JOURNAL OF THE AMERICAN COLLEGE OF TOXICOLOGY
Volume 9, Number 2, 1990
Mary Ann Liebert, Inc., Publishers

7

Final Report on the Safety Assessment of Diazolidinyl Urea

Diazolidinyl Urea is a heterocyclic-substituted urea used as a preservative in a variety of cosmetic products at a normal product use concentration of 0.2 to 0.4%, up to a maximum of 1.0%.

Diazolidinyl Urea was slightly toxic to rats in acute oral studies but was relatively non-toxic in subchronic studies. At 5%, Diazolidinyl Urea was not an ocular or skin irritant in rabbits. In three studies using a maximization procedure, Diazolidinyl Urea was a mild sensitizer in guinea pigs, but was not a sensitizer in a fourth study in which a nonmaximization procedure was used.

Diazolidinyl Urea was nonmutagenic when tested in the Ames test, or in the micronucleus assay.

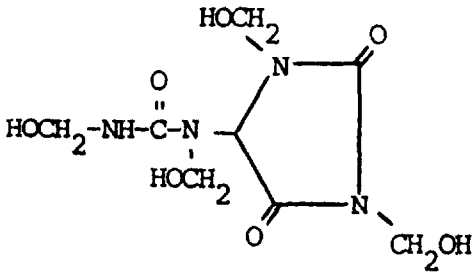
At concentrations up to 0.4%, Diazolidinyl Urea was a mild cumulative skin irritant in humans. In was not a sensitizer in an RIPT study on nonpatient volunteers. Fifty-seven of 2385 patients had allergic reactions to 1.0% Diazolidinyl Urea. It was not a photosensitizer at 0.25%.

This report notes that Diazolidinyl Urea is a formaldehyde releaser. It has been previously concluded that the use of formaldehyde in cosmetic products is safe to the great majority of consumers. There is no indication that the use of Diazolidinyl Urea as used in cosmetic products would release formaldehyde at concentrations which would exceed the limits recommended for formaldehyde. The report concludes that Diazolidinyl Urea may be safely used in cosmetic products at the minimum effective concentration, not to exceed 0.5%.

CHEMISTRY

Definition and Structure

Diazolidinyl Urea (CAS No. 78491-02-8) is a heterocyclic-substituted urea which has a molecular formula of $C_8H_{14}N_4O_7$ and a molecular weight of 278.26. It conforms to the following structure:[1]



Diazolidinyl Urea

Other names for Diazolidinyl Urea include N-(hydroxymethyl)-*N*-(1,3-dihydroxymethyl-2,5-dioxo-4-imidazolidinyl)-*N'*-(hydroxymethyl) urea;[2] *N*-[1,3]*bis*(hydroxymethyl)-2,5-dioxo-4-imidazolidinyl]-*N,N'-bis*(hydroxymethyl) urea;[1] imidazolidinyl urea II.[3]

Chemical and Physical Properties

Diazolidinyl Urea is a fine white powder with a slight characteristic odor. It dissolves easily in water and is insoluble in fats. Diazolidinyl Urea is 19 to 21% nitrogen, has a loss upon drying of 3% maximum, residue upon ignition of 3% maximum, and a maximum concentration of 10 ppm heavy metals.[4–6]

Method of Manufacture

Diazolidinyl Urea is prepared from the reaction of allantoin and formaldehyde. The allantoin is treated with 37% formaldehyde and 10% sodium hydroxide to form Diazolidinyl Urea.[7]

Analytical Methods

A colorimetric assay for Diazolidinyl Urea has been described.[6]

Reactions

Diazolidinyl Urea is compatible with most cosmetic ingredients. It is not inactivated by anionic, cationic, or nonionic surfactants or proteins.[6]

The formaldehyde released from Diazolidinyl Urea in protein and nonprotein shampoos was studied. Diazolidinyl Urea was added to anionic shampoos, both with and without protein, at concentrations of 0.1, 0.2, 0.4, and 0.8%. The amount of formaldehyde was measured at both 23 and 60°C. After five minutes of reaction time, Diazolidinyl Urea released a total of 2.1 mole of formaldehyde per mole of preservatives as determined by the Hantzsch reaction. This differed from the predicted value of 4.0 mole, but the value of 2.0 mole was used for all of the further calculations. As the concentration of the Diazolidinyl Urea increased, so did the amount of free formaldehyde released. From the nonprotein shampoo, 150 ppm free formaldehyde was recovered with a Diazolidinyl Urea concentration of 0.1% and 740 ppm from a

concentration of 0.8%. In the protein shampoo, 58 ppm free formaldehyde was recovered with a Diazolidinyl Urea concentration of 0.1% and 384 ppm with a concentration of 0.8%. These values were measured at 23°C but the values did not differ significantly at 60°C. The amounts of free formaldehyde were less in the protein shampoo because the formaldehyde was complexed by the protein. The percentage of free formaldehyde released increased as the concentration of preservative decreased in the nonprotein shampoo. The order of formaldehyde release among the preservatives studied was Imidazolidinyl urea < DMDM hydantoin < diazolidinyl urea <quaternium 15.[3]

USE

Cosmetic

Diazolidinyl Urea, in the 1987 FDA computer listing, was reported to be used in a total of 95 cosmetic preparations. It is used as a preservative[6] in a variety of formulations, including infant care preparations, eye makeup, facial makeup, aftershave, and nail, bath, hair, and skin care preparations. Of the 95 reported uses, 90 were at the ≤ 1% concentration while 5 were in the > 1–5% range[8] (Table 1). It has also been reported that Diazolidinyl Urea was used in 130 cosmetic preparations. The concentration of use, and/or, type of cosmetic preparation in which the ingredient was used was not stated.[9]

The FDA cosmetic product formulation computer printout[8] is compiled through voluntary filing of such data in accordance with Title 21 part 720.4 of the Code of Federal Regulations.[10] Ingredients are listed in preset concentration ranges under

TABLE 1. Product Formulation Data for Diazolidinyl Urea[8]

Product category	*Total no. of formulations in category*	*Total no. containing ingredient*	*No. of product formulations within each concentration range (%)*	
			>1–5	*≤1*
Baby care preparations	71	3	—	3
Bubble baths and other bath preparations	665	10	—	10
Eye makeup preparations	495	11	—	11
Powders (dusting and talcum, excluding aftershave talc)	348	8	5	3
Hair preparations	1497	3	—	3
Facial makeup preparations	1692	16	—	16
Nail preparations	196	3	—	3
Aftershave lotions	221	1	—	1
Skin cleansing preparations (cold creams, lotions, liquids, and pads)	707	7	—	7
Moisturizing and related skin care preparations	2020	26	—	26
Other skin care preparations	990	7	—	7
1987 Totals		95	5	90

specific product type categories. Since certain cosmetic ingredients are supplied by the manufacturer at less than 100% concentration, the value reported by the cosmetic formulator may not necessarily reflect the actual concentration found in the finished product; the actual concentration would be a fraction of that reported to the FDA. Data submitted within the framework of preset concentration ranges provides the opportunity for overestimation of the actual concentration of an ingredient in a particular product. An entry at the lowest end of a concentration range is considered the same and one entered at the highest end of that range, thus introducing the possibility of a two- to tenfold error in the assumed ingredient concentration.

Diazolidinyl Urea is listed in Annex VI, Part 2 of the European Economic Community (EEC) Cosmetics Directive as a preservative provisionally allowed for use in cosmetics. The maximum authorized concentration for Diazolidinyl Urea is 0.5%.[11]

Cosmetic products formulated with Diazolidinyl Urea are typically applied to the eye area, skin, face, nails, and hair. Cosmetic products containing Diazolidinyl Urea may be applied as often as several times a day and may stay in contact with the skin for several hours. The formulations also have the potential for repeated application over the course of many years.

Noncosmetic

The use of Diazolidinyl Urea in an ointment for eye and ear infections, ointments for the treatment of skin diseases, and enteric-coated tablets and capsules has been patented.[12] Its use as a preservative in ophthalmic solutions and contact lens solutions has also been patented.[13] Diazolidinyl Urea has also been patented as a preservative in a compound to be used in the water of an aquarium to promote the healing of damaged tissue in salt water, tropical, and cold water fish.[14]

ANTIMICROBIAL EFFECTIVENESS

Diazolidinyl Urea was effective as a preservative at concentrations of 0.1 to 0.3%. It is effective against bacteria, especially gram-negative species, yeast, and molds.[6] Normal product use concentrations of 0.2% to 0.4% up to a maximum of 1.0% have also been reported.[15] The antimicrobial spectrum of Diazolidinyl Urea is presented in Table 2.

Three microorganisms, *Pseudomonas aeruginosa, Candida albicans,* and *Aspergillus niger,* were instilled into several types of shampoo: model testing shampoo, baby shampoo, acid pH shampoo, conditioning shampoo, and protein shampoo. Diazolidinyl Urea, tested at concentrations of 0.1 and 0.2% produced complete kill of all microorganisms within 72 h in all types of shampoo.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

Diazolidinyl Urea was tested for acute oral toxicity in three groups of 10 CD-1 mice (5 males, 5 females). The mice were fasted for 4 h and each group received a single dose

TABLE 2. Antimicrobial Spectrum for Diazolidinyl Urea[12]

Test organisms (~10^6 CFU/ml)	*Minimal germicidal concentration(μg/ml) (suspension test; contact times of 24 and 72 h)*	*Minimal inhibitory concentration (μg/ml) (serial dilution test; incubation times of 24 and 72 h)*
Staphylococcus aureus	1000	250
Escherichia coli	4000	1000
Klebsiella pneumoniae	4000	500
Pseudomonas aeruginosa	4000	1000
Pseudomonas fluorescens	2000	1000
Pseudomonas cepacia	2000	1000
Candida albicans	8000	8000
Aspergillus niger	8000	4000
Penicillium notatum	8000	4000

of different concentrations of Diazolidinyl Urea. The doses given were 2.0, 3.2, and 4.0 g/kg. The mice weighed between 18 and 25 g and were observed for 14 days following the administration. An LD_{50} value for Diazolidinyl Urea was 3.7 g/kg with 95% confidence limits of 3.0 to 4.4 g/kg.[16]

The acute oral toxicity of Diazolidinyl Urea was tested in three groups of five male and five female Charles River CD rats. The groups received doses of either 2.0, 2.5, or 3.0 g/kg Diazolidinyl Urea after a fast of 18 h. The rats were observed for seven days after the administration. An LD_{50} value for Diazolidinyl Urea of 2.6 g/kg was calculated.[17]

Dermal

Diazolidinyl Urea was tested for its acute dermal toxicity using the procedure outlined in the CFR 16:1500.40(a)(b)(c). A dose of 2.0 g/kg Diazolidinyl Urea (solvent not specified) was applied, using a sleeve made of rubber dam or other impervious material, to the intact and abraded skin of five male and five female rabbits. The rabbits were observed for 14 days after the application was made. None of the rabbits died during the study. Moderate erythema and edema were observed at both intact and abraded sites. The cutaneous alterations had decreased in severity by the third day, at which time scabs had formed. The scabs had disappeared by day 14. No macroscopic changes were observed at necropsy.[18]

Short-Term Toxicity

Oral

Sprague-Dawley rats were used in a 7-day toxicity test. The rats were divided into six groups of 5 males and 5 females each. Each group was given either 10 ml/kg distilled water (vehicle control) or 0.1, 0.2, 0.4, 0.8, or 1.6 g/kg Diazolidinyl Urea orally once daily for seven consecutive days. The rats were weighed at the beginning and end of the study. Feed consumption was measured on days 4 and 7. The rats were sacrificed on day 7 for necropsy. The males of the 1.6 g/kg group had a significant reduction in body weight at the termination of the study. Feed consumption was significantly reduced by male and female rats of the 1.6 g/kg group on day 4 and by the males on day 7. No

treatment-related toxic effects were observed in rats of the vehicle control or 0.1 g/kg groups. Rats (8/10) of the 0.4 g/kg group had decreased activity, wobbly gait, and an abnormal stance. The majority (9/10) of the rats of the 0.8 and 1.6 g/kg groups had similar signs of toxicity. These changes in appearance and behavior were observed from day 3 to day 7. No lesions were observed at necropsy of the rats of the control, 0.1, 0.2, 0.4, or 0.8 g/kg groups. At necropsy, a foreign material was adhered to the gastric wall in 6/10 rats of the 1.6 g/kg group. This was accompanied by a linear red lesion.[19]

Diazolidinyl Urea was administered orally to three groups of 5 male and 5 female rats for 29 consecutive days. A fourth group given deionized water served as the control group. The groups were given doses of 0.1, 0.3, or 0.9 g/kg Diazolidinyl Urea in deionized water. Appearance and behavior were evaluated daily; body weight and feed consumption were measured weekly. At the end of the study, the rats were sacrificed for necropsy, and blood was collected for hematologic and clinical chemistry determinations. None of the animals died during the study. The male rats of the 0.9 g/kg dose group had a significant reduction in body weight gain. Signs of toxicity, seen in both males and females of the 0.9 g/kg group, included abnormal stance and gait, salivation, decreased activity, diarrhea, dyspnea, flaccid muscle tone, poor grooming, and lacrimation. Females of the high-dose group had a significant increase in absolute adrenal weights and both males and females had an increase in relative adrenal weights. At microscopic examination of the tissues of some of the rats of the 0.9 g/kg group, a compound-related increase in the incidence and severity of focal gastritis of the glandular portion of the stomach was observed. Animals of the 0.3 g/kg group had abnormal stance and gait, salivation, decreased activity, diarrhea, and flaccid muscle tone. No significant compound-related effects were seen in animals of the 0.1 g/kg group; this dose was considered the dose which produced no toxic effects.[20]

Subchronic Toxicity

Oral

A subchronic oral toxicity study was conducted for Diazolidinyl Urea using Sprague-Dawley rats. Four groups of rats were used, each consisting of 15 males and 15 females. The rats were fed either an untreated diet (the control group) or diets containing 0.01, 0.025, or 0.10 g/kg Diazolidinyl Urea for 90 days. Body weights and feed consumption were measured weekly. Hematological studies were conducted at 0, 30, 60, and 90 days using 5 male and 5 female rats of the control, low-, and high-dose groups. Clinical chemistries and urinalyses were conducted using rats of the control and high-dose groups at the termination of the study. The rats were then sacrificed for necropsy. Tissues were removed and prepared for microscopic examination. The administration of Diazolidinyl Urea did not produce any significant changes in growth rate, general appearance, hematology, organ weights, urinalysis, clinical chemistry, or lesions in the test animals when compared with controls.[21]

Dermal

Female Sprague-Dawley rats were used in a dermal toxicity test of a cosmetic formulation containing 0.2% Diazolidinyl Urea. A dose of 3.14 g/kg of the cosmetic product was administered dermally five days per week for 13 consecutive weeks to an unspecified number of rats. All of the rats survived the study. Approximately one third of the animals treated with the product had minimal cellular desquamation on the dose

site for the duration of the study. No statistically significant changes were seen in hematologic, clinical chemistry, or urinalysis determinations for treated rats as compared with untreated controls. No changes other than the previously noted dermal lesions were found at necropsy. No toxicologically significant differences in body or organ weights were seen between treated and control animals. Changes in the skin suggested a mild irritating effect, but no other microscopic changes were found. The cutaneous lesions were considered directly related to treatment with the cosmetic, but were not considered toxicologically significant because of the large dose of the cosmetic used. The cosmetic formulation containing 0.2% Diazolidinyl Urea did not produce cumulative systemic toxic effects and was considered safe for marketing.[22]

Irritation

Ocular

Diazolidinyl Urea was tested for ocular irritation in six albino rabbits. In each animal, 0.1 ml of a 5.0% solution (solvent not specified) of Diazolidinyl Urea was instilled into the conjunctival sac of one eye. The other untreated eye served as the control. The instillation of the solution was not followed by a water rinse. The eyes were examined for irritation every 24 h for four days and then after seven days. No ocular irritation was observed in any of the animals at any of the observation periods. The 5.0% solution of Diazolidinyl Urea was nonirritating to rabbit eyes when tested by this procedure.[23]

A 30% solution of Diazolidinyl Urea in propylene glycol caused minor conjunctival irritation, with a return to normal by the third day, when it was instilled into rabbit eyes without a water rinse. This irritation was similar to that observed after the instillation of propylene glycol alone. When the solution of 30% Diazolidinyl Urea in propylene glycol was instilled and followed by a water rinse after 20–30 s, no eye irritation was observed.[24]

Dermal

A 1.0% aqueous solution of Diazolidinyl Urea was tested for dermal irritancy by application of 0.5 ml under an occlusive patch to the intact and abraded skin of two albino rabbits for 24 h. Dermal irritation reactions were scored when the patches were removed and again at 48 h. No signs of irritation were seen in either rabbit at either observation period. The 1.0% aqueous solution of Diazolidinyl Urea was not a primary dermal irritant in rabbits.[25]

A second study was conducted to determine the dermal irritancy of a 5.0% aqueous solution of Diazolidinyl Urea. The procedures were the same as described in the paragraph above with the exception that three albino rabbits were used. No signs of irritation were seen in any of the rabbits tested. Diazolidinyl Urea as a 5.0% aqueous solution was not a primary dermal irritant in rabbits.[26]

Ten female Dunkin-Hartley guinea pigs were used to determine the irritancy of Diazolidinyl Urea in a dose range evaluation for a sensitization test. The backs of guinea pigs were shaved and an occlusive patch containing 0.2 ml of various concentrations of Diazolidinyl Urea was applied to the shaved area. The concentrations of Diazolidinyl Urea used in the study were 5, 10, and 25% in petrolatum, and 25, 50, and 75% in 25% aqueous ethanol. All of the concentrations of Diazolidinyl Urea in petrolatum and the 25% concentration in ethanol were essentially nonirritating to the guinea pig skin. The

50% concentration in ethanol caused irritation with a score of 3 (denoting bright red erythema with accompanying edema, petechiae, or papules) in 4/10 animals at the 24-h and 3/10 animals at 48- and 72-h observations. Marked irritation with a score of 3 was also observed in 6/10 animals treated with 75% Diazolidinyl Urea in ethanol after 24 h, 5/10 animals after 48 h, and 6/10 animals after 72 h. In many of the animals reacting to the 50% and 75% concentrations, the skin surrounding the patch site was black-green.[27]

A range-finding study was conducted to determine the irritancy of Diazolidinyl Urea to establish the dose to be used for a sensitization study. Aqueous solutions of 10%, 25%, 50%, or 100% Diazolidinyl Urea were applied to the skin of six Hartley albino guinea pigs (3 males and 3 females). The occlusive patches were left on the skin for 24 h. Dermal reactions were scored 24 and 48 h after the patches had been removed. No irritation was seen from any of the test concentrations in any of the guinea pigs.[28]

Sensitization

A modified Magnusson-Kligman maximization procedure was carried out to determine the sensitizing potential of Diazolidinyl Urea. In the induction phase, 10 female Dunkin-Hartley guinea pigs received single 0.5 ml intradermal injections on six sites of the upper back, three on the left and three on the right. The paired injections consisted of either a 50% aqueous solution of Freund's complete adjuvant (FCA), a 5% solution of Diazolidinyl Urea in propylene glycol, or a 5% solution of Diazolidinyl Urea in 50% aqueous FCA. After one week, the animals received a topical booster of 50% Diazolidinyl Urea in petrolatum with a pretreatment of 5% sodium lauryl sulfate 24 h before the booster application. Two weeks after the booster application, occlusive challenge patches containing 25% and 50% Diazolidinyl Urea were applied to the backs of the guinea pigs for 24 h. Reactions at 24 and 48 h were scored when the patches were removed. At challenge, 2/10 animals reacted to the 25% concentration and 4/10 reacted to the 50% concentrations. None of the control animals, receiving only the challenge patches, reacted to a 25% concentration of Diazolidinyl Urea and 1/10 reacted to the 50% concentration. Diazolidinyl Urea had a weak to moderate allergenic potential in guinea pigs when tested at a concentration of 25% in petrolatum.[27]

Diazolidinyl Urea was tested for its sensitization potential in Hartley albino guinea pigs using a modified Magnusson-Kligman maximization procedure. The induction phase consisted of intradermal injections followed by topical applications. Each animal received injections at six sites on the upper back: two injections of 0.1 ml of a 50% aqueous solution of Freund's Complete Adjuvant, two injections of 0.1 ml of a 5% aqueous solution of Diazolidinyl Urea, and two injections of 5% Diazolidinyl Urea in 50% Freund's complete adjuvant. After one week, occlusive patches containing 100% Diazolidinyl Urea were applied to the animals at the injection sites following a 24-h pretreatment with a 10% solution of sodium lauryl sulfate. The patches were left on the skin for 48 h. Occlusive challenge patches containing 50% aqueous Diazolidinyl Urea were applied to previously untreated sites two weeks later. A positive control substance, 2,4-dinitrochlorobenzene, was administered in the same manner as the Diazolidinyl Urea. Six animals were used as irritation controls and received only the challenge patches. At challenge, 3/10 animals had dermal scores of 1 or greater after 24 h and 1/10 had a score of 1 after 48 h. The Draize[29] scoring scale was used. The other

tested animals had ± or equivocal scores. In the irritation controls, 2/6 animals had ± scores after 24 h. Diazolidinyl Urea had a "slight potential to produce dermal sensitization in guinea pigs" under these test conditions. The investigators predicted under normal use conditions, "little or no sensitization potential appears likely in humans."[28]

Diazolidinyl Urea was tested for sensitization in Hartley albino guinea pigs using a modified Magnusson-Kligman maximization test. Each animal received three pairs of intradermal injections in the clipped shoulder area. These consisted of one pair of 50 μl injections of Freund's complete adjuvant and water, one pair of 50-μl injections of a 2.0% w/v solution of Diazolidinyl Urea in water, and one pair of 50-μl injections of a 2.0% w/v solution of Diazolidinyl Urea in water and Freund's complete adjuvant. Controls received the same treatment without Diazolidinyl Urea. No positive controls were reported. One week later, the same area was clipped and a 10% mixture of sodium lauryl sulfate in petrolatum was massaged into the test site and left for 24 h. An occlusive patch containing 0.3 ml of a 50% w/v solution of Diazolidinyl Urea was then applied to the site for 48 h. Controls again received the same treatment without Diazolidinyl Urea. Two weeks later, the challenge patches were applied. The flanks of the guinea pigs were shaved and an occlusive patch containing 0.3 ml of a 50% w/v solution of Diazolidinyl Urea was applied to the left flank while a patch containing only distilled water was applied for 24 h to the right flank. Controls were equally treated. Reactions were scored at 48 and 72 h (max = 3). Five of the 25 test guinea pigs had a reaction score of ≥ 1 (at either scoring period) to Diazolidinyl Urea. The maximum reaction score was also 1. None of the test guinea pigs reacted to the vehicle and none of the 11 control guinea pigs had any reactions. An additional challenge was conducted two weeks later with those guinea pigs having a score of ≥ 0.5 at the first challenge (8 animals). Each animal was patched with a 50% w/v solution of imidazolidinyl urea and a 1.0% w/v solution of formaldehyde; some degree of responsiveness was observed in 5/8 and 6/8 animals to imidazolidinyl urea and formaldehyde, respectively. Two weeks later, a third challenge was conducted with the same eight guinea pigs. Patches containing a 50% w/v solution of Diazolidinyl Urea were applied to new test sites. Only one guinea pig had a reaction: scores of 0.5 at 24 h and 0 at 48 h. Diazolidinyl Urea appeared to be a mild sensitizer according to the allergenicity scale of Magnusson and Kligman. Cross reactivity may occur between Diazolidinyl Urea and imidazolidinyl urea and Diazolidinyl Urea-sensitized animals will cross react to formaldehyde. Diazolidinyl Urea can produce contact sensitization under controlled experimental conditions; however, recognizing that the procedure used is the most sensitive for producing sensitization in the guinea pig and considering the low level of the reactions seen, Diazolidinyl Urea used "as part of a cosmetic preservative system should not present a significant risk to the consumer population; however, confirmatory sensitization studies are recommended, prior to marketing."[30]

Diazolidinyl Urea, as a 0.1% solution in saline, was tested for its sensitization potential in nine guinea pigs. Using the Landsteiner-Jacobs procedure, the solution was injected intracutaneously every 48 h for a total of 10 induction injections. The first injection was 0.05 ml; subsequent induction injections were 0.1 ml. After a two-week nontreatment period, a challenge injection of 0.05 ml of the solution was administered. The reactions were observed 24 h after the challenge injection. The average response to the challenge reaction was not greater than the average response seen to the induction injections and Diazolidinyl Urea, as assessed by this study, was not sensitizing to guinea pigs.[31]

MUTAGENICITY

Diazolidinyl Urea was nonmutagenic when tested in a *Salmonella*/mammalian microsome assay following the Ames[32] procedure. *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 were used in the study both with and without rat liver metabolic activation (S-9). 2-Aminoanthracene was the positive control for all strains with metabolic activation. Without activation, the positive controls were 2-nitrofluorene for strains TA98 and TA1538, sodium azide for strains TA100 and TA1535, and 9-aminoacridine for strain TA1537. Preliminary toxicity studies indicated that Dizolidinyl Urea could be tested at doses up to 600 μg/plate. A two- to three-fold increase in revertants per plate was observed for TA1537, and a slight increase in TA98 revertants per plate in the presence of rat liver metabolic activation. In an attempt to clarify the response observed with TA1537, the tests were repeated with TA97, a more sensitive strain, as well as TA98 and TA1537. Diazolidinyl Urea was tested at concentrations ranging from 150 to 700 μg/plate with metabolic activation. Increases in revertants were noted at the 500 and 600 μg/plate dose concentrations in all three strains; the increase was less than twofold in TA97 and TA98 and 2.5-fold in TA1537. However, the increases seen were not dose related and did not meet the criteria for a positive mutagenic response.[33]

A second study was designed to investigate what effect the S-9 concentrations and the species from which the S-9 was derived had on the number of revertants per plate. This specially designed study used the TA98 and TA1537 strains of *S. typhimurium*. Diazolidinyl Urea did not cause a positive mutagenic response in either of these strains. The increases in the number of revertants per plate were similar to those seen in the study described above. Neither the concentration of S-9 used nor the species from which it was derived greatly influenced the magnitude of the increases in the number of revertants.[34]

A micronucleus test for chromosomal aberrations in CD-1 mice was performed with Diazolidinyl Urea. The mice, nine groups of 5 males and 5 females, were given oral doses of 1200, 2000, or 2800 mg/kg Diazolidinyl Urea in 0.25% methylcellulose. The mice were sacrificed at either 30, 48, or 72 h after the administration of the Diazolidinyl Urea and bone marrow slides were prepared. The control animals had been given either 0.25% methylcellulose (vehicle control) or 60 mg/kg cyclosphosphamide (positive control). Approximately 1000 erythrocytes were scored per animal. Diazolidinyl Urea was nonmutagenic in this micronucleus assay.[35]

CLINICAL ASSESSMENT OF SAFETY

Dermal Irritation and Sensitization

Predictive Tests

Jordan[36] reported that a 2% concentration of Diazolidinyl Urea sensitized 20 of 151 volunteers, whereas concentrations of 0.3 and 0.1% sensitized 3 and 0 of 150 volunteers, respectively. Imidazolidinyl urea, Diazolidinyl Urea's predecessor, sensitized 2 of 150 when tested at a 2% concentration. Fifty percent of the Diazolidinyl Urea-sensitized subjects were reported to cross react to imidazolidinyl urea (Table 3).

A test for the cumulative irritancy potential of a white lotion containing 0.4% Diazolidinyl Urea was conducted using a panel consisting of one male and nine female

TABLE 3. Clinical Assessment of Safety: Dermal Irritation, Sensitization, and Photosensitization of Diazolidinyl Urea

Concentration tested	*Type of test*	*No. of subjects*	*Results/comments*	*Reference*
Diazolidinyl Urea, 2%	Experimental sensitization	151	20 Sensitized	36
0.3%		150	3 Sensitized	
0.1%		150	0 Sensitized	
Diazolidinyl Urea, 0.4% in lotion	Cumulative irritation	10	Total irritation 298/630, mild cumulative irritation	37
Diazolidinyl Urea, 0.2% in moisturizer	Mini-cum test	17	Primary Irritation Index = 0.03, nonirritating	38
Diazolidinyl Urea, 0.3% in lotion	Intensified RIPT[a]	54	Faint to intense erythema and edema, moderately intense cumulative irritant, nonsensitizing	39
Diazolidinyl Urea, 0.4% in moisturizer	RIPT	91	Nonirritating, nonsensitizing	40
Diazolidinyl Urea, 0.4% in moisturizer	RIPT	103	Nonirritating, nonsensitizing	41
Diazolidinyl Urea, 0.25% in lotion	RIPT	108	Mildly irritating, nonsensitizing, although possible sensitization in 1/108 subjects, no changes in skin pigmentation	42
Diazolidinyl Urea, 2.0% in petrolatum	SIPT[b]	501	No reactions in contact dermatitis patients	43
Diazolidinyl Urea, 0.5% and 1.0% in water or petrolatum	SIPT	71	No reactions in patients previously sensitized to preservatives or other chemicals	44
Diazolidinyl Urea, unspecified conc.	SIPT	126	3 Positive reactions	45
Diazolidinyl Urea, 1% in water	SIPT	2385 (1397 with relevancy data)	57 Allergic reactions; 2 irritant reactions (33 allergic reactions; 21/33 relevant; 0 irritant reactions)	46
Diazolidinyl Urea, 1% in petrolatum	SIPT	2485 (1495 with relevancy data)	49 Allergic reactions; 1 irritant reaction. (33 allergic reactions; 23/33 relevant; 0 irritant reactions)	46
Diazolidinyl Urea, 0.25% in lotion	Photosensitization	26	Nonphotosensitizing	47

[a]RIPT = repeat insult patch test.
[b]SIPT = single insult patch test.

subjects ranging in age from 30 to 59 years. Applications of the lotion were made under occlusive patches for 21 consecutive 23-h periods. A total irritation score of 298/630 was reported for the lotion. This indicates that the lotion would possibly be a mild irritant under normal use conditions and had "evidence of a moderate potential for mild cumulative irritation under conditions of this test."[37]

A moisturizer containing 0.2% Diazolidinyl Urea was tested for its cumulative irritation in a four-day study. An application of the moisturizer was made to 17 subjects for an unspecified length of time for four consecutive days. One subject tested had a ± (equivocal) reaction to the moisturizer and a primary irritation index score of 0.03 (maximum unspecified) was calculated. The moisturizer was judged "essentially nonirritating."[38]

The irritation and sensitization potential of a lotion containing 0.3% Diazolidinyl Urea was studied using 54 subjects. Patches containing 0.2 g of the lotion were applied to intact and abraded skin of the subjects for four, 24-h consecutive periods each week for three weeks of an induction phase. During the fourth week of the study, challenge patches were applied to a previously untreated site for four, 24-h consecutive periods. During the induction period, faint erythema was noted at 16 intact and 21 abraded sites, moderate erythema at 13 intact and 15 abraded sites, intense erythema at 3 intact sites, and intense erythema and edema at 2 intact and 1 abraded sites. At challenge, faint erythema was noted at 13 intact and 15 abraded sites, moderate erythema at 3 intact and abraded sites, and intense erythema at 1 intact and abraded site. These responses were considered those of a "moderately intense cumulative irritant" and did not establish that the lotion was capable of sensitizing any of the subjects.[39]

A moisturizer with sunscreen containing 0.4% Diazolidinyl Urea was tested in a repeated insult patch test (RIPT) to determine its sensitization potential. The moisturizer was applied under an occlusive patch to the skin of 91 subjects, 7 males and 84 females, every Monday, Wednesday, and Friday for three consecutive weeks. The patches were left on the skin for 24 h. After a two-week nontreatment period, a challenge patch was applied to a previously untreated site. The challenge patch was left on the skin for 24 h and reactions were scored 24 and 48 h after the patch was removed. Of the 91 subjects tested, one had a ± reaction to the sixth induction patch and another had a ± reaction 24 h after the challenge patch had been removed. The moisturizer with sunscreen was not a sensitizer under these test conditions.[40]

An RIPT was completed to determine the sensitization potential of a moisturizer containing 0.4% Diazolidinyl Urea. A total of 103 subjects, 21 male and 82 female, completed the study. The moisturizer was applied under occlusive patches to the backs of the subjects on Tuesdays, Thursdays, and Saturdays for three consecutive weeks. Each patch remained in contact with the skin for 24 h after its application. A challenge patch was applied to a previously untreated site after a 13-21-day nontreatment period. The reactions to the challenge patch were scored 24 and 48 h after application. During the induction phase, scattered ± (equivocal) reactions were observed in 6 of 103 subjects and mild irritant reactions were observed in 1 of 103 subjects. At challenge, 1 of 103 subjects had a ± reaction to the moisturizer. The cosmetic formulation "did not induce significant irritation nor allergic contact dermatitis in human subjects."[41]

The sensitization potential of a lotion formulation containing 0.25% Diazolidinyl Urea was investigated in an RIPT. Semiocclusive patches containing the lotion were applied to the backs of 108 subjects for 10 consecutive periods of 48 or 72 h. After a two-week nontreatment period, a semiocclusive challenge patch was applied for 48 h to previously untreated sites on the subjects. Changes in skin pigmentation due to the treatment with the cosmetic product were evaluated before the challenge patch was applied. Positive results at challenge were followed with a second challenge patch after one week. Diazolidinyl Urea was given a mean cumulative irritation score of 0.278 (maximum not given) as compared with the nonirritating control, mineral oil, at 0.111 and the mildly irritating control, propylene glycol, at 0.519. At challenge, 1 of 108 subjects had a grade 3 reaction, denoting erythema and edema. This subject was challenged a second time and had a score of 1, denoting questionable erythema not covering the complete patch site. Reactions to propylene glycol of grades 1 and 3 were observed in this same subject at the first and second challenges, respectively. The inconsistent nature of the responses from the one reactor at challenge "did not support

the induction of contact sensitization." No changes in pigmentation were observed in any of the subjects.[42]

Provocative Tests

Patch testing of Diazolidinyl Urea, 2.0% in petrolatum, as well as 13 other preservatives, was carried out according to the International Contact Dermatitis Research Group recommended procedures. The preservatives were tested on 501 consecutive patients undergoing routine patch testing because of suspected contact dermatitis. None of the 501 patients reacted to 2.0% Diazolidinyl Urea in petrolatum[43] (Table 3).

Diazolidinyl Urea was used in patch tests of 71 patients who previously had sensitization reactions to various chemicals and cosmetic preservatives. None of the subjects had any reaction of Diazolidinyl Urea tested at concentrations of 0.5% and 1.0% in either water or petrolatum.[44]

Patch tests were performed on 126 patients with an unspecified concentration of Diazolidinyl Urea. The reactions were scored on a scale of 1+ to 3+. Three patients had 1+ reactions to Diazolidinyl Urea. On patch testing, the first patient responded positively to 1.0% Diazolidinyl Urea and a hair gel containing Diazolidinyl Urea, and did not respond to any cosmetic product that did not contain Diazolidinyl Urea. (No positive sensitization reactions were seen in any of 19 control subjects patch tested with the hair gel although three subjects had irritant reactions.) The second patient also had a 2+ reaction to imidazolidinyl urea, a 3+ reaction to *p*-phenylenediamine, and a 1+ reaction to ethylenediamine. The third patient with a reaction to Diazolidinyl Urea had numerous preservative sensitivities.[45]

In a 1986–1987 study conducted by the North American Contact Dermatitis Group (NACDG), 1.0% Diazolidinyl Urea in water elicited 57 allergic and two irritant reactions in 2385 patients. Of the subset of 1397 patients for which a history was taken, 21 of the 33 allergic reactions were relevant and no irritant reactions were observed. Patch testing with 1.0% Diazolidinyl Urea in petrolatum produced 49 allergic and 1 irritant reactions in 2485 patients. Again, of the subset of 1495 patients for which a history was taken, 23 of the 33 allergic reactions were relevant and no irritant reactions were observed. Comparable numbers were observed in patients patched with 2% imidazolidinyl urea in either water or petrolatum. Of those 2321 patients simultaneously patched with Diazolidinyl Urea and imidazolidinyl urea in water, 36 had allergic reactions to both ingredients, 21 had allergic reactions to Diazolidinyl Urea but had negative reactions to imidazolidinyl urea, and 18 had negative responses to Diazolidinyl Urea but allergic responses to imidazolidinyl urea. All other patients had no cutaneous response to either ingredient. Of 2116 patients simultaneously patched with Diazolidinyl Urea and imidazolidinyl urea in petrolatum, 31 had allergic reactions to both ingredients, 12 had allergic reactions to Diazolidinyl Urea but no reactions to imidazolidinyl urea, and 18 had no responses to Diazolidinyl Urea, but had allergic responses to imidazolidinyl urea. All other patients had no reactions to either ingredient. The NACDG views Diazolidinyl Urea as a definite and probably significant contact allergen.[46]

Photosensitization

Diazolidinyl Urea, 0.25% in a lotion, was tested for photoallergenic potential using a panel of 26 female subjects, ages 18–65. A Xenon Arc Solar Simulator used as the light

source emitted a continuous spectrum in the UVA and UVB range (290–400 nm). Each subject was tested for minimal erythemal dose (MED) before the study began. Occlusive patches containing the lotion were applied to each subject for 24 h. After the patches were removed, the sites were scored and irradiated with three times each subject's MED. The reactions were read 48 h after the irradiation and patches were again applied. This procedure was repeated twice weekly for three weeks. An occlusive challenge patch was applied to a previously untreated site after a 10-day nontreatment period. The challenge patch was removed after 24 h and the site was irradiated, using a Schott WG345 filter over the light source, for 3 min. The reactions were observed 15 min, and 24, 48, and 72 h after the irradiation. Two control sites on each subject were treated by the same procedure but without irradiation to one and without the product application to the other. None of the subjects had any reactions during the study and the lotion formulation was not a photosensitizer (Table 3).[47]

SUMMARY

Diazolidinyl Urea is a heterocyclic-substituted urea used as a preservative in a variety of cosmetic products at a normal product use concentration of 0.2 to 0.4%, up to a maximum of 1.0%. In 1987, Diazolidinyl Urea was listed by the FDA as a component in 95 cosmetic formulations including eye, facial, nail, hair, and infant care products. The majority of these reported uses were at concentrations of $\leq$ 1.0%; however, some dusting and talcum powders were reported to contain between 1 and 5% Diazolidinyl Urea.

Diazolidinyl Urea was slightly toxic when administered orally to rats in acute studies. In a short-term oral study in rats, doses of 100 mg/kg or less of Diazolidinyl Urea produced no toxicity. This compound also was relatively nontoxic in oral and dermal subchronic studies in rats.

When tested at 5%, Diazolidinyl Urea was not an ocular irritant in rabbits. At 30% in propylene glycol, Diazolidinyl Urea was mildly irritating to rabbit eyes. Diazolidinyl Urea as a powder was not an irritant to rabbit skin at concentrations of 5%. In guinea pigs, 25 to 100% Diazolidinyl Urea (aqueous vehicle) produced no irritation in one study, while in another study, mild to severe erythema and edema were produced by concentrations of 50% and 75% Diazolidinyl Urea in ethanol. No irritation was seen with 25% Diazolidinyl Urea in ethanol. The ethanol may have contributed to the difference in irritancy rating.

In three studies using a modified maximization procedure, Diazolidinyl Urea was a mild sensitizer in guinea pigs. Diazolidinyl Urea was not a sensitizer to guinea pigs in a fourth study in which a nonmaximization procedure was used.

Diazolidinyl Urea was nonmutagenic when tested in the Ames test using *Salmonella typhimurium* strains TA98, TA100, and TA1535. Slight mutagenic activity was noted with *Salmonella typhimurium* strain TA1537. Diazolidinyl Urea was nonmutagenic in a micronucleus assay.

At concentrations of up to 0.4% in cosmetic formulations, Diazolidinyl Urea was a mild to moderate cumulative irritant in humans and was not a sensitizer in repeated insult patch tests with a total of 356 subjects. However, results of the NACDG's 1986–1987 patient testing period were 57/2385 allergic reactions to 1% Diazolidinyl Urea in water and 49/2485 allergic reactions to 1% Diazolidinyl Urea in petrolatum.

Diazolidinyl Urea produced 0/150, 3/150, and 20/151 allergic reactions at concentrations of 0.1, 0.3, and 2.0% in experimental sensitization studies.

Diazolidinyl Urea was not a photosensitizer at a concentration of 0.25% in a cosmetic formulation.

DISCUSSION

The Expert Panel noted that Diazolidinyl Urea is a formaldehyde releaser. The Panel has previously concluded that the use of formaldehyde in cosmetic products is safe to the great majority of consumers. However, due to skin sensitivity of some individuals to formaldehyde, it should be used at the minimum effective concentration (not to exceed 0.2%). There is no indication that the use of Diazolidinyl Urea as used in cosmetic products would release formaldehyde at concentrations which would exceed the limits recommended for formaldehyde. The Panel noted that the results of tests with Diazolidinyl Urea, at low concentrations, were indicative of a potential for sensitization. A comment received in the first issuance of the Tentative Final Report stated that the normal use of Diazolidinyl Urea was between 0.2% and 0.4% with a maximum of 1.0%. Another comment indicated that a safe use level of 1.0% was inconsistent with the test data at 1.0% on dermatologic patients. Repeat Insult Patch Test (RIPT) sensitization studies using cosmetic products at concentrations up to 0.4% on normal subjects were essentially negative. The results of Single Insult Patch Testing (SIPT) of patients at concentrations up to 2.0% have varied (Diazolidinyl Urea was a significant sensitizer in one study at 1.0% in petrolatum and was negative in a second). Results of sensitization studies (SIPT) on Diazolidinyl Urea using water as the vehicle were also inconsistent.

The Expert Panel re-evaluated the safety test data in the first issuance of the Tentative Final Report on Diazolidinyl Urea along with the comments that were received. The Panel concluded that this ingredient could be safely used in cosmetic products at the minimum effective concentration. The effective use and safety test data indicate that the potential of this ingredient to produce adverse reactions should be minimized. In cosmetic formulations, Diazolidinyl Urea should not exceed a maximum concentration of 0.5%.

CONCLUSION

On the basis of the animal and clinical data presented in this report, the CIR Expert Panel concludes the Diazolidinyl Urea is safe as a cosmetic ingredient up to a maximum concentration of 0.5%.

REFERENCES

1. WHELAN, J.M. (EDITOR). *CTFA Cosmetic Ingredient Dictionary*, 3rd ed., Supplement. Washington, DC: CTFA, Inc.
2. WALLHAUSSER, K.H. (1984). Appendix B: antimicrobial preservatives used by the cosmetic industry. In: Kabara, J.J. (ed.), *Cosmetic and Drug Preservation*. New York: Marcel Dekker.
3. ROSEN, M. and MCFARLAND, A.G. (1984). Free formaldehyde in anionic shampoos. J. Soc. Cosmet. Chem. **35**,157–69.
4. FIEDLER, H.P. (1983). New preservatives with broad antimicrobial spectrum for cosmetics. Aerztl. Kosmetol. **13**(3),249–51.

5. SUTTON LABORATORIES, INC. (May 29, 1987). Specifications for Germall II. Submission of unpublished data by CTFA.*
6. BERKE, P.A. and ROSEN, W.E. (1982). Germall II—a new broad spectrum cosmetic preservative. Cosmet. Toilet. **97**(6),49–53.
7. BERKE, P.A. and ROSEN, W.E. (1981). *N*-(Hydroxymethyl)-*N*-(1,3-dihydroxy-methyl-2,5-dioxo-4-imidazolidinyl)-*N'*-(hydroxymethyl)urea and its use. PCT. Int. Appl. WO 81/566, 5 March. (Abstract).
8. FOOD AND DRUG ADMINISTRATION (FDA). (1987). Cosmetic product formulation data. FDA computer printout.
9. DECKER, R.L. and WENNINGER, J.A. (1987). Frequency of Preservative Use in Cosmetic Formulas as Disclosed to FDA—1987. Cosmet. Toilet. **102**(12), 21.
10. CODE OF FEDERAL REGULATIONS (CFR). (Revised as of April 1, 1984). Title 21 Part 720.4; Title 16 Part 1500.50. Washington, DC: U.S. Government Printing Office.
11. EUROPEAN ECONOMIC COMMUNITY (EEC). (1986). The EEC Cosmetics Directive. Updated version—incorporating all amendments until 15th June 1986. J Dupuis (ed.). Annex VI, Part 2, No. 17.
12. HARRISON, A.R. and MORRISON, A.M. (1983). Therapeutic use of allantoin-formaldehyde condensation products. Eur. Pat. Appl. Patent No. 80281 (Abstract).
13. TRAGER, S.F. and CHYLINSKI, V.S. (1985). Imidazolidinylurea and its derivatives for use in opthalmic solutions. U.S. Patent No. 4539330. (Abstract).
14. GOLDSTEIN, J. (1985). Damaged fish tissue treatment with a composition containing aloe vera extract. U.S. Patent No. 4500510. (Abstract).
15. ROSEN, W.E. (1988). Letter of July 7, 1988 to R. Elder commenting on the Tentative Final Report on Diazolidinyl Urea dated April 4, 1988.
16. PHARMAKON RESEARCH INTERNATIONAL, INC. (October 14, 1986). Acute oral toxicity study. Submission of unpublished data by CTFA.*
17. LEBERCO LABORATORIES. (January 19, 1981). Acute oral toxicity test. Submission of unpublished data by CTFA.*
18. LEBERCO LABORATORIES. (January 28, 1981). Acute dermal toxicity test. Submission of unpublished data by CTFA.*
19. PHARMAKON RESEARCH INTERNATIONAL, INC. (November 17, 1986). Repeated oral toxicity study—7 day. Submission of unpublished data by CTFA.*
20. PHARMAKON RESEARCH INTERNATIONAL, INC. (December 12, 1986). Repeated oral toxicity study—28 day. Submission of unpublished data by CTFA.*
21. LEBERCO LABORATORIES. (December 30, 1981). 90 day subacute oral toxicity test. Submission of unpublished data by CTFA.*
22. COSMETIC, TOILETRY AND FRAGRANCE ASSOCIATION (CTFA). (February 12, 1987). Submission of unpublished data by CTFA. Subchronic dermal toxicity study—13 weeks.*
23. LEBERCO LABORATORIES. (December 30, 1980). Ocular irritation study. Submission of unpublished data by CTFA.*
24. BERKE, P.A., STEINBERG, D.C., and ROSEN, W.E. (November 1982). Germaben II a complete preservation system in clear liquid form. Cosmet. Toilet. **97**, 89–93.
25. LEBERCO LABORATORIES. (November 21, 1980). Dermal irritation study. Submission of unpublished data by CTFA.*
26. LEBERCO LABORATORIES. (December 29, 1980). Dermal irritation study. Submission of unpublished data by CTFA.*
27. CTFA. (May 14, 1984). Submission of unpublished data by CTFA. Contact sensitization test.*
28. BIODYNAMICS, INC. (January 28, 1983). Guinea pig maximization test. Submission of unpublished data by CTFA.*
29. DRAIZE, J.H. (1959). Dermal Toxicity. In: *Appraisal of the Safety of Chemicals in Foods, Drugs and Cosmetics*. Austin, TX: The Association of Food and Drug Officials of the United States; Bureau of Food and Drugs.
30. STEPHEN, T.J., DRAKE, K.D., and DROTMAN, R.B. (1987). Experimental delayed contact sensitization to diazolidinyl urea (Germall II) in guinea pigs. Contact Dermatitis **16**, 164–8.
31. LEBERCO LABORATORIES. (February 4, 1981). Intracutaneous sensitization study. Submission of unpublished data by CTFA.*
32. AMES, B.N., MCCANN, J., and YAMASAKI, E. (1975). Methods for detecting carcinogens and mutagens with the *Salmonella*/mammalian-microsome mutagenicity test. Mutat. Res. **31**, 347–64.
33. MICROBIOLOGICAL ASSOCIATES. (July 29, 1983). *Salmonella*/mammalian-microsome mutagenicity assay. Submission of unpublished data by CTFA.*
34. MICROBIOLOGICAL ASSOCIATES. (September 15, 1983). *Salmonella*/mammalian-microsome mutagenicity assay. Submission of unpublished data by CTFA.*
35. PHARMAKON RESEARCH INTERNATIONAL, INC. (December 12, 1986). Micronucleus test. Submission of unpublished data by CTFA.*

*Available for review: Director, Cosmetic Ingredient Review, 1110 Vermont Ave., N.W., Suite 810, Washington, DC 20005.

36. JORDAN, W.P., JR. (October 1984). Human Studies That Determine the Sensitizing Potential of Haptens. Experimental Allergic Contact Dermatitis. Dermatol. Clin. **2**(4), 533–8.
37. HILL TOP RESEARCH, INC. (March 5, 1984). Human skin test of cumulative irritation. Submission of unpublished data by CTFA.*
38. CTFA. (August 19, 1985). Submission of unpublished data by CTFA. Clinical 4-Day mini-cum test.*
39. PRODUCT INVESTIGATIONS, INC. (June 17, 1986). Clinical irritation and sensitization study. Submission of unpublished data by CTFA.*
40. CTFA. (October 19, 1984). Submission of unpublished data by CTFA. Clinical contact sensitization test.*
41. FOOD AND DRUG HUMAN CLINICAL LABS, INC. (August 2, 1983). Clinical repeated insult patch test. Submission of unpublished data by CTFA.*
42. CTFA. (June 4, 1982). Submission of unpublished data by CTFA. Clinical sensitization test.*
43. DE GROOT, A.C., BOS, J.D., JAGTMAN, B.A., BRUYNZEEL, D.P., VAN JOOST, T., and WEYLAND, J.W. (1986). Contact allergy to preservative—II. Contact Dermatitis **15**, 218–22.
44. CTFA. (April 30, 1984). Submission of unpublished data by CTFA. Clinical patch test.*
45. KANTOR, G.R., TAYLOR, J.S., RATZ, J.L., and EVEY, P.L. (1985). Acute allergic contact dermatitis from diazolidinyl urea (Germall II) in a hair gel. J. Am. Acad. Dermatol. **13**(1), 116–9.
46. STORRS, F.J. and RIETSCHEL, R. (Sept. 8, 1987). Personal correspondence to R. Elder from Storrs (Manager, NACDG studies) and Rietschel (Secretary, NACDG).*
47. CTFA. (September 16, 1983). Submission of unpublished data by CTFA. Clinical photosensitization test.*