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

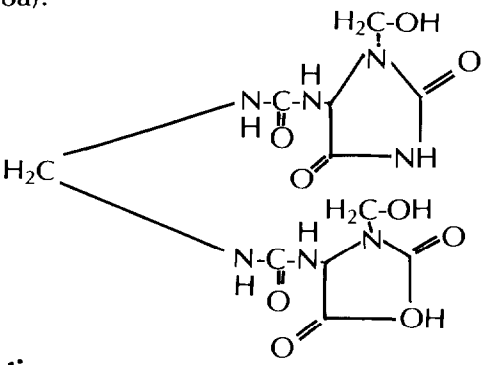
Imidazolidinyl Urea is the name used by the Cosmetic, Toiletry and Fragrance Association, Inc. for a member of a patented family of substituted imidazolidinyl urea compounds (Berke and Rosen, 1970).

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 (Sheppard 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No published or unpublished literature was reported on the reactivity of Imidazolidinyl Urea.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 Rfs 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 $K_3[Fe(CN)_6]$-$Na_2[Fe(CN)_5NO]$. $2H_20$ 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 HC1, phenylhydrazine-HC1, and $K_3[F_e(CN)_6]$. 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,). 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 fregert (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)

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

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 months 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 H_2O.

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, irridiated, 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 Ceasarean 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 July1, 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 photosensitization 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.

REFERENCES

Avon Products, Inc.: Submission of data by CTFA. Eye irritation study with rabbits, 1970a.[1]

Avon Products, Inc.: Submission of data by CTFA. Repeat patch test with rabbits, 1970b.[1]

Avon Products, Inc.: Submission of data by CTFA. Human occlusive patch test - single insult, 1972.[1]

Avon Products, Inc.: Submission of data by CTFA. Human repeated insult patch test, 1973.[1]

Berke, P.A., and Rosen, W.E.: Germall®, a new family of antimicrobial preservatives for cosmetics. Am. Perfum. Cosmet. 85(3):55-9, 1970.

CTFA: Submission of data by CTFA. Human predictive patch test study and clinical usage study on liquid makeup, 1974a.[1]

CTFA: Submission of data by CTFA. Repeat insult-occlusive patch test (Maibach) with a night cream (64050), 1974b.[1]

CTFA: Submission of data by CTFA. Primary skin irritation study with rabbits, March 8, 1976a.[1]

CTFA: Submission of data by CTFA. Acute oral study in rats, March 23, 1976b.[1]

CTFA: Submission of data by CTFA. Personal communication with A.A. Fisher. Results of patch testing 30 formaldehyde-sensitive individuals with 2 percent Germall 115 aqueous solution, April 15, 1977.[1]

CTFA: Submission of data by CTFA. Cosmetic ingredient description for Imidazolidinyl urea, 1978a.[1]

CTFA: Submission of data by CTFA. Human photo-in-use study on moisturizing cream, Sept. 5, 1978b.[1]

CTFA: Submission of data by CTFA. Human photo-in-use study on hand and body lotion, Sept. 5, 1978c.[1]

Dahlquist, I., and Fregert, S.: Formaldehyde releasers. Contact Dermatitis 4(3):173, 1978.

Douglas, M.L., Kabacoff, B.L., Anderson, G.A., and Cheng, M.C.: The chemistry of nitrosamine formation and destruction. J. Soc. Cosmet. Chem. 29:581-606, 1978.

FDA: Cosmetic product formulation data. Washington, D.C.: Food and Drug Administration, Aug. 31, 1976.

FDA: Summary prepared by FDA. Contact dermatitis cases reported to FDA by nine dermatologists in the North American Contact Dermatitis Group, Quarters 3-6, Nov. 15, 1976 - Nov. 15, 1977.

Federal Register: Final Order, Enforcement Regulations. Fed. Reg. 26(155): 7336, Aug. 21, 1961.

Fisher, A.A.: Allergic contact dermatitis from Germall 115, a new cosmetic preservative. Contact Dermatitis 1:126, 1975.

Fisher, A.A.: Dermatitis due to formaldehyde-releasing agents in cosmetics and medicaments. Cutis 22(6):655, 658, 662, 664, 708, 1978.

Gottschalck, H., and Oelschlager, T.: Indentifizierung und quantitative Bestimmung von Konservierungsmitteln in kosmetischen Produkten. J. Soc. Cosmet. Chem. 28:497-520, 1977.

Maguire, H.C., Jr.: Letter to Frank Marzulli. "Quarterly report Number 4 on FDA Contract 223-77-2341." Sept. 22, 1978.

Mandy, S.H.: Letter to the Editor. Contact dermatitis to substituted Imidazolidinyl Urea - a common preservative in cosmetics. Arch. Dermatol. 110:463, 1974.

Mandy, S.H.: Personal communication to A.A. Fisher, 1978.

Martelli, A., and Proserpio, G.: Color reaction for the thin-layer chromatographic identification and recognition of an antimicrobial compound widely used in the cosmetic field. Imidazolidinyl Urea. Riv. Ital. Essenze Profumi Piante Off. Aromi Saponi Cosmet. Aerosol 58(1):23-7, 1976.

North American Contact Dermatitis Group (NACDG): Unpublished patch test results, July 1, 1976 - June 30, 1977.

Richardson, E.L.: Preservatives: Frequency of use in cosmetic formulas as disclosed to FDA. Cosmet. Toiletries 92(3):85-6, 1977.

Rosen, W.E., and Berke, P.A.: Germall 115 - a safe and effective modern cosmetic preservative. Cosmet. Toiletries 92(3):88-9, 1977a.

Rosen, W.E., Matzin, T., and Peterson, A.F.: Preservation of cosmetic lotions with Imidazolidinyl Urea plus parabens. J. Soc. Cosmet. Chem. 28(2): 83-7, 1977b.

Rudner, E.J.: North American Contact Dermatitis Group results. Contact Dermatitis 3(4):208-9, 1977.

Ryder, D.S.: The thin-layer chromatographic detection and determination of an Imidazolidinyl Urea antmicrobial preservative. J. Soc. Cosmet. Chem. 25(10):535-44, 1974.

Schmidt, G.: Customary cosmetic bactericidal agents. Seifen ole Fette Wachse 102(19):557-8, 1976.

Sheppard, E.P., and Wilson, C.H.: Fluorometric determination of formaldehyde-releasing cosmetic preservatives. J. Soc. Cosmet. Chem. 25(12):655-66, 1974.

Sutton Laboratories: Submission of data by CTFA. I. Acute dermal study with rabbits, 1972.[1]

Sutton Laboratories: Submission of data by CTFA. Acute oral study in rats, 1973a.[1]

Sutton Laboratories: Submission of data by CTFA. II. Acute dermal study with rabbits, 1973b.[1]

Sutton Laboratories: Submission of data by CTFA. Primary irritation study with rabbits, 1973c.[1]

Sutton Laboratories: Submission of data by CTFA. Rabbit eye irritation study, 1973d.[1]

Sutton Laboratories: Submission of data by CTFA. Acute inhalation study in rats, 1973e.[1]

Sutton Laboratories: Submission of data by CTFA. Ninety-day study in rats, 1973f.[1]

Sutton Laboratories: Submission of data by CTFA. Subacute dermal study with rabbits, 1973g.[1]

Sutton Laboratories: Submission of data by CTFA. Teratology study in mice, 1973h.[1]

Takasago Perfumery Co.: Submission of data by CTFA. Acute oral study in rats and mice, 1974a.[1]

Takasago Perfumery Co.: Submission of data by CTFA. Dermal toxicity study with rabbits, 1974b.[1]

Takasago Perfumery Co.: Submission of data by CTFA. Eye irritation study with rabbits, 1974c.[1]

Takasago Perfumery Co.: Submission of data by CTFA. Phototoxicity study with guinea pigs, 1974d.[1]

Takasago Perfumery Co.: Submission of data by CTFA. Primary skin irritation study with humans, 1974e.[1]

United States Pharmacopeia Convention: The United States Pharmacopeia, 19th rev. ed. Rockville, Md., 1975

Wilson, C.H.: Identification of preservatives in cosmetic products by thin-layer chromatography. J. Soc. Cosmet. Chem. 26(2):75-81, 1975.

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[1]Cosmetic, Toiletry and Fragrance Association, Inc.

[2]Available upon request. Administrator, Cosmetic Ingredient Review, Suite 212, 1133 15th St., NW, Washington, D C 20005.