Safety Assessment of Hydroxyethyl Urea As Used in Cosmetics

Status: Draft Report for Panel Review
Release Date: August 29, 2018
Panel Meeting Date: September 24-25, 2018

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.

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Inhalation

In an acute study performed in accord with the Office of Prevention, Pesticides and Toxic Substances (OPPTS) protocol 870.1300 (Acute Inhalation Toxicity Limit Test), the inhalation toxicity of a tradename mixture containing approximately 50% Hydroxyethyl Urea (which corresponds to > 4 mg/l of Hydroxyethyl Urea) was studied in Sprague-Dawley rats.[2,3] Groups of 5 male and 5 female rats were exposed nose-only for 4 hours. 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). There were no deaths reported during the exposure or observation period, however, 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_{50} 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).[2,3] 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 finding 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 potential adverse effect of Hydroxyethyl Urea on developmental and reproductive functions was tested in 4 groups of 25 female Sprague-Dawley rats.[2,3] An aqueous solution containing 57.58% Hydroxyethyl Urea was dermally applied using open applications of 0, 100, 330, and 1000 mg/kg bw/day in deionized water and then applied for 6 h/day on days 6 through 19 of gestation. Elizabethan collars were placed around the neck of each animal during the exposure period to minimize ingestion. 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.[2,3] Doses of 75 - 5000 µg/plate were tested with and without metabolic activation. Dosage was adjusted for the purity of the aqueous solution containing Hydroxyethyl Urea (57.58%). In the initial toxicity mutation assay, the maximum dose tested was 5000 µg per plate; this dose was achieved using a concentration of 50 mg/mL and of the test

article. 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 Crl:CD-1 (ICR) BR mice in accordance with OECD TG 474.[2,3] 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.[3] Each treatment was conducted in duplicate. Following the treatment, a negative control (1% octoxinol (an ethoxylated alkyl phenol)) was performed in duplicate for the 4 and 24 h exposure times. The ET_{50} (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 mildly irritating to the skin.[3]

Animal

The dermal irritation potential of an aq. solution containing 57.58% Hydroxyethyl Urea was evaluated using 6 male New Zealand white rabbits.[2,3] Occlusive patches containing 0.5 mL of the test material (at 52% and undiluted) 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^2. 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.[2,3] Ten male and ten female guinea pigs received 0.1 ml intradermal injections of the test material at a concentration of 5% in deionized water, 5.0% test material and Freund's complete adjuvant (FCA), 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 ocular irritation of an aq. solution containing 57.58% Hydroxyethyl Urea was evaluated by instilling 0.1 ml of 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).[2,3] 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 *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 are in bath soaps and detergent products. The results of the concentration of use survey conducted in 2017 by the Council only reported leave-on uses, and indicated that the highest concentration of Hydroxyethyl Urea is 20.6% in 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 P_{ow} estimated to be -2.06).

The acute dermal and oral LD_{50}s of an aq. solution containing 57.58% Hydroxyethyl Urea were both > 2000 mg/kg. The LC_{50} of a mixture that contained approximately 50% Hydroxyethyl Urea was > 5.152 mg/l in 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 *S. typhimurium* (TA1535, TA1537, TA98, TA100) and *E. 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 given a single dose 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 (tested at 52% and undiluted) was slightly irritating to rabbit skin however it was not a sensitizer in guinea pigs when administered intradermal injections of 5.0% Hydroxyethyl Urea in deionized water along with injections of FCA and 5.0%.

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.

DISCUSSION

To be developed.

CONCLUSION

To be determined.

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^3 at 22.3^{o}C	1.36	3
Vapor pressure mm Hg at 25^{0}C	0.00021	3
Melting Point ^{o}C	94 - 95	13
Boiling Point ^{o}C at 772.1mm Hg	Decomposed at 150	3
Water Solubility g/l at 20 ^{o}C	699	3
Log P_{ow}	-2.06	4
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[6]	*Max Conc of Use (%)*[7]
Totals*	**641**	**0.00046 – 20.6%**
Duration of Use		
Leave-On	*209*	*0.00046 – 20.6%*
Rinse-Off	*432*	*NR*
Diluted for (Bath) Use	*NR*	*NR*
Exposure Type		
Eye Area	5	NR
Incidental Ingestion	2	0.009
Incidental Inhalation-Spray	13; 106[a]; 46[b]	5; 0.5-2.5[a]
Incidental Inhalation-Powder	13; 46[b]	0.0091-5[c]
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.
[a] Includes products that can be sprays, but it is not known whether the reported uses are sprays
[b] 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
[c] 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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CATEGORY	CAS #	MAINTERM	COUNT
03D - Eye Lotion	1320510	HYDROXYETHYL UREA	5
04A - Cologne and Toilet waters	1320510	HYDROXYETHYL UREA	1
04E - Other Fragrance Preparation	1320510	HYDROXYETHYL UREA	12
05A - Hair Conditioner	1320510	HYDROXYETHYL UREA	1
05F - Shampoos (non-coloring)	1320510	HYDROXYETHYL UREA	2
05G - Tonics, Dressings, and Other Hair Grooming Aids	1320510	HYDROXYETHYL UREA	6
05I - Other Hair Preparations	1320510	HYDROXYETHYL UREA	7
07A - Blushers (all types)	1320510	HYDROXYETHYL UREA	1
07B - Face Powders	1320510	HYDROXYETHYL UREA	13
07C - Foundations	1320510	HYDROXYETHYL UREA	2
07E - Lipstick	1320510	HYDROXYETHYL UREA	2
07I - Other Makeup Preparations	1320510	HYDROXYETHYL UREA	2
08G - Other Manicuring Preparations	1320510	HYDROXYETHYL UREA	1
10A - Bath Soaps and Detergents	1320510	HYDROXYETHYL UREA	407
10E - Other Personal Cleanliness Products	1320510	HYDROXYETHYL UREA	4
11A - Aftershave Lotion	1320510	HYDROXYETHYL UREA	2
11E - Shaving Cream	1320510	HYDROXYETHYL UREA	3
11G - Other Shaving Preparation Products	1320510	HYDROXYETHYL UREA	7
12A - Cleansing	1320510	HYDROXYETHYL UREA	3
12C - Face and Neck (exc shave)	1320510	HYDROXYETHYL UREA	28
12D - Body and Hand (exc shave)	1320510	HYDROXYETHYL UREA	17
12E - Foot Powders and Sprays	1320510	HYDROXYETHYL UREA	1
12F - Moisturizing	1320510	HYDROXYETHYL UREA	87
12G - Night	1320510	HYDROXYETHYL UREA	11
12H - Paste Masks (mud packs)	1320510	HYDROXYETHYL UREA	5
12I - Skin Fresheners	1320510	HYDROXYETHYL UREA	1
12J - Other Skin Care Preps	1320510	HYDROXYETHYL UREA	9
13A - Suntan Gels, Creams, and Liquids	1320510	HYDROXYETHYL UREA	1

Personal Care Products Council
Committed to Safety, Quality & Innovation

Memorandum

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

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

DATE: July 31, 2018

SUBJECT: Hydroxyethyl Urea

Anonymous. 2018. Hydroxyethyl Urea (method of manufacture, impurities).

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July 31, 2018

Hydroxyethyl Urea

- method of manufacture:
  - Hydroxyethyl urea is manufactured by reacting ethanolamine with excess urea. The product as sold to the cosmetics industry is prepared by diluting the hydroxyethyl urea with water and neutralizing the excess ammonia generated in the reaction with lactic acid.
  - Specifically, 2-hydroxyethyl urea is made by the deamination of urea and monoethanolamine. This is an equilibrium reaction with the product strongly favored. Ammonia and unreacted monoethanolamine are removed from the reaction by sparging with nitrogen. Lactic acid is added to neutralize any ammonia or monoethanolamine remaining in the product. The product also contains unreacted urea, which can decompose to ammonia and carbon dioxide. CO_2 evolves from the product into the head space; ammonia remains in solution as ammonium lactate. Keeping the pH below 8.25 keeps more than 90% of the ammonia and ethanolamine ionized, preventing decomposition (ammonolysis) of hydroxyethyl urea.

- impurities data
  - Urea <3.0%
  - Ethanolamine: <0.5%
  - 2-oxazolidone: <1.0%
  - N,N 'bis (2-hydroxyethyl urea: <5.0%
  - Diethanolamine <0.025% (residue from ethanolamine

- dermal absorption data:
  - Hydroxyethyl urea is a small molecule with a low molecular weight and high solubility, therefore, dermal absorption may occur. However, this is expected to be limited based on the partition coefficient (log Pow), which is estimated to be -2.06.

- Hydroxyethyl Urea is sold as an aqueous solution of about 50-60%

Concentration of Use by FDA Product Category – Hydroxyethyl Urea

Product Category	Maximum Concentration of Use
Tonics, dressings and other hair grooming aides	0.5%
Other hair preparations (noncoloring)	0.25-2%
Foundations	0.042%
Lipstick	0.009%
Deodorants Not spray	 0.00046%
Face and neck products Not spray	 0.5-2%
Body and hand products Not spray Spray	 0.0091-5% 5%
Moisturizing products Not spray	 1-20.6%
Skin fresheners	2.5%
Other skin care preparations	0.5%

Information collected in 2017

Table prepared September 27, 2017

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Memorandum

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

FROM: Alexandra Kowcz, MS, MBA
Industry Liaison to the CIR Expert Panel

DATE: July 13, 2018

SUBJECT: Scientific Literature Review: Safety Assessment of Hydroxyethyl Urea As Used in Cosmetics (posted June 22, 2018)

The Council respectfully submits the following comments on the Scientific Literature Review Safety Assessment of Hydroxyethyl Urea as Used in Cosmetics.

Physical Chemical Properties - It should be made clear that the mixture that was tested was an aqueous solution.

Impurities - It should also be noted that the NICNAS summary indicated that the purity of the Hydroxyethyl Urea in the aqueous solution "is likely >90%".

Acute, Dermal and Oral - The difference between the 3473 mg/kg and 2000 mg/kg doses is not clear. Does 3473 mg/kg represent mg formulation/kg body weight and 2000 mg/kg/represent mg Hydroxyethyl Urea/kg body weight?

Acute, Inhalation - It does not make sense that the group of rats exposed to the diluted Hydroxyethyl Urea was exposed to the higher concentration. The summary in the NICNAS report says that group 2 was exposed to 5.152 mg/L and that group 3 was exposed to 0.132 mg/L.

DART Studies - Please revise the following sentence: "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."

Summary - It should be made clear that the 1000 mg/kg/day dose NOAEL in the 90-day dermal study in rats was the highest dose tested.

In the description of the micronucleus study please change "2000 mg/kg of an aq. solution containing 57.58% Hydroxyethyl Urea" to "2000 mg/kg <u>as</u> an aq. solution containing 57.58% Hydroxyethyl Urea". This makes it clearer that 2000 mg/kg is the dose of Hydroxyethyl Urea rather than the dose of the aqueous solution containing 57.58% Hydroxyethyl Urea.

Please include the doses used in the guinea pig maximization study.

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