# Safety Assessment of Sodium Hyaluronate Crosspolymers as Used in Cosmetics

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*All interested persons are provided 60 days from the above release date (i.e., **May 25, 2026**) to comment on this safety assessment, and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available for review by any interested party, and may be cited in a peer-reviewed scientific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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## ABBREVIATIONS

| | |
|---|---|
| BDDE | 1,4-butanediol diglycidyl ether |
| CCK-8 | cell counting kit-8 |
| CIR | Cosmetic Ingredient Review |
| Council | Personal Care Products Council |
| *Dictionary* | *International Cosmetic Ingredient Dictionary* |
| FDA | Food and Drug Administration |
| HAM | hyaluronic acid membrane |
| HCEC | human corneal epithelial cells |
| L929 | murine fibroblast cells |
| LDH | lactate dehydrogenase |
| l.o. | leave-on |
| LPS | lipopolysaccharide |
| MoCRA | Modernization of Cosmetics Regulation Act of 2022 |
| MC3T3-E1 | mouse pre-osteoblastic cells |
| MTT | 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide |
| NR | not reported |
| Panel | Expert Panel for Cosmetic Ingredient Safety |
| RLD | Registration and Listing Data |
| r.o. | rinse-off |
| US | United States |

## INTRODUCTION

This assessment reviews the safety of the following 6 ingredients as used in cosmetic formulations:

| | |
|---|---|
| Sodium Hyaluronate Crosspolymer | Sodium Hyaluronate Crosspolymer-4 |
| Sodium Hyaluronate Crosspolymer-2 | Sodium Hyaluronate Crosspolymer-6 |
| Sodium Hyaluronate Crosspolymer-3 | Sodium Hyaluronate Crosspolymer-7 |

According to the *International Cosmetic Ingredient Dictionary* (*Dictionary*), all of these ingredients are reported to function as skin conditioning agents in cosmetic products, with the exception of Sodium Hyaluronate Crosspolymer-2, which is reported to function as a humectant (Table 1).[1] The ingredients above are all sodium salts of either hyaluronic acid or a polymer of hyaluronic acid before being crosslinked.

The Expert Panel for Cosmetic Ingredient Safety (Panel) has reviewed the safety of hyaluronic acid and sodium hyaluronate. In the original review of hyaluronic acid, potassium hyaluronate, and sodium hyaluronate that was published in 2009, the Panel concluded that these ingredients are safe in the present practices of use and concentration, as described in the safety assessment.[2] In 2023, a re-review was conducted for hyaluronic acid, potassium hyaluronate, and sodium hyaluronate with the addition of hydrolyzed calcium hyaluronate, hydrolyzed hyaluronic acid, hydrolyzed sodium hyaluronate, and sodium acetylated hyaluronate.[3] The Panel concluded that these ingredients are also safe in the present practices of use and concentration, as described in the safety assessment.

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 extensive search of the world's literature; a search was last conducted March 2026. 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.

## CHEMISTRY

### Definition and Structure

The definitions and idealized structures of the ingredients included in this review are provided in Table 1. According to the *Dictionary*, each of these ingredients share the same polyhyaluronate salt backbone and differ only by the crosslinker (i.e., vinyl sulfone for Sodium Hyaluronate Crosspolymer; diglycidyl ether for Sodium Hyaluronate Crosspolymer-2; propylbisoxyamine for Sodium Hyaluronate Crosspolymer-3; 1,4-butanediol diglycidyl ether for Sodium Hyaluronate Crosspolymer-4; PEG-9 diglycidyl ether for Sodium Hyaluronate Crosspolymer-6; and sodium trimetaphosphate for Sodium Hyaluronate Crosspolymer-7).[1] Hyaluronic acid is a linear mucopolysaccharide (glycosaminoglycan) comprising disaccharide repeat units of *N*-acetyl-D-glucosamine and D-glucuronic acid; sodium hyaluronate is the sodium salt thereof and serves as the monomer for the polyhyaluronate salt backbone in these ingredients. Crosslinking of these linear polymers results in a 3D network.

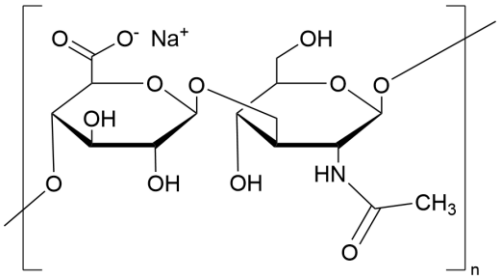



**Figure 1.** Sodium hyaluronate polymer backbone.[CIR Staff]

### Chemical Properties

Sodium Hyaluronate Crosspolymer (CAS No. 105524-32-1) is reported to be a colorless to slightly yellow clear viscous liquid.[4] No further details were provided. Chemical properties were not found in the published literature on the other sodium hyaluronate crosspolymer ingredients, and unpublished data were not submitted.

### Method of Manufacture

Methods of manufacture data, specific to the cosmetics industry, were not found in the published literature, and unpublished data were not submitted. However, manufacture of these same chemicals for use as soft-tissue fillers is documented in the published literature.[5,6]

### Impurities

According to a specification, the heavy metal content of Sodium Hyaluronate Crosspolymer is not to exceed 10 ppm.[4] No further details were provided. For the purification of soft-tissue fillers comprising hyaluronate crosspolymers, dialysis is a common technique. [5]

## USE

### Cosmetic

The safety of the cosmetic ingredient/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 sodium hyaluronate crosspolymers in cosmetics. Registration and Listing Data (RLD) obtained from the FDA report frequency of use, and responses to a survey conducted by the Personal Care Products Council (Council) indicate maximum reported concentrations of use; it is these values that define the present practices of use and concentration that are assessed by the Panel. Since 2024, as a result of the Modernization of Cosmetics Regulation Act of 2022 (MoCRA), manufacturers and processors are required to register facilities and list their products (and ingredients therein) with the FDA (i.e., RLD). An exception is made for small businesses (average gross annual sales in the US of cosmetic products for the previous 3-yr period is less than $1,000,000, adjusted for inflation), which are exempt from MoCRA reporting for most cosmetic product categories. Eye area products, injected products, internal use products, or products that alter appearance for more than 24 h, and the facilities that manufacture these products, are not included in this exemption.[7] Another change resulting from MoCRA is the addition of tattoo preparations (permanent tattoo inks, temporary tattoo inks, and other tattoo products) to the product categories for which companies need to list their products with FDA. However, evaluating the safety of ingredients as used in tattoo preparations is not within the purview of the Panel; accordingly, such use is not included as part of the present practices of use that are assessed by the Panel.

According to RLD obtained from the FDA in 2025, Sodium Hyaluronate Crosspolymer has the most reported uses at 5396 formulations. (Table 2).[8,9] The results of the concentration of use survey conducted by the Council in 2025 indicated that Sodium Hyaluronate Crosspolymer also had the highest reported concentration of use, resulting in leave-on exposure at 0.47% in non-spray face and neck products and moisturizing products.[10] Sodium Hyaluronate Crosspolymer-2 and Sodium Hyaluronate Crosspolymer-3 did not have any concentrations of use reported. The concentration of use survey by the Council for Sodium Hyaluronate Crosspolymer-4, Sodium Hyaluronate Crosspolymer-6 and Sodium Hyaluronate Crosspolymer-7 is being conducted, and the results will be added once received.

Some ingredients in this report are used in products that are applied near the eye, that can be incidentally ingested, and are used near mucous membranes. For example, Sodium Hyaluronate Crosspolymer has been used in eye lotions (concentrated of use not reported), lipsticks and lip glosses at up to 0.00035%, and in bath soaps and body washes at up to 0.0000007%.

These ingredients may be used in sprays and powder. For example, Sodium Hyaluronate Crosspolymer is used in hair sprays (concentration of use not reported) and face powders (concentration of use not reported). In practice, as stated in the Panel's respiratory exposure resource document (https://www.cir-safety.org/cir-findings), most droplets/particles incidentally inhaled from cosmetic sprays would be deposited in the nasopharyngeal and tracheobronchial regions and would not be respirable (i.e., they would not enter the lungs) to any appreciable amount. 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.

With the advent of MoCRA and the current product categories outlined therein, it is now mandatory that cosmetic products used in airbrush delivery systems be reported as such for some, but not all, product categories in the RLD. In other words, a reliable source of frequency of use data regarding the use of cosmetic ingredients in conjunction with airbrush delivery systems is now available in some instances. Additionally, the concentration of use surveys are conducted based on the same product categories as identified in the RLD. Based on RLD, some products containing Sodium Hyaluronate Crosspolymer are marketed for use with airbrush delivery systems. However, no consumer habits and practices data or particle size data are publicly available to evaluate the exposure associated with this use type, thereby preempting the ability to evaluate risk or safety. Without information regarding the consumer habits and practices data or product particle size data (or other relevant particle data, e.g., diameter) related to this use technology, the data profile is incomplete, and the Panel is not able to determine safety for use in airbrush formulations. Accordingly, the data are insufficient to evaluate the exposure resulting from cosmetics applied via airbrush delivery systems.

The sodium hyaluronate crosspolymers named in this report are not restricted from use in any way under the rules governing cosmetic products in the European Union.[11]

### Non-Cosmetic

The FDA lists hyaluronic acid, as an "absorbable (temporary) material" that is often crosslinked before being used as a dermal filler.[12] There is published literature available on hydrogels with a similar composition to Sodium Hyaluronate Crosspolymer-4 (hyaluronic acid crosslinked with 1,4-butanediol diglycidyl ether (BDDE)) with use found in soft tissue

fillers.[5] Currently, the hydrogels are also being researched for use as a vitreous substitute and for wound healing applications.[13,14]

## TOXICOKINETIC STUDIES

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

## TOXICOLOGICAL STUDIES

Acute and repeated-dose toxicity studies were not found in the published literature, and unpublished data were not submitted.

## DEVELOPMENTAL AND REPRODUCTIVE TOXICITY STUDIES

Developmental and reproductive toxicity studies were not found in the published literature, and unpublished data were not submitted.

## GENOTOXICITY STUDIES

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

## CARCINOGENICITY STUDIES

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

## OTHER RELEVANT STUDIES

### Cytotoxicity

Sodium Hyaluronate Crosspolymer-4

The cytotoxicity studies summarized below are described in Table 3.

A hyaluronic acid membrane (HAM) was developed with the same crosslinker as Sodium Hyaluronate Crosspolymer-4 (i.e., BDDE).[15] The cell viability of a primary culture of human corneal epithelial cells (HCECs) was assessed through cell counting kit-8 (CCK-8) analysis. The HCECs were incubated with the HAM for 12, 24, and 48 h. At 48 h, there was an increase of cell viability of 50% and the cells expressed more MK167, a cellular marker for proliferation. A hyaluronic acid hydrogel crosslinked with BDDE was incubated with mouse pre-osteoblastic cells (MC3T3-E1) at 0.1 ml for 24 h.[16] The MC3T3-E1 cells were assessed through CCK-8 analysis to test cell viability and a lactate dehydrogenase (LDH) assay to measure cytotoxicity. The hyaluronic acid-BDDE crosslinked hydrogel had a cell viability of 105% (control was 100%) and was slightly more cytotoxic than the control, but the difference was not statistically significant. Multiple biphasic gel formulations were created with 5 - 15% (w/w) citric acid – hyaluronic acid content.17 From the formulations, only the steam-sterilized biphasic gel formulation containing 6% hyaluronic acid crosslinked with BDDE and 12% citric acid-hyaluronic acid non-crosslinked was evaluated using a 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay in L929 mouse fibroblast cells for 24 h. There was no adverse effect on cell viability detected.

### Immunotoxicity

Sodium Hyaluronate Crosspolymer-4

Crosslinked hyaluronic acid products utilizing BDDE, the same crosslinker used in Sodium Hyaluronate Crosspolymer-4, were evaluated in six mice with a lipopolysaccharide (LPS)-induced low-grade inflammatory phenotype.[18] LPS (5 µg/ml) l9was also used as a positive control at 20 µl. The mice received an acute intradermal injection of 20 µl of the vehicle control (inactivated hyaluronidase), VYC-15L (low and high molecular weight hyaluronic acid crosslinked with BDDE), VYC-15L fragments, HYC-24L+ (high molecular weight hyaluronic acid crosslinked with BDDE), or HYC-24L+ fragments. The fragments treatments were degraded. After 24 h, the mouse skin was examined microscopically. The VYC-15L and VYC-15L fragments had moderate inflammation. HYC-24L+ and its fragments induced less inflammation, and the vehicle control produced minimal inflammation.

## DERMAL IRRITATION AND SENSITIZATION STUDIES

Dermal irritation and sensitization studies were not found in the published literature, and unpublished data were not submitted.

## OCULAR IRRITATION STUDIES

Ocular irritation studies were not found in the published literature, and unpublished data were not submitted.

## SUMMARY

The assessment reviews the safety of the following 6 sodium hyaluronate crosspolymer ingredients as used in cosmetic formulations: Sodium Hyaluronate Crosspolymer, Sodium Hyaluronate Crosspolymer-2, Sodium Hyaluronate Crosspolymer-3, Sodium Hyaluronate Crosspolymer-4, Sodium Hyaluronate Crosspolymer-6 and Sodium Hyaluronate Crosspolymer-7. These ingredients are reported to function in cosmetics as humectants and skin conditioning agents.

According to RLD obtained from the FDA in 2025, Sodium Hyaluronate Crosspolymer is the ingredient in this group with the most reported uses at 5396 formulations. The results of the concentration of use survey conducted by the Council in 2025 indicated that Sodium Hyaluronate Crosspolymer also had the highest reported concentration of use resulting in leave-on exposure in 2025 at 0.47% in leave-on face and neck products (not spray) and in moisturizing products (not spray). Sodium Hyaluronate Crosspolymer-2 and Sodium Hyaluronate Crosspolymer-3 did not have any concentration of use reported. The concentration of use survey by the Council for Sodium Hyaluronate Crosspolymer-4, Sodium Hyaluronate Crosspolymer-6 and Sodium Hyaluronate Crosspolymer-7 is being conducted, and the results will be added once received.

A HAM was developed with the same crosslinker as Sodium Hyaluronate Crosspolymer-4 (i.e., BDDE). The cell viability of a primary culture of HCECs was assessed through CCK-8 analysis. The HCECs were incubated with the HAM for 12, 24, and 48 h. At 48 h, there was an increase of cell viability of 50% and the cells expressed more MK167, a cellular marker for proliferation. A hyaluronic acid hydrogel crosslinked with BDDE was incubated with MC3T3-E1 cells for at 0.1 ml for 24 h. The MC3T3-E1 cells were assessed through CCK-8 analysis to test cell viability and an LDH assay to measure cytotoxicity. The HA-BDDE crosslinked hydrogel had a cell viability of 105% (control was 100%) and was slightly more cytotoxic than the control, but the difference was not statistically significant. Multiple biphasic gel formulations were created with 5-15% (w/w) citric acid – hyaluronic acid content. From the formulations, only the steam-sterilized biphasic gel formulation containing 6% hyaluronic acid crosslinked with BDDE and 12% citric acid-hyaluronic acid non-crosslinked was evaluated using a MTT assay using L929 cells for 24 h. There was no adverse effect on cell viability detected.

A group of six mice with a LPS-induced low-grade inflammatory phenotype received an acute intradermal injection of 20 µl of the vehicle control (inactivated hyaluronidase), VYC-15L (low and high molecular weight hyaluronic acid crosslinked with BDDE), HYC-24L+ (high molecular weight hyaluronic acid crosslinked with BDDE), or the degraded fragments of the latter two formulations. Histological evaluation at 24 h concluded that the VYC-15L and fragments treatment produced the most inflammation followed by HYC-24L and its fragments treatment. The vehicle control had the least inflammation in comparison.

## INFORMATION SOUGHT

The following information on the sodium hyaluronate crosspolymer ingredients is being sought for use in the resulting safety assessment:

- Chemistry (including UV absorption), especially formula weights, formula weight distributions
- Impurities and method of manufacture
- Concentration of use
- Toxicokinetics data, specifically dermal absorption and/or penetration
- Repeated-dose toxicity data
- Inhalation toxicity data, if the ingredient is used in a product that can be incidentally inhaled
- Reproductive/developmental toxicity data
- Genotoxicity data; if positive, carcinogenicity data may be needed
- Dermal irritation and sensitization data at maximum concentration of use

# TABLES

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

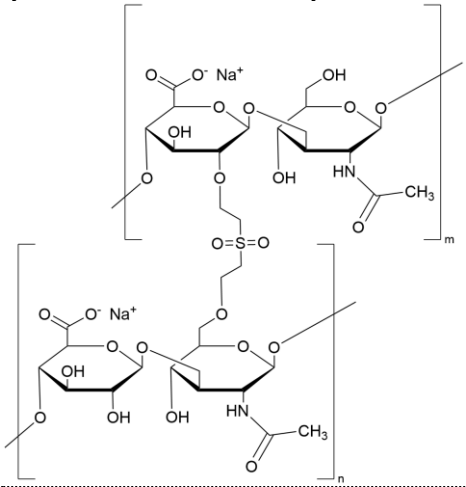
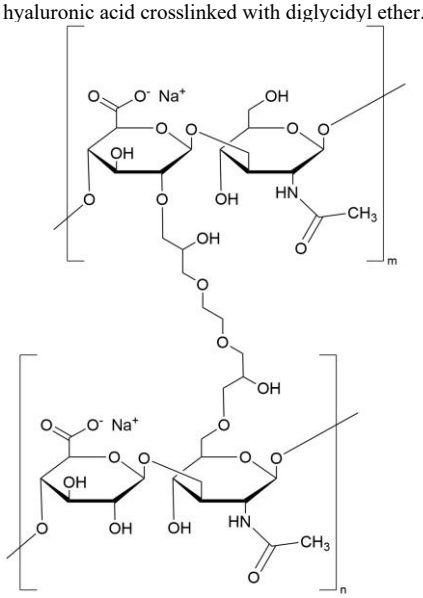
| Ingredient (CAS No.) | Definition | Function(s) |
|---|---|---|
| Sodium Hyaluronate Crosspolymer (105524-32-1) | Sodium Hyaluronate Crosspolymer is the sodium salt of a polymer of hyaluronic acid crosslinked with vinyl sulfone.  | Skin-Conditioning Agents – Humectant<br>Skin-Conditioning Agents – Miscellaneous |
| Sodium Hyaluronate Crosspolymer-2 (113797-47-0) | Sodium Hyaluronate Crosspolymer-2 is the sodium salt of a polymer of hyaluronic acid crosslinked with diglycidyl ether.  | Humectants |

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

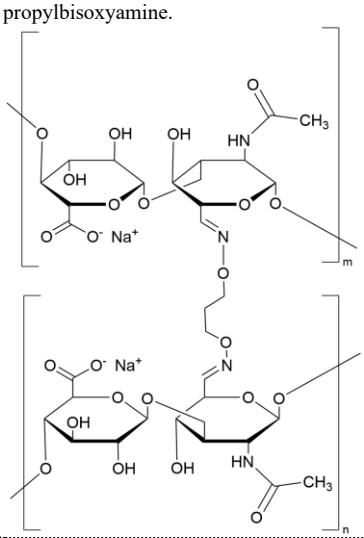
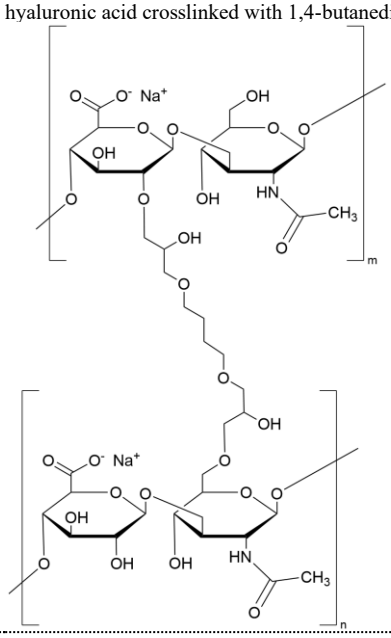
| Ingredient (CAS No.) | Definition | Function(s) |
|---|---|---|
| Sodium Hyaluronate Crosspolymer-3 | Sodium Hyaluronate Crosspolymer-3 is the sodium salt of hyaluronic acid that has been oxidized to facilitate the subsequent crosslinking by propylbisoxyamine.  | Skin-Conditioning Agents – Humectant<br>Skin-Conditioning Agents – Miscellaneous |
| Sodium Hyaluronate Crosspolymer-4 (781214-94-6) | Sodium Hyaluronate Crosspolymer-4 is the sodium salt of a polymer of hyaluronic acid crosslinked with 1,4-butanediol diglycidyl ether.  | Skin-Conditioning Agents – Emollient<br>Skin-Conditioning Agents – Humectant |

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

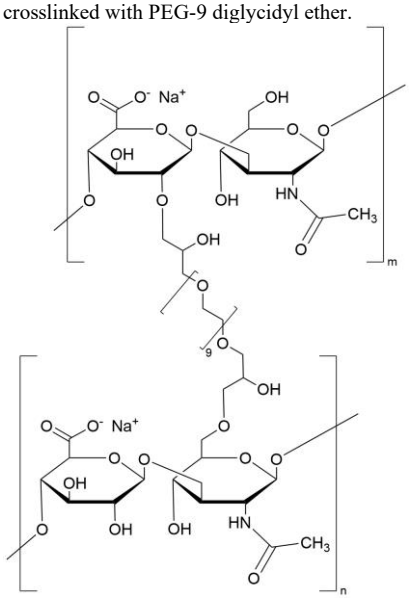
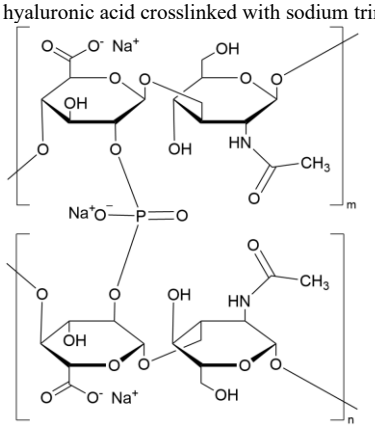
| Ingredient (CAS No.) | Definition | Function(s) |
|---|---|---|
| Sodium Hyaluronate Crosspolymer-6 | Sodium Hyaluronate Crosspolymer-6 is the polymer of sodium hyaluronate crosslinked with PEG-9 diglycidyl ether.  | Skin-Conditioning Agents – Miscellaneous |
| Sodium Hyaluronate Crosspolymer-7 | Sodium Hyaluronate Crosspolymer-7 is the sodium salt of a polymer of hyaluronic acid crosslinked with sodium trimetaphosphate.  | Skin-Conditioning Agents – Humectant<br>Skin-Conditioning Agents – Miscellaneous |

**Table 2. Frequency and concentration of use according to likely duration and exposure and by product category**

| | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] |
|---|---|---|---|---|---|---|
| | Sodium Hyaluronate Crosspolymer | | Sodium Hyaluronate Crosspolymer-2 | | Sodium Hyaluronate Crosspolymer-3 | |
| **Totals*** | **5396** | **0.0000007-0.47** | **8** | **NR** | **23** | **NR** |
| **summarized by likely duration and exposure**** | | | | | | |
| ***Duration of Use*** | | | | | | |
| *Leave-On* | *4747* | *0.00013-0.47* | *7* | *NR* | *24* | *NR* |
| *Rinse-Off* | *1470* | *0.0000007-0.47* | *1* | *NR* | *10* | *NR* |
| *Diluted for (Bath) Use* | *9* | *NR* | *NR* | *NR* | *NR* | *NR* |
| *Unknown* | *45* | *NR* | *NR* | *NR* | *NR* | *NR* |
| ***Exposure Type*** | | | | | | |
| Baby Products | 6 | NR | NR | NR | NR | NR |
| Children's Makeup | NR | NR | NR | NR | NR | NR |
| Eye Area | 67 | NR | NR | NR | 1 | NR |
| Incidental Ingestion | 234 | 0.00035 | NR | NR | NR | NR |
| Mucous Membrane | 351 | 0.0000007-0.00035 | NR | NR | 2 | NR |
| Incidental Inhalation-Spray | 7; 1389[a]; 2922[b] | 0.0001[a]; 0.2[b] | 7[b] | NR | 10[a]; 15[b] | NR |
| Incidental Inhalation-Airbrush | 1 | NR | NR | NR | NR | NR |
| Incidental Inhalation-Powder | 15; 2922[b]; 2[c] | 0.2[b]; 0.00013-0.47[c] | 7[b] | NR | 15[b] | NR |
| Dermal Contact | 5417 | 0.0000007-0.47 | 8 | NR | 33 | NR |
| Deodorant (underarm) | NR | NR | NR | NR | NR | NR |
| Hair - Non-Coloring | 200 | NR | NR | NR | NR | NR |
| Hair-Coloring | 371 | 0.003 | NR | NR | NR | NR |
| Nail | 4 | NR | NR | NR | NR | NR |
| Other Preparations (Unknown Exposure Type) | 45 | NR | NR | NR | NR | NR |
| **as reported by product category** | | | | | | |
| ***Baby Products*** | | | | | | |
| Baby Shampoos | | | | | | |
| Baby Lotions/Oils/Powders/Creams | 2 | NR | | | | |
| Other Baby Products | 1 (l.o.); 3 (r.o.) | NR | | | | |
| ***Bath Preparations (diluted for use)*** | | | | | | |
| Bath Oils, Tablets, and Salts | 2 | NR | | | | |
| Bubble Baths | 3 | NR | | | | |
| Other Bath Preparations | 4 | NR | | | | |
| ***Eye Makeup Preparations (not children's)*** | | | | | | |
| Eyebrow Pencil | 4 | NR | | | | |
| Eye Shadow | | | | | | |
| Eye Lotion | 22 | NR | | | 1 | NR |
| Mascara | 1 | NR | | | | |
| Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers) | 13 | NR | | | | |
| Eyelash Cleansers | 4 | NR | | | | |
| Other Eye Makeup Preparations | 23 | NR | | | | |
| ***Children's Eye Makeup Preparations*** | | | | | | |
| Other Children's Eye Makeup | | | | | | |
| ***Fragrance Preparations*** | | | | | | |
| Perfumes | 4 | NR | | | | |
| Other Fragrance Preparation | 1 | NR | | | | |
| ***Hair Preparations (non-coloring)*** | | | | | | |
| Hair Conditioners | 16 (l.o); 35 (r.o.) | NR | | | | |

**Table 2. Frequency and concentration of use according to likely duration and exposure and by product category**

| | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] |
|---|---|---|---|---|---|---|
| Hair Sprays (aerosol fixatives) | 1 | NR | | | | |
| Hair Straighteners | 2 | NR | | | | |
| Permanent Waves | 1 | NR | | | | |
| Rinses (non-coloring) | 21 | NR | | | | |
| Shampoos (non-coloring) | 60 (r.o.) | NR | | | | |
| Tonics, Dressings, Other Hair Grooming Aids | 22 | NR | | | | |
| Other Hair Preparations | 22 (l.o); 20 (r.o.) | NR | | | | |
| ***Hair Coloring Preparations*** | | | | | | |
| Hair Dyes and Colors (all types requiring caution statements and patch tests) | 368 | 0.003 | | | | |
| Hair Rinses (coloring) | 2 (r.o.) | NR | | | | |
| Hair Shampoos (coloring) | 1 (r.o.) | NR | | | | |
| Other Hair Coloring Preparation | | | | | | |
| ***Makeup Preparations (not eye or children's)*** | | | | | | |
| Blushers and Rouges (all types) | 31 | NR | | | | |
| Face Powders | 15 | NR | | | | |
| Foundations | 294 (traditional) | NR | | | | |
| Lipsticks and Lip Glosses | 234 | 0.00035 | | | | |
| Makeup Bases | 38 (traditional) | NR | | | | |
| Makeup Fixatives | 33 | NR | | | | |
| Other Makeup Preparations | 44 (traditional); 1 (airbrush) | 0.0035 (traditional) | | | | |
| ***Manicuring Preparations*** | | | | | | |
| Cuticle Softeners | 1 | NR | | | | |
| Nail Creams and Lotions | | | | | | |
| Nail Polish and Enamel Removers | 1 | NR | | | | |
| Other Manicuring Preparations | 2 | NR | | | | |
| ***Personal Cleanliness*** | | | | | | |
| Bath Soaps and Body Washes | 60 | 0.0000007 | | | | |
| Deodorants (underarm) | | | | | | |
| Douches | | | | | 1 | NR |
| Disposable Wipes | 5 | NR | | | | |
| Other Personal Cleanliness Products | 11 (l.o.); 32 (r.o.) | NR | | | 1 (r.o.) | NR |
| ***Shaving Preparations*** | | | | | | |
| Aftershave Lotions | 1 | NR | | | | |
| Beard Softeners | | | | | | |
| Pre-shave Lotions (all types) | | | | | | |
| Shaving Cream (aerosol, brushless, lather) | 2 | NR | | | | |
| Other Shaving Preparations | | | | | | |
| ***Skin Care Preparations*** | | | | | | |
| Cleansing | 358 | 0.00035-0.47 | 1 | NR | 4 | NR |
| Depilatories | 23 | NR | | | | |
| Face and Neck (excluding shaving preps) | 2384 (l.o.); 226 (r.o.) | not spray: 0.00013-0.47 (l.o.); 0.00013 (r.o.) | 6 (l.o.) | NR | 9 (l.o.) | NR |
| Body and Hand (excluding shaving preps) | 201 (l.o); 36 (r.o.) | not spray: 0.0011 (l.o.) | | | 3 (l.o.) | NR |
| Foot Powders and Sprays | 5 | NR | | | 1 | NR |
| Moisturizing | 850 | 0.0035-0.47 (not spray) | | | 4 | NR |
| Night | 55 | NR | | | 3 | NR |
| Paste Masks (mud packs) | 130 | NR | | | 2 | NR |

**Table 2. Frequency and concentration of use according to likely duration and exposure and by product category**

| | # of Uses | Max Conc of Use | # of Uses | Max Conc of Use | # of Uses | Max Conc of Use |
|---|---|---|---|---|---|---|
| | RLD (2025)[8,9] | % (2025)[10] | RLD (2025)[8,9] | % (2025)[10] | RLD (2025)[8,9] | % (2025)[10] |
| Skin Fresheners | 105 | NR | | | 1 | NR |
| Other Skin Care Preparations | 288 (l.o); 84 (r.o.) | 0.2 (l.o); 0.0001 (r.o.) | 1 (l.o.) | NR | 2 (l.o); 2 (r.o.) | NR |
| ***Suntan Preparations*** | | | | | | |
| Suntan Gels, Creams, and Liquids | 11 | NR | | | | |
| Indoor Tanning Preparations | 4 (traditional); 1 (spray) | NR | | | | |
| Other Suntan Preparations | 2 | NR | | | | |
| ***Other Preparations (i.e., those that do not fit another category)*** | 45 | NR | | | | |
| | **Sodium Hyaluronate Crosspolymer-4** | | **Sodium Hyaluronate Crosspolymer-6** | | **Sodium Hyaluronate Crosspolymer-7** | |
| **Totals*** | **3** | *** | **715** | *** | **3** | *** |
| **summarized by likely duration and exposure**** | | | | | | |
| ***Duration of Use*** | | | | | | |
| *Leave-On* | *3* | *** | *677* | *** | *4* | *** |
| *Rinse-Off* | *NR* | *** | *240* | *** | *NR* | *** |
| *Diluted for (Bath) Use* | *NR* | *** | *5* | *** | *NR* | *** |
| *Unknown* | *NR* | *** | *18* | *** | *NR* | *** |
| ***Exposure Type*** | | | | | | |
| Baby Products | NR | *** | 8 | *** | NR | *** |
| Children's Makeup | NR | *** | 1 | *** | NR | *** |
| Eye Area | NR | *** | 28 | *** | NR | *** |
| Incidental Ingestion | NR | *** | 28 | *** | NR | *** |
| Mucous Membrane | NR | *** | 51 | *** | NR | *** |
| Incidental Inhalation-Spray | 3[b] | *** | 7; 265[a]; 365[b] | *** | 1[a]; 1[b] | *** |
| Incidental Inhalation-Airbrush | NR | *** | NR | *** | NR | *** |
| Incidental Inhalation-Powder | 3[b] | *** | 2; 365[b]; 5[c] | *** | 1[b] | *** |
| Dermal Contact | 3 | *** | 857 | *** | 4 | *** |
| Deodorant (underarm) | NR | *** | 2 (not spray) | *** | NR | *** |
| Hair - Non-Coloring | NR | *** | 28 | *** | NR | *** |
| Hair-Coloring | NR | *** | 5 | *** | NR | *** |
| Nail | NR | *** | 2 | *** | NR | *** |
| Other Preparations (Unknown Exposure Type) | NR | *** | 18 | *** | NR | *** |
| **as reported by product category** | | | | | | |
| ***Baby Products*** | | | | | | |
| Baby Shampoos | | | 2 | *** | | |
| Baby Lotions/Oils/Powders/Creams | | | 5 | *** | | |
| Other Baby Products | | | 1 (r.o.) | *** | | |
| ***Bath Preparations (diluted for use)*** | | | | | | |
| Bath Oils, Tablets, and Salts | | | 2 | *** | | |
| Bubble Baths | | | | | | |
| Other Bath Preparations | | | 3 | *** | | |
| ***Eye Makeup Preparations (not children's)*** | | | | | | |
| Eyebrow Pencil | | | | | | |
| Eye Shadow | | | 2 | *** | | |
| Eye Lotion | | | 5 | *** | | |
| Mascara | | | 3 | *** | | |
| Eyelash and Eyebrow Preparations (primers, conditioners, serums, fortifiers) | | | 11 | *** | | |

**Table 2. Frequency and concentration of use according to likely duration and exposure and by product category**

| | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] |
|---|---|---|---|---|---|---|
| Eyelash Cleansers | | | 1 | *** | | |
| Other Eye Makeup Preparations | | | 5 | *** | | |
| ***Children's Eye Makeup Preparations*** | | | | | | |
| Other Children's Eye Makeup | | | 1 | *** | | |
| ***Fragrance Preparations*** | | | | | | |
| Perfumes | | | 3 | *** | | |
| Other Fragrance Preparation | | | 3 | *** | | |
| ***Hair Preparations (non-coloring)*** | | | | | | |
| Hair Conditioners | | | 1 (l.o.) | *** | | |
| Hair Sprays (aerosol fixatives) | | | 1 | *** | | |
| Hair Straighteners | | | 1 | *** | | |
| Permanent Waves | | | | | | |
| Rinses (non-coloring) | | | 2 | *** | | |
| Shampoos (non-coloring) | | | 1 (l.o.); 2 (r.o.) | *** | | |
| Tonics, Dressings, Other Hair Grooming Aids | | | 10 | *** | | |
| Other Hair Preparations | | | 5 (l.o.); 3 (r.o.) | *** | | |
| ***Hair Coloring Preparations*** | | | | | | |
| Hair Dyes and Colors (all types requiring caution statements and patch tests) | | | 1 | *** | | |
| Hair Rinses (coloring) | | | | | | |
| Hair Shampoos (coloring) | | | | | | |
| Other Hair Coloring Preparation | | | 4 (l.o.) | *** | | |
| ***Makeup Preparations (not eye or children's)*** | | | | | | |
| Blushers and Rouges (all types) | | | 2 | *** | | |
| Face Powders | | | 2 | *** | | |
| Foundations | | | 40 (traditional) | *** | 2 (traditional) | *** |
| Lipsticks and Lip Glosses | | | 28 | *** | | |
| Makeup Bases | | | 10 (traditional) | *** | | |
| Makeup Fixatives | | | 5 | *** | | |
| Other Makeup Preparations | | | 3 (traditional) | *** | | |
| ***Manicuring Preparations*** | | | | | | |
| Cuticle Softeners | | | 1 | *** | | |
| Nail Creams and Lotions | | | 1 | *** | | |
| Nail Polish and Enamel Removers | | | | | | |
| Other Manicuring Preparations | | | | | | |
| ***Personal Cleanliness*** | | | | | | |
| Bath Soaps and Body Washes | | | 7 | *** | | |
| Deodorants (underarm) | | | 2 (not spray) | *** | | |
| Douches | | | | | | |
| Disposable Wipes | | | 2 | *** | | |
| Other Personal Cleanliness Products | | | 1 (l.o.); 8 (r.o.) | *** | | |
| ***Shaving Preparations*** | | | | | | |
| Aftershave Lotions | | | 1 | *** | | |
| Beard Softeners | | | 3 | *** | | |
| Pre-shave Lotions (all types) | | | 1 | *** | | |
| Shaving Cream (aerosol, brushless, lather) | | | 2 | *** | | |
| Other Shaving Preparations | | | 5 | *** | | |

**Table 2. Frequency and concentration of use according to likely duration and exposure and by product category**

| | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] | # of Uses RLD (2025)[8,9] | Max Conc of Use % (2025)[10] |
|---|---|---|---|---|---|---|
| ***Skin Care Preparations*** | | | | | | |
| Cleansing | | | 93 | *** | | |
| Depilatories | | | 2 | *** | | |
| Face and Neck (excluding shaving preps) | 3 (l.o.) | *** | 251 (l.o.); 47 (r.o.) | *** | | |
| Body and Hand (excluding shaving preps) | | | 21 (l.o.); 3 (r.o.) | *** | | |
| Foot Powders and Sprays | | | | | | |
| Moisturizing | | | 120 | *** | 1 | *** |
| Night | | | 12 | *** | | |
| Paste Masks (mud packs) | | | 13 | *** | | |
| Skin Fresheners | | | 25 | *** | | |
| Other Skin Care Preparations | | | 69 (l.o.); 45 (r.o.) | *** | 1 (l.o.) | *** |
| ***Suntan Preparations*** | | | | | | |
| Suntan Gels, Creams, and Liquids | | | 8 | *** | | |
| Indoor Tanning Preparations | | | 4 (traditional) | *** | | |
| Other Suntan Preparations | | | 2 | *** | | |
| ***Other Preparations (i.e., those that do not fit another category)*** | | | 18 | *** | | |

NR – not reported
l.o. – leave-on; r.o. – rinse-off
*The sum of the counts given for duration of use and by exposure type, and the sum of the frequency reported by product category, may not equal the sum of total uses because each ingredient may be used in cosmetic formulations that are reported under more than one product category.
**Likely duration and exposure are derived from survey data based on product category (see Use Categorization https://www.cir-safety.org/cir-findings)
***concentration of use survey is in-progress; results will be added when received
[a] It is possible these products are sprays, but it is not specified whether the reported uses are sprays.
[b] 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
[c] It is possible these products are powders, but it is not specified whether the reported uses are powders.

**Table 3. Cytotoxicity studies**

| Test Article | Vehicle | Animals/Group | Dose/Concentration | Procedure | Results | Reference |
|---|---|---|---|---|---|---|
| **IN VITRO** | | | | | | |
| Hyaluronic acid membrane (6%) crosslinked with BDDE (0.01%) | NR | HCECs | NR | CCK-8 assay; cells were treated for 12, 24, and 48 h. Controls were untreated. | At 48 h, the HAM crosslinked with BDDE had a 50% increase in cell viability and expression of MK167 (cell marker for proliferation) | [15] |
| Hyaluronic acid hydrogel crosslinked with BDDE | NR | MC3T3-E1 cells | 0.1 ml | CCK-8 assay; cells were treated for 24 h. Negative controls were untreated. Positive controls were treated with Triton X-100. | Cell viability for the cells treated with hyaluronic acid hydrogel crosslinked with BDDE was 105% compared to control which was 100%. | [16] |
| Hyaluronic acid hydrogel crosslinked with BDDE | NR | MC3T3-E1 cells | 0.1 ml | LDH assay; cells were treated for 24 h. Negative controls were untreated. Positive controls were treated with Triton X-100. | Hyaluronic acid hydrogel crosslinked with BDDE was slightly more cytotoxic than the control, but the difference was not statistically significant. | [16] |
| Hyaluronic acid (6%) gel with citric acid (12%) and crosslinked with BDDE | NR | L929 mouse fibroblast cells | 5 – 15% | Multiple biphasic gel formations were created. The MTT assay was only performed on the steam-sterilized biphasic gel formation containing 6% HA crosslinked with BDDE and 12% citric acid non-crosslinked; cells were treated for 24 h. Controls were untreated. | No adverse effect on cell viability detected with the steam-sterilized hyaluronic acid (6%) gel with citric acid (12%) and crosslinked with BDDE | [17] |

BDDE – 1,4-butanediol diglycidyl ether; CCK-8 - cell counting kit-8; HA – hyaluronic acid; HAM – hyaluronic acid membrane; HCECs – human corneal epithelial cells; L929 cells - murine fibroblast cells; LDH - lactate dehydrogenase; MC3T3-E1 – mouse pre-osteoblastic cells; MTT - (3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide

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