
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 (i.e., August 17, 2020) to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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.

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ABSTRACT

The Expert Panel for Cosmetic Ingredient Safety (Panel) assessed the safety of Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate. These ingredients are reported to function as skin-conditioning agents – miscellaneous. The Panel considered the available data and concluded that the five adenosine ingredients reviewed in this report are safe in cosmetics in the present practices of use and concentration described in this safety assessment.

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 being reviewed together due to their structurally similarities.

This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that the Panel typically evaluates, is provided on the Cosmetic Ingredient Review (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 Unpublished data are provided by the cosmetics industry, as well as by other interested parties.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.² 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 (CAS No. 58-61-7; Figure 1) as the core structure.

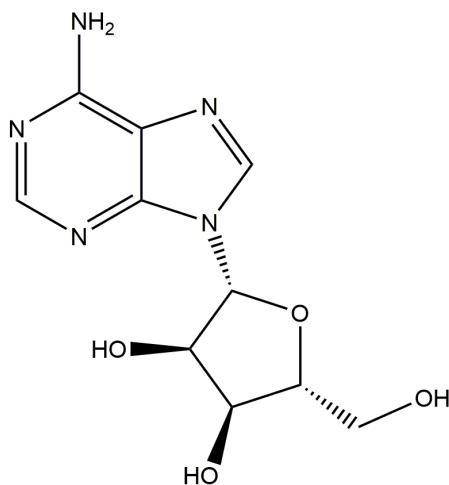


Figure 1. Adenosine

Adenosine Triphosphate (ATP; CAS No. 56-65-5) is composed of a purine nucleoside esterified with a triphosphate.³ Adenosine Triphosphate is a ubiquitous organophosphate that connects anabolism and catabolism, but also fuels processes such as motile contraction, phosphorylations, and active transport.⁴ Both Adenosine and Adenosine Phosphate (AMP; CAS No. 61-19-8) are formed when Adenosine Triphosphate is consumed in metabolic processes. Adenosine, a ribonucleoside comprising adenine and ribose, exerts pleiotropic functions throughout the body, primarily by interaction with G-protein coupled receptors.⁵ Adenosine Phosphate is an ester of phosphoric acid and Adenosine. Like Adenosine Triphosphate, Adenosine Phosphate plays an important role in many cellular metabolic processes, and is an intermediate in the synthesis of nucleic acids.

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.⁶ *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.⁷

Impurities

Adenosine

A supplier reported that Adenosine has a purity of $\geq 99\%$.⁸

Adenosine Triphosphate

A supplier reported the following impurities for Adenosine Triphosphate: $< 2\%$ Adenosine Phosphate, $< 2\%$ Adenosine diphosphate, and $< 0.01\%$ methanol.⁹

Disodium Adenosine Triphosphate

Disodium Adenosine Triphosphate used in a trade name mixture sold to the cosmetic industry was reported to be free from carcinogens, mutagens, and reproductive toxicants (CMR) as defined by European Union (EU) chemical regulations, and from phthalates, pesticides, and glycol ether.¹⁰ Additional details were not provided.

USE

Cosmetic

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

According to 2020 VCRP survey data, Adenosine has the highest frequency of use, with a total of 905 formulations (Table 3).¹¹ Adenosine is most commonly used in face and neck products (313 formulations) and moisturizing products (262 formulations). Disodium Adenosine Triphosphate is reported to be used in 116 formulations, 100 of which are leave-on formulations. The remaining in-use ingredients are reported to be used at 96 formulations or less. The results of the concentration of use survey conducted by the Council indicate that Adenosine has the highest concentration of use; it is used at up to 1% in body and hand products.¹² 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 0.5% Adenosine Phosphate in mascara). In addition, Adenosine could result in incidental ingestion as it is used in lipstick and dentifrices (concentrations of use 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 $> 10 \mu\text{m}$, with propellant sprays yielding a greater fraction of droplets/particles $< 10 \mu\text{m}$ compared with pump sprays.^{13,14} 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.^{15,16} Adenosine is reported to be 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.¹⁷⁻¹⁹

All of the adenosine ingredients named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.²⁰

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.²¹ Adenosine is typically given intravenously at a dose of 3 mg/mL.²² 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.^{23,24}

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.²⁵⁻²⁷ Adenosine Triphosphate has been previously reported to treat acute kidney failure, high blood pressure, cystic fibrosis, and lung cancer.^{28,29}

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.³⁰ 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 min, 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 a low concentration of Adenosine to skin (thickness of 2 mg/cm²) would result in absorption of up to 2% Adenosine.³¹

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 [¹⁴C]-Adenosine Phosphate dissolved in 9% aqueous sodium chloride via gavage.³² The specific activity of the [¹⁴C]-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 min 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.³³ 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 min) as compared to the pellet administration (150 - 390 min).

TOXICOLOGICAL STUDIES

Acute Toxicity Studies

Oral

Adenosine

An LD₅₀ of > 2000 mg/kg bw was established for mice given Adenosine orally.³¹ No other details regarding this study were provided.

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) 423.² 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 LD₅₀ was reported to be > 2000 mg/kg bw.

Adenosine Triphosphate

The oral LD₅₀ of Adenosine Triphosphate was reported to be > 2000 mg/kg in rats.³⁴ 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.³⁵ 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 (PaO₂).

Disodium Adenosine Triphosphate

An oral LD₅₀ of > 2000 mg/kg was reported for both mice and rats treated with Disodium Adenosine Triphosphate.³⁶ 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 (n = 12) Adenosine Triphosphate mixed with cellulose, or 20 mg/kg/d adenosine hemisulfate salt (n = 4) for 14 days.³⁵ 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 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.³¹ Decreased spermatogenesis and increased numbers of abnormal sperm were noted. No other details regarding this study were provided.

GENOTOXICITY

In Vitro

Adenosine

The potential mutagenicity of Adenosine (up to 333 µg/plate, vehicle not stated), was evaluated in *Salmonella typhimurium* (TA98, TA 100) in an Ames assay performed without metabolic activation.³⁷ The test material was considered to be non-genotoxic. Similarly, negative results were obtained in an Ames assay performed with and without metabolic activation on Adenosine in dimethyl sulfoxide (DMSO; up to 5000 µg/plate) using *S. typhimurium* (TA97, TA98, TA100, TA1535, TA1537, TA1538) and *Escherichia coli* (WP2 uvrA).²

The genotoxicity of Adenosine was also evaluated in a Chinese hamster ovary cell/hypoxanthine-guanine phosphoribosyl-transferase (CHO/HGPRT) assay.³⁸ Adenosine in DMSO was not genotoxic when tested 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 immortalized cervical cancer (HeLa) cells, cultured with and without adenosine deaminase, was studied.³⁹ [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.⁴⁰ 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-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 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.⁴¹ 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 < 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.

The effects of intradermal injections of Adenosine Phosphate and Adenosine Triphosphate, as compared to intradermal injections of histamine, were evaluated.⁴² 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-min intervals. The area of erythema induced by the injection was delineated at 30 seconds and after 4.5 min. 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 min, and was replaced by slightly darker erythema that lasted for up to 2 hours. The extent of these reactions was dose-dependent. No wheals were formed after injection with Adenosine Phosphate or phosphate-buffered saline. Adenosine Triphosphate produced wheals in 5 out of 7 subjects injected with 180 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 either 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 439.² 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 contact between the powder and the 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.³¹ No other details regarding these studies were provided.

Human

Adenosine

A 48-hour patch test was performed on 10 subjects.⁴³ 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.³¹ 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).⁴⁴ 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.⁴³ 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 2-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.⁴⁴ 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 2 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.

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.⁴⁴ 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 min; 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.⁴⁴ For 3 weeks, six 24-hour induction patches were applied containing a 2% aqueous solution (i.e., 0.3% mannitol, 0.3% Disodium Adenosine Triphosphate) of the trade name mixture. Applications were performed in duplicate; one site was subsequently irradiated with UV light (260 - 400 nm) for 15 min 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.

OCULAR IRRITATION STUDIES

In Vitro

Adenosine

According to a risk profile from the NFSA, Adenosine was predicted to be slightly irritating to the eyes in an in vitro hen's egg test-chorioallantoic membrane (HET-CAM) assay.³¹ No other details were provided for this study.

Animal

Adenosine

A Draize assay was performed on 3 Japanese White rabbits according to OECD TG 405.² 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.

CLINICAL STUDIES

Effects of Inhalation

Adenosine

The effect of inhaled Adenosine was studied in 8 asthmatic subjects.⁴⁵ 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 sample 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 min. 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/cm²/water, were observed at 3 and 30 min, 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.⁴⁶ 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 min 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.⁴⁷ 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.

Adenosine Triphosphate in Resistance-Trained Athletes

Adenosine Triphosphate

The effect of Adenosine Triphosphate in resistance-trained athletes was investigated in a 12-week, 3-phase randomized, double-blind, and placebo- and diet-controlled intervention.⁴⁸ Phase 1 consisted of a periodized resistance-training program. Phase 2 was a 2-week overreaching cycle in which volume and frequency were increased, followed by a 2-week taper (Phase 3). Biochemical parameters were evaluated on weeks 0, 4, 8 and 12 to assess the chronic effects of the test substance. Twenty-four males were randomly assigned to receive either 400 mg/day of Adenosine Triphosphate or maltodextrin (placebo), consumed orally via a two-piece gelatin capsule 30 minutes prior to resistance training sessions. On non-training days, participants were instructed to consume one dose on an empty stomach prior to breakfast. No statistically or clinically significant changes in blood chemistry or hematology were observed. No adverse effects were reported in this study.

SUMMARY

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

According to 2020 VCRP survey data, Adenosine, Adenosine Phosphate, Adenosine Triphosphate, and Disodium Adenosine Triphosphate are reported to be used in 905, 96, 42, and 116 formulations, respectively. The results of the concentration of use survey conducted by the Council indicate that Adenosine has the highest concentration of use; it is used at up to 1% in body and hand products. Disodium Adenosine Phosphate is not reported to be in use.

The penetration ability of Adenosine in different vehicles was evaluated in human skin. The observed optimal $K_{p,s}$ 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 low concentrations of Adenosine would result in an absorption of up to 2% Adenosine.

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 were observed when Wistar rats were orally given 2000 mg/kg bw Adenosine in methylcellulose, however, pale kidneys were observed in all females in one group given 2000 mg/kg Adenosine. In a different study, the reported oral LD_{50} of Adenosine in mice was > 2000 mg/kg. The acute oral LD_{50} of Adenosine Triphosphate was reported to be > 2000 mg/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 LD₅₀ of > 2000 mg/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. Administrations occurred via gastric cannula. 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.

Adenosine was non-genotoxic in Ames assays performed with and without metabolic activation on *S. typhimurium* and *E. coli* at up to 5000 µg/plate. Adenosine was also non-genotoxic in a CHO/HGRPT assay 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-[³H]-thymidine (final concentrations, 1 µCi/mL, 1 µM). DNA synthesis and cell proliferation were stimulated in all cell lines tested, with an EC₅₀ of 2.8 - 30 µM, and a maximum stimulation was reached at 10 - 100 µM.

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 180 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 of guinea pigs. 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.

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.

Adenosine was predicted to be slightly irritating to the eyes in a HET-CAM assay. It was considered to be non-irritating to rabbit eyes in a different 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/water were observed at 3 and 30 min, 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.

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 only at high concentrations. Adenosine Triphosphate released histamine at concentrations > 1 mg/mL, while 48/80 stimulated histamine release in skin at concentrations > 1 µg/mL.

The effect of orally ingested Adenosine Triphosphate (400 mg/day) in resistance-trained athletes was evaluated over a 12-week period. No significant changes in blood chemistry or hematology were observed, and no adverse effects were reported.

DISCUSSION

The ingredients reviewed in this document are naturally-occurring, ubiquitous chemicals. Because the noted, safe use of these ingredients in the diet and in therapeutics results in significantly greater systemic exposures than could be possible from cosmetic use, the concern for systemic toxicity is mitigated. The Panel determined that the available human sensitization data on Disodium Adenosine Triphosphate and Adenosine can be used as read-across sources to mitigate any concerns for the ingredients lacking these data. The safety of these ingredients was further supported by low concentrations of use, sufficient impurities data, negative animal oral toxicity assays, and human clinical studies.

The Panel discussed the issue of incidental inhalation exposure from powders and hair sprays. The Council survey results indicate that Adenosine is being used in face powders at concentrations up to 0.1%. In addition, Adenosine is used in spray moisturizing products at up to 0.041%, and Adenosine Phosphate is used at up to 0.04% in hair sprays. The Panel noted that in aerosol products, 95% – 99% of droplets/particles would not be respirable to any appreciable amount. Furthermore, droplets/particles deposited in the nasopharyngeal or bronchial regions of the respiratory tract present no toxicological concerns based on the chemical and biological properties of these ingredients. Coupled with the small actual exposure in the breathing zone and the concentrations at which the ingredients are used, the available information indicates that incidental inhalation would not be a significant route of exposure that might lead to local respiratory or systemic effects. A detailed discussion and summary of the Panel's approach to evaluating incidental inhalation exposures to ingredients in cosmetic products is available at <https://www.cir-safety.org/cir-findings>.

CONCLUSION

The Expert Panel for Cosmetic Ingredient Safety concluded that Adenosine, Adenosine Phosphate, Adenosine Triphosphate, Disodium Adenosine Phosphate, and Disodium Adenosine Triphosphate are safe in cosmetics in the present practices of use and concentrations described in the safety assessment.

TABLES

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

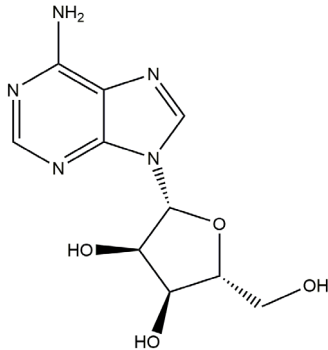
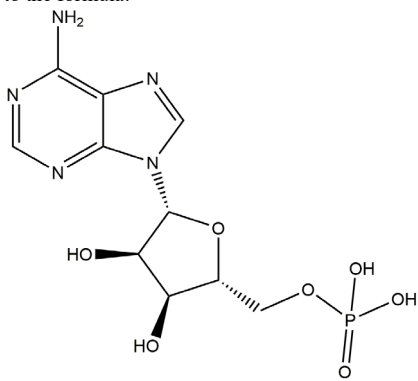
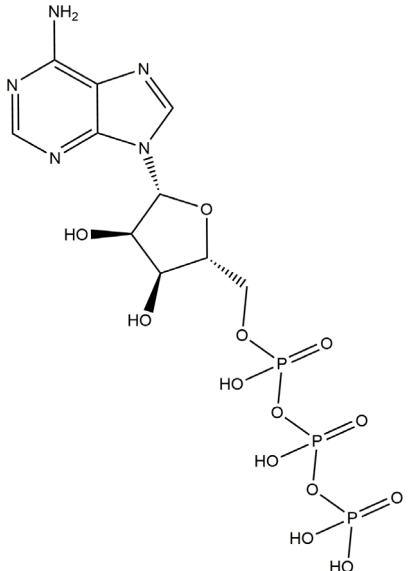
Ingredient	Definition	Function
Adenosine (58-61-7)	Adenosine is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning Agents – Miscellaneous
Adenosine Phosphate (61-19-8)	Adenosine Phosphate is the heterocyclic organic compound that conforms to the formula: 	Skin-Conditioning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

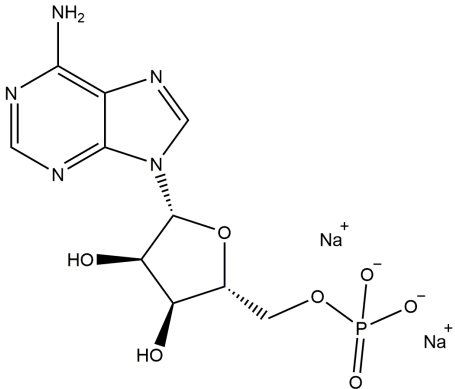
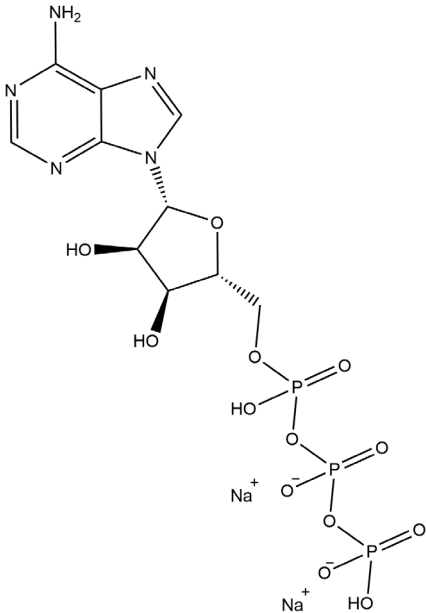
Ingredient	Definition	Function
Disodium Adenosine Phosphate (4578-31-8)	Disodium Adenosine Phosphate is the disodium salt of Adenosine Phosphate  <p>The structure shows the adenosine moiety (adenine base attached to a ribose sugar) linked to a phosphate group. The phosphate group is shown as a phosphorus atom double-bonded to one oxygen and single-bonded to three others, two of which carry a negative charge. Two sodium ions (Na+) are shown nearby to indicate the disodium salt form.</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 chain consists of three phosphate groups connected in series. The terminal phosphate has a hydroxyl group and a negative charge. The middle phosphate has a negative charge. The terminal phosphate has a hydroxyl group and a negative charge. Two sodium ions (Na+) are shown to indicate the disodium salt form.</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	49
Color	White	49
Odor	Odorless	50
Molecular Weight (g/mol)	267.25	51
Vapor pressure (mmHg @ 25 °C)	6.0×10^{-15}	52
Melting Point (°C)	235.5	53
Water Solubility (g/L @ 25 °C)	5.1	53
log K _{ow}	-1.05	53
Λ_{\max} (@ pH = 7.0; nm)	14.6 – 15.2 nm	8
Adenosine Phosphate		
Physical Form	Solid	54
Molecular Weight (g/mol)	347.22	51
Melting Point (°C)	195	54
Water Solubility (g/L)	3.31	55
log K _{ow}	-3.1	55
Adenosine Triphosphate		
Physical Form	Solid	56
Molecular Weight (g/mol)	507.18	51
Water Solubility (g/L)	1000	57
Disodium Adenosine Phosphate		
Formula Weight (g/mol)	391.19	51
Disodium Adenosine Triphosphate		
Formula Weight (g/mol)	551.15	51

Table 3. Frequency and concentration of use^{11,12}

	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)	# of Uses	Max Conc of Use (%)
	Adenosine		Adenosine Phosphate		Adenosine Triphosphate	
Totals*	905	0.04 - 1	96	0.001 - 0.5	42	NR
Duration of Use						
<i>Leave-On</i>	868	0.04 - 1	81	0.0048 - 0.5	35	NR
<i>Rinse-Off</i>	37	0.041	15	0.001 - 0.04	7	NR
<i>Diluted for (Bath) Use</i>	NR	NR	NR	NR	NR	NR
Exposure Type						
Eye Area	87	0.041	12	0.04 - 0.5	2	NR
Incidental Ingestion	2	NR	NR	NR	NR	NR
Incidental Inhalation-Spray	326 ^a ; 301 ^b	0.04 - 0.041	1; 10 ^a ; 54 ^b	0.04; 0.11 ^b	8 ^a ; 17 ^b	NR
Incidental Inhalation-Powder	326 ^a	0.1; 0.04 - 1 ^c	10 ^a	0.058 ^c	8 ^a	NR
Dermal Contact	897	0.04 - 1	68	0.001 - 0.058	35	NR
Deodorant (underarm)	NR	NR	NR	NR	NR	NR
Hair - Non-Coloring	5	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*	116	0.003 - 0.1				
Duration of Use						
<i>Leave-On</i>	100	0.003 - 0.1				
<i>Rinse Off</i>	16	0.003 - 0.005				
<i>Diluted for (Bath) Use</i>	NR	NR				
Exposure Type						
Eye Area	11	0.003				
Incidental Ingestion	NR	NR				
Incidental Inhalation-Spray	41 ^a ; 43 ^b	NR				
Incidental Inhalation-Powder	41 ^a	0.003 ^c				
Dermal Contact	116	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

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