate, with 15 reaching C5. Eight out of 20 chronic cough patients coughed with Adenosine Phosphate, two reaching C5. Eighteen of 19 chronic cough patients reached C5 after inhalation of Adenosine Triphosphate. The C5 in chronic cough patients was predominately distributed between 1 mM and 100 mM, as all patients who reached C5, did so by a concentration of 100 mM.

SUMMARY

The safety of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate as used in cosmetics is reviewed in this CIR safety assessment. According to the *Dictionary*, these ingredients are reported to function as skin-conditioning agents – miscellaneous.

According to 2019 VCRP survey data, Adenosine, Adenosine Phosphate, Adenosine Triphosphate, and Disodium Adenosine Triphosphate are reported to be used in 737, 98, 41, and 111 formulations, respectively. The results of the concentration of use survey conducted by the Council indicate that Adenosine has the highest concentration of use in a leave-on formulation; it is used at up to 1% in body and hand products. Disodium Adenosine Phosphate is not reported to be in use.

In an in vitro study, Adenosine in various vehicles was observed for penetration ability in human skin. The observed optimal K_ps of Adenosine from a binary vehicle (propionic and hexanoic acid), propionic acid solution, and hexanoic acid solution were 0.004, 0.012, and 0.016 cm/min, respectively. According to a risk profile from the NFSA, a cream containing Adenosine at low concentrations would be absorbed by the skin at a maximum of 2%.

Wistar rats were given 10 mg/kg [^{14}C]-Adenosine Phosphate dissolved in 9% aqueous sodium chloride via gavage. Within 72 hours of administration, 28% of the injected activity was excreted in the urine and 6% was recovered in the feces. Eight volunteers were given singles doses of 5000 mg Adenosine Triphosphate or placebo via an ingested pellet targeted at release in the proximal or distal small intestine, or via a naso-duodenal tube. Concentrations of uric acid were significantly increased compared to placebo after administration via proximal-release pellets and naso-duodenal tube, but not after administration via distal-release pellets.

No treatment-related symptoms other than pale kidneys were observed when Wistar rats were given 2000 mg/kg bw Adenosine in methylcellulose. In a different study, the reported LD_{50} of Adenosine in mice was > 2000 mg/kg. The acute oral LD_{50} of Adenosine Triphosphate was reported to be > 2 g/kg in rats. No changes in diastolic aortic pressure, heart rate, central venous pressure, IVBF, lung resistance, or Pa_{O2} were observed in New Zealand White rabbits given a single dose of up to 20 mg/kg Adenosine Triphosphate orally. An oral LD_{50} of > 2 g/kg was reported for both mice and rats for Disodium Adenosine Triphosphate in two different studies.

In a short-term toxicity study, New Zealand White rabbits were given doses of either 3 mg/kg/d or 20 mg/kg/d Adenosine Triphosphate mixed with cellulose, or 20 mg/kg/d adenosine hemisulfate salt, for 14 days. The LVWI was significantly increased by 10% in animals given 20 mg/kg/d Adenosine Triphosphate. In addition, treatment with the highest dose level led to a 12.5% decrease of the spontaneous respiratory frequency. A 26% reduction of lung resistance was noted in all Adenosine Triphosphate -treated groups. Increases of 22 and 23% of Pa_{O2} were observed in rabbits treated with 3 mg/kg/d and 20 mg/kg/d Adenosine Triphosphate, respectively.

In a reproductive study, Adenosine (50, 100, and 150 mg/kg) administered intraperitoneally in mice and rats cause decreased spermatogenesis and an increased number of abnormal sperm.

No genotoxicity was reported when Adenosine was used on *S. typhimurium* and *E. coli* at up to 5000 µg/plate in Ames assays performed with and without metabolic activation. Adenosine was non-genotoxic in CHO/HGRPT assays at up to 2000 µg/mL, with and without metabolic activation.

The cytotoxic effects of Adenosine in Swiss albino mouse embryo 3T3 and 3T6 and in HeLa cells cultured with and without adenosine deaminase were studied. Cells were exposed to Adenosine at concentrations of 0, 0.002, 0.005, 0.01, 0.02, 0.20, 1.0, and 2.0 mM. When Adenosine was added to cell cultures in a medium containing horse serum (does not contain adenosine deaminase), it was found to be toxic at low concentrations. Cell inhibition in calf serum was observed when Adenosine was used at concentrations of 1.0 mM and higher.

The effect of Adenosine on DNA synthesis and cell growth in human HT-29, T84, HRT-18, and Colo320HSR and mouse MCA-38 cell lines was studied. Adenosine was added with methyl-[^{3}H]-thymidine (final concentrations, 1 µCi/mL, 1 µM). DNA synthesis and cell proliferation were stimulated in all cell lines tested, with an EC_{50} of 2.8 - 30 µM, and a maximum stimulation was reached at 10 - 100 µM.

Thirty-nine patients with various dermatoses were used in a study evaluating histamine release from human cutaneous mast cells following intracutaneous injection with 48/80 (1 mg/mL water), Adenosine Triphosphate (60 mg/mL water), Adenosine Diphosphate (30 mg/mL water), or Adenosine Phosphate (37 mg/mL water). In addition, 3 concentrations of histamine dihydrochloride were also injected (1, 3, and 10 µg/mL), and used to compare the responses elicited from the test substance. Injection of Adenosine Triphosphate in the skin caused a response similar to that of histamine, but high concentrations of

ATP were needed to elicit this response. Adenosine Triphosphate released histamine in concentrations > 1 mg/mL, while 48/80 stimulated histamine release in skin in concentrations > 1 µg/mL.

The effects of intradermal injections of Adenosine Phosphate and Adenosine Triphosphate compared to intradermal injections of histamine were evaluated. The backs of volunteers were injected with 50 µL isosmotic phosphate buffered saline containing Adenosine Triphosphate, Adenosine Phosphate, histamine, compound 48/80, or saline. Adenosine Triphosphate produced wheals in 5 out of 7 subjects injected with 10 nmol, and in all subjects at higher doses, in a dose-dependent manner. Wheals that resulted from 1080 nmol Adenosine Triphosphate were approximately equal to wheals due to histamine (1.63 nmol). Injections of Adenosine Triphosphate at high doses produced sensations of persistent pain which was not observed with injection of saline or histamine.

Adenosine (10 mg) was considered to be non-irritating in an in vitro skin irritation study performed using reconstructed human epidermis, according to OECD TG 439. According to a risk profile from the NFSA, Adenosine was non-irritating to animal skin in multiple conventional tests. According to the same risk profile, Adenosine was considered to be non-sensitizing to the skin. A 48-hour patch test performed using 0.2% Adenosine on 10 subjects yielded negative results. Negative results were also observed in an HRIPT performed on 205 subjects using the same test substance. A trade name material consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate was used in different aqueous dilutions in a Magnusson-Kligman maximization test (0.075% mannitol and 0.075% Disodium Adenosine Triphosphate (challenge); 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate (induction)) and HRIPT (1.5% mannitol, 1.5% Disodium Adenosine Triphosphate). No signs of sensitization were observed in either study.

Adenosine was slightly irritating to the eyes in a HET-CAM assay, and was considered to be non-irritating to rabbit eyes in a different study.

A phototoxicity and photosensitization study was performed with a trade name mixture consisting of 15% mannitol and 15% Disodium Adenosine Triphosphate. The test substances were applied at 10% (i.e., 1.5% mannitol, 1.5% Disodium Adenosine Triphosphate and 2% (i.e., 0.3% mannitol, 0.3% Disodium Adenosine Triphosphate) aqueous dilutions in the phototoxicity and photosensitization studies, respectively. No skin reactions were noted in either study.

The effect of inhaled Adenosine (0.6 to 6.7 mg/mL) was studied in 8 asthmatic subjects. Significant falls in SG_{aw} from a mean baseline of 0.124 ± 0.024 to 0.046 ± 0.008 and 0.066 ± 0.012 s/cm/H_2O were observed at 3 and 30 minutes, respectively. Inhalation did not produce significant changes in levels of histamine, neutrophil chemotactic factor, or cyclic adenosine phosphate in the blood.

The effects of aerosolized Adenosine Triphosphate and Adenosine Phosphate on dyspnea and airway caliber were studied. The PD_{20} was 26.9 mg/mL and 39.6 mg/mL for Adenosine Triphosphate and Adenosine Phosphate, respectively, in responsive subjects. The perception of dyspnea assessed by the Borg score increased from 0.1 to 3.3 and 0.2 to 2.5 after Adenosine Triphosphate and Adenosine Phosphate, respectively, in patients with asthma. In a different study, two out of 19 healthy patients coughed after inhalation of Adenosine Phosphate, none reaching C5. Two out of 18 volunteers coughed after administration of Adenosine Triphosphate, with 15 reaching C5. Eight out of 20 chronic cough patients coughed with Adenosine Phosphate, two reaching C5. Eighteen of 19 chronic cough patients reached C5 after inhalation of Adenosine Triphosphate.

DISCUSSION

To be formulated.

CONCLUSION

To be determined.

TABLES

Table 1. Definitions, structures, and functions of adenosine ingredients.[1, CIR Staff]

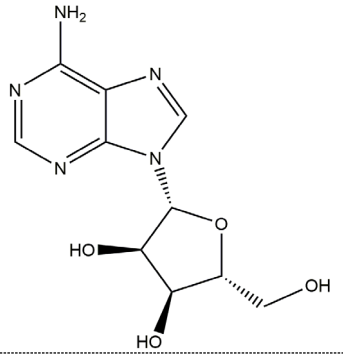
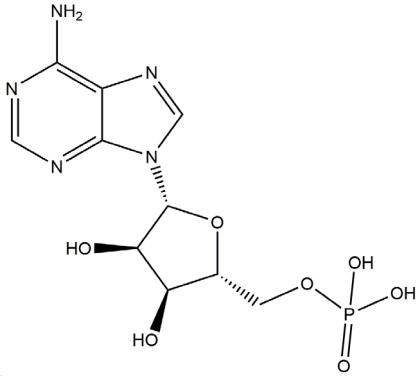
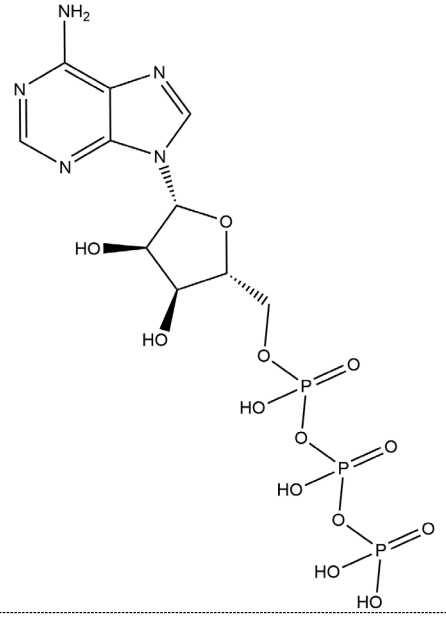
Ingredient	Definition	Function
Adenosine (58-61-7)	Adenosine is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous
Adenosine Phosphate (61-19-8)	Adenosine Phosphate is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous
Adenosine Triphosphate (56-65-5)	Adenosine Triphosphate is the organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous

Table 1. Definitions, structures, and functions of adenosine ingredients.[1, CIR Staff]

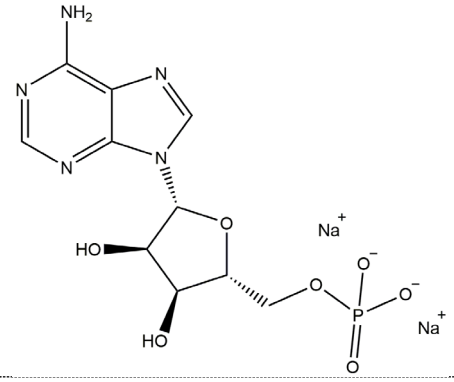
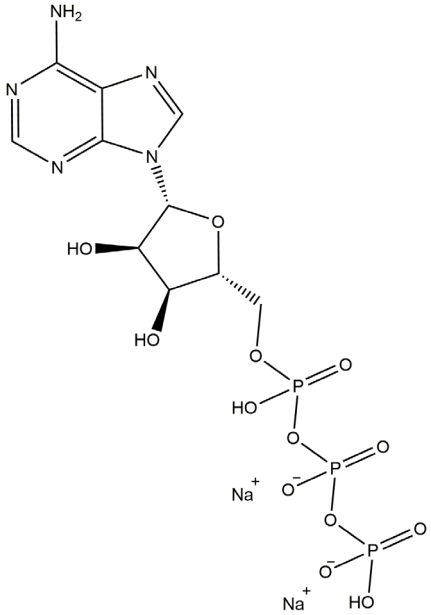
Ingredient	Definition	Function
Disodium Adenosine Phosphate (4578-31-8)	Disodium Adenosine Phosphate is the disodium salt of Adenosine Phosphate 	Skin-Conditioning Agents – Miscellaneous
Disodium Adenosine Triphosphate (987-65-5)	Disodium Adenosine Triphosphate is the disodium salt of Adenosine Triphosphate 	Skin-Conditioning Agents – Miscellaneous

Table 2. Chemical Properties of the Adenosine ingredients in this safety assessment

Property	Value	Reference
Adenosine		
Physical Form	Crystalline powder	45
Color	White	45
Odor	Odorless	46
Molecular Weight (g/mol)	267.25	47
Vapor pressure (mmHg @ 25 ºC)	6.0×10^{-15}	48
Melting Point (ºC)	235.5	49
Water Solubility (g/L @ 25 ºC)	5.1	49
log K_{ow}	-1.05	49
Adenosine Phosphate		
Physical Form	Solid	50
Molecular Weight (g/mol)	347.22	47
Melting Point (ºC)	195	50
Water Solubility (g/L)	3.31	51
log K_{ow}	-3.1	51
Adenosine Triphosphate		
Physical Form	Solid	52
Molecular Weight (g/mol)	507.18	47
Water Solubility (g/L)	1000	53
Disodium Adenosine Phosphate		
Formula Weight (g/mol)	391.19	47
Disodium Adenosine Triphosphate		
Formula Weight (g/mol)	551.15	47

Table 3. Frequency and concentration of use[9,10]

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Adenosine		Adenosine Phosphate		Adenosine Triphosphate	
Totals*	**737**	**0.04 - 1**	**98**	**0.001 – 0.5**	**41**	**NR**
Duration of Use						
Leave-On	*710*	*0.04 – 1*	*83*	*0.0048 – 0.5*	35	*NR*
Rinse-Off	*27*	*0.041*	*15*	*0.001 – 0.04*	6	*NR*
Diluted for (Bath) Use	*NR*	*NR*	*NR*	*NR*	NR	*NR*
Exposure Type						
Eye Area	80	0.041	12	0.04 – 0.5	2	NR
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	269[a]; 222[b]	0.04 – 0.041	1; 12[a]; 54[b]	0.04; 0.11[b]	8[a]; 17[b]	NR
Incidental Inhalation-Powder	269[a]	0.1; 0.04 – 1[c]	12[a]	0.058[c]	8[a]	NR
Dermal Contact	732	0.04 - 1	70	0.001 – 0.058	34	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	2	NR	27	0.0095 – 0.11	1	NR
Hair-Coloring	NR	NR	NR	NR	NR	NR
Nail	NR	NR	NR	NR	6	NR
Mucous Membrane	3	NR	NR	NR	NR	NR
Baby Products	NR	NR	NR	NR	NR	NR

	Disodium Adenosine Triphosphate	
Totals*	**111**	**0.003 – 0.1**
Duration of Use		
Leave-On	*95*	*0.003 – 0.1*
Rinse Off	*16*	*0.003 – 0.005*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	10	0.003
Incidental Ingestion	NR	NR
Incidental Inhalation-Spray	39[a]; 41[b]	NR
Incidental Inhalation-Powder	39[a]	0.003[c]
Dermal Contact	111	0.003 – 0.1
Deodorant (underarm)	NR	NR
Hair - Non-Coloring	NR	0.005
Hair-Coloring	NR	NR
Nail	NR	NR
Mucous Membrane	3	NR
Baby Products	NR	NR

*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] Not specified whether a spray or a powder, but it is possible the use can be as a spray or a powder, therefore the information is captured in both categories
[b] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders
NR – no reported use

Table 4. Genotoxicity studies

Test Article	Concentration/Dose	Vehicle	Test System	Procedure	Results	Reference
IN VITRO						
Adenosine	3.3 – 333 µg/plate	NR	*S. typhimurium* (TA 98 and TA 100)	Ames assay without metabolic activation	Non-genotoxic	54
Adenosine	0 - 5000 µg/plate	DMSO	*S. typhimurium* TA 97, TA98, TA100, TA1535, TA1537, TA 1538 and *E. coli* WP2 uvrA	Ames assay with and without metabolic activation	Non-genotoxic	3
Adenosine	25 – 2000 µg/mL	DMSO	Chinese hamster ovary (CHO-KL-BH4)	CHO/HGPRT assay with and without metabolic activation	Non-genotoxic	35

NR = Not Reported; DMSO = Dimethyl sulfoxide; CHO/HGPRT = Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase

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2019 FDA Frequency of Use:

Adenosine (737)

03D - Eye Lotion	58617	43
03G - Other Eye Makeup Preparations	58617	37
05I - Other Hair Preparations	58617	2
07C - Foundations	58617	24
07E - Lipstick	58617	1
07F - Makeup Bases	58617	2
07I - Other Makeup Preparations	58617	6
09A - Dentifrices	58617	1
10C - Douches	58617	1
11A - Aftershave Lotion	58617	1
11G - Other Shaving Preparation Products	58617	1
12A - Cleansing	58617	7
12C - Face and Neck (exc shave)	58617	259
12D - Body and Hand (exc shave)	58617	10
12F - Moisturizing	58617	186
12G - Night	58617	33
12H - Paste Masks (mud packs)	58617	17
12I - Skin Fresheners	58617	3
12J - Other Skin Care Preps	58617	103

Adenosine Phosphate (98)

03D - Eye Lotion	61198	8
03F - Mascara	61198	1
03G - Other Eye Makeup Preparations	61198	3
04E - Other Fragrance Preparation	61198	1

05A - Hair Conditioner	61198	6
05F - Shampoos (non-coloring)	61198	6
05G - Tonics, Dressings, and Other Hair Grooming Aids	61198	14
05I - Other Hair Preparations	61198	1
07I - Other Makeup Preparations	61198	1
12C - Face and Neck (exc shave)	61198	10
12D - Body and Hand (exc shave)	61198	2
12F - Moisturizing	61198	32
12G - Night	61198	8
12H - Paste Masks (mud packs)	61198	3
12J - Other Skin Care Preps	61198	2

Adenosine Triphosphate (41)

03D - Eye Lotion	56655	1
03G - Other Eye Makeup Preparations	56655	1
05G - Tonics, Dressings, and Other Hair Grooming Aids	56655	1
08A - Basecoats and Undercoats	56655	1
08E - Nail Polish and Enamel	56655	4
08G - Other Manicuring Preparations	56655	1
12A - Cleansing	56655	2
12C - Face and Neck (exc shave)	56655	6
12D - Body and Hand (exc shave)	56655	2
12F - Moisturizing	56655	10
12G - Night	56655	3
12H - Paste Masks (mud packs)	56655	4
12I - Skin Fresheners	56655	1
12J - Other Skin Care Preps	56655	2
13B - Indoor Tanning Preparations	56655	1
13C - Other Suntan Preparations	56655	1

Disodium Adenosine Triphosphate (111)

03D - Eye Lotion	987655	7
03E - Eye Makeup Remover	987655	2
03G - Other Eye Makeup Preparations	987655	1
10A - Bath Soaps and Detergents	987655	1
10E - Other Personal Cleanliness Products	987655	2
12A - Cleansing	987655	10
12C - Face and Neck (exc shave)	987655	31
12D - Body and Hand (exc shave)	987655	8
12F - Moisturizing	987655	30
12G - Night	987655	3
12H - Paste Masks (mud packs)	987655	1
12I - Skin Fresheners	987655	2
12J - Other Skin Care Preps	987655	7
13A - Suntan Gels, Creams, and Liquids	987655	4
13B - Indoor Tanning Preparations	987655	1
13C - Other Suntan Preparations	987655	1

Disodium Adenosine Phosphate (0)

Concentration of Use by FDA Product Category – Adenosine Ingredients*

Adenosine
Adenosine Phosphate
Adenosine Triphosphate
Disodium Adenosine Phosphate
Disodium Adenosine Triphosphate

Ingredient	Product Category	Maximum Concentration of Use
Adenosine	Eye lotions	0.041%
Adenosine	Face powders	0.1%
Adenosine	Foundations	0.04%
Adenosine	Other makeup preparations	0.041%
Adenosine	Face and neck products Not spray	 0.04-0.041%
Adenosine	Body and hand products Not spray	 1%
Adenosine	Moisturizing products Not spray Spray	 0.1% 0.04-0.041%
Adenosine	Night products Not spray	 0.041%
Adenosine	Paste masks and mud packs	0.041%
Adenosine	Other skin care preparations	0.04-0.044%
Adenosine	Suntan products Not spray	 0.04%
Adenosine Phosphate	Eye lotions	0.04%
Adenosine Phosphate	Mascaras	0.5%
Adenosine Phosphate	Hair conditioners	0.01%
Adenosine Phosphate	Hair sprays Aerosol	 0.04%
Adenosine Phosphate	Shampoos (noncoloring)	0.0095%
Adenosine Phosphate	Tonics, dressings and other hair grooming aids	0.11%
Adenosine Phosphate	Foundations	0.015%
Adenosine Phosphate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.04%
Adenosine Phosphate	Face and neck products Not spray	 0.058%
Adenosine Phosphate	Paste masks and mud packs	0.001%
Adenosine Phosphate	Suntan products Not spray	 0.0048%
Disodium Adenosine Triphosphate	Eye lotions	0.003%
Disodium Adenosine Triphosphate	Hair conditioners	0.005%
Disodium Adenosine Triphosphate	Shampoos (noncoloring)	0.005%
Disodium Adenosine Triphosphate	Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.003%
Disodium Adenosine Triphosphate	Face and neck products	

	Not spray	0.003%
Disodium Adenosine Triphosphate	Other skin care preparations	0.1%

*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: May 31, 2018

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: June 19, 2019

SUBJECT: Mannitol and Disodium Adenosine Triphosphate

Anonymous. 2019. Summary of studies of a trade name mixture containing: 15% Mannitol and 15% Disodium Adenosine Triphosphate.

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

June 2019

Summary of Studies of a Trade Name Mixture Containing: 15% Mannitol and 15% Disodium Adenosine Triphosphate

Phototoxicity

A phototoxicity study (completed in 1993) was conducted with the trade name mixture (10% aqueous solution of the mixture [1.5% Mannitol, 1.5% Disodium Adenosine Triphosphate]) in 10 volunteers. The test item (0.2 ml) was applied under occlusive conditions to two different areas of the forearm, one designated as non-irradiated, the other as the irradiated test site. After a 24-hour exposure, one treated site was irradiated with UVA light (320-400 nm) for 15 minutes. The other site served as the non-irradiated control. Skin reactions were scored immediately after light exposure as well as 24 and 48 hours later.

Results: No reactions were noted on either the irradiated or non-irradiated test material contact site in any subject.

Skin Sensitization

Guinea Pig Maximization Test

In a study completed in 1992, a test according to the Magnusson Kligman method was completed with the trade name mixture in male and female albino guinea pigs (strain Pirbright white). Concentrations were 0.5% (w/w) (0.075% Mannitol and 0.075% Disodium Adenosine Triphosphate) in adjuvant and water, and 10% in water (w/v) (1.5% Mannitol, 1.5% Disodium Adenosine Triphosphate) for the intracutaneous induction, and epicutaneous induction and challenge, respectively.

Results: No signs of irritation and skin reactions indicative of an immune response were seen at the readings 24 and 48 hours after removal of the challenge patch

Human Repeated Insult Patch Test

In a study completed in 1992, a 10% aqueous solution of the trade name material (1.5% Mannitol, 1.5% Disodium Adenosine Triphosphate) was repeatedly applied (total of 9 applications within 3 weeks) for 24 hours under occlusive conditions to the backs of 52 volunteers during the induction phase. The challenge took place two weeks later with the same concentration and the same area as well as a naïve site of the back. Readings were taken 24 hours after removal of the patches during induction, as well as 48 and 96 hours after removal of the challenge patches.

Results: Among the 50 volunteers completing the study, no skin reactions were noted during both induction and challenge.

Photosensitization

A photosensitization test (completed in 1994) with the trade name mixture (2% solution in water [0.3% Mannitol, 0.3% Disodium Adenosine Triphosphate]) was conducted on 36 volunteers. For 3 weeks, 6 induction patches with the test item were applied in duplicate to the same site of the skin for 24 hours each time, one site subsequently irradiated with UV light (260-400 nm) for 15 minutes each session,

while the other site was left non-irradiated. After two weeks, the challenge patch was applied at virgin sites with and without irradiation.

Results: At the challenge phase, no skin reactions were exhibited on either the irradiated or the non-irradiated test material contact site. No reactions were observed on the irradiated or non-irradiated control site of the 34 individuals completing the study.

Personal Care Products Council
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Memorandum

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

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

DATE: August 2, 2019

SUBJECT: Adenosine

Anonymous. 2019. Summaries of studies on adenosine.

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

August 2019

Summaries of Studies on Adenosine

Forty-eight Hour Patch Test (completed in 2015)
In a 48-hour patch test completed by 10 human subjects, a cosmetic ingredient containing 0.2% adenosine did not indicate a potential for dermal irritation.

Each of 10 human subjects received an occlusive patch with 15 µl of 100% cosmetic ingredient containing 0.2% adenosine to the inside upper arm for 48 hours. The skin reaction was observed 1h, 24h and 48h after patch removal and the clinical examination was conducted by the trained expert. One hour after patch removal, a slight erythema (intensity 1) was observed on one volunteer. However, 24h and 48h after patch removal, no skin reaction such as irritation (erythema and edema) was observed on the volunteers on the patch area. The results were considered negative from the assessment of the clinical observation by the trained expert and volunteers. Therefore, it can be concluded that throughout the test, the cosmetic ingredient containing 0.2% adenosine was well tolerated on the skin.

Human Repeated Insult Patch Test (HRIPT) (completed in 2016)
In an HRIPT completed by 205 human subjects, a cosmetic ingredient containing 0.2% adenosine demonstrated no potential for dermal irritation or allergic contact sensitization.

Each of 205 human subjects received 0.2 ml of 100% cosmetic ingredient containing 0.2% adenosine on the upper back area (semi-occlusive patch). Following a 24-hour exposure period, test patches were removed and sites scored for erythema and edema. A series of nine induction patches was applied three times a week for three weeks. Following a two-week rest period, challenge patches were applied to a virgin site on the back and allowed to remain in skin contact for 24 hours. Challenge sites were scored for erythema and edema at 24 and 72 hours post patching. Under the conditions of the study, the cosmetic ingredient containing 0.2% adenosine indicated no potential for dermal irritation or allergic contact sensitization.

Personal Care Products Council
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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: June 25, 2019

SUBJECT: Scientific Literature Review: Safety Assessment of Adenosine Ingredients as Used in Cosmetics (release date May 31, 2019)

The Personal Care Products Council (PCPC) has no suppliers listed for Disodium Adenosine Phosphate.

The Council respectfully submits the following comments on the scientific literature review, Safety Assessment of Adenosine Ingredients as Used in Cosmetics.

Key Issue

As Adenosine and Adenosine Triphosphate are used as drugs, it would be helpful to include information about the doses and routes of administration. Information about the kinetics of the drugs should also be added to the ADME section. For example, PubChem indicates that the plasma half-life of Adenosine is less than 10 seconds.

Additional Considerations

Introduction - The normal presence of these ingredients in living organisms should reduce concerns regarding systemic toxicity no matter the route of exposure, not just mitigate safety concerns following oral exposure as stated in the Introduction.

Cosmetic Use - Please provide a reference for the European Union Inventory of cosmetic ingredients. An update of the inventory was recently published and can be found at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32019D0701&from=EN

Dermal Penetration, In Vitro; Summary - The abstract of reference 26 indicates that the K_p values were 0.4×10^{-3}, 0.12×10^{-3}, and 0.16×10^{-3}, or 0.0004, 0.00012 and 0.00016 cm/min; not 0.004, 0.0012 and 0.0016 cm/min as stated in the Scientific Literature Review.

Short-Term - Please define "IVBF"

Clinical Studies, Effects of Inhalation - It would be helpful to state at the beginning of the description of the study what was measured in the blood.