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8

Final Report on the Safety Assessment of Drometrizole

Drometrizole is used in cosmetics as an ultraviolet (UV) light absorber and stabilizer, primarily at concentrations below 0.1%. Drometrizole is appreciably absorbed and metabolized. Repeated oral administration of Drometrizole for 14 or 28 days caused a significant increase in relative liver weight but did not affect the body weight gain. Drometrizole was relatively nontoxic in acute oral and dermal studies and only moderately irritating after direct instillation into the rabbit eye.

Drometrizole was not mutagenic in either the Ames test with *Salmonella typhimurium* or in the mouse bone marrow micronucleus test.

In clinical studies, Drometrizole tested at 1% was nonirritating in a single insult patch test. Twice daily applications of Drometrizole for 8 weeks produced no irritation. Only two hypersensitivity reactions were observed in a separate clinical study involving 145 patients. Cosmetic products containing up to 1.0% Drometrizole produced no irritation, sensitization, photosensitization, or phototoxicity.

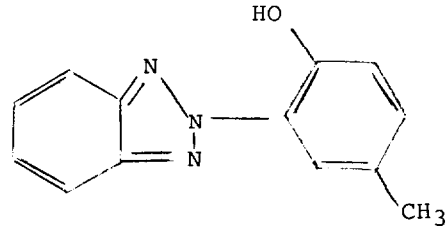
It is concluded that a 90-day subchronic oral toxicity study and mutagenicity testing in two systems other than the Ames assay and the mouse bone marrow micronucleus test are needed before an adequate safety assessment can be made. On the basis of the available data included in the report, it cannot be concluded that Drometrizole is safe for use in cosmetic products until such time that the appropriate safety data have been obtained and evaluated.

INTRODUCTION

The following report documents all of the relevant published and unpublished data available to the Cosmetic Ingredient Review (CIR) on Drometrizole. The CIR Expert Panel reviewed these data and concluded that additional information is required to substantiate the safety of Drometrizole for use in cosmetic products. The types of data needed to assess the safety of this cosmetic ingredient are outlined in the Discussion section of this report.

CHEMICAL AND PHYSICAL PROPERTIES

Drometrizole is a benzotriazole derivative that conforms to the following structure[1]:



Also called 2-(2′-hydroxy-5′-methylphenyl)benzotriazole, it occurs as an odorless, off-white to yellow, crystalline powder with a melting point of 131–133°C and a boiling point of 225°C. Drometrizole has a molecular weight of 225.25 and is soluble in ethyl acetate, acetone, caprolactam solutions, dioctylphthalate, oleyl alcohol, hot petrolatum, methyl ethyl ketone, methyl methacrylate, chloroform, toluene, and styrene. It is insoluble in water.[2–5] The physicochemical properties of Drometrizole are presented in Table 1.

Drometrizole (in ethanol) has its maximum absorbance at wavelengths of approximately 243 ± 2 nm, 298 ± 2 nm, and 340 ± 2 nm; minimum absorbance occurs at wavelengths of 259 ± 2 nm and 214 ± 2 nm.[4] Drometrizole exposed to light in the UV and visible range has only an insignificant luminescence.[6] Identification and assay methods are given in the *Japanese Standards of Cosmetic Ingredients*.[4] Gas chromatography mass spectrometry (GCMS) has been used to analyze Drometrizole.[7]

Drometrizole is both light and heat stable. The chemical reactivity of the phenolic hydroxyl is reduced, since it forms a hydrogen bond with either nitrogen N-1 or N-3 of the triazole ring.[5] Drometrizole's high degree of environmental stability is indicated by its high accumulation (40 ppm; 2000-fold accumulation factor) in river sediment near industrial wastewater outlets.[7] It is also stable to conditions and chemicals used in polymerization or compounding of plastics.[3]

USE

Cosmetic Use

Drometrizole is used as a UV light absorber and stabilizer in cosmetics.[3,5] It is primarily used at concentrations below 0.1% in the following product categories: bath, fragrance, coloring and noncoloring hair, manicuring, shaving, skin care, and suntan preparations.[8]

Table 2 presents the Food and Drug Administration (FDA) product formulation data for Drometrizole.[8] These data, made available by the FDA, are compiled through voluntary filing of such data in accordance with Title 21 part 720.4 (d)(1) of the Code of Federal Regulations (1982). Ingredients are listed in prescribed concentration ranges under 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 con-

TABLE 1. Physicochemical Properties of Drometrizole

Property	*Value*	*Reference*
Physical occurrence	Off-white to yellow crystalline powder	2,4,5
Empirical formula	$C_{13}H_{11}N_3O$	2–5
Molecular weight	225.25	3,4
Melting range (°C)	131–133	3
Boiling point (°C)	225 (10 mm Hg)	2,5
Particle size	2.5% max retained on 200 mesh screen 7.5% max retained on 325 mesh screen	5
Specific gravity	151	5
Ash	1% max	5
Loss on drying	≤0.5%	4
Residue on ignition	≤0.1%	4
Solubility[a]		
Acetone	S	3–5
Caprolactam solutions	S	3
Chloroform	S	5
Dioctylphthalate	S	3
Ethanol	S	4
Ethyl acetate	S	3,5
Methyl ethyl	S	2
Methyl methacrylate	S	2
Oleyl alcohol	S	3
Petrolatum (hot) ketone	S	3
Styrene	S	5
Toluene	S	5
Water	I	2,5

[a]S, soluble; I, insoluble.

centration in such a case would be a fraction of that reported to the FDA. The fact that data are only submitted within the framework of preset concentration ranges also 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 as one entered at the highest end, thus introducing the possibility of a two- to ten-fold error in the assumed ingredient concentration.

In 1981, 77% of the 217 reported uses of Drometrizole were in nail polishes and enamels, and 11% were in noncoloring hair shampoos. Of this total, 53% were at concentrations ≤0.1%, 4% at >0.1–1%, and 43% at unknown concentrations.[8]

The formulation data presented in Table 2 indicate that cosmetic products containing Drometrizole may contact all external body surfaces and hair, as well as the eyes and mucous membranes. These products may be used daily or occa-

TABLE 2. Product Formulation Data[8]

Product category	Total no. of formulations in category	Total no. containing ingredient	No. of product formulations within each concentration range (%)		
			Unreported concentration	>0.1–1	≤0.1
Drometrizole					
Bath oils, tablets, and salts	237	8	–	–	8
Colognes and toilet waters	1120	1	–	–	1
Hair rinses (noncoloring)	158	1	–	–	1
Hair shampoos (noncoloring)	909	24	–	–	24
Other hair preparations (non-coloring)	177	1	–	–	1
Hair shampoos (coloring)	16	2	–	–	2
Nail basecoats and undercoats	44	5	–	3	2
Nail polish and enamel	767	169	94	2	71
Nail polish and enamel remover	41	1	–	–	1
Other manicuring preparations	50	2	–	2	–
Preshave lotions (all types)	29	1	–	–	1
Moisturizing skin care preparations	747	2	–	–	2
Other skin care preparations	349	1	–	–	1
Suntan gels, creams, and liquids	164	1	–	1	–
1981 TOTALS		217	94	8	115

sionally over a period of up to several years. The frequency and length of application could result in continuous exposure.

Noncosmetic Use

Drometrizole is used as a UV light absorber and stabilizer in plastics, polyesters, polystyrene, polyvinyls, polypropylene, alkyds, cellulose acetate, ethyl cellulose, acrylates, dyes, rubber, synthetic and natural fibers, waxes, and detergent solutions.[2,3,9–11] It is used in orthodontic adhesives and dental restorations as well as in polyurethane elastomers for maxillofacial use.[12–16]

Drometrizole is used as a UV absorber in agricultural products for the prevention of leaf burn and apple peel spot.[17,18] It is also formulated as a stabilizer in insecticides.[19–21]

Drometrizole is approved as an indirect food additive for use as an antioxidant and/or stabilizer in polymers. Its use is subject to the limitations set forth in the Code of Federal Regulations (1982), Title 21, part 178.2010.

BIOLOGICAL EFFECTS

Epstein et al.[22,23] studied the cytotoxicity of Drometrizole to *Tetrahymena pyriformis* and its antioxidant potency as measured by the *T. pyriformis* photodynamic assay. Drometrizole had very low cytotoxicity to *T. pyriformis*, with a median ID_{50} of 640 μg/ml. Drometrizole, as a UV absorber, inhibited photodynamic

injury to *T. pyriformis* by the standard photosensitizing agent benzo(a)pyrene. With a relative antioxidant potency of 0.2 (α-tocopherol = 1), 159 μg/ml Drometrizole doubled the irradiation time required to immobilize 90% of *T. pyriformis*. It was found that 100% of the protection afforded by Drometrizole was due to light absorption.

The effects of Drometrizole on rat liver were studied by Schmid et al.[24] Drometrizole in corn oil was administered by gavage to three groups of 10 male rats each in a daily dose of 300 mg/kg: the first and second groups were treated for 14 and 28 days, respectively, and were killed 1 day after the last administration; the third group was treated for 14 days and killed after a 28-day recovery period. Comparable control groups received an equal volume of corn oil. Additionally, groups of four rats each were tested to determine the O-dealkylation of ethoxycoumarin and the activities of NADPH-cytochrome c reductase and acid hydrolases. Hepatic subcellular fractions were prepared, and biochemical determinations were made. Tissues were prepared for and examined by electron microscopy.

The repeated administration of Drometrizole to rats caused a significant increase in relative liver weights in all three dose groups, although it did not influence body weight gains. Microsomal protein content was slightly decreased at 14 days and significantly increased at 28 days; however, the latter control value (from the paired control group) was lower than those of the other control groups. No change was noted in the content of microsomal phospholipid or activity of cytochrome P-450. The activity of several mixed-function oxidases remained unchanged. Drometrizole administration significantly increased the activity of aminopyrine N-demethylase after 28 days and UDP glucuronosyltransferase activity at 14 and 28 days. Glucose 6-phosphatase activity was decreased at 14 days only. Addition of 7,8-benzoflavone to liver microsomal fractions prepared from control, phenobarbital-treated, or Drometrizole-treated rats stimulated the activity of ethoxycoumarin 0-deethylase, whereas it inhibited the enzymic activity when added to liver microsomes of rats treated with 3-methylcholanthrene. Drometrizole treatment had no appreciable effect on free and total activity of the various acid hydrolases. No major alterations were seen in the organelles of hepatocytes from rats of any of the dose groups. The proliferative response of the smooth endoplasmic reticulum was moderate in comparison to those rats treated with phenobarbital as an enzyme inducer. The investigators concluded that Drometrizole was an enzyme inducer with a slight stimulant effect on the formation of mixed-function oxidases.[24]

The distribution and elimination of Drometrizole in the rat also was studied by Schmid et al.[24] ^{14}C-Drometrizole (5.07 μCi/mg), labeled in the benzene ring and in the 5′-methyl group in an unstated ratio, was administered to four male rats as a single oral dose of 10 mg/kg dissolved in polyethylene glycol 400. Urine and feces were collected every 24 h for 7 days. The rats were then killed, and the organs and tissues were analyzed for radioactivity. Ninety-one percent of the radioactivity was eliminated from the body within the first 48 h; recovery was essentially complete by the seventh day, with about 73% of the radioactivity in the urine and 27% in the feces. Residual radioactivity measured in the tissues (at 7 days) was negligible, for the most part below the blood concentration of 0.017 μg/g, with the exceptions of the kidney, the aorta, and the liver (0.10–0.22 μg/g). The chemical nature of the radioactive excretion products was not identified.

ANIMAL TOXICOLOGY

Acute Toxicity

Oral

The acute oral LD_{50} of Drometrizole in mice has been reported to be >5.0 g/kg body weight[23] and 6.5 g/kg.[25] Acute oral toxicity test results are presented in Table 3.

Komarova and Maksimova[11] administered 5.0 and 10.0 g/kg Drometrizole (in sunflower oil) by stomach tube to white mice and rats. Sunflower oil was given to the control animals. During the 3-week observation period, behavior and body weights of the test animals were comparable to controls. Drometrizole was considered a substance of low toxicity.

Four cosmetic nail products containing Drometrizole at concentrations of 1.0, 1.0, 0.30, and 0.03% were evaluated for oral toxicity in rats. Doses of each product were administered by oral intubation. The resultant LD_{50}s were >15.0 g/kg for the two products containing 1% Drometrizole and >5.0 g/kg for the products containing 0.30 and 0.03% Drometrizole. All products were considered practically nontoxic by ingestion.[26-29]

Dermal

A nail polish containing 1.0% Drometrizole was evaluated for acute dermal toxicity in six albino guinea pigs. A 10% aqueous solution of the product was applied under occlusive patches at a dose of 3.0 g/kg to the clipped and abraded (three only) skin of each guinea pig for 24 h. The animals were observed for toxic effects and mortality for 14 days. No deaths occurred. Necropsy was performed on Day 14. The nail polish was considered nontoxic by percutaneous application.[30]

TABLE 3. Acute Oral Toxicity

Compound	*Animal*	*LD_{50}*	*Comments*	*Reference*
Drometrizole	Mice	6.5 g/kg	---	25
Drometrizole	Mice	>5.0 g/kg	---	23
Drometrizole	Mice	5.0, 10.0 g/kg administered	Low toxicity	11
	Rats	5.0, 10.0 g/kg administered		
Drometrizole 1.0% in a nail polish	Rats, 5	>15.0 g/kg	Practically nontoxic	27
Drometrizole 1.0% in a nail polish	Rats, 5	>15.0 g/kg	Practically nontoxic	28
Drometrizole 0.30% in a nail product	Rats, 10 or more	>5.0 g/kg	Nontoxic	29
Drometrizole 0.03% in a nail product	Rats, 10 or more	>5.0 g/kg	Nontoxic	26

A nail product containing 0.3% Drometrizole was evaluated for dermal toxicity using 10 rabbits. The product was applied under occlusive patches to the clipped and abraded (five only) skin of each rabbit for 24 h. The animals were observed for 14 days. The LD_{50} was >2 g/kg; the product was considered nontoxic under the conditions of the test.[26]

Irritation

Ocular

Instillation of 500 mg Drometrizole into the eye of a rabbit produced moderate irritation after 24 h.[31] Ocular irritation test results are reported in Table 4.

A nail polish containing 1.0% Drometrizole was evaluated for ocular irritation in two Draize tests. In each test, a 0.1 ml sample of the polish was instilled into one eye of each rabbit; the other eye served as the control. Three and six rabbits were used in the first and second tests, respectively. The eyes of the rabbits in the first test were rinsed with water 4 seconds after instillation, and the total score was 1 on Days 1 and 2 and 0 on Day 3 (max = 110). The eyes of the rabbits in the second test were not rinsed, and the total scores were 32, 27, 31, 24, and 24 on Days 1, 2, 3, 4, and 7, respectively. By the Draize classification of irritation, the polish was minimally irritating under conditions of the first test (rinsed) and moderately to severely irritating under conditions of the second test (unrinsed).[32,33]

TABLE 4. Ocular Irritation

Ingredient	*Test method*	*Results*	*Reference*
Drometrizole	500 mg instilled into one eye	Moderately irritating after 24 h	31
Drometrizole 1.0% in a nail polish	Draize, 3 rabbits/rinsed	Scores of 1, 1, and 0 on days 1, 2, and 3, respectively[a]; minimally irritating	33
Drometrizole 1.0% in a nail polish	Draize, 6 rabbits/unrinsed	Scores of 32, 27, 31, 24, and 24 on Days 1, 2, 3, 4, and 7, respectively[a]; moderately to severely irritating	32
Drometrizole 1.0% in a nail polish	Draize, 3 rabbits/rinsed	Scores of 11, 9, 5, 1, and 0 on Days 1, 2, 3, 4, and 7, respectively[a]; mildly irritating	35
Drometrizole 1.0% in a nail polish	Draize, 6 rabbits/unrinsed	Scores of 16, 8, 2, and 0 on Days 1, 2, 3, and 4, respectively[a]; mildly irritating	34
Drometrizole 0.03% in a nail product	Draize, 6 rabbits/unrinsed	All scores of 0[a]; nonirritating	29

[a]Maximum score = 110.

Another nail polish containing 1.0% Drometrizole was evaluated for ocular irritation in two Draize tests, as outlined above. In three rabbits, the eyes were rinsed after instillation, and the scores were 11, 9, 5, 1, and 0 on Days 1, 2, 3, 4, and 7, respectively. In six rabbits the eyes were unrinsed, and the scores were 16, 8, 2, and 0 on Days 1, 2, 3, and 4, respectively. By the Draize classification of irritation, the polish was mildly irritating under the conditions of either test (rinsed or unrinsed).[34,35]

A nail product containing 0.03% Drometrizole was evaluated for ocular irritation using six albino rabbits. A 0.1 ml sample of the product was instilled into one eye of each rabbit; the other eye served as the control. Eyes were scored at 24, 48, and 72 h; all rabbits had a score of 0. The nail product was considered nonirritating under the test conditions.[29]

Dermal

A nail polish containing 1.0% Drometrizole was evaluated for primary skin irritation in nine albino rabbits. A 0.5 ml sample of the polish was applied under occlusive patches to the clipped skin of each rabbit for 24 h. Sites were scored 2 and 24 h after patch removal; all scores were 0. The polish was considered nonirritating under the test conditions.[36]

Sensitization

Drometrizole was evaluated for sensitization in guinea pigs by two separate Magnusson-Kligman maximization tests.[37,38] The induction phase in each test consisted of three 0.05 ml intradermal injections into the shaved upper back of each guinea pig. The experimental group of 10 animals received injections of 50% aqueous Freund's adjuvant, 5% Drometrizole in corn oil, and 5% Drometrizole in 50% aqueous Freund's adjuvant. The control group of 10 guinea pigs received injections of 50% aqueous Freund's adjuvant, corn oil, and a 1:1 mixture of corn oil and 50% aqueous Freund's adjuvant.

A dose range phase was conducted in each test to determine the slightly irritating and subirritating concentrations for use in the booster and challenge phases, respectively. Occlusive patches containing 5, 10, and 100% Drometrizole (in petrolatum) were applied to 10 additional guinea pigs in the first test. All scores were 0; the concentrations for the booster and challenge phases were set at 100 and 10%, respectively. In the second test, concentrations of 0.5, 1.0, and 5% Drometrizole (in petrolatum) were administered. Two of the 10 guinea pigs had a ± score at the 5% concentration. The booster and challenge phase concentrations were set at 10 and 5%, respectively.[37,38]

The booster phase was conducted 1 week after the induction phase. Guinea pigs of the second test received a pretreatment of 10% sodium lauryl sulfate (SLS), applied to the site 24 h before the test booster application. Topical booster applications containing 0.1 g of 100% Drometrizole (first test) or 0.1 g of 10% Drometrizole in petrolatum (second test) were applied to the same induction sites under occlusive patches for 48 h. The control groups received applications of petrolatum.[37,38]

The challenge phase was conducted 2 weeks after the booster phase. Topical patches containing 0.1 g of 10% (first test) or 5% (second test) Drometrizole in petrolatum were applied to previously untreated sites on all animals under oc-

clusive patches for 24 h. Sites were scored 24 and 48 h after patch removal. No reactions were observed in the first control group, and one guinea pig in the first experimental group had a score of 1 (max = 4) at 24 h and ± at 48 h. In the second test, the control group had five and two ± reactions at 24 and 48 h, respectively. The experimental group had five and three ± reactions at 24 and 48 h, respectively, as well as a score of 1 at 24 h. The investigators in both studies observed no discernible potential for allergic skin sensitization and considered Drometrizole safe for use in nail product formulations at a 1% concentration.[37,38]

MUTAGENICITY AND CARCINOGENICITY

Drometrizole was evaluated for mutagenicity in the Ames test using *Salmonella typhimurium* strains TA 1538 and TA98 with metabolic activation. Both the spot test (with Drometrizole concentrations of 10 and 100 μg/plate) and the top agar method (with Drometrizole concentrations of 50 and 100 μg/plate) were used. Saline or dimethyl sulfoxide (DMSO) were used as solvents. Drometrizole was not mutagenic.[39]

The Ames test as well as a mouse bone marrow micronucleus test were used to evaluate the mutagenic potential of Drometrizole alone and in a mixture with methylmethacrylate, methylacrylate, stearyl alcohol, and DMSO or olive oil. *S. typhimurium* strains TA1535, TA1537, TA1538, TA98, and TA100 were used with and without metabolic activation to test concentrations of Drometrizole ranging from 0 to 20 μg/plate. The mouse bone marrow test evaluated micronucleated erythrocytes from mice given single oral doses of 0.63–2.5 g/kg or three doses of 0.63 g/kg. All results were negative.[40]

CLINICAL ASSESSMENT OF SAFETY

Irritation, Sensitization, and Photosensitization

Drometrizole was evaluated for primary skin irritation as a 1% solution in peach kernel oil using a panel of 100 females. Samples of 0.1 ml were applied under occlusive patches to the back of each subject for 48 h. Reactions were scored 15 minutes and 24 h after patch removal. No erythema or edema was noted. Drometrizole was not a primary irritant.[41] Results of clinical irritation, sensitization, and photosensitization tests are reported in Table 5.

Drometrizole was applied daily for 8 weeks by means of an occlusive dressing to 300 patients with and without dermatosis. No irritation or eczematous reactions were observed.[6]

A nail polish containing 1.0% Drometrizole was evaluated for primary skin irritation using a panel of 20 subjects. Occlusive patches containing samples of the polish were applied to a site on the arm for 24 or 48 h. A commercially marketed product was simultaneously applied as the control. Reactions were scored 2 and 24 h after patch removal. Only one panelist had a ± score (max = 4) for the nail polish and for the control product, giving an average irritation score of 0.03 for both products. The investigators concluded that there were no significant differences in irritancy between the nail polish and the reference control.[42]

TABLE 5. Clinical Irritation, Sensitization, Photosensitization, and Phototoxicity

Ingredient	*Test*	*No. of subjects*	*Results*	*Reference*
Drometrizole 1% in peach kernel oil	SIPT[a]	100 females	No erythema or edema noted; nonirritating	41
Drometrizole	Daily occlusive application for 8 weeks	300 with or without dermatosis	No irritating or eczematous reactions	6
Drometrizole 1.0% in a nail polish	SIPT	20	One subject with score of ± (max = 4); no difference in irritancy between polish and control; nonirritating	42
Drometrizole 5% in a UV light-absorbing preparation 1.5 parts by weight in a UV light-absorbing preparation	3-year trial—445 topical applications with radiation	145—some suffering from light dermatoses and sensitivity	Hypersensitivity reactions in 2 cases	6
Drometrizole 0.5% in a nail polish	RIPT[b]—Modified Draize-Shelanski-Jordan	148–59 males 89 females	All scores of 0; nonirritating and nonsensitizing	43

Drometrizole 0.30% in a nail product	Controlled use study–2× weekly for 4 weeks	53	No adverse reactions; nonirritating	44
Drometrizole 0.03% in a nail product	Controlled use study–1× weekly for 4 weeks	48	No adverse reactions; nonirritating	45
Drometrizole 0.03% in a nail product	Prophetic patch test with UV exposure	99	All scores of 0; nonirritating, nonsensitizing, and nonphotosensitizing	46
Drometrizole 0.03% in a nail product	RIPT with UV exposure	48	A total of 5 scores of 1 (max = 3) and 1 score of 2 during induction; 1 score of 1 at challenge, and 1 reaction at challenge with UV exposure; nonirritating, nonsensitizing, and nonphotosensitizing	46
Drometrizole 0.1% in a suntan oil	Phototoxicity with UVA and UVB exposure	10–2 males 8 females	All scores of 0; nonphototoxic	47
Drometrizole 0.1% in a suntan oil	Phototoxicity with UVA and UVB exposure	10–2 males 8 females	All scores of 0; nonphototoxic	48

[a]SIPT, Single Insult Patch Test.
[b]RIPT, Repeated Insult Patch Test.

A 3-year clinical therapeutic trial of two UV light-absorbing preparations was conducted using 145 patients. Preparation I was an ointment containing 5% Drometrizole; Preparation II was a lacquer containing 1.5 parts by weight Drometrizole. These two preparations were tested for their light-protective capabilities in numerous patients (some suffering from light dermatoses and light sensitivity) by means of radiation with an Osram Ultra Vitalux lamp or with sunlight; 445 successful applications indicated that the preparations were highly effective. Hypersensitivity reactions were observed in only two cases.[6]

A nail polish containing 0.5% Drometrizole was evaluated for irritation and sensitization by a Modified Draize-Shelanski-Jordan repeated insult patch test (RIPT). Topical occlusive patches were applied to the upper back of each of 148 subjects (59 males, 89 females) on Monday, Wednesday, and Friday for 3 consecutive weeks. Patches were removed and sites were scored before each new patch application. Following a 2-week rest period, each subject received two consecutive challenge patches each applied for 48 h on a previously untreated site. Reactions were scored at 48 and 96 h; all subjects had a score of 0. The polish was neither an irritant nor a sensitizer under the conditions of the test.[43]

Two nail products containing 0.30 and 0.03% Drometrizole were evaluated in controlled use studies. A panel of 53 subjects used the nail product with 0.30% Drometrizole twice weekly for 4 weeks. A panel of 48 subjects used the product with 0.03% Drometrizole once a week for 4 weeks. No adverse reactions were noted in either study. Both nail products were considered nonirritating.[44,45]

A nail product containing 0.03% Drometrizole was evaluated in a prophetic patch test and a RIPT, both with UV exposure. A panel of 99 subjects participated in the prophetic patch test, receiving single induction and challenge patches with UV exposure. All scores were 0. The RIPT was conducted using 48 subjects, each receiving 10 induction patches and a single challenge patch, with UV exposure. A total of five scores of 1 (max = 3) and one score of 2 were observed in the induction phase, one score of 1 at challenge, and one reaction was noted at challenge with UV exposure. The nail product was considered nonirritating, nonsensitizing, and nonphotosensitizing.[46]

Phototoxicity

Two suntan oils, each containing 0.1% Drometrizole, were evaluated for phototoxicity in identical panels of two males and eight females. Occlusive patches containing 0.2 ml samples of each suntan oil were applied to duplicate sites (one test, one control) on the back of each subject for 24 h. The oils were reapplied to each test site after patch removal. Five minutes later, the test site of each subject was irradiated with the equivalent of 1 MED of UVB followed by 12 minutes of exposure to UVA. An additional untreated site on each subject was irradiated as a second control. The light source used in this experiment was a xenon arc solar simulator (150 W) giving a continuous emission of 290–400 nm. A Schott WG345 filter was used to screen out UVB. All sites were scored at 15 minutes and 24 and 48 h. All scores for both suntan oils were 0. Neither product produced evidence of phototoxicity[47,48] (Table 5).

Case Reports

A 37-year-old woman was patch tested with various cosmetic products after developing swelling of the eyelids and a mild papular eruption on the cheeks. All tests were negative after 48 h; however, at 96 h a positive reaction was seen to one nail varnish. The woman was found to be allergic to Drometrizole after patch testing with the individual ingredients of the varnish. Positive reactions were seen at 48 and 96 h after patch testing with 1% and 5% Drometrizole in petrolatum. Drometrizole tested at 5% in petrolatum was negative in eight controls.[49]

Drometrizole in facial creams has been reported to be the cause of allergic contact dermatitis in four women. Each had eczema of the face, although it was confined to the eyelids in one woman. Two the the women had used the creams on other areas of the body, and these, also, were affected. Each of the women reacted to patch tests with 1% Drometrizole in petrolatum; two of three reacted when tested with their facial cream. One particular brand of cosmetics had been used by three of the women, and these manufacturers have since discontinued the use of Drometrizole in their products.[50]

SUMMARY

Drometrizole, a benzotriazole derivative, is an odorless, off-white to yellow, crystalline powder. It is insoluble in water and soluble in ethyl acetate, acetone, oleyl alcohol, caprolactam solutions, dioctylphthalate, hot petrolatum, methyl ethyl ketone, methyl methacrylate, chloroform, toluene, and styrene.

Drometrizole has maximum absorbance at wavelengths of approximately 243, 298, and 340 nm; minimum absorbance occurs at 214 and 259 nm.

Drometrizole is both light stable and heat stable and has a high degree of environmental stability. It is also stable to conditions and chemicals used in polymerization or compounding of plastics.

Drometrizole is used in cosmetics as a UV light absorber and stabilizer, primarily at concentrations below 0.1%. Of the total 217 uses reported in 1981, 77% were in nail polishes and enamels and 11% were in noncoloring hair shampoos. Products containing Drometrizole may contact all external body surfaces and hair, as well as the eyes and mucous membranes. Frequency and length of application could result in continuous exposure.

Drometrizole is used widely as a UV absorber and stabilizer in plastics, polyesters, celluloses, acrylates, dyes, rubber, synthetic and natural fibers, waxes, detergent solutions, and orthodontic adhesives. It is similarly used in agricultural products and insecticides. Drometrizole is approved as an indirect food additive for use as an antioxidant and/or stabilizer in polymers.

Drometrizole has low cytotoxicity to *Tetrahymena pyriformis* and inhibited photodynamic injury to the protozoon by the photosensitizing agent benzo(a)pyrene.

Drometrizole was administered orally to rats to determine its effects on the liver; repeated administration for 14 or 28 days caused a significant increase in relative liver weight but did not affect the body weight gain of the rats. The activities of enzymes aminopyrine N-demethylase and UDP glucuronosyltransferase

were significantly increased. No significant effects were noted in the activities of various acid hydrolases or in the organelles of hepatocytes. Drometrizole was found to be an enzyme inducer with a slight stimulant effect on the formation of mixed-function oxidases.

The results of a distribution and elimination study of ^{14}C-Drometrizole in rats indicated that Drometrizole was appreciably absorbed and metabolized. Recovery of radioactivity was essentially complete by the seventh day, with about 73% recovered from the urine and 27% from the feces. Residual radioactivity in the tissues was negligible.

Drometrizole and products containing Drometrizole were relatively nontoxic in acute oral and dermal studies.

Drometrizole was moderately irritating 24 h after instillation of 500 mg into the rabbit eye. Nail polishes containing 1.0% Drometrizole were minimally to mildly irritating to rabbit eyes when instillation was followed by a rinse, and mildly to severely irritating in unrinsed eyes. A nail product containing 0.03% Drometrizole was nonirritating to rabbit eyes when instillation was not followed by a water rinse.

A nail polish containing 1.0% Drometrizole was nonirritating to rabbit skin. Drometrizole was negative for sensitization in two Magnusson-Kligman maximization tests in guinea pigs.

Drometrizole was not mutagenic in two Ames tests using *Salmonella typhimurium* both with and without metabolic activation or in a mouse bone marrow micronucleus test.

In clinical studies, Drometrizole tested at 1% in peach kernel oil was nonirritating to 100 females in a single insult patch test. No irritation or eczematous reactions were observed in 300 patients (with or without dermatosis) treated with daily applications of Drometrizole for 8 weeks. In a 3-year clinical therapeutic trial conducted to evaluate the effectiveness of two UV-absorbing preparations containing up to 5% Drometrizole, two hypersensitivity reactions were observed during 445 applications. A total of 145 patients were used, some of whom suffered from light dermatoses and light sensitivity. Cosmetic products containing 0.03–1.0% Drometrizole produced no irritation, sensitization, photosensitization, or phototoxicity in a total of 436 subjects.

Drometrizole was considered the sensitizing agent in five case reports of allergic contact dermatitis due to cosmetic use.

DISCUSSION

Section 1 paragraph (p) of the CIR Procedures states that "A lack of information about an ingredient shall not be sufficient to justify a determination of safety." In accordance with Section 30(j)(2)(A) of the Procedures, the Expert Panel informed the public of its decision that the data on Drometrizole were insufficient to determine that this ingredient, under each relevant condition of use, was either safe or not safe. The Panel released a "Notice of Insufficient Data" on July 2, 1985, outlining the data needed to assess the safety of Drometrizole. The types of data required included:

1. 90-day subchronic oral toxicity
2. Mutagenicity testing in two systems other than the Ames assay and the mouse bone marrow micronucleus test

There has been no response or indication of intent to supply the aforementioned information.

CONCLUSION

The safety of this ingredient has not been documented and substantiated. The CIR Expert Panel cannot conclude that Drometrizole is safe for use in cosmetic products until such time that the appropriate safety data have been obtained and evaluated.

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