
Safety Assessment of Adenosine Ingredients as Used in Cosmetics

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All interested persons are provided 60 days from the above release date (July 30, 2019) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included. Information may be submitted without identifying the source or the trade name of the cosmetic product containing the ingredient. All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a peer-reviewed scientific journal. Please submit data, comments, or requests to the CIR Executive Director, Dr. Bart Heldreth.

The 2019 Cosmetic Ingredient Review Expert Panel members are: Chair, Wilma F. Bergfeld, M.D., F.A.C.P.; Donald V. Belsito, M.D.; Ronald A. Hill, Ph.D.; Curtis D. Klaassen, Ph.D.; Daniel C. Liebler, Ph.D.; James G. Marks, Jr., M.D., Ronald C. Shank, Ph.D.; Thomas J. Slaga, Ph.D.; and Paul W. Snyder, D.V.M., Ph.D. The CIR Executive Director is Bart Heldreth, Ph.D. This safety assessment was prepared by Priya Cherian, Scientific Analyst/Writer.

INTRODUCTION

This scientific literature review is the initial step in preparing 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, significant safety concern following oral exposure is mitigated. This safety assessment focuses predominantly on the chemistry and exposure of these adenosine ingredients as they are used in cosmetics.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated.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.

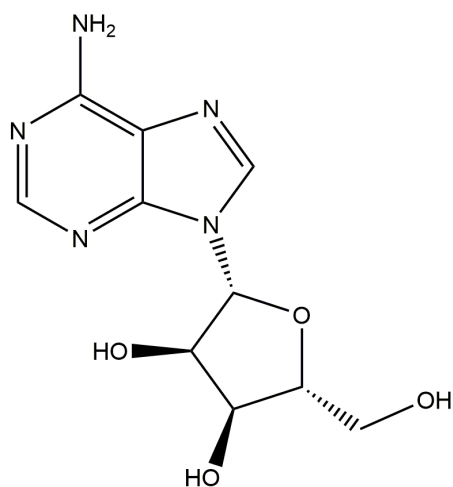


Figure 1. Adenosine

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

These ingredients are solids at room temperature and are soluble in water. Available information of the physical and chemical properties of adenosine, phosphates, and phosphate salts thereof 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.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.

Non-Cosmetic

Medicine

Adenosine

According to the 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.¹⁸ 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.^{19,20}

Adenosine Phosphate and Adenosine Triphosphate

Adenosine Phosphate is used in the therapeutic treatment of herpes, post-herpetic neuralgia, photosensitivity, and porphyria cutanea tarda.²¹⁻²³ 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 Triphosphate

Adenosine Triphosphate is given orally and intravenously to treat acute kidney failure, high blood pressure, cystic fibrosis, and lung cancer.^{24,25}

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.²⁶ 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 0.004, 0.012, and 0.016 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%.²⁷

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.²⁸ 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 single 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.²⁹ 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 acute oral toxicity study on Adenosine was performed on 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. An LD_{50} of greater than 2000 mg/kg bw was also reported in a different study involving mice given Adenosine orally.²⁷ No other details regarding this study were provided.

Adenosine Triphosphate

The oral LD_{50} of Adenosine Triphosphate was reported to be > 2 g/kg in rats.³⁰ 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.³¹ The test substance did not have an effect on diastolic aortic pressure, heart

rate, central venous pressure, iliac venous blood flow (IVBF), lung resistance, or the arterial partial pressure of oxygen (PaO₂).

Disodium Adenosine Triphosphate

An oral LD₅₀ of > 2 g/kg was reported for both mice and rats in two different studies.³² 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.³¹ 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 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 PaO₂ 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 PaO₂ 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.²⁷ 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.^{33,34} 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.

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 cervical cancer (HeLa) cells, cultured with and without adenosine deaminase, was studied.³⁵ [¹⁴C]-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.³⁶ Cells were seeded in 24-well plates at 20,000 cells/well. Adenosine was added at final concentrations of 1 μ Ci/mL, 1 μ M, with [methyl-³H]-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 (EC₅₀) of 2.8 - 30 μ M, and a maximum stimulation being reached at 10 -100 μ M.

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.³⁷ 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 μ g/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 μ g/mL. Adenosine Triphosphate released histamine in concentrations > 1 mg/mL, while compound 48/80 stimulated histamine release in skin in concentrations > 1 μ g/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.³⁸ The backs of subjects were injected with 50 μ L 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 extents of these reactions were 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 milligrams of Adenosine (in powder form; concentration not provided) was applied to the epidermal surface. (The epidermal surface was first moistened with 5 μ L 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 the skin in multiple conventional tests.²⁷ No other details regarding these studies were provided.

Sensitization

In Vitro

Animal

Adenosine

According to a risk profile from the NFSA, Adenosine was non-sensitizing in a Magnusson and Kligman maximization study.²⁷ No other details regarding this study were provided.

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.²⁷ 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. They eyes, which were not rinsed, were observed for 21 days. The test substance was considered to be non-irritating to the eye.

CLINICAL STUDIES

Effects of Inhalation

Adenosine

The effect of inhaled Adenosine was studied in 8 asthmatic subjects.³⁹ 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/H₂O, 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.⁴⁰ The perception of dyspnea quantified by a modified Borg score 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, Borg score was determined, and symptoms other than dyspnea were recorded. In order to determine the Borg score, 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, whereas 90% of patients with asthma experienced dyspnea when given Adenosine Phosphate. The geometric mean provocative dose (PD₂₀) 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.⁴¹ 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.

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 [¹⁴C]-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 single 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 LD₅₀ of Adenosine in mice was > 2000 mg/kg. The acute oral LD₅₀ 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 PaO₂ were observed in New Zealand White rabbits given a single dose of up to 20 mg/kg Adenosine Triphosphate orally. An oral LD₅₀ 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 PaO₂ 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 effect of Adenosine in Swiss albino mouse embryo fibroblasts (3T3 and 3T6) and cervical cancer (HeLa) cells cultured with and without adenosine deaminase was 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, Colo320HSR) and mouse (MCA-38) colorectal carcinoma cell lines was studied. Adenosine was added with methyl-[³H]-thymidine (final concentrations, 1 μ Ci/mL, 1 μ M). DNA synthesis and cell proliferation was stimulated in all cell lines tested, with an EC₅₀ of 2.8 - 30 μ M, and a maximum stimulation was reached at 10 - 100 μ M.

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 μ g/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 μ g/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 microliters 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 the skin in multiple conventional tests. According to the same risk profile, Adenosine was considered to be non-sensitizing to the skin and slightly irritating to the eyes when used in a HET-CAM assay. In an in vivo ocular irritation study, Adenosine was considered to be non-irritating.

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/H₂O 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 PD₂₀ 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.

INFORMATION SOUGHT

The CIR is seeking the following information on Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate:

- Dermal absorption data; if absorbed, other studies may be requested
- Skin irritation and sensitization data at concentration of use
- Ocular irritation data, if available, at concentration of use

TABLES

Table 1. Definitions, structures, and functions of adenosine ingredients.^{1, CIR Staff}

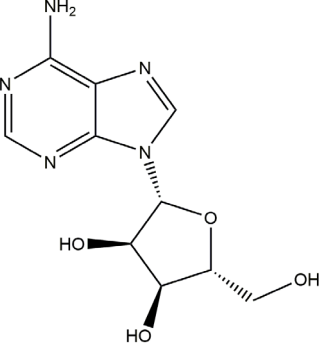
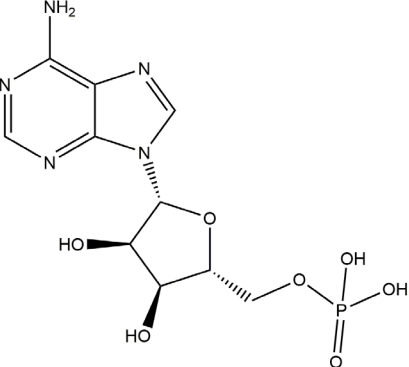
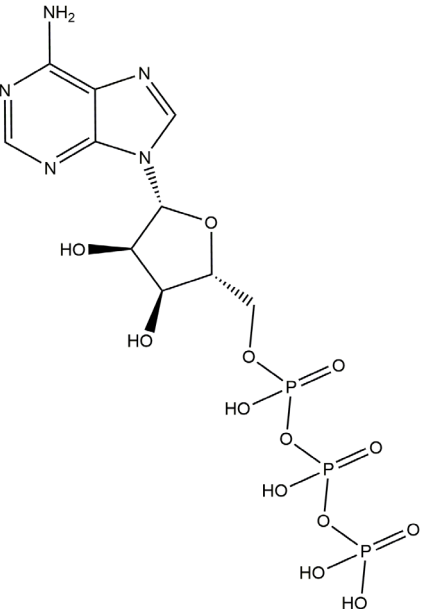
Ingredient	Definition	Function
Adenosine (58-61-7)	Adenosine is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous
Adenosine Phosphate (61-19-8)	Adenosine Phosphate is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning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

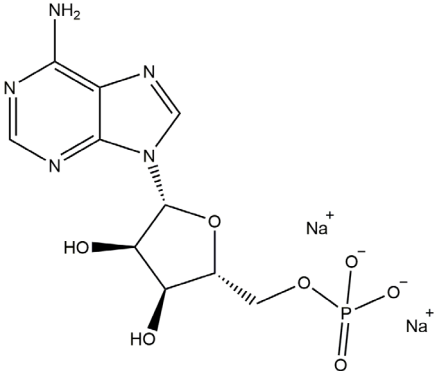
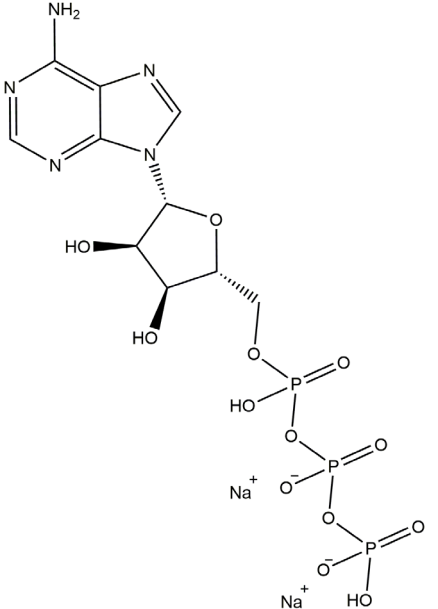
Ingredient	Definition	Function
Disodium Adenosine Phosphate (4578-31-8)	Disodium Adenosine Phosphate is the disodium salt of Adenosine Phosphate  <p>The structure shows the adenosine moiety (adenine base attached to a ribose sugar) linked to a phosphate group. The phosphate group is shown as a phosphorus atom double-bonded to one oxygen and single-bonded to three others, two of which are negatively charged and associated with sodium ions (Na+).</p>	Skin-Conditioning Agents – Miscellaneous
Disodium Adenosine Triphosphate (987-65-5)	Disodium Adenosine Triphosphate is the disodium salt of Adenosine Triphosphate  <p>The structure shows the adenosine moiety (adenine base attached to a ribose sugar) linked to a triphosphate chain. The triphosphate chain consists of three phosphate groups connected in series. The terminal phosphate group is shown with two negatively charged oxygens, each associated with a sodium ion (Na+).</p>	Skin-Conditioning Agents – Miscellaneous

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

Property	Value	Reference
Adenosine		
Physical Form	Crystalline powder	42
Color	White	42
Odor	Odorless	43
Molecular Weight (g/mol)	267.25	44
Vapor pressure (mmHg @ 25 °C)	6.0×10^{-15}	45
Melting Point (°C)	235.5	46
Water Solubility (g/L @ 25 °C)	5.1	46
log K _{ow}	-1.05	46
Adenosine Phosphate		
Physical Form	Solid	47
Molecular Weight (g/mol)	347.22	44
Melting Point (°C)	195	47
Water Solubility (g/L)	3.31	48
log K _{ow}	-3.1	48
Adenosine Triphosphate		
Physical Form	Solid	49
Molecular Weight (g/mol)	507.18	44
Water Solubility (g/L)	1000	50
Disodium Adenosine Phosphate		
Formula Weight (g/mol)	391.19	44
Disodium Adenosine Triphosphate		
Formula Weight (g/mol)	551.15	44

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	<i>S. typhimurium</i> (TA 98 and TA 100)	Ames assay without metabolic activation	Non-genotoxic	33
Adenosine	0 - 5000 µg/plate	DMSO	<i>S. typhimurium</i> TA 97, TA98, TA100, TA1535, TA1537, TA 1538 and <i>E. coli</i> 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	34

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

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