
Safety Assessment of Imidazolidinyl Urea as Used in Cosmetics

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



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Memorandum

To: CIR Expert Panel Members and Liaisons
From: Christina Burnett, Senior Scientific Writer/Analyst
Date: May 10, 2019
Subject: Re-Review of the Safety Assessment of Imidazolidinyl Urea

Imidazolidinyl Urea was one of the first ingredients reviewed by the CIR Expert Panel, and the final safety assessment was published in 1980 with the conclusion “safe when incorporated in cosmetic products in amounts similar to those presently marketed” (*imurea062019origrep*). In 2001, after considering new studies and updated use data, the Panel determined to not re-open the safety assessment (*imurea062019RR1sum*). The minutes from the Panel deliberations of that re-review are included (*imurea062019min_RR1*). Minutes from the deliberations of the original review are unavailable.

Because it has been at least 15 years since the first re-review summary was published, in accord with CIR Procedures, the Panel should again consider whether the safety assessment of Imidazolidinyl Urea should be re-opened. An exhaustive search of the world’s literature was performed for studies dated 1999 forward. A brief synopsis of the relevant data is enclosed (*imurea062019new data*).

Also included for your review are current and historical use data (*imurea062019use tbl*). The frequency of use has decreased since the initial re-review was considered. According to VCRP data, Imidazolidinyl Urea was reported to be used in 2025 formulations in 2001. In 2019, the VCRP indicates that Imidazolidinyl Urea is used in 1558 formulations (*imurea062019fda*). The current maximum concentration of use in leave-on products (0.6%) is nearly the same as that reported in 2001 (0.7%). The maximum concentrations of use by exposure type (e.g., eye area, nails) have decreased in most categories (*imurea062019data1-data2*).

A data profile is included for the original (1980) report and for the data discovered since the first re-review (*imurea062019prof_orig rpt*).

If, upon review of the new studies and updated use data, the Panel determines that a re-review is warranted, a full draft amended report will be presented at an upcoming meeting.

Imidazolidinyl Urea Data Profile* - June 2019 - Christina Burnett

Imidazolidinyl Urea Data Profile* - June 2019 - Christina Burnett																													
				Toxicokinetics			Acute Tox			Repeated Dose Tox			DART		Genotox		Carci		Dermal Irritation			Dermal Sensitization				Ocular Irritation		Clinical Studies	
	Reported Use	Method of Mfg	Constituents/ Impurities	log P/log K _{ow}	Dermal Penetration	ADME	Dermal	Oral	Inhalation	Dermal	Oral	Inhalation	Dermal	Oral	In Vitro	In Vivo	Dermal	Oral	In Vitro	Animal	Human	In Vitro	Animal	Human	Phototoxicity	In Vitro	Animal	Retrospective/ Multicenter	Case Reports
1980 Report Data	X		X				X	X	X	X	X			X						X	X		X	X	X		X	X	X
2019 Re-review	X		X												X								X		X			X	X

* "X" indicates that data were available in a category for the ingredient

Imidazolidinyl Urea RR

SciFin	PubMed	FDA	EU	ECHA	SIDS	ECETOC	HPVIS	NICNAS	NTIS	NTP	WHO	FAO	NIOSH	Web
similar to PubMed results	66 hits		√	√				√						

Search Strategy/PubMed – 3/29/2019 - from 1999 on

Imidazolidinyl Urea or CAS No. 39236-46-9 = 66 hits, 41 ordered or downloaded, 28 relevant

Minutes from the 1st Re-Review of Imidazolidinyl Urea – September 10-11, 2001

Dr. Belsito noted that Imidazolidinyl Urea has been reviewed by CIR, and that the Panel issued a Final Report with the following conclusion in 1980: It is the opinion of the Expert Panel, based on the evidence at hand, which it believes to be relevant and accumulated in a reasonable manner, that the cosmetic ingredient, Imidazolidinyl Urea, is safe when incorporated in cosmetic products in amounts similar to those presently marketed.

After reviewing summaries of studies that have been published since the original Final Report on Imidazolidinyl Urea was issued, the Panel unanimously concluded that the safety assessment should not be reopened and that original conclusion should not be changed.

Current and historical frequency and concentration of use of Imidazolidinyl Urea according to duration and exposure.

	# of Uses		Max Conc of Use (%)	
	2019 ¹	2001 ²	2018 ³	2001 ²
Totals*	1558	2025	0.0000004-0.6	0.01-1
<i>Duration of Use</i>				
<i>Leave-On</i>	1217	1576	0.0002-0.6	0.01-0.7
<i>Rinse-Off</i>	335	363	0.0000004-0.5	0.1-1
<i>Diluted for (Bath) Use</i>	6	86	NR	0.2-0.5
<i>Exposure Type</i>				
Eye Area	336	433	0.2-0.5	0.01-0.6
Incidental Ingestion	2	11	0.2	0.4
Incidental Inhalation-Spray	2; 367 ^a ; 269 ^b	32; 369 ^a ; 202 ^b	0.2-0.6 ^a	0.4-0.5; 0.2-0.6 ^{a,b}
Incidental Inhalation-Powder	82; 269 ^b ; 2 ^c	88; 202 ^b ; 2 ^c	0.2; 0.3-0.5 ^c	0.2-0.4; 0.2-0.6 ^b ; 0.3-0.6 ^c
Dermal Contact	1277	1814	0.000024-0.5	0.01-1
Deodorant (underarm)	3 ^a	4 ^a	0.3 ^a	0.4 ^a
Hair - Non-Coloring	152	125	0.0000004-0.6	0.2-0.5
Hair-Coloring	91	6	0.0006-0.3	0.2-0.4
Nail	6	10	0.0002-0.35	0.2-0.5
Mucous Membrane	42	138	0.00008-0.3	0.2-0.5
Baby Products	4	4	NR	0.3-0.6

*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 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.

NR – not reported

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3. Personal Care Products Council. 2018. Concentration of Use by FDA Product Category: Imidazolidinyl Urea. (Unpublished data submitted by Personal Care Products Council)

New Data – Imidazolidinyl Urea

Definition and Structure

Imidazolidinyl Urea (CAS No. 39236-46-9) is the heterocyclic substituted urea that conforms to the following structure:¹

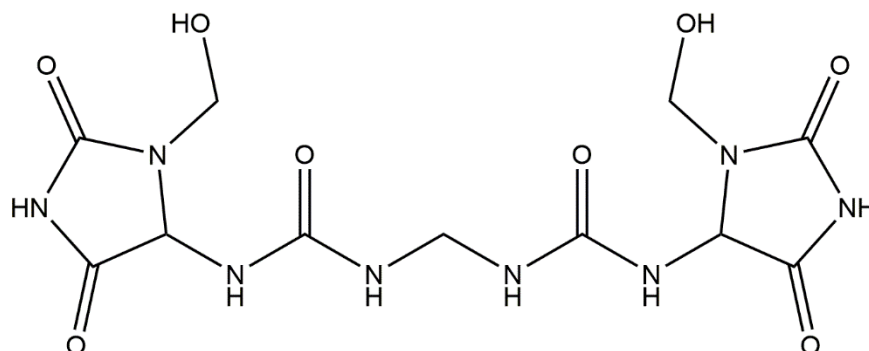


Figure 1. Imidazolidinyl Urea

Formaldehyde Release

The amount of formaldehyde released from Imidazolidinyl Urea and seven other formaldehyde releasing preservatives was dependent on matrix, pH, time, and (mainly) temperature.² The releasing effect was also cosmetic-specific, with more formaldehyde being released in products such as hand cleansers, shampoos, and bath gels than in products such as toothpaste, nail polish, and perfume.

Constituents

Approximately 30 - 40% of Imidazolidinyl Urea has been characterized as a mixture of allantoin, (4-hydroxymethyl-2,5-dioxo-imidazolidine-4-yl)-urea, and 1-(3,4-bis-hydroxymethyl-2,5-dioxo-imidazolidine-4-yl)-1,3-bis-hydroxymethyl-urea.³ The remaining fraction is believed to be polymers of allantoin-formaldehyde condensation products.

Another characterization study of Imidazolidinyl Urea from three different sources (dissolved in aqueous solutions, from patch test materials, and from cosmetics) found the composition to be allantoin, (4-hydroxymethyl-2,5-dioxo-imidazolidine-4-yl)-urea, (3,4-bis-hydroxymethyl-2,5-dioxo-imidazolidine-4-yl)-urea, and (3-hydroxymethyl-2,5-dioxo-imidazolidine-4-yl)-urea.⁴ The two former urea constituents are also common in diazolidinyl urea and may be possible causative agents in cross-reactivity between the two different urea ingredients.

Cosmetic Use

In the European Union, Imidazolidinyl Urea is listed as a preservative in Annex V that is limited to a maximum concentration of 0.6% in ready for use preparations.⁵

The Australian government's National Industrial Chemicals Notification and Assessment Scheme (NICNAS) concluded that Imidazolidinyl Urea should be classified as a hazardous substance with respect to sensitization by skin contact.⁶ The recommended concentration cutoff is $\geq 1\%$.

Non-Cosmetic Use

Imidazolidinyl Urea and other formaldehyde releasers have been researched for use as therapeutic corneal and scleral tissue cross-linking agents.⁷

Genotoxicity

Imidazolidinyl Urea in water (0 - 10,000 $\mu\text{g}/\text{plate}$) was not mutagenic in Ames tests using *Escherichia coli* WP2 uvr A and *Salmonella typhimurium* strains TA 98, TA 100, TA 1535, and TA 1537, with and without metabolic activation.⁸ Additionally, Imidazolidinyl Urea in water (at up to 10.0 $\mu\text{g}/\text{ml}$) did not significantly increase in the proportion of cells showing chromosome aberrations in Chinese hamster ovary cells, with and without metabolic activation.

Dermal Irritation and Sensitization

Imidazolidinyl Urea in dimethylformamide was considered to be sensitizing in the local lymph node assay (LLNA).⁸ The concentrations tested were 10%, 25%, and 50%. Stimulation indices (SI) were greater than 3 at test concentrations of 25% and 50%. No EC₃ values were calculated.

Photomutagenicity and Phototoxicity

Imidazolidinyl Urea (0.2%) was not photomutagenic in an in vitro analysis with *Saccharomyces cerevisiae* FF18733 cells and solar simulated light (0 - 561.6 kJ/m² for long-wave ultraviolet (UVA) light and 0 - 44kJ/m² for mid-wavelength UV (UVB) light).⁹ The cells were incubated with the test material for 2 h without light.

In another in vitro study, Imidazolidinyl Urea was not phototoxic to human erythrocytes.¹⁰ The cells were irradiated with UVA-rich or UVB-rich lamps at 320 - 460 nm or 275 - 365 nm, respectively.

Clinical Assessment of Safety

The optimal patch test concentration in hydrophilic dried-in vehicle (TRUE test) for Imidazolidinyl Urea was determined to be 600 µg/cm².¹¹ This determination was based on randomized, blinded patch testing in 181 patients (12 with previous positive patch tests to Imidazolidinyl Urea) with a dilution series of 0, 7, 22, 67, 200, or 600 µg/cm² of 2% (pet. or aq.) Imidazolidinyl Urea in Finn chambers.

Retrospective and Baseline Assessments

Retrospective and baseline studies that included testing of Imidazolidinyl Urea are summarized in Table 1. Global investigations indicate the positive sensitization rate for Imidazolidinyl Urea ranges from 0.3% to 8.1%.

A retrospective analysis performed by the North American Contact Dermatitis Group (NACDG) on the sensitivity of different vehicles for detecting allergy in different formaldehyde-releasing preservatives determined that petrolatum is significantly more sensitive than an aqueous vehicle in detecting allergy to Imidazolidinyl Urea in patch tests.¹² This study also noted that most patients allergic to Imidazolidinyl Urea are also allergic to formaldehyde; however, most formaldehyde-allergic patients are not allergic to Imidazolidinyl Urea. These results are likely due to the amount of formaldehyde released in patch tests in contrast to the amount that patients are exposed to in products containing these preservatives, and due to the threshold concentration for the elicitation of reactions for formaldehyde.

Case Studies

A 51-year-old woman reported intense itching and acute dermatitis following an ultrasound treatment on her shoulder.¹³ The patient had previously tested positive (++) to Imidazolidinyl Urea (2% pet.). Patch testing with the ultrasound gel had a ++ reaction. The manufacturer of the ultrasound gel reported that it contained Imidazolidinyl Urea.

A 14-year-old girl presented with persistent eczematous lesions on her hands, neck, and face that had been occurring for 3 months.¹⁴ The patient had been using skin and body creams that were marketed for treating eczema. Patch testing was conducted using the Spanish series, the patient's skin products, the cosmetics series, and formaldehyde. Results showed positive reactions to Imidazolidinyl Urea (2% in pet.; D2 +, D4 ++), diazolidinyl urea (2% in pet; D2 ++, D4 +++), and the patient's skin products (as is; D2 ++, D4 +++).

Table 1. Retrospective and baseline studies with Imidazolidinyl Urea

Number of Patients	Clinical Testing Type	Country and Time Span	Results	References
1235	Hermal standard series; no further details provided	Massachusetts from 1990 to 2006	Cross reactions observed between formaldehyde and Imidazolidinyl Urea; positivity rates for the former and latter were 15.6% and 5.4%, respectively	¹⁵
6845	Retrospective study; Finn chambers on Scanpor tape; Imidazolidinyl Urea tested at 2.0% in petrolatum	Australia (3 centers) from 1993 to 2006	Positivity rate to Imidazolidinyl Urea was 1.9%	¹⁶
2453; 342 of which had atopic dermatitis	Patients tested with NACDG standard screening series; Finn chambers on Scanpor tape; concentrations tested not reported	Kansas City and New York City from July 1, 1994 to June 3, 2013	Positivity rate to Imidazolidinyl Urea in patients with atopic dermatitis was 3.80% and in patients without was 1.94%	¹⁷
31,942; comprised of 5306 older patients, 25,028 adult patients, and 1608 child patients	Patients tested with NACDG standard screening series; Imidazolidinyl Urea tested at 2.0% in petrolatum	NACDG from July 1, 1994 to December 31, 2008	Clinically relevant patch test reactions to Imidazolidinyl Urea in older patients was 4.9%, in adult patients was 2.1%, and in children was 0.8%	¹⁸
11,271	European baseline series using Finn chambers on Scanpor tape; Imidazolidinyl Urea was tested at 2.0% in petrolatum; applied to upper back and occluded for 2 days; readings made on day 2, 3 or 4, and 7	Denmark from 1994-2008	Positivity rate to Imidazolidinyl Urea was 0.8%	¹⁹
78,670	Retrospective analysis of patch testing of special preservative series including 2% pet. Imidazolidinyl Urea	Germany, Switzerland, and Austria (IVDK) from 1996-2009	Positivity rate to Imidazolidinyl Urea was 0.6%; concomitant reactions between formaldehyde and Imidazolidinyl Urea were observed	²⁰
3062	Patients tested with British standard series and the European standard series; Imidazolidinyl Urea tested at 2.0% in petrolatum	7 centers in the United Kingdom in 2000	Positivity rate to Imidazolidinyl Urea was 0.5%	²¹
308	Patients tested with European standard series and additional chemicals, including 2% pet. Imidazolidinyl Urea; Finn chambers on Scanpor tape on upper back with readings on day 2 and 4	Turkey from 2000 to 2004	Positivity rate to Imidazolidinyl Urea was 0.3%	²²
1927; with chronic eczema	Patients tested with Hermal series; patches applied for 48 h and test sites were evaluated after 72 and 96 h; Imidazolidinyl Urea tested at 2% in petrolatum	Czech Republic from 2001 to 2006	Positivity rate to Imidazolidinyl Urea was 0.7%	²³
1354	Retrospective analysis of patients patch tested with modified European baseline series. Concentration not provided	China from 2001 to 2006	Positivity rate to Imidazolidinyl Urea was 3.0%	²⁴
5134	Baseline series patch testing performed according to the International Contact Dermatitis Research Group recommendations; Finn chambers on Scanpor tape; Imidazolidinyl Urea tested at 2.0% in petrolatum; readings on days 2 and 4	Australia from January 1, 2001 to December 31, 2010	Positivity rate to Imidazolidinyl Urea was 1.0 % (authors rounded to nearest whole number)	²⁵
6958	Patch tested with the extended British Contact Dermatitis Society Standard series with Finn chambers or IQ chambers; reactions scored on days 2 and 4; Imidazolidinyl Urea	9 centers in the United Kingdom from 2004 to 2005	Positivity rate to Imidazolidinyl Urea was 0.7% in males and 1.0% in females; mean rates for both sexes was 0.9% (95% CI 0.5-1.3)	²⁶

Table 1. Retrospective and baseline studies with Imidazolidinyl Urea

Number of Patients	Clinical Testing Type	Country and Time Span	Results	References
	tested at 2.0% in petrolatum			
350	Patients patch tested with preservatives and a modified European standard series; Finn chambers on Scanpor tape; Imidazolidinyl Urea tested at 2.0% in petrolatum	Singapore from 2006 to 2011	Positivity rate to Imidazolidinyl Urea was 0.57%	²⁷
4232	Screening series patch tests with standardized technique using Finn chambers on Scanpor Tape; Imidazolidinyl Urea tested at 2.0% in petrolatum	NACDG from January 1, 2011 to December 31, 2012	Positivity rate to Imidazolidinyl Urea was 1.6%; rate is decreasing from previous study years (e.g. 3.1% from 2001-2002, 2.9% from 2005-2006)	²⁸
378 eczema patients	Patients patch tested with a modified European standard series. Concentration not provided	China for a 2-year period	Positivity rate to Imidazolidinyl Urea for confirmed allergic contact dermatitis was 8.1%	²⁹

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FINAL REPORT OF THE SAFETY ASSESSMENT FOR IMIDAZOLIDINYL UREA

Imidazolidinyl Urea is used as a preservative in cosmetic formulations. The compound has low acute toxicity by oral, dermal, intraperitoneal, intravenous, and inhalation routes in animals tested. Repeated insult patch tests with 10% Imidazolidinyl Urea on 200 human subjects showed no irritation or sensitization; however, one case of allergic contact sensitization was verified by patch testing with product formulations.

Imidazolidinyl Urea is safe when incorporated in cosmetic products in amounts similar to those presently marketed.

CHEMICAL AND PHYSICAL PROPERTIES

Structure

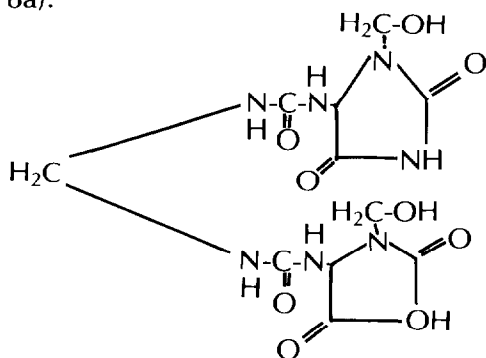
Imidazolidinyl Urea is the name used by the Cosmetic, Toiletry and Fragrance Association, Inc. for a member of a patented family of substituted imidazolidinyl urea compounds (Berke and Rosen, 1970).

Other chemical and trade names for this material include:

Methane bis [N,N' (5-ureido-2,4-diketotetrahydro imidazole)N,N-dimethylol]

N,N'-Methylenebis [N'-[1-(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl] urea]

Imidazolidinyl Urea is a heterocyclic substituted urea with the structure (CTFA, 1978a):



Properties

Imidazolidinyl Urea is a non-aromatic, polar, hydrophilic antimicrobial compound (Ryder, 1974). It is a stable white, water-soluble powder which is odorless, tasteless, and of neutral pH (Berke and Rosen, 1970). It does not absorb ultraviolet light, and decomposes at temperatures above 160°C (Shepard and Wilson, 1974). In aqueous solution the pH is close to neutrality.

No published or unpublished literature was reported on the reactivity of Imidazolidinyl Urea. Theoretically, in the presence of nitrites, *in vivo* and *in vitro* reactions with Imidazolidinyl Urea can lead to N-nitroso ureas and N-nitrosamides. However, to date there are no published data in support of

such hypotheses. Nitrosamides, once formed, are less stable in an aqueous environment than are nitrosamines, and can be hydrolyzed, especially in neutral or alkaline solution (Douglas *et al.*, 1978).

Analytical Methods

Imidazolidinyl Urea can be detected in a wide range of products using thin-layer chromatography (TLC).

The method described by Ryder (1974) uses silica gel 'G'F thin-layer plates; the flow solvent is chloroform:methanol:acetic acid:water (50:30:10:10); the spray reagent is ninhydrin. The plate is heated to 150°C, cooled and viewed under UV light at 366 nm. Imidazolidinyl Urea appears as two pale yellow fluorescent zones at R_fs of 0.27 and 0.35.

Gottschalck and Oelschlager (1977) have described an assay using polyamide thin-layer plates. The ingredient is first detected with K₃[Fe(CN)₆]-Na₂[Fe(CN)₅NO]·2H₂O or with phenyl hydrazine-4-sulfonic acid. Reflectance densitometry at 550 nm is then used to measure the concentration of Imidazolidinyl Urea on the plate.

Martelli and Proserpio (1976) describe a TLC method using heat and spray reagents of HCl, phenylhydrazine-HCl, and K₃[Fe(CN)₆]. With this procedure, Imidazolidinyl Urea (purity unspecified) appears as a red color spot.

Wilson (1975) describes a rapid screening procedure using TLC with 4-methyl umbelliferone and iodine vapor as indicator reagents.

Sheppard and Wilson (1974) describe a fluorometric method for determining the presence of Imidazolidinyl Urea. This method involves the oxidation of the hydroxymethylene groups under mild conditions of temperature (60°C) and pH. The released formaldehyde is reacted with 2,4 pentanedione and ammonia to form 3,5-diacetyl-1,4-dihydrolutidine, which is measured fluorometrically. When the authors applied this method to shampoos and skin creams at concentrations of 0.05, 0.1, and 1.0%, the amount they determined ranged from 104-110% of the amount originally present.

A colorimetric procedure has been developed for the quantitative assay of Imidazolidinyl Urea incorporated in cosmetic emulsions (CTFA, 1978a). Following a series of extractions, the absorbance of the emulsion extract is measured at approximately 520 nm. This absorbance is then compared to the absorbance of standard solutions of Imidazolidinyl Urea. Using the known quantities of Imidazolidinyl Urea in the standard solution and the weight of the test sample, the actual concentration of Imidazolidinyl Urea in the cosmetic emulsion can be determined.

Impurities

Heavy metal (as lead) content of Imidazolidinyl Urea is less than 10 ppm (CTFA, 1978a). Dahlquist and Jergert (1978) list Imidazolidinyl Urea as a formaldehyde-releaser. Sheppard and Wilson (1974) have demonstrated through the use of fluorometric determination that the ingredient releases formaldehyde under the non-physiologic conditions of 60°C and pH 6. Fisher (1978) suggests that such elevated temperatures may give false-positive results due to chemical decomposition of Imidazolidinyl Urea that does not otherwise take place at 37°C as seen using the USP test for formaldehyde (United States Pharmacopeia, 1975).

USE

Purpose and Extent of Use in Cosmetics

Imidazolidinyl Urea is used in cosmetics for its antimicrobial properties. It acts synergistically with other preservatives resulting in a preservative system which gives a wider range of antimicrobial protection. It is effective against both gram-positive and gram-negative bacteria (Berke and Rosen, 1970). The synergistic behavior has been most often observed in combination with the parabens (Berke and Rosen, 1970; Rosen and Berke, 1977a; Rosen et al., 1977b), but has also been reported with sorbic acid, dehydroacetic acid, quaternary ammonium compounds and triclosan (Rosen and Berke, 1977a). Used alone, it is more effective against gram-negative bacteria than other cosmetic preservatives and has strong activity against the deactivating effects of certain common cosmetic components (emulsifiers and proteins) (Rosen and Berke, 1977a). The material is bacteriostatic and/or bactericidal against a wide range of organisms (Table 1) (Berke and Rosen, 1970). The antimicrobial activity of Imidazolidinyl Urea is apparently increased by the presence of proteins, surfactants, and other cosmetic additives (Berke and Rosen, 1970). Imidazolidinyl Urea is one of the most frequently used preservatives in cosmetics (Richardson, 1977). It is used in a wide variety of products including lotions, creams, hair conditioners, shampoos, deodorants, etc., at concentrations of ≤ 0.1 to 5% (Table 2) (FDA, 1976).

TABLE 1. Organisms Susceptible to Bactericidal and/or Bacteriostatic Control by Imidazolidinyl Urea (Berke and Rosen, 1970)

<i>S. aureus</i>	<i>C. albicans</i>
<i>S. aureus</i> (penicillin resistant)	<i>L. casei</i>
<i>E. coli</i>	<i>P. vulgaris</i>
<i>B. ammoniogenes</i>	<i>L. bifidus</i>
<i>B. subtilis</i>	<i>N. asteroides</i>
<i>S. albus</i>	<i>M. gypseum</i>
<i>P. ovale</i>	<i>T. mentagrophytes</i>
<i>C. acnes</i>	<i>St. pyogenes</i>
<i>S. faecalis</i>	<i>S. typhosa</i>
<i>S. epidermis</i>	<i>M. rubens</i>
<i>A. aerogenes</i>	<i>M. luteus</i>
<i>Ps. aeruginosa</i>	<i>B. cereus</i>
	<i>Flavobacterium solari</i>

Frequency or Duration of Application

Products containing Imidazolidinyl Urea (Table 2) are used on all body surfaces and around all body orifices.

Imidazolidinyl Urea is applied to the body as often as several times a day in lipsticks, face, body, and hand creams and lotions, or as infrequently as once each month or two in hair coloring preparations. It remains on the skin from a few minutes to several days.

TABLE 2. Product Formulation Data (FDA, 1976)

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product Formulations
Imidazolidinyl Urea	Baby shampoos	>0.1 to 1	1
		≤0.1	1
	Lotions, oils, powders, and creams	>0.1 to 1	1
	Bath oils, tablets, and salts	>0.1 to 1	12
	Bubble baths	>0.1 to 1	12
		≤0.1	3
	Bath capsules	>0.1 to 1	1
	Other bath preparations	>0.1 to 1	11
		≤0.1	1
	Eyebrow pencil	>0.1 to 1	11
		≤0.1	2
	Eyeliner	>0.1 to 1	72
		≤0.1	27
	Eye shadow	>1 to 5	1
		>0.1 to 1	167
		≤0.1	86
	Eye makeup remover	>0.1 to 1	3
	Mascara	>0.1 to 1	37
		≤0.1	9
	Other eye makeup preparation	>0.1 to 1	16
		≤0.1	2
	Colognes and toilet waters	≤0.1	1
	Powders (dusting and talcum) (excluding after shave talc)	>0.1 to 1	44
		≤0.1	8
	Sachets	>0.1 to 1	12
		≤0.1	1
	Other fragrance preparations	≤0.1	2
	Hair conditioners	>1 to 5	2
		>0.1 to 1	20
		≤0.1	13
	Permanent waves	>0.1 to 1	1
	Rinses (noncoloring)	>1 to 5	1
		>0.1 to 1	4
		≤0.1	1
	Shampoos (noncoloring)	>1 to 5	3
		>0.1 to 1	37
		≤0.1	3
	Tonics, dressings, and other hair grooming aids	>0.1 to 1	4
		≤0.1	4
	Wave sets	>0.1 to 1	1
		≤0.1	3

TABLE 2. (continued) Product Formulation Data

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product Formulations
Imidazolidinyl Urea (continued)	Other hair preparations	>0.1 to 1	2
		≤0.1	2
	Hair shampoos (coloring)	>0.1 to 1	1
	Other hair coloring preparations	≤0.1	1
	Blushers (all types)	>1 to 5	1
		>0.1 to 1	37
		≤0.1	16
	Face powders	>1 to 5	1
		>0.1 to 1	93
		≤0.1	13
	Foundations	>1 to 5	1
		>0.1 to 1	58
		≤0.1	9
	Leg and body paints	>0.1 to 1	1
	Lipstick	≤0.1	5
	Makeup bases	>0.1 to 1	27
		≤0.1	3
	Rouges	>0.1 to 1	12
		≤0.1	6
	Makeup fixatives	>0.1 to 1	1
		≤0.1	1
	Other makeup preparations	>0.1 to 1	3
		≤0.1	4
	Basecoats and undercoats	≤0.1	1
	Cuticle softeners	>0.1 to 1	4
		≤0.1	6
	Bath soaps and detergents	≤0.1	3
	Deodorants (underarm)	>0.1 to 1	2
		≤0.1	2
	Other personal cleanliness products	≤0.1	1
	Men's talcum	>0.1 to 1	1
	Shaving cream (aerosol, brushless, and lather)	≤0.1	1
	Cleansing (cold creams, cleansing lotions, liquids, and pads)	>1 to 5	2
		>0.1 to 1	51
		≤0.1	18
	Face, body, and hand (excluding shaving preparations)	>0.1 to 1	42
		≤0.1	16
	Foot powders and sprays	>0.1 to 1	1
	Moisturizing	>1 to 5	1
		>0.1 to 1	64
		≤0.1	29
	Night	>1 to 5	1
		>0.1 to 1	18
		≤0.1	9

TABLE 2. (continued) Product Formulation Data

Ingredient	Cosmetic Product Type	Concentration (%)	Number of Product Formulations
Imidazolidinyl Urea (continued)	Paste masks (mud packs)	>0.1 to 1	20
		≤0.1	3
	Skin fresheners	>0.1 to 1	16
		≤0.1	5
	Wrinkle smoothing (removers)	>0.1 to 1	3
	Other skin care preparations	>0.1 to 1	30
		≤0.1	12
	Suntan gels, creams, and liquids	>0.1 to 1	10
		≤0.1	4
	Other suntan preparations	>0.1 to 1	1

BIOLOGICAL PROPERTIES

Animal Toxicology

General Studies

Acute

Oral Sherman-Wistar rats, fasted 24 hours before treatment, were given doses of Imidazolidinyl Urea ranging from 3.15 to 7.90 g/kg by stomach tube. Animals were observed for 14 days; all deaths occurred in the first day. The acute oral LD50 was calculated by the Thompson Moving Average Method to be 5.2 (4.2—6.4) g/kg (Sutton Laboratories, 1973a).

In a second study, Imidazolidinyl Urea, dissolved in water, was administered to Wistar rats by stomach tube at seven dose levels (6.2—18.7 g/kg); the animals were then fasted for six hours. The LD50 was calculated by the Litchfield and Wilcoxin method as 11.3 g/kg (95% confidence limits 9.7—13.2 g/kg). In each dose group, observed spontaneous activity decreased and/or disappeared. The righting reflex and lacrimation decreased and/or disappeared, respiration was slow and deep and the hind legs showed signs of ataxia and paralysis (Takasago, 1974a). In a similar study conducted with mice given 4.3 to 13 g/kg, the LD50 was calculated to be 7.2 g/kg (confidence limits 6.2—8.4 g/kg). A dose of 9.0 g/kg decreased spontaneous and reflex activity 30 minutes after dosing in about 50% of the animals. The righting reflex and withdrawal reflex of the hind legs disappeared 60 minutes after dosing at the 12.96 g/kg dose level. The animals had diarrhea, showed hyperemia of the gastric and duodenal mucosae, and had bloody intestinal contents (Takasago, 1974a).

Fasted male and female Wistar rats were given single doses of Imidazolidinyl Urea (1.0, 2.0, 4.0, 5.0, and 8.0 g/kg) by gastric intubation and observed for 14 days; none died. Although no untreated controls were used for comparison, animals receiving doses up to 5.0 g/kg gained weight normally. Those receiving 5.0 g/kg had diarrhea one hour after dosing, but recovered in 20 to 44

hours. The 8.0 g/kg dose caused diarrhea, lethargy, and temporary loss of weight two to 40 hours after intubation. They recovered completely by 48 hours (Berke and Rosen, 1970).

Ten female Holtzman rats (200-300 g) were given 5 g/kg of the ingredient by gastric intubation and observed for 14 days. One animal died (Berke and Rosen, 1970).

An oral dose of Imidazolidinyl Urea of 8 g/kg to rats produced no lasting toxic effects (Schmidt, 1976).

Dermal Acute dermal toxicity studies in rabbits were conducted (Sutton, 1972, 1973b) with the methods described under Section 191.10 of the Final Order, Enforcement Regulations (Fed. Reg. 1961). The first study consisted of dose levels of 2 and 4 g/kg applied as a 50% w/w solution in water (Sutton, 1972). The second study consisted of five dose levels ranging from 0.5 to 8.0 g/kg of the solid (Sutton, 1973b). The animals were observed for 14 days; none died. No symptoms were reported. The acute dermal LD50 in rabbits is greater than 8.0 g/kg.

A number of primary skin irritation studies have been conducted (Berke and Rosen, 1970; Sutton, 1973c, Takasago, 1974b). When the methods prescribed for classification under the Federal Hazardous Substances Labeling Act, Imidazolidinyl Urea (50% w/w solution in water) were used, no erythema or edema occurred at the intact skin sites in any of six albino rabbits used. There were moderate to severe erythema and edema at the abraded skin sites in all animals. The Primary Irritation Index was calculated to be 3.08 out of a maximum 8.00 (Sutton, 1973c).

No irritancy occurred when a dose of 0.5 g of the dry ingredient was applied to normal and abraded skin on three rabbits. The animals were examined at 24 and 72 hours and evaluated by the Draize method for erythema and edema (Berke and Rosen, 1970).

Imidazolidinyl Urea was applied to the shaved backs of six albino rabbits at concentrations of 0, 1, 2.5, and 5%. Irritation indices of zero were obtained at all levels during the seven days of observation. It was concluded that Imidazolidinyl urea is non-irritating to the skin at concentrations up to 5% (Takasago, 1974b).

Eye Three groups of three albino rabbits were tested and scored according to the Draize procedure. Each group received 0.1 ml of test solution in the right eye. The eyes were scored and examined for up to seven days. The aqueous solutions containing 5, 10, and 20% Imidazolidinyl Urea produced no irritation (Berke and Rosen, 1970).

An eye irritation study was performed on six albino rabbits using procedures recommended by the Federal Hazardous Substances Labeling Act. Imidazolidinyl Urea used as a fine white powder, produced mild transient conjunctival irritation which cleared by the second or third day. The material had no effect on the cornea or iris (Sutton, 1973d).

In another test on five rabbits, single instillations of 10 or 20% Imidazolidinyl Urea in the left eye had no irritant effect on the cornea, iris, or conjunctiva after three and 24 hours (Takasago, 1974c). The right eye acted as the control and received doses of distilled H₂O.

Three albino rabbits were used in a standard Draize eye test procedure. A 5% solution of Imidazolidinyl Urea (0.1 ml) was instilled into the eye on three successive days. None of the animals had any visible irritation and the author concluded that 5% Imidazolidinyl Urea is non-toxic to the eye (Avon, 1970a).

Intraperitoneal Intraperitoneal injections of a 50% solution of the ingredient were given in doses of 1.0, 2.0, and 4.0 g/kg to female rats, one rat per dose. The rat receiving the high dose died within 21 hours. The other two showed ataxia, lethargy, abnormal posture, and abdominal swelling but recovered in 21 hours. No further signs of toxicity were seen in the following two weeks (Berke and Rosen, 1970).

Intravenous A dose of approximately 160 mg/kg was injected intravenously into a rabbit as 1.0 ml of a 50% aqueous solution. There was no evidence of toxicity during one week of observation (Berke and Rosen, 1970). A second rabbit received an intravenous injection of 2.0 g/kg of a 50% aqueous solution. In the first day, the animal showed signs of pain and lethargy, and had increased body temperature. The effects had disappeared in 24 hours, and no further signs of toxicity were noted during the subsequent two weeks (Berke and Rosen, 1970).

An intravenous injection of 2 g/kg of body weight of Imidazolidinyl Urea administered to rabbits had no lasting toxic effects (Schmidt, 1976).

Inhalation Ten Wistar-Sherman rats were exposed to Imidazolidinyl Urea in the air as a dust. The animals were placed in a testing chamber and an atmosphere of 5.5 mg/l Imidazolidinyl Urea (nominal concentration of 5.1 mg/l) established. The one-hour exposure time was measured from the moment a fog was observed in the testing chamber (about eight minutes). In 40 minutes, the rats had watery eyes and noses, and labored and slow breathing; several animals were gasping. At the end of fifty minutes, most of the animals' eyes were nearly closed and all were gasping. All animals survived the one-hour exposure and the 14-day observation period that followed. Another group of ten Wistar-Sherman rats was similarly exposed to an aerosol of a 50% aqueous solution of Imidazolidinyl urea. The concentration measured in the exposure chamber was 4.3 mg/l. These rats were not as severely affected as those in the above test. It was concluded that Imidazolidinyl Urea has an LC50 greater than 5 mg/l when administered to rats by continuous inhalation for one hour (Sutton, 1973e).

Subchronic

Oral Two male and two female adult rats received a 0.5% aqueous solution of Imidazolidinyl Urea in lieu of drinking water for 25 days. The animals were then placed on water alone for 14 days. Four control animals received regular drinking water. There was no evidence of toxicity (Berke and Rosen, 1970).

In a 90-day feeding study, 70 weanling albino rats were assigned to five groups each consisting of seven males and seven females. The animals received diets containing graded amounts of the test material that provided daily

intakes of 0, 6, 28, 130, and 600 mg/kg of body weight. During the 90-day period of this experiment, no deaths occurred although male rats on 28, 130, and 600 mg/kg diets had lower weight gains but showed no toxic effects. The hematology, biochemistry, urinalysis, and pathology of these animals did not differ significantly from those of the control animals. Imidazolidinyl Urea, when fed to rats for 90 days, inhibits growth, particularly in doses above 28 mg/kg/day in males; it has no effect on females at dose levels up to 600 mg/kg/day. It is essentially non-toxic to rats under the conditions used in the study (Sutton, 1973f).

Dermal Imidazolidinyl Urea was applied daily to the shaved backs of albino rabbits. Five groups consisting of five male and five female animals each were exposed to the material for six hours per day, five days per week, for three weeks. Intact skin was exposed in three males and two females of each group, and abraded skin in the remaining two males and three females. One group was sham treated as a control, the other four groups received the following graded levels of the undiluted test material: 20, 45, 90, and 200 mg/kg/day. Imidazolidinyl Urea was introduced as a fine white powder under a patch of surgical gauze and the entire trunk was wrapped with impervious cloth. Exposure sites were observed before each treatment and tissue reactions were scored quantitatively for gross signs of erythema and/or edema, using the Draize system of scoring. Daily skin scores indicated occasional slight erythema with no score exceeding one (4 maximum score), and no edema for animals for either abraded or intact skin in all five groups. On microscopic examination, treated skin showed slight to mild, superficial acute or chronic dermatitis, sometimes with focal ulceration and pustule formation. There was no evidence of any effect on growth, hematology, urinalysis, or gross pathology related to treatment. There was a slight to mild inflammatory and focal ulcerative effect from Imidazolidinyl Urea (Sutton, 1973g).

Eight male guinea pigs received ten intracutaneous injections of 0.1% Imidazolidinyl Urea in physiological saline. The first injection was 0.05 ml, the others 0.1 ml on alternate days into the same 3-4 sq. cm area. Two weeks after the last injection, another 0.05 ml of fresh solution was injected. Twenty-four hours after each injection, the animals were examined and the results scored. The average reading after the last injection was less than the average of the previous ten readings. It was concluded that this ingredient did not produce sensitization in this test (Berke and Rosen, 1970).

In a phototoxicity study, Imidazolidinyl Urea (5, 2.5, 1%, and control) was injected intradermally into the shaved backs of female Hartley guinea pigs. After the injection, the animals were irradiated with FL20E and FL20BLB light (emission spectra or energy output not given) for a total of 30 minutes, but no reaction occurred. Twenty-four hours after the first injection, the animals were again injected, irradiated, and observed, again with no reactions. The procedure was carried out again 48 hours after the first injection with still no results. The authors concluded that Imidazolidinyl Urea has no phototoxicity under these conditions (Takasago, 1974d).

In a repeated open patch test, 5% Imidazolidinyl Urea was applied daily (.5 ml) for three successive days to the shaved skin of rabbits. There was no visible evidence of skin irritation (Avon, 1970b).

Preliminary results have been reported on an experimental study to evaluate new methods for identifying weak contact allergens in the guinea pig. Imidazolidinyl Urea was tested by five different assay procedures, each of which used ten Hartley female guinea pigs (Maguire, 1978). Ten and 50% concentrations of Imidazolidinyl Urea in petrolatum were not found to be sensitizers or contact allergens when tested by the Buehler, Magnusson-Kligman guinea pig maximization, or cyclophosphamide-CFA tests. The Draize intradermal technique (0.5 ml injections of 0.1% Imidazolidinyl Urea in saline) also failed to elicit any sensitization or contact allergy from the compound. It was found that the ingredient at 10% concentration was not a sensitizer by the split adjuvant method. A 50% solution of Imidazolidinyl Urea was shown to be a contact allergen according to the latter test method. Two of ten guinea pigs showed definite positive reactions at second challenge with 50% Imidazolidinyl Urea and appropriate controls. The author raises the question of whether a high concentration of the material is needed to bring out the sensitivity and/or whether the guinea pigs were boosted in sensitivity by previous application of 10% concentrations of the material (Maguire, 1978).

Special Studies

Teratology After virgin adult female albino mice were mated with young adult males, the appearance of vaginal sperm plugs established day zero of gestation. Beginning on day six and continuing through day 15, the females received by oral intubation graded doses of 30, 95, and 300 mg/kg Imidazolidinyl Urea. Negative control animals were sham-treated. Apsirin served as a positive control. On day 17, the embryos were removed post mortem by Cesarean section and the number of implant sites, resorption sites, and live and dead fetuses recorded. Imidazolidinyl Urea appeared to cause a slight increase in the number of resorptions and/or fetal deaths *in utero*, but the number of abnormalities in either soft or skeletal tissue did not differ from that which occurred in the sham-treated controls. In these experiments at least, Imidazolidinyl Urea was slightly fetotoxic but not teratogenic in mice (Sutton, 1973h).

Other Studies Acute oral and primary irritation studies on rats and rabbits, respectively, have been conducted with cosmetic formulations containing Imidazolidinyl Urea. The results of these studies showed no adverse effects that could be attributed to Imidazolidinyl Urea (CTFA, 1976b, a).

Clinical Assessment of Safety

Skin Irritation and Sensitization Single insult 24-hour occlusive patch tests using 0.1, 1, and 10% aqueous solutions of Imidazolidinyl Urea were performed on 29 human volunteers. All of these doses gave irritation indices of zero (Takasago, 1974). In another single insult 24-hour occlusive patch test,

10% aqueous Imidazolidinyl Urea was applied to 20 human volunteers. An index of zero was obtained for 19 subjects, and an index of 0.5 obtained for the other subject. Imidazolidinyl Urea was considered to be essentially nonirritating under these conditions (Avon, 1972).

A repeated insult patch test was conducted on a group of 200 subjects with a 10% aqueous solution of Imidazolidinyl Urea. Lintine disks moistened with the test solution were placed on predesignated sites, covered, and sealed with overlapping strips of Blenderm tape. After 24 hours, the patch was removed and the site examined. Contact sites were left undisturbed for 24 hours and then re-examined for any changes since the previous reading. If the sites manifested no changes, the test material was reapplied. This cycle was repeated on Mondays, Wednesdays, and Fridays. A 48-hour rest period between removal and reapplication was permitted on weekends. Following the 15th application, the subjects were rested for two weeks before being challenged. The test material was reapplied to the previous test sites and left for 24 hours under occlusion. At the end of the 24 hours, the contact site was read immediately and again after intervals of 24 and 48 hours. There were no visible skin changes after any of the 15 applications or challenges. The authors concluded that Imidazolidinyl Urea does not cause primary irritation or sensitization when conditions of contact do not exceed those of the test procedures (Avon, 1973).

A repeat insult patch test was conducted with a liquid makeup preparation containing Imidazolidinyl Urea in a 0.50% concentration. Occlusive patches impregnated with the test material were applied to the backs of 189 Caucasian subjects and left on the skin for 48 hours. Upon removal of the patches, the skin sites were observed for signs of immediate reaction and then again one to two hours later for signs of delayed reaction. New patches were applied following the second examination and the sequence was repeated. Eleven applications of the test material were made. No evidence of primary irritation or allergic contact sensitization was observed (CTFA, 1974a).

Imidazolidinyl Urea (0.5%) in a night cream was tested for accumulation irritancy with Maibach's repeat insult patch test on eight human subjects. An average irritancy index of 0.003 (4.0 max.) was obtained for the formulation, leading the author to conclude that the formulation was exceptionally mild, evoking little or no irritation (CTFA, 1974b).

In a recent study of 30 formaldehyde-sensitive patients, Imidazolidinyl Urea as a 2% aqueous solution produced a positive patch test in one patient. The author concludes that from this series of tests, Imidazolidinyl Urea is safe for use in formaldehyde-sensitive individuals, and should not be classified as a "formaldehyde donor." The investigator, a dermatologist, also noted that another patient, not included in the above test, who had shown a positive patch test reaction to Imidazolidinyl Urea was negative when tested with only formaldehyde. These findings would support the view that sensitization to Imidazolidinyl Urea and formaldehyde are distinct and separate sensitization (CTFA, 1977).

Use Test In a clinical usage study, a liquid makeup preparation containing 0.5% Imidazolidinyl Urea was given to 84 subjects with instructions to use the product for one month on a regular basis in the same manner as they would use a comparable preparation. No adverse reactions were reported after one month (CTFA, 1974a).

Photo In-Use Test Studies for photo sensitization under conditions of use were conducted in southern Florida with a moisturizing cream and a hand and body lotion both containing Imidazolidinyl Urea at a 0.5% concentration. Women (50 in each study) were instructed to use the products daily for four weeks, discontinue for one week, and reapply the preparations for one week. There was no evidence of any contact or photoallergic sensitivity in any of the subjects (CTFA, 1978b, c).

Usage Experience A case of allergic contact sensitivity to Imidazolidinyl Urea has been reported in a 49-year old white woman from the use of a moisturizing lotion and an eyeliner. Diagnostic patch testing gave a 3+ reaction to a 1% solution of Imidazolidinyl Urea. Two plus (2+) reactions were observed with the products. No positive reactions were obtained from the other unspecified product components tested or to formaldehyde (Mandy, 1974, 1978; Fisher, 1975).

Six cases of cosmetic ingredient related allergic contact dermatitis involving Imidazolidinyl Urea were reported to the Food and Drug Administration (FDA) by dermatologists in the North American Contact Dermatitis Group. These cases were observed following examination of over 2000 contact dermatitis cases from November 15, 1976, through November 15, 1977 (FDA, 1976, 1977).

The North American Contact Dermatitis Group (NACDG) has reported that in their diagnostic patch testing studies using 27 allergens conducted between July 1, 1975, and June 30, 1976, Imidazolidinyl Urea, 2% (aqueous), had a 0.9% frequency of reaction (Rudner, 1977). Unpublished results for patch testing by the Group from July 1, 1976, to June 30, 1977 showed 2% aqueous Imidazolidinyl Urea to have a 1% reactivity of 2,080 male and female patients tested (NACDG, 1977).

SUMMARY

1. Imidazolidinyl Urea is a widely used preservative in cosmetic formulations at concentration ranges of ≤ 0.1 , >0.1 to 1, and >1 to 5%.
2. These cosmetic formulations are applied to many skin areas.
3. The compound has low acute toxicity by oral, dermal, intraperitoneal, intravenous, and inhalation routes in animals tested.
4. Single applications produce little or no irritation in eyes or on the skin of rabbits.
5. It has low subchronic toxicity by oral routes of administration in rats.
6. The powder is mildly irritating but nontoxic in subchronic occluded skin painting of rabbits.
7. It is not phototoxic by repeated intradermal injection of guinea pigs.

8. There are no data on chronic studies available nor is there information on absorption, excretion, and metabolism.
9. Imidazolidinyl Urea is slightly fetotoxic, but not teratogenic in mice at daily dose levels of 300 mg/kg administered from day 6 to 15 of gestation.
10. Repeated insult patch tests with 10% Imidazolidinyl Urea on 200 human subjects showed no irritation or sensitization.
11. One case of allergic contact sensitization was verified by patch testing with product formulations.
12. Six cases of allergic contact dermatitis attributable to Imidazolidinyl Urea were reported to the Food and Drug Administration in the period 1976-77. These six cases were observed following examination of over 2000 allergic contact dermatitis cases reported to the FDA in that 12-month period.
13. The North American Contact Dermatitis Group reports 2% aqueous Imidazolidinyl Urea to have a 1% reactivity in 2,080 patients patch tested during 1976-77.

The safety assessment of this ingredient rests on the information at hand and on its considerable usage at various concentrations in a variety of cosmetic products. Results of studies reviewed show a very low toxicity and the absence of important risk at present levels of use. Additional biological assessment might reasonably be considered to include animal studies in absorption, metabolism, chronic toxicity, and mutagenicity and human studies in photo-sensitization and phototoxicity.

CONCLUSIONS

It is the opinion of the Expert Panel, based on the evidence at hand, which it believes to be relevant and accumulated in a reasonable manner, that the cosmetic ingredient, Imidazolidinyl Urea, is safe when incorporated in cosmetic products in amounts similar to those presently marketed.

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¹Cosmetic, Toiletry and Fragrance Association, Inc.²Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, DC 20005.

Table 11 presents the available use information for Glycol Distearate.

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IMIDAZOLIDINYL UREA

A safety assessment of Imidazolidinyl Urea was published in 1980 with the conclusion that this ingredient is “safe when incorporated in cosmetic products in amounts similar to those presently marketed” (Elder 1980). New studies, along with the updated information below regarding uses and use concentrations, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

In 1976, Imidazolidinyl Urea was used in 1061 cosmetic products, with the largest single use in face powder products in the concentration range of $\leq 0.1\%$ to 5%. In 2001, there were uses reported in 2025 products, with the largest single use in eye shadow (FDA 2001). In 2001, the maximum use concentration

TABLE 12
 Imidazolidinyl Urea use

Product category	1976 use (Elder 1980)	2001 use (FDA 2001)	1976 concentrations (Elder 1980)	2001 concentrations (CTFA 2001)
Baby shampoos	2	1	$\leq 0.1\%$ –1%	0.5%
Baby lotions, oils, powders, etc.	1	2	$> 0.1\%$ –1%	0.3%–0.6%
Other baby products	—	1	—	0.3%
Bath oils, tablets, and salts	12	—	$> 0.1\%$ –1%	0.2%–0.5%
Bubble baths	15	26	$\leq 0.1\%$ –1%	0.3%–0.4%
Other bath preparations	12	60	$\leq 0.1\%$ –1%	0.5%
Eyebrow pencil	13	4	$\leq 0.1\%$ –1%	0.3%
Eyeliners	99	18	$\leq 0.1\%$ –5%	0.01%–0.6%
Eye shadow	—	301	—	0.2%–0.5%
Eye lotion	—	7	—	0.5%
Eye makeup remover	3	16	$\leq 0.1\%$ –1%	0.1%–0.5%
Mascara	46	59	$\leq 0.1\%$ –1%	0.3%–0.5%
Other eye makeup preparations	18	28	$\leq 0.1\%$ –1%	0.3%–0.5%
Colognes and toilet waters	1	3	$\leq 0.1\%$	0.4%
Perfumes	—	11	—	0.4%–0.5%
Powders	52	19	$\leq 0.1\%$ –1%	0.2%–0.4%
Sachets	13	—	$\leq 0.1\%$ –1%	0.1%
Other fragrance preparations	2	17	$\leq 0.1\%$	0.4%–0.5%
Hair conditioners	35	35	$\leq 0.1\%$ –5%	—
Hair sprays (aerosol fixatives)	—	1	—	0.4%
Permanent waves	1	6	$\leq 0.1\%$ –1%	—
Rinses (noncoloring)	6	2	$\leq 0.1\%$ –5%	0.2%
Shampoos (noncoloring)	43	46	$\leq 0.1\%$ –5%	0.2%–0.5%
Hair tonics, dressings, etc.	8	24	$\leq 0.1\%$ –1%	0.4%
Wave sets	4	3	$\leq 0.1\%$ –1%	0.3%
Other hair preparations	4	7	$\leq 0.1\%$ –1%	0.2%
Hair dyes and colors	—	3	—	—

(Continued on next page)

²Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

TABLE 12
Imidazolidinyl Urea use (*Continued*)

Product category	1976 use (Elder 1980)	2001 use (FDA 2001)	1976 concentrations (Elder 1980)	2001 concentrations (CTFA 2001)
Hair tints	—	—	—	0.4%
Hair rinses (coloring)	—	1	—	0.2%
Hair bleaches	—	—	—	0.4%
Hair shampoos (coloring)	1	1	>0.1%–1%	—
Other hair-coloring preparations	1	1	≤0.1%	—
Blushers (all types)	54	120	≤0.1%–5%	0.2%–0.4%
Face powders	107	69	≤0.1%–5%	0.2%–0.3%
Foundations	68	98	≤0.1%–5%	0.2%–0.5%
Leg and body paints	1	2	>0.1%–1%	0.2%
Lipstick	5	11	≤0.1%	0.4%
Makeup bases	30	38	≤0.1%–1%	0.3%
Rouges	18	2	≤0.1%–1%	0.3%–0.5%
Makeup fixatives	2	3	≤0.1%–1%	0.3%
Other makeup preparations	7	27	≤0.1%–1%	0.2%–0.5%
Basecoats and undercoats	1	—	≤0.1%–1%	—
Cuticle softeners	10	4	≤0.1%–1%	0.3%
Nail creams and lotions	—	4	—	0.2%
Nail polish and enamel	—	—	—	0.2%–0.5%
Other manicuring preparations	—	2	—	0.2%
Bath soaps and detergents	3	36	≤0.1%	0.4%–0.5%
Deodorants (underarm)	4	4	≤0.1%–1%	0.4%
Feminine deodorants	—	—	—	0.2%
Other personal cleanliness products	1	5	≤0.1%	0.2%–0.3%
Aftershave lotion	—	19	—	0.3%–0.6%
Men's talcum	1	—	>0.1%–1%	—
Shaving cream	1	15	≤0.1%	0.1%–1%
Other shaving preparation products	—	4	—	—
Skin cleansing preparations	71	128	≤0.1%–5%	0.2%–0.6%
Face and neck skin preparations ^a	58	41	≤0.1%–1%	0.3%–0.6%
Body and hand skin preparations ^a	—	157	≤0.1%–1%	0.3%–0.6%
Foot powders and sprays	1	4	≤0.1%–1%	0.3%–0.4%
Moisturizing preparations ^b	94	215	≤0.1%–5%	0.4%–0.6%
Wrinkle smoothing (removers) ^b	3	—	0.1%–1%	—
Night creams, lotions, etc.	28	60	≤0.1%–5%	0.5%
Paste masks (mud packs)	23	60	≤0.1%–1%	0.3%–0.5%
Skin fresheners	21	35	≤0.1%–1%	0.3%–0.5%
Other skin care preparations	42	124	≤0.1%–1%	0.1%–0.7%
Suntan gels, creams, and liquids	14	15	≤0.1%–1%	0.3%–0.5%
Indoor tanning preparations	—	12	—	0.2%–0.5%
Other suntan preparations	1	8	>0.1%–1%	0.2%–0.5%
Totals/ranges	1061	2025	≤0.1%–5%	0.1%–1%

^aOriginally, Face and Neck and Body and Hand were combined as one category, but now they are separated.

^bWrinkle smoothing (removers) is now part of the Moisturizing category.

was 1% (CTFA 2001). Table 12 presents the available use information for Imidazolidinyl Urea.

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ISOPROPYL LANOLATE

A safety assessment of Isopropyl Lanolate was published in 1980 with the conclusion that this ingredient is “safe as currently used in cosmetic products” (Elder 1980). New studies, along with the updated information below regarding types and concentrations of use, were considered by the CIR Expert Panel. The Panel determined to not reopen this safety assessment.

The CIR Expert Panel did note that a safety assessment of Lanolin itself and eight derivatives were completed in 1980 (Elder 1980) and safety assessments of polyethylene glycol lanolins were published in 1982 (Elder 1982) and 1996 (Andersen 1996). In all cases, the lanolin ingredients were found safe as used in cosmetic formulations.

As with plant-derived cosmetic ingredients, the CIR Expert Panel has a long history of reviewing animal-derived cosmetic ingredients. It is now common to remind manufacturers that cosmetic products containing any animal-derived ingredient should be formulated to limit the presence of pesticide/heavy metal residues as follows: lead ≤ 0.1 ppm; arsenic ≤ 3 ppm; mercury ≤ 1 ppm; total PCB/pesticide contamination ≤ 40 ppm with ≤ 10 ppm for any specific residue (Andersen 1998). Likewise, the Panel has concluded that cosmetic products containing any animal-derived ingredient should be formulated to be free of detectable pathogenic viruses or infectious agents (CIR 1999).

In 1976, Isopropyl Lanolate was used in 1194 cosmetic products, with the largest single use in lipsticks. In 2001, there were 415 reported uses (FDA 2001), again with the largest single use in lipstick products in a concentration range of 2% to 14% (CTFA 2001). Table 13 presents the available use information for Isopropyl Lanolate.

²Available from Director, Cosmetic Ingredient Review, 1101 17th Street NW, Suite 310, Washington, DC 20036, USA.

2019 VCRP RAW DATA

01A - Baby Shampoos	IMIDAZOLIDINYL UREA	1
01B - Baby Lotions, Oils, Powders, and Creams	IMIDAZOLIDINYL UREA	2
01C - Other Baby Products	IMIDAZOLIDINYL UREA	1
02B - Bubble Baths	IMIDAZOLIDINYL UREA	1
02D - Other Bath Preparations	IMIDAZOLIDINYL UREA	5
03A - Eyebrow Pencil	IMIDAZOLIDINYL UREA	1
03B - Eyeliner	IMIDAZOLIDINYL UREA	13
03C - Eye Shadow	IMIDAZOLIDINYL UREA	245
03D - Eye Lotion	IMIDAZOLIDINYL UREA	21
03E - Eye Makeup Remover	IMIDAZOLIDINYL UREA	7
03F - Mascara	IMIDAZOLIDINYL UREA	30
03G - Other Eye Makeup Preparations	IMIDAZOLIDINYL UREA	19
04C - Powders (dusting and talcum, excluding aftershave talc)	IMIDAZOLIDINYL UREA	19
05A - Hair Conditioner	IMIDAZOLIDINYL UREA	18
05B - Hair Spray (aerosol fixatives)	IMIDAZOLIDINYL UREA	2
05C - Hair Straighteners	IMIDAZOLIDINYL UREA	2
05D - Permanent Waves	IMIDAZOLIDINYL UREA	4
05F - Shampoos (non-coloring)	IMIDAZOLIDINYL UREA	76
05G - Tonics, Dressings, and Other Hair Grooming Aids	IMIDAZOLIDINYL UREA	26
05H - Wave Sets	IMIDAZOLIDINYL UREA	1
05I - Other Hair Preparations	IMIDAZOLIDINYL UREA	22
06A - Hair Dyes and Colors (all types requiring caution statements and patch tests)	IMIDAZOLIDINYL UREA	65
06B - Hair Tints	IMIDAZOLIDINYL UREA	2
06C - Hair Rinses (coloring)	IMIDAZOLIDINYL UREA	21
06D - Hair Shampoos (coloring)	IMIDAZOLIDINYL UREA	1
06F - Hair Lighteners with Color	IMIDAZOLIDINYL UREA	1
06H - Other Hair Coloring Preparation	IMIDAZOLIDINYL UREA	1
07A - Blushers (all types)	IMIDAZOLIDINYL UREA	48
07B - Face Powders	IMIDAZOLIDINYL UREA	63
07C - Foundations	IMIDAZOLIDINYL UREA	8
07E - Lipstick	IMIDAZOLIDINYL UREA	2
07F - Makeup Bases	IMIDAZOLIDINYL UREA	2
07I - Other Makeup Preparations	IMIDAZOLIDINYL UREA	7
08B - Cuticle Softeners	IMIDAZOLIDINYL UREA	3
08C - Nail Creams and Lotions	IMIDAZOLIDINYL UREA	1
08E - Nail Polish and Enamel	IMIDAZOLIDINYL UREA	1
08G - Other Manicuring Preparations	IMIDAZOLIDINYL UREA	1
10A - Bath Soaps and Detergents	IMIDAZOLIDINYL UREA	25
10B - Deodorants (underarm)	IMIDAZOLIDINYL UREA	3
10E - Other Personal Cleanliness Products	IMIDAZOLIDINYL UREA	9

11A - Aftershave Lotion	IMIDAZOLIDINYL UREA	5
11E - Shaving Cream	IMIDAZOLIDINYL UREA	4
11F - Shaving Soap	IMIDAZOLIDINYL UREA	1
11G - Other Shaving Preparation Products	IMIDAZOLIDINYL UREA	2
12A - Cleansing	IMIDAZOLIDINYL UREA	73
12B - Depilatories	IMIDAZOLIDINYL UREA	2
12C - Face and Neck (exc shave)	IMIDAZOLIDINYL UREA	111
12D - Body and Hand (exc shave)	IMIDAZOLIDINYL UREA	157
12E - Foot Powders and Sprays	IMIDAZOLIDINYL UREA	1
12F - Moisturizing	IMIDAZOLIDINYL UREA	274
12G - Night	IMIDAZOLIDINYL UREA	24
12H - Paste Masks (mud packs)	IMIDAZOLIDINYL UREA	19
12I - Skin Fresheners	IMIDAZOLIDINYL UREA	16
12J - Other Skin Care Preps	IMIDAZOLIDINYL UREA	62
13A - Suntan Gels, Creams, and Liquids	IMIDAZOLIDINYL UREA	6
13B - Indoor Tanning Preparations	IMIDAZOLIDINYL UREA	20
13C - Other Suntan Preparations	IMIDAZOLIDINYL UREA	1



Memorandum

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

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

DATE: June 1, 2018

SUBJECT: Concentration of Use by FDA Product Category: Imidazolidinyl Urea

Concentration of Use by FDA Product Category – Imidazolidinyl Urea

Product Category	Maximum Concentration of Use
Eye shadows	0.2-0.3%
Eye lotions	0.2%
Eye makeup removers	0.3%
Mascaras	0.5%
Hair conditioners	0.001-0.02%
Shampoos (noncoloring)	0.0000004%
Tonics, dressings and other hair grooming aids	0.25-0.6%
Hair dyes and colors	0.3%
Hair bleaches	0.0006%
Blushers	0.3%
Face powders	0.2%
Foundations	0.1-0.25%
Lipstick	0.2%
Other makeup preparations	0.2%
Nail polish and enamel removers	0.0002%
Other manicuring preparations	0.35%
Bath soaps and detergents	0.00008-0.0012%
Deodorants Not spray	0.3%
Other personal cleanliness products	0.3%
Shaving cream	0.000024%
Skin cleansing (cold creams, cleansing lotions, liquids and pads)	0.3-0.5%
Depilatories	0.0002%
Face and neck products Not spray	0.3%
Body and hand products Not spray	0.3-0.5%
Moisturizing products Not spray	0.2%
Night products Not spray	0.4%
Paste masks and mud packs	0.3%
Other skin care preparations	0.3-0.4%

Information collected in 2018

Table prepared June 26, 2018