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## Safety Assessment of Hydroxyethyl Urea As Used in Cosmetics

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*All interested persons are provided 60 days from the above release date to comment on this safety assessment and to identify additional published data that should be included or provide unpublished data which can be made public and included.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 All unpublished data submitted to CIR will be discussed in open meetings, will be available at the CIR office for review by any interested party and may be cited in a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 2018 Cosmetic Ingredient Review Expert Panel members are: Chairman, 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 Alice Akinsulie, Scientific Analyst/Writer.

## **INTRODUCTION**

This Scientific Literature Review is the initial step in preparing a safety assessment of Hydroxyethyl Urea as used in cosmetic formulations. According to the web-based *International Cosmetic Ingredient Dictionary and Handbook* (wINCI *Dictionary*), Hydroxyethyl Urea is reported to function as a humectant and hair- and skin-conditioning agent for use in cosmetic products.<sup>1</sup>

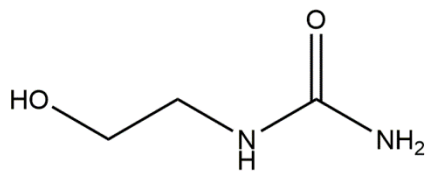
This safety assessment includes relevant published and unpublished data that are available for each endpoint that is evaluated. Published data are identified by conducting an exhaustive search of the world's literature. A listing of the search engines and websites that are used and the sources that are typically explored, as well as the endpoints that CIR typically evaluates, is provided on the CIR website (<http://www.cir-safety.org/supplementaldoc/preliminary-search-engines-and-websites>; <http://www.cir-safety.org/supplementaldoc/cir-report-format-outline>). Unpublished data are provided by the cosmetics industry, as well as by other interested parties.

Much of the data included in this safety assessment was obtained from the European Chemicals Agency (ECHA)<sup>2</sup> website and from the Australian Government Department of Health National Industrial Chemicals Notification and Assessment Scheme (NICNAS)<sup>3</sup> hazard assessments. Both of these sources provide summaries of data generated by industry, and ECHA and NICNAS, respectively, are cited as the sources of the summary data in this safety assessment as appropriate.

## **CHEMISTRY**

### **Definition and Structure**

Hydroxyethyl Urea (CAS No. 2078-71-9;1320-51-0) is the organic compound that conforms to the structure in Figure 1.<sup>1</sup> Urea is the simplest diamide of carbonic acid. Hydroxyethyl Urea is a derivative of urea, singly substituted with 2-ethanol.



**Figure 1. Hydroxyethyl Urea**

### **Physical and Chemical Properties**

This ingredient is a low molecular weight, highly water soluble, hygroscopic solid.<sup>3</sup> Light microscopic examination revealed that the particles of Hydroxyethyl Urea are flakes with a wide various particle size. The currently available toxicity data on Hydroxyethyl Urea describe a tradename mixture containing up to 60% Hydroxyethyl Urea. Additional information on the physical and chemical properties is found in Table 1.

### **Method of Manufacture**

Method of manufacture data, specific to the cosmetic ingredient, were not found in the published literature, and unpublished data were not submitted. However, Hydroxyethyl Urea could be synthesized via N-carbamoylation of ethanolamine with potassium cyanate.<sup>4</sup> Alternatively, this ingredient could be synthesized via transamidation of urea with ethanolamine.<sup>5</sup>

### **Impurities**

Impurities data for Hydroxyethyl Urea were not found in the published literature, and unpublished data were not submitted. However, retail raw material suppliers indicate that this chemical is available with at least 95% purity.<sup>6</sup>

## **USE**

### **Cosmetic**

The safety of the cosmetic ingredient addressed in this assessment is evaluated based on data received from the U.S. Food and Drug Administration (FDA) and the cosmetics industry on the expected use of this ingredient in cosmetics. Use frequencies of individual ingredients in cosmetics are collected from manufacturers and reported by cosmetic product category in 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 2018 VCRP data, Hydroxyethyl Urea is reported to be used in a total of 641 cosmetic formulations; the majority of the uses (407) are in bath soaps and detergent products (Table 2).<sup>7</sup> The results of the concentration of use survey conducted by the Council indicate the highest use concentration of Hydroxyethyl Urea for products applied to the skin is 20.6%, in leave-on products (moisturizing products).<sup>8</sup>

Hydroxyethyl Urea is reported to be used in lipstick products at up to 0.009%; use in lipsticks can result in incidental ingestion.<sup>8</sup> It is also used in cosmetic sprays and could possibly be inhaled; Hydroxyethyl Urea is reported to be used at 5% in spray body and hand product formulations. 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.<sup>9,10</sup> 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. they would not enter the lungs) to any appreciable amount.<sup>11,12</sup>

Hydroxyethyl Urea is not classified as hazardous according to Australia's *Approved Criteria for Classifying Hazardous Substances*.<sup>3</sup> Hydroxyethyl Urea is not restricted from use in any way under the rules governing cosmetic products in the European Union.<sup>13</sup>

### **Non-Cosmetic**

Hydroxyethyl Urea has been approved for use as an indirect food additive for use only as a component of adhesives. (21 CFR 175.105)

## **TOXICOKINETIC STUDIES**

### **Absorption, Distribution, Metabolism, and Excretion (ADME)**

Hydroxyethyl Urea has a low molecular weight and high water solubility; therefore dermal absorption may occur.<sup>3</sup> However, based on the partition coefficient (log P<sub>ow</sub> estimated to be -2.06), absorption is expected to be limited. In the gastrointestinal tract, Hydroxyethyl Urea may pass through aqueous pores or be carried through the epithelial barrier by the passage of water.

## **TOXICOLOGICAL STUDIES**

### **Acute Toxicity Studies**

#### **Dermal**

In an acute dermal toxicity study, occlusive patches of an aqueous (aq.) solution containing 57.58% Hydroxyethyl Urea were applied to 5 male and 5 female Sprague-Dawley rats in accord with Organization for Economic Co-operation and Development (OECD) TG 402.<sup>2</sup> Dermal administration of the test substance at a dose of 3473 mg/kg formulation corresponded to 2000 mg/kg Hydroxyethyl Urea. Dermal irritation was noted at the site of test article application. Clinical abnormalities observations included few feces, and dark materials were observed around the facial area. A slight body weight loss was recorded for 1 male and 1 female in the first week of observation. The dermal LD<sub>50</sub> was > 3473 mg/kg of the test material, corresponding to > 2000 mg/kg Hydroxyethyl Urea.

#### **Oral**

Groups of 5 male and 5 female Sprague-Dawley rats were dosed by gavage with 3473 mg/kg of an aq. solution containing 57.58% Hydroxyethyl Urea; this dose corresponded to 2000 mg/kg Hydroxyethyl Urea.<sup>2,3</sup> Clinical abnormalities included transient incidences of fecal stain, mucoid stools and dark material around the nose. The LD<sub>50</sub> of the aq. solution was > 3473 mg/kg, corresponding to > 2000 mg/kg Hydroxyethyl Urea.

#### **Inhalation**

In an acute inhalation toxicity study performed in accord with the Office of Prevention, Pesticides and Toxic Substances (OPPTS) 870.1300 (Acute Inhalation Toxicity Limit Test), a tradename mixture containing approximately 50% Hydroxyethyl Urea was studied in Sprague-Dawley rats.<sup>2,3</sup> Groups of 5 male and 5 female rats were exposed nose-only for 4 hours. Test material was approx. 50% solids. For Groups 1 and 2, the test material was undiluted, and mean aerosol mass concentrations were 0.59 and 0.125 mg/l, respectively. For Group 3, the aerosol was a 1:1 dilution of the test material with water; the mean aerosol mass concentration was 5.152 mg/l. In each instance, test concentrations were based on the non-volatile fraction (i.e., 50% for the material tested as supplied; 25% for the test material that was diluted). The mean mass median aerodynamic diameters (MMAD) (and geometric standard deviation) for each exposure were: 1.06 µm (1.80; group 1); 1.90 µm (2.87; group 2); and 1.63 µm (2.33; group 3). Animals from all groups had lungs with foci. Histopathologic evaluation of the lungs from two animals with lung foci in Group 2 showed no hemosiderophages in the lymph node of either animal. Since small foci of peracute hemorrhage in the lung are not rare in rodents, the lung foci found in animals from this study were not considered related to treatment with the test substance. With the exception of the observation of redness/red

material around the nose, observations were determined not to be attributable to the test article. The LC<sub>50</sub> for inhalation exposure to Hydroxyethyl Urea in rats was greater than > 5.152 mg/L of the test material; this was calculated as corresponding to >4 g/ml Hydroxyethyl Urea.

### **Short-Term Toxicity Studies**

No relevant published short-term toxicity studies on Hydroxyethyl Urea were identified in a literature search for this ingredient, and no unpublished data were submitted.

### **Subchronic Toxicity Studies**

#### **Dermal**

In a 90-day dermal study using semi-occlusive patches, an aqueous solution containing 57.58% of Hydroxyethyl Urea (0, 100, 330, or 1000 mg/kg bw/day) was administered to groups of 10 male and 10 female Sprague-Dawley rats (6 h/day, 7 days/wk in deionized water).<sup>2,3</sup> Minor treatment-related dermal effects were observed during the study, including a dose-related increase in the incidence of focal/pinpoint eschar, desquamation and red pinpoint areas (a slightly higher incidence is noted in females). These were deemed to be superficial in nature. A statistically-significant increase in phosphorus (all test groups) and calcium (1000 mg/kg bw/day group) were noted on day 90 in males; these findings were deemed to be possibly related to the test article, but not of biological significance. No effects on organ weights and no test article-related microscopic lesions were noted at necropsy. The no-observed-adverse-effect-level (NOAEL) was established as 1000 mg/kg bw/day, based on the absence of any toxicologically significant effects at this dose level.

### **Chronic Toxicity Studies**

No relevant published chronic toxicity studies on Hydroxyethyl Urea were identified in a literature search for this ingredient, and no unpublished data were submitted.

## **DEVELOPMENTAL AND REPRODUCTIVE TOXICITY (DART) STUDIES**

#### **Dermal**

The developmental and reproductive toxicity of an aq. solution containing 57.58% Hydroxyethyl Urea was dermally-applied using 4 groups of 25 female Sprague-Dawley rats.<sup>2,3</sup> Open applications of 0, 100, 330, and 1000 mg/kg bw/day of the test substance in deionized water were applied 6 hours a day on days 6 through 19 of gestation. Elizabethan collars were placed around the neck of each animal during the exposure period. None of the animals died during the study. Mean feed consumption for females in the 1000 mg/kg bw/day group was statistically significantly lower than that of controls during the treatment period. However, there were no statistically significant differences in mean body weights or body weight gain between the control and test groups. No reproductive or developmental effects were observed. The NOAEL was established as 1000 mg/kg bw/day for both maternal and developmental toxicity.

## **GENOTOXICITY**

### **In Vitro**

An Ames test was conducted in accordance with OECD TG 471 using *Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and *Escherichia coli* (WP2uvrA) to evaluate the mutagenicity of an aq. solution containing 57.58% Hydroxyethyl Urea.<sup>2,3</sup> Doses of 75 - 5000 µg/plate were tested with and without metabolic activation. Dosage was adjusted for the purity of the test substance. All dose levels of test article, vehicle controls and positive controls were plated in triplicate. The test article was not mutagenic under the conditions of the test.

### **In Vivo**

A mammalian micronucleus test of an aq. solution containing 57.58% Hydroxyethyl Urea was performed in CrI:CD-1 (ICR) BR mice in accordance with OECD TG 474.<sup>2,3</sup> Groups of 6 male mice were dosed by gavage with 0, 500, 1000 and 2000 mg/kg bw of the test substance in deionized water, and the animals were killed 24 h after dosing. A second group of 6 males was dosed with 2000 mg/kg bw of the test substance and killed 48 h after dosing. No clinical signs of toxicity were observed at any dose level. A statistically significant increase in micronucleated polychromatic erythrocytes (PCEs) was not observed for any group. As expected, the positive control (cyclophosphamide) induced a statistically significant increase in micronucleated PCEs.

## **CARCINOGENICITY STUDIES**

No relevant published carcinogenicity studies on Hydroxyethyl Urea were identified in a literature search for this ingredient, and no unpublished data were submitted.

## **DERMAL IRRITATION AND SENSITIZATION**

### **Irritation**

#### **In Vitro**

In an EpiDerm™ study, tissue samples were exposed to 100 µL of a test material containing ≤ 50% Hydroxyethyl Urea for 1, 4, and 24 h.<sup>2,3</sup> Each treatment was conducted in duplicate. A negative control was performed at the 4 h time point and a positive control (1% octoxinol (an ethoxylated alkyl phenol)) was performed in duplicate for the 4 and 24 h exposure times. The ET<sub>50</sub> (the time at which the EpiDerm™ tissue viability was reduced 50% compared to control tissues) was determined to be 12.1 h. The test substance is expected to be very mild to the skin.<sup>3</sup>

#### **Animal**

The dermal irritation potential of an aq. solution containing 57.58% Hydroxyethyl Urea was evaluated using 6 male New Zealand white rabbits.<sup>2,3</sup> Occlusive patches containing 0.5 mL of the test material (100% and 52%) were applied for 24 h to one intact and one abraded site (i.e. total of four test sites). The skin surface area treated per site was approximately 6.5 cm<sup>2</sup>. Slight erythema and edema were reported. Desquamation was also noted in 2/6 animals treated with 100% test substance at abraded sites. All reactions were fully reversible within 10 days. The test substance is slightly irritating to the skin.

### **Sensitization**

#### **Animal**

The dermal sensitization potential of an aq. solution containing 57.58% Hydroxyethyl Urea was evaluated in Hartley derived albino guinea pigs.<sup>2,3</sup> Ten male and ten female guinea pigs received 0.1 ml intradermal injections of the test material at concentration of 5% in deionized water, 5.0% test material and Freund's complete adjuvant (FCA) emulsion, and FCA only. One week later, a topical induction application of 0.8 mL neat test material was applied for 48 hours. After a 2 week non-treatment period, animals were challenged with a 24 hours exposure to 0.3 ml of Hydroxyethyl Urea, applied neat; the challenge sites were pretreated with sodium lauryl sulfate. A control group of 5 male and 5 female guinea pigs were exposed to deionized water during induction and the test material at challenge. No reactions were observed; the test material was not a sensitizer. A historical study using alpha-hexylcinnamaldehyde served as the positive control.

## **OCULAR IRRITATION STUDIES**

#### **Animal**

The potential irritation effect of an aq. solution containing 57.58% Hydroxyethyl Urea was evaluated by instilling the test material into the conjunctival sac of one eye of 3 male and 3 female New Zealand White rabbits, in accord with OECD TG 405(Acute Eye Irritation/Corrosion).<sup>2,3</sup> Each of the 6 rabbits received a 0.1mL dose of Hydroxyethyl Urea. Iritis was noted in 3/6 animals at the 1 hour scoring interval, which resolved completely in all test eyes by the 48 hour scoring interval. Conjunctivitis (was noted in 6/6 animals at the 1 hour scoring interval. The conjunctival irritation was resolved completely in all test eyes by study day 7. The test substance was classified as slightly irritating to the eye.

### **SUMMARY**

This is a review of the safety of Hydroxyethyl Urea as used in cosmetics. According to the WINCI *Dictionary*, this ingredient is reported to function in cosmetics as a humectant and a hair and skin conditioning agent. Based on 2018 VCRP data, Hydroxyethyl Urea is used in a total of 641 cosmetic formulations, the majority (407) of which are in bath soaps and detergent products. The results of the concentration of use survey conducted in 2017 by the Council indicate that the highest concentration of Hydroxyethyl Urea for products applied to the skin is 20.6%, in leave-on products (moisturizing products).

Given the low molecular weight and high water solubility (>699 g/L) of Hydroxyethyl Urea, dermal absorption may occur. However, dermal absorption is expected to be limited based on the partition coefficient (log Pow estimated to be -2.06).

The acute dermal and oral and LD<sub>50</sub>s of an aq. solution containing 57.58% Hydroxyethyl Urea were both > 2000 mg/kg. The L<sub>C50</sub> of a 50% dilution of a tradename mixture that contained approximately 50% Hydroxyethyl Urea was > 5.152 mg/l male and female rats; this was calculated as corresponding to >4 g/ml Hydroxyethyl Urea. In a 90-day dermal toxicity study with semi-occlusive patches of an aq. solution containing 57.58% Hydroxyethyl Urea in rats, the NOAEL was 1000 mg/kg bw/day.

In a dermal developmental toxicity study in which open applications of an aq. solution containing 57.58% Hydroxyethyl Urea were made on days 6 through 19 of gestation, a dosage level of 1000 mg/kg/day was considered to be the NOAEL for maternity and developmental toxicity. No reproductive or developmental effects were observed.

The genotoxic potential of Hydroxyethyl Urea was evaluated in an Ames test using *Salmonella typhimurium* (TA1535, TA1537, TA98, TA100) and *Escherichia coli* (WP2uvrA). Hydroxyethyl Urea was not mutagenic to bacteria under the conditions of the test. Hydroxyethyl Urea also was not genotoxic in a micronucleus study in which mice were dosed by gavage with up to 2000 mg/kg of an aq. solution containing 57.58% Hydroxyethyl Urea.

Based on the results of an EpiDerm™ study, a test material containing ≤ 50% Hydroxyethyl Urea is expected to be very mild to skin. An aq. solution containing 57.58% Hydroxyethyl Urea was slightly irritating to rabbit skin; it was not a sensitizer in guinea pigs.

In an ocular irritation study, an aq. solution containing 57.58% Hydroxyethyl Urea was instilled into the sac of one eye of 3 male and 3 female New Zealand White rabbits. The test material was slightly irritating in rabbit eye.

#### **DATA NEEDS**

CIR is seeking any data that would help the CIR Expert Panel assess the safety of this ingredient as it is used in cosmetics and would improve the resulting safety assessment. Particularly, methods of manufacture and impurities data and dermal absorption data are requested.

## TABLES

**Table 1.** Physical and chemical properties of Hydroxyethyl Urea

Property	Value	Reference
Physical Form	Solid	3
Color	Light yellow	3
Molecular Weight (Da)	104.11	3
Density/Specific Gravity g/cm <sup>3</sup> at 22.3°C	1.36	3
Vapor pressure mm Hg at 25°C	0.00021	3
Melting Point °C	94-95	14
Boiling Point °C at 772.1mm Hg	Decomposed, 150	3
Water Solubility g/l at 20°C	699	3
Disassociation constants 25 °C		2
pKa – 1 (N-H)	14.72 est.	
pKa – 2 (O-H)	14.83 est.	
pKa – 3 (N-H)	16.20 est.	

**Table 2.** Frequency and concentration of use according to duration and exposure

	# of Uses <sup>7</sup>	Max Conc of Use (%) <sup>8</sup>
<b>Totals*</b>	<b>641</b>	<b>0.00046 – 20.6%</b>
<b>Duration of Use</b>		
Leave-On	209	0.00046 – 20.6%
Rinse-Off	432	NR
Diluted for (Bath) Use	NR	NR
<b>Exposure Type</b>		
Eye Area	5	NR
Incidental Ingestion	2	0.009
Incidental Inhalation-Spray	13; 106 <sup>a</sup> ; 46 <sup>b</sup>	0.5-5; 2.5 <sup>a</sup> ;
Incidental Inhalation-Powder	13; 46 <sup>b</sup>	0.0091-5 <sup>c</sup>
Dermal Contact	622	0.00046-20.6%
Deodorant (underarm)	NR	0.00046
Hair - Non-Coloring	16	0.25-2%
Hair-Coloring	NR	NR
Nail	1	NR
Mucous Membrane	413	0.009
Baby Products	NR	NR

\*Because an ingredient may be used in cosmetics with multiple exposure types, the sum of all exposure types may not equal the sum of total uses.

<sup>a</sup> Includes products that can be sprays, but it is not known whether the reported uses are sprays

<sup>b</sup> Not specified whether this product is a spray or a powder or neither, but it is possible it may be a spray or a powder, so this information is captured for both categories of incidental inhalation

<sup>c</sup> Includes products that can be powders, but it is not known whether the reported uses are powders

NR – no reported use

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