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Risk Assessment of Drometrizole, a Cosmetic Ingredient used as an Ultraviolet Light Absorber

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Abstract

As the use of cosmetics has greatly increased in a daily life, safety issues with cosmetic ingredients have drawn an attention. Drometrizole [2-(2′-hydroxy-5′-methylphenyl)benzotriazole] is categorized as a sunscreen ingredient and is used in cosmetics and non-cosmetics as a UV light absorber. No significant toxicity has been observed in acute oral, inhalation, or dermal toxicity studies. In a 13-week oral toxicity study in beagle dogs, No observed adverse effect level (NOAEL) was determined as 31.75 mg/kg bw/day in males and 34.6 mg/kg bw/day in females, based on increased serum alanine aminotransferase activity. Although drometrizole was negative for skin sensitization in two Magnusson-Kligman maximization tests in guinea pigs, there were two case reports of consumers presenting with allergic contact dermatitis. Drometrizole showed no teratogenicity in reproductive and developmental toxicity studies in which rats and mice were treated for 6 to 15 days of the gestation period. Ames tests showed that drometrizole was not mutagenic. A long-term carcinogenicity study using mice and rats showed no significant carcinogenic effect. A nail product containing 0.03% drometrizole was nonirritating, non-sensitizing and non-photosensitizing in a test with 147 human subjects. For risk assessment, the NOAEL chosen was 31.75 mg/kg bw/day in a 13-week oral toxicity study. Systemic exposure dosages were 0.27228 mg/kg bw/day and 1.90598 mg/kg bw/day for 1% and 7% drometrizole in cosmetics, respectively. Risk characterization studies demonstrated that when cosmetic products contain 1.0% of drometrizole, the margin of safety was greater than 100. Based on the risk assessment data, the MFDS revised the regulatory concentration of drometrizole from 7% to 1% in 2015. Under current regulation, drometrizole is considered to be safe for use in cosmetics. If new toxicological data are obtained in the future, the risk assessment should be carried out to update the appropriate guidelines.

Key words: Risk, Safety, Drometrizole, Cosmetics, Toxicity, Skin

INTRODUCTION

Cosmetics are a part of everyday life for people of all ages around the world. People use cosmetics to maintain their personal hygiene or to care for their personal appearance (1). Cosmetics contain many ingredients with various functionalities. As the use of cosmetics has expanded, the safety issues of cosmetic ingredients have drawn

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List of Abbreviations: CTFA, Cosmetic, Toiletry and Fragrance Association; EPA, Environmental Protection Agency; FDA, Food and Drug Administration; MFDS, Ministry of Food and Drug Safety; MHLW, Ministry of Health, Labor and Welfare; MOS, Margin of safety; NMRI, Nuclear Magnetic Resonance Imaging; NOAEL, No observed adverse effect level; NOEL, No observed effect level; PEG, Polyethylene glycol; RIPT, Repeat insult patch test; SED, Systemic exposure dosage; UDP, Uridine diphosphate; UV, Ultra violet.

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extensive attention. Therefore, certain cosmetic ingredients are under regulation, requiring that human health be safe when using cosmetics under normal or predictable conditions of use (2). Drometrizole is categorized as an ingredient of sunscreen and is known to be used in various cosmetics and non-cosmetics. The purpose of this review is to investigate the toxicological data and risk assessment of drometrizole using the available published data.

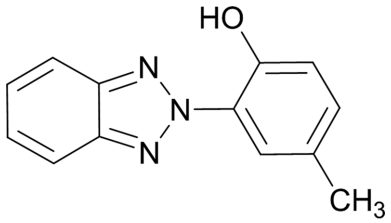

Fig. 1. Chemical structure of drometrizole.

Physical and chemical properties. Drometrizole (CAS no. 2440-22-4) called 2-(2′-hydroxy-5′-methylphenyl) benzotriazole, is an odorless benzotriazole compound that appears as an off-white to yellow crystalline powder with a structure as shown in Fig. 1. It is also known as 2-(2H-benzotriazol-2-yl)-4-methylphenol, 2-(2H-benzotriazol-2-yl)-p-cresol, benazol P, and tinuvin P. Molecular weight is 225.25. Its melting point is 131°C to 133°C and its boiling point is 225°C. The Log P (octanol/water) of drometrizole is 4.31 and it is soluble in organic solvents such as acetone, chloroform, dioctylphthalate, ethanol, ethyl acetate, but insoluble in water (3-7).

Other physical and chemical properties are presented in Table 1.

Cosmetic use. Drometrizole is used in a variety of cosmetics and personal care products in addition to non-cosmetic products. In cosmetics, drometrizole is categorized as a sunscreen ingredient and used as a UV light absorber and stabilizer (8). It prevents the deterioration of cosmetics and personal care products because it absorbs, reflects, and scatters UV rays (9). It is also used as a fragrance ingredient in consumer goods by International Fragrance Association-affiliated members (10). According to the US Food and Drug Administration (FDA), in 1981, drometrizole was used in the following cosmetics: bath, fragrances, coloring and noncoloring hair care, manicuring, shaving, skin care, and suntan preparations. Of the 217 reported drometrizole use cases, 77% were used in nail polishes and enamels, and 11% were used in noncoloring hair shampoos. According to voluntary industry reports to the US FDA in 2005, there were two uses of drometrizole: in noncoloring shampoos and in other noncoloring hair preparations (11). In 2006, the International Cosmetic Ingredient Dictionary and Handbook indicated the uses of drometrizole in nail polishes and enamels (8).

Table 1. Physical and chemical properties of drometrizole

Properties	Value	Reference
INCI name	Drometrizole	7
CAS number	2440-22-4	7
EINECS number	219-470-5	7
Molecular weight	225.23	4
Empirical formula	$C_{13}H_{11}N_3O$	3
Physical appearance	Off-white to yellow crystalline powder	3
Melting point (°C)	131-133	4
Boiling point (°C)	225	3
Log P (octanol-water)	4.31	7
Vapor pressure	7.95×10^{-8} mmHg (p 25°C)	7
Particle size	2.5% max retained on 200 mesh screen 7.5% max retained on 325 mesh screen	6
Specific gravity	151	6
Ash	1% max	6
Loss on drying	< 0.5%	5
Residue on ignition	< 0.1%	5
Solubility	Soluble in Acetone, caprolactam solutions, chloroform, dioctylphthalate, ethanol, ethyl acetate, methyl ethyl ketone, methyl methacrylate, oleyl alcohol, petrolatum (hot) ketone, styrene, toluene. Insoluble in water (25.6 mg/L at 25°C)	3
Henry's law constant	6.12×10^{-14} atm-m^3/mol	7
Synonyms	2-(2′-Hydroxy-5′-methylphenyl) benzotriazole; 2-(2H-benzotriazol-2-yl)-4-methylphenol; 2-(2H-Benzotriazolyl)-p-cresol; Benazol P; Tinuvin P	7

Based on the list of cosmetics ingredients reported by manufacturers to the Ministry of Food and Drug Safety (MFDS) in 2015, drometrizole was used in 184 products of the 100,190 products manufactured in Korea. Most of these are nail care products while it is not used as the main ingredient of sunscreens in Korea.

In non-cosmetic products, drometrizole is used as a UV absorber and stabilizer in plastics, polyesters, celluloses, acrylates, dyes, rubber, synthetic and natural fibers, waxes, detergent solutions, and orthodontic adhesives. Because of its high degree of environmental stability, it is used in polymerization or compounding of plastics (12). Due to its stability in the presence of light and heat, it may be used in agricultural applications as a UV absorber to prevent leaf burn and apple peel spot. It is formulated in insecticides as a stabilizer (13). In addition, it has antioxidant and stabilizing effects and is approved as an indirect food additive. It is used as a UV absorber in food packaging (14).

According to the Global Cosmetic Ingredient Information database, drometrizole is regulated to be used up to 7% in cosmetics other than those washed immediately after use, such as soap or shampoo in Japan (15). It is not included in restricted ingredient lists in the European Union and USA (16).

According to the US Food and Drug Administration (FDA) in 1981, about half of the products were used at concentrations below 0.1%, 4% were used at 0.1-1%, and 43% at unknown concentrations (17). In a survey carried out by the Cosmetic, Toiletry and Fragrance Association (CFTA), drometrizole is used at 0.07% in nail care products (basecoats and undercoats) (18). In Korea, the regulation of drometrizole concentration in cosmetics as an ultraviolet sunscreen agent was revised from 7.0% to 1.0% in 2015.

HAZARD IDENTIFICATION

Acute toxicity. Mice and rats were administered 5.0 or 10.0 g/kg of drometrizole in sunflower oil by stomach tube intubation. After body weight and behavior were monitored for 3 weeks, acute toxicity of drometrizole was evaluated to be low (19). The oral lethal dose (LD_{50}) of drometrizole in mice was reported to be 6.5 g/kg and > 5.0 g/kg by Labor Hygiene and Occupational Diseases (20) and Epstein *et al.* (21), respectively (20,21). Oral toxicity was evaluated in rats for nail care cosmetics containing 1%, 0.3% and 0.03% of drometrizole. The LD_{50} of products containing 1% of drometrizole was > 15.0 g/kg. LD_{50} of products containing 0.3% and 0.03% of drometrizole was > 5.0 g/kg. No acute toxicity was observed in these treatments (22-25).

Tif:Ralf (SPF) rats were orally treated with 4,640, 7,750, or 10,000 mg/kg of drometrizole suspended in polyethylene glycol (PEG) 400. Rats were observed for clinical symptoms and mortality for 14 days after treatment. Rats showed sedation, dyspnea, curved position, and ruffled fur within 2 hr after administration. Two females of 10,000 mg/kg group died within one week and all other animals recovered within 10 days after treatment. The animals showed no symptoms associated with administration at necropsy. The Environmental Protection Agency (EPA) concluded that the oral LD_{50} of drometrizole in rats was > 10,000 mg/kg (26).

Five male and five female Charles River rats were exposed to drometrizole/air mixture at 1,420 mg/m^3 for 4 hr. Drometrizole aerosol was produced through a Ferris wheel dust system. The animals showed no clinical signs, toxicity, or mortality for 14 days after exposure. There were no effects or changes related to exposure at necropsy. Thus, LC_{50} (4 hr) of drometrizole was evaluated to be > 1,420 mg/m^3 (26).

A nail product containing 0.3% drometrizole was applied under occlusive patches to the clipped skin of 10 rabbits for 24 hr. After application, the animals were observed for 14 days. Dermal LD_{50} was estimated to be > 2 g/kg (22). Nail polish products containing 1% drometrizole were applied to six albino guinea pigs under occlusive patches at 3.0 g/kg doses for 24 hr. There were no toxic effects or

Table 2. Acute toxicity studies of drometrizole

Route	Animal, number	Compound	LD50/LC50	Results	Reference
Oral	Mice	Drometrizole	6.5 g/kg	-	20
Oral	Mice	Drometrizole	> 5 g/kg	-	21
Oral	Mice	Drometrizole	> 10 g/kg	Low toxicity	19
Oral	Rats	Drometrizole	> 10 g/kg	Low toxicity	19
Oral	Rats	Drometrizole	> 10 g/kg	-	26
Oral	Rats, 5	Drometrizole 1.0% in a nail polish	> 15 g/kg	Nontoxic	23
Oral	Rats, 5	Drometrizole 1.0% in a nail polish	> 15 g/kg	Nontoxic	24
Oral	Rats, 10 or more	Drometrizole 0.3% in a nail polish	> 5 g/kg	Nontoxic	25
Oral	Rats, 10 or more	Drometrizole 0.03% in a nail polish	> 5 g/kg	Nontoxic	22
Inhalation	Rats, 5	Drometrizole/air mixture	> 1,420 mg/m^3	Nontoxic	26
Dermal	Rabbits, 10	Drometrizole 0.3% in a nail polish occlusive patches	> 2 g/kg	-	22
Dermal	Guinea pigs, 6	Drometrizole 1% in a nail polish occlusive patches	> 3 g/kg	-	27

Table 3. Repeated toxicity studies of drometrizole

Period	Animal, number	Compound	Dosage (mg/kg bw/day)	Results	Reference
14 days to 28 days	Rats, 30	Drometrizole	300	Increase in liver weight, change of several enzyme activity	28
13 weeks	Dogs	Drometrizole	Male: 31.75, 95.25, 317.5 Female: 34.6, 103.8, 346	Decrease in food intake and body weight gain, increase of serum enzyme activity	26
2 years	Rats	Drometrizole	4, 14, 47, 142	Decrease in body weight in male and food intake in female	26

mortality for 14 days after treatment (27).

Acute toxicity test results are summarized in Table 2.

Repeated dose toxicity. Three groups of 10 male rats were orally administered 300 mg/kg drometrizole in corn oil every day. The first and second groups were treated for 14 and 28 days, respectively, the third group had a recovery period of 28 days after 14 days of treatment. There was no significant effect on body weight gain in any of the three groups, but a significant increase in liver weight was observed. Liver microsomal protein content was significantly increased in the 28 days group, but slightly decreased in the 14 days group. Microsomal phospholipids showed no significant difference compared to controls in any of the treatment groups. The activity of cytochrome P450, ethylmorphine N-demethylase, (3-methyl-4-methylamino-azobenzene)-N-demethylase, and biphenyl 4-hydroxylase was not changed significantly by drometrizole treatment. Drometrizole did not affect the activity of a variety of acid hydrolases in the liver, nor did it alter the organelles of hepatocytes in any of the groups. In contrast, the activity of aminopyrine N-demethylase in the liver was significantly increased in the 14 days group. Liver UDP-glucuronosyltransferase was significantly increased in both the 14 days and the 28 days groups. Hepatic glucose 6-phosphatase activity was decreased in the 14 days group. These results suggest that drometrizole is an enzyme inducer for the formation of mixed function oxidases with a slight stimulatory effect (28).

The EPA reported a 13-week study of drometrizole administration in four groups of beagle dogs. Drometrizole dosage was 0, 1,000, 3,000, and 10,000 ppm (male: 0, 31.75, 95.25, 317.5 mg/kg bw/day, female: 0, 34.6, 103.8, 346 mg/kg bw/day) for each group. No mortalities or clinical symptoms were observed upon treatment. Decreased food intake and body weight gain were observed in the 10,000 ppm group. The 3,000 and 10,000 ppm group showed increased serum alanine aminotransferase activity. Serum gamma-glutamyltranspeptidase activity was increased only in the 10,000 ppm group. The EPA concluded that the no observed effect level (NOEL) of drometrizole was 31.75 mg/kg bw/day (26).

CFY rats were administered 0, 100, 300, 1,000, or 3,000 ppm (4, 14, 47, 142 mg/kg bw/day) of drometrizole for 2 years. The 3,000 ppm group showed a slight decrease in weight gain in male rats in the second year of treatment and a slight reduction in food consumption in female rats at 53 to 80 weeks of the treatment period. No differences in body weight, food intake or mortality were observed in the other treatment groups. Based on the results, EPA reported that the NOEL of drometrizole was 47 mg/kg bw/day (26).

Repeated toxicity test results are presented in Table 3.

Ocular irritation. Application of 500 mg drometrizole on rabbit eyes caused a moderate irritation response after 24 hr (29).

Two Draize tests were reported by the CTFA to evaluate the ocular irritation of nail polish products containing 1% drometrizole. Four seconds after instilling 0.1 mL of product into one eye of three rabbits, the eyes were washed with water. The score measured was "1" on days 1 and 2. The score on day 3 was "0" (max = 110). Then, 0.1 mL of the product was instilled into one eye of six rabbits without washing. The scores were measured as 32, 27, 31, 24, and 24 on days 1, 2, 3, 4 and 7, respectively. CTFA concluded that the nail polish was minimally irritating under test conditions with washing and moderately to severely irritating without washing (30,31).

Another nail polish product containing 1.0% drometrizole was tested for ocular irritation in two Draize tests. With washing, the scores were 11, 9, 5, 1 and 0 on days 1, 2, 3, 4 and 7, respectively. Without washing, the scores were 16, 8, 2 and 0 on days 1, 2, 3 and 4, respectively. The nail polish was mildly irritating under both test conditions by the Draize classification of irritation (32,33).

A nail product containing 0.03% drometrizole in 0.1 mL was tested in the eye of rabbits without washing. The scores were 0 at 24, 48 and 72 hr. The nail product was nonirritating under all test conditions (25).

Ocular irritation results are presented in Table 4.

Dermal irritation. A nail polish product containing 1.0% drometrizole was evaluated for dermal irritation with

Table 4. Ocular irritation studies of drometrizole

Method	Animal, number	Compound	Results	Reference
Instilled into one eye	Rabbit	Drometrizole 500 mg	Moderately irritating after 24 hr	29
Draize, rinsed	Rabbits, 3	Drometrizole 1.0% in a nail polish	Minimally irritating	31
Draize, unrinsed	Rabbits, 6	Drometrizole 1.0% in a nail polish	Moderately to severely irritating	30
Draize, rinsed	Rabbits, 3	Drometrizole 1.0% in a nail polish	Mildly irritating	33
Draize, unrinsed	Rabbits, 6	Drometrizole 1.0% in a nail polish	Mildly irritating	32
Draize, unrinsed	Rabbits, 6	Drometrizole 0.03% in a nail polish	Nonirritating	25

Table 5. Dermal irritation studies of drometrizole

Method	Subject, number	Compound	Results	Reference
Occlusive patches for 24 hr	Rabbits, 9	Drometrizole 1.0% in a nail polish	Nonirritating	34
Daily occlusive application for 8 weeks	Human with or without dermatosis, 300	Drometrizole	Nonirritating or eczematous reactions	35
Single-insult patch test	Human, 100 female	Drometrizole 1.0% in peach kernel oil	Nonirritating; no erythema or edema	36
Controlled use study twice weekly for 4 weeks	Human, 53	Drometrizole 0.30% in a nail product	Nonirritating; no adverse reactions	37
Controlled use study once weekly for 4 weeks	Human, 48	Drometrizole 0.03% in a nail product	Nonirritating; no adverse reactions	38
Single-insult patch test	Human, 20	Drometrizole 1.0% in a nail polish	Nonirritating; no differences in irritancy between polish and control	39

nine albino rabbits. A volume of 0.5 mL of the polish was applied to clipped rabbit skin under occlusive patches for 24 hr. The scores that were measured at 2 and 24 hr were zero. The nail polish product was nonirritating under this test condition (34).

Drometrizole was applied to 300 patients with or without dermatosis by occlusive dressing for 8 weeks. The patients showed no irritation or eczematous reactions (35).

To evaluate the primary skin irritation of drometrizole, 0.1 mL of 1% drometrizole solution in peach kernel oil was applied to the backs of 100 women by an occlusive patch for 48 hr. The reactions were observed 15 min and 24 hr after patch removal. There was no erythema or edema observed at these time points (36).

To evaluate the irritation of nail products containing drometrizole, 101 subjects used products containing 0.3% drometrizole twice a week for 4 weeks, or 0.03% drometrizole once a week for 4 weeks. Since no adverse responses were seen in the subjects, the two nail products were considered nonirritating (37,38).

Occlusive patches containing 1.0% drometrizole in a nail polish product were applied on one of the arms of 20 subjects for 24 or 48 hr. The reactions were observed at 2 and 24 hr after patch removal. The average irritation score was 0.03 for both product group and control group, showing no significant differences in irritancy between the product and control (39).

Dermal irritation results are presented in Table 5.

Skin sensitization. CTFA reported two separate Magnusson-Klingman maximization tests to evaluate sensitization of drometrizole. For each test, 5% of drometrizole in corn oil and/or 0.05 mL of drometrizole in 50% aqueous Freund's adjuvant was injected three times into the shaved back of guinea pigs in the induction phase. After one week of induction, the booster phase was conducted. Topical booster was applied to the induction site under occlusive patches for 48 hr. The first test used 0.1 g of 100% drometrizole and the second test used 0.1 g of 10% drometrizole in petrolatum as a booster. After two weeks of the booster phase, the challenge phase was conducted with 0.1 g of 10% or 5% of drometrizole in petrolatum, applied to previously untreated sites under occlusive patches for 24 hr. The score was measured 24 or 48 hr after patch removal. No significant allergic skin sensitization potential was observed in either study. Two tests on guinea pigs indicated no allergic skin sensitization potential when induced with 5% drometrizole the, and concluded that it was safe to use at 1% concentration of drometrizole in nail products (40,41).

A nail polish containing 0.5% drometrizole was applied to the upper back of 148 subjects by topical occlusive patches on every Monday, Wednesday, and Friday for 3 weeks. Scores were measured before new patches were attached. After a two-week break, new patches were applied to untreated sites for 48 hr. Reaction scores were determined at 48 and 96 hr. All subjects showed a zero score.

Table 6. Skin sensitization tests of drometrizole

Method	Subject, number	Compound	Results	Reference
Magnusson-Klingman maximization tests	Guinea pigs	Drometrizole 5% (induction) Drometrizole 10, 100% (booster) Drometrizole 5%, 10% (challenge)	Nonsensitizing	40,41
Occlusive patches: three times weekly for 3 weeks (induction)/new patches for 48 hr (challenge)	Human, 148	Drometrizole 0.5% in a nail polish product	Nonirritating and nonsensitizing	36
Patch test	Human (Female), 4	Drometrizole 1%	Sensitizing	43
Patch test	Human (Female), 1	Drometrizole 1%, 5%	Sensitizing	44

These show that the polish product was neither an irritant nor a sensitizer (42).

Allergic contact dermatitis has been reported in four women who used a facial cream containing drometrizole. All women exhibited eczema on their face. One woman had eczema only on her eyelids. Two of the women who used a cream on their whole body developed eczema on their body. All women reacted to a patch test of 1% drometrizole in petrolatum (43).

A patch test was performed with a 37-year-old woman who had developed eyelid-swelling and mild papular eruption on the cheeks. Her response to various cosmetic products was tested 48 and 96 h after patch application. A positive response was observed with one nail varnish at 96 h. Upon testing with individual ingredients of the nail varnish, drometrizole was found to be responsible for the allergy of this woman. Positive responses in this woman were observed at 48 and 96 hr after patch testing with 1% and 5% drometrizole in petrolatum while control subjects did not develop a reaction to 5% drometrizole (44).

A 57-year old woman had developed an eczematous rash after using sunscreens containing drometrizole trisiloxane. The photopatch test was conducted with the sunscreens, and a positive response to drometrizole trisiloxane was observed (45).

A 27-year old woman had eczema in three situations using plastic products containing drometrizole. First, eczema occurred in the nose pad part of the sunglasses. Eczema also occurred at the tops of her feet when she used flip-flops with rubber straps. Finally, after using a wristwatch with a rubber strap, eczema occurred on her wrist (46).

Skin sensitization test results are presented in Table 6.

Reproductive and developmental toxicity. Reproductive and developmental toxicity study was conducted with NMRI-derived albino mice. Mice were orally administered 150, 500 or 1,000 mg/kg of drometrizole for 6 to 15 days of the gestation period. General condition, weight gain, food consumption and symptomology were checked every day during treatment period, and fetuses were removed by caesarian section on the 18th day of gestation. Drometrizole administration did not induce toxicity in pregnant dams during gestation. Implantation rates and embryotoxicity were not significantly affected by the treatment. No teratogenicity was observed. In this study, NOEL was reported as 1,000 mg/kg bw/day (26).

Sprague-Dawley rats were used to study reproductive and developmental toxicity. Rats were administered drometrizole for 6 to 15 days of gestation at 150, 500 or 1,000 mg/kg dose, and fetuses were removed by caesarian section on the 21st day of gestation. No teratogenicity or response to administration was noted, and NOEL was reported at 1,000 mg/kg/day (26).

A dominant lethal assay with male NMRI albino mice was performed. Mice were administered a single dose of drometrizole at a concentration of 0, 1,000, or 3,000 mg/kg. Each male was placed in a cage with two untreated females immediately after dosing, and one week later two females were replaced by other females for a total of six weeks. On the 14th day of pregnancy, females were necropsied, and the number of live embryos and dead embryos noted. There was no dominant lethal effect and no differences in mating ratio, number of implantations, or embryonic deaths, compared with the control group (26).

Results of reproductive and developmental toxicity study are presented in Table 7.

Table 7. Reproductive and developmental toxicity studies of drometrizole

Subject	Compound (mg/kg bw/day)	Exposure period	Results	Reference
Mice	Drometrizole 150, 500, 1,000	6 to 15 days of gestation	No effect on the rates of implantation No embryotoxicity and teratogenicity	26
Rats	Drometrizole 150, 500, 1,000	6 to 15 days of gestation	No teratogenicity	26
Mice	Drometrizole 1,000, 3,000	A single dose	No dominant lethal effect	26

Table 8. Genotoxicity studies of drometrizole

Method	Subject	Compound	Results	Reference
Ames test	*Salmonella typhimurium* TA1538, TA98	Spot test (10, 100 mg/plate) Top agar method (50, 100 mg/plate)	Negative	47
Ames test	*Salmonella typhimurium* TA1535, TA1537, TA1538, TA98, TA100	0-20 mg/plate	Negative	48
Ames test	*Salmonella typhimurium* TA98, TA100, TA1535, TA1537	10, 30, 90, 270, 810 mg/0.1 mL	Negative	26
Somatic mutation assay	Hamsters	500, 1,000, 2,000 mg/kg	Negative	26

Table 9. Carcinogenicity studies of drometrizole

Subject	Compound (mg/kg bw/day)	Exposure period	Results	Reference
Mice	Male: 0.8, 6.5, 64 Female: 0.8, 6.7, 62	2 years	No differences compared to control	26
Rats	Male: 4, 14, 47, 142 Female: 6, 17, 53, 169	-	No differences compared to control	26

Genotoxicity. Mutagenicity study of drometrizole was performed using *Salmonella typhimurium* strains TA1538 and TA98 with metabolic activation in the Ames' test. Spot test (10 and 100 mg drometrizole/plate) and top agar method (50 and 100 mg drometrizole/plate) were conducted. The results showed that drometrizole was not mutagenic (47).

Ames' test with the *Salmonella typhimurium* strains TA1535, TA1537, TA98, and TA100 was conducted at 0 to 20 mg drometrizole/plate with or without metabolic activation. Test results were negative (48).

Ames' test was performed using *Salmonella typhimurium* strains TA98, TA100, TA1535, and TA1537, with or without metabolic activation, with 10, 30, 90, 270, and 810 mg drometrizole/0.1 mL. The test results showed that drometrizole was not mutagenic (26).

Mouse bone marrow micronucleus test was performed to evaluate the production of micronucleated erythrocytes in mice treated with a single oral dose of 0.63 to 2.5 g/kg or three doses of 0.63 g/kg drometrizole. All test results were negative (48).

A somatic mutation assay was performed in Chinese hamsters (3 males and 3 females per group). The hamsters were treated with 500, 1,000, or 2,000 mg/kg/day of drometrizole by gavage daily for two consecutive days. Bone marrow cells were harvested 24 hr after the second treatment and scored for chromosomal anomalies. The test results showed that drometrizole was nonmutagenic (26).

Genotoxicity study results are presented in Table 8.

Carcinogenicity. MAGf (SPF) mice were administered drometrizole at doses of 0, 5, 50, and 500 ppm (0.8, 6.5 and 64 mg/kg/day in males and 0.8, 67 and 62 mg/kg/day in females) for 24 months with meals. All treatment groups showed similar mean body weight gain, food consumption and food conversion, as well as median survival time and mortality distribution compared to the control group. There were no clinical signs of local and/or systemic toxicity related to treatment. A significant liver weight decrease in the 50 ppm male group and a slight adrenal weight increase in treated female groups were observed, but this was considered a part of the natural aging process. Microscopic changes in organs and tissues were not significantly different from the control group. Benign and malignant tumors were observed in both control and treatment groups. This study concluded that drometrizole has no effect on inflammation, degeneration, proliferation or neoplasia formation (26).

CFY rats were administered drometrizole at doses of 0, 100, 300, 1,000, 3,000 ppm (4, 14, 47 and 142 mg/kg/day in males and 6, 17, 53 and 169 mg/kg/day in females) in the long-term feeding study. The 300 and 1,000 ppm treatment female groups showed a slight but statistically insignificant increase in tumor incidence when compared to controls. In conclusion, tumor incidence was similar in the treatment and control groups (26).

Carcinogenicity study results are presented in Table 9.

Phototoxicity. A three-year clinical therapeutic trial was performed to evaluate the light-protective effect of UV light-absorbing preparations containing drometrizole in 145 patients with light dermatoses and light sensitivity. An ointment containing 5% drometrizole or a lacquer containing 1.5 parts by weight of drometrizole was tested with radiation of an OsramUltra Vitalux lamp or sunlight. Drometrizole was proven to be highly effective in 445 applications with only two cases of hypersensitivity reactions (35).

Two suntan oils, each containing 0.1% drometrizole were applied on the backs of human subjects (2 males and 8

Table 10. Phototoxicity studies of drometrizole

Subject/Number	Compound	Method	Results	Reference
Human patients suffering from light dermatoses and sensitivity, 145	Drometrizole 5% or 1.5 parts by weight	445 topical applications with radiation for 3 years	Hypersensitivity reactions in 2 cases	35
Human, 2 males and 8 females	Drometrizole 0.1% in suntan oil	Phototoxicity with UVA and UVB exposure	Nonphototoxic	49
Human, 2 males and 8 females	Drometrizole 0.1% in suntan oil	Phototoxicity with UVA and UVB exposure	Nonphototoxic	50
Human, 99	Drometrizole 0.03% in a nail product	Prophetic patch test with UV exposure	Nonirritating, nonsensitizing, and nonphotosensitizing	51
Human, 48	Drometrizole 0.03% in a nail product	RIPT with UV exposure	Nonirritating, nonsensitizing, and nonphotosensitizing	51

females) for phototoxicity evaluation. An occlusive patch containing 0.2 mL samples was applied for 24 hr and the oil was reapplied after the patch was removed. The test site was irradiated with 1 minimal erythema dose (MED) of UVB followed by exposure to UVA for 12 min. The scores measured at 15 min, 24 hr, and 48 hr, were all zero. None of the products used in the tests showed phototoxicity (49,50).

A prophetic patch test was performed to evaluate phototoxicity of a nail product containing 0.03% drometrizole. Single induction and challenge patches with UV exposure were applied to 99 human subjects. The test scores were all zero (51).

A repeat insult patch test (RIPT) with UV exposure was performed to evaluate phototoxicity of nail product containing 0.03% drometrizole in 48 human subjects. Ten induction patches and a single challenge patch with UV exposure were applied. Five cases with score 1 (max. = 3) and one case of score 2 were observed in the induction phase. One case of score 1 at challenge was reported. In addition, one case was noted at challenge with UV exposure. In conclusion, the nail product containing 0.03% drometrizole was evaluated as nonirritating, nonsensitizing, and nonphotosensitizing (51).

Phototoxicity study results are presented in Table 10.

TOXICOKINETICS

Tissue distribution and elimination. Schmid *et al.* (28) reported the distribution and elimination of drometrizole in rats. Four male rats were administered a single oral dose of 10 mg/kg of ^{14}C-drometrizole, which was labeled in the benzene ring and in the 5′-methyl group, dissolved in PEG 400. For 7 days, urine and feces were collected every day. At day 7, the organs and tissues were collected and evaluated for radioactivity. Within the first 48 hr, 91% of the radioactivity was eliminated and the recovery was completed by the 7th day. The radioactivity in urine and feces were about 73% and 27%, respectively.

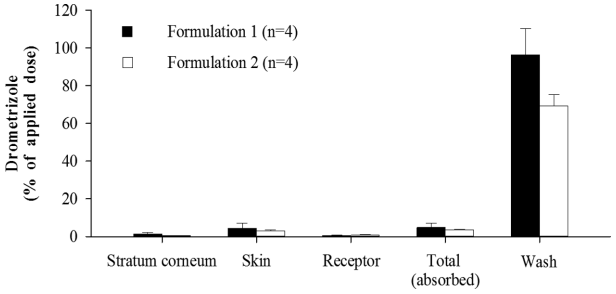

Fig. 2. Dermal absorption study of drometrizole.

The residual radioactivity measured in the tissues was negligible and was lower than blood levels of 0.017 mg/g, except for the kidney, the aorta, and the liver (0.10 to 0.22 mg/g) (28).

Dermal absorption rate. Human and animal *in vivo* studies of skin permeability of drometrizole are currently not available.

Franz diffusion cell with the back skin of the rat was used to determine *in vitro* skin permeability of drometrizole (Fig. 2). Two formulations (named 1 and 2), containing 2% of drometrizole in 200 mg were applied to the rat skins. The total absorbed fractions of drometrizole versus the base applied were 4.81 ± 2.40% and 3.42 ± 0.53%, for formulation 1 and 2, respectively. The *in vitro* skin permeability was determined to be 105.59 ± 52.69 mg/cm^2 and 79.07 ± 12.25 mg/cm^2, for formulations 1 and 2, respectively. Therefore, the skin absorption rate for the risk assessment of drometrizole was estimated as 9.61 mg/cm^2 according to the calculation of "Mean + 2xStandard Deviation = 4.81 + 2x2.40".

DOSE-RESPONSE ASSESSMENT

After toxicological data were reviewed to determine the optimal toxicity reference value, the NOAEL of drometrizole was selected from the 13 weeks repeated dose tox-

Table 11. Systemic exposure dosage (SED) of drometrizole at different concentrations in cosmetics

Cosmetics category	Concentration of cosmetic ingredient (%)	Amount of cosmetics daily used (g/day)	Dermal absorption rate (%)	Body weight (kg)	SED (mg/kg bw/day)
Sunscreens	1.0	17.0	9.61	60	0.27228
	1.2				0.32674
	7.0				1.90598

Table 12. Estimation of margin of safety (MOS) of drometrizole by product concentrations

Subject cosmetics	Concentration of cosmetic ingredient (%)	Amount of cosmetics daily used (g/day)	SED (mg/kg bw/day)	NOAEL (mg/kg bw/day)	MOS
Sunscreens	1.0	17.0	0.27228	31.75	116.6
	1.2		0.32674		97.2
	7.0		1.90598		16.7

icity study in beagles. Based on the increase of serum alanine aminotransferase activity in the 3,000 and 10,000 ppm group, the NOAEL was determined to be 1,000 ppm (male: 31.75 mg/kg/day, female: 34.6 mg/kg/day), at which dosage no toxicity was observed (26).

EXPOSURE ASSESSMENT

Since drometrizole is a sunscreen ingredient, the dermal route is a major exposure pathway when it is used in cosmetics. Systemic exposure dosage (SED) was calculated based on the amount of cosmetics used daily by Korean adults according to the following equation:

$$SED = \frac{A(g/day) \times 1{,}000\ mg/g \times C(\%)/100 \times DAp(\%)/100}{60\ kg}$$

SED (mg/kg/day) : Systemic exposure dosage
A (g/day) : Amount of cosmetics daily used
C (%) : Maximum allowed concentration of cosmetic ingredient
DAp (%) : Dermal absorption rate of cosmetic ingredient
60 kg : Average body weight

The amount of cosmetics used daily (A) by adults was 17.0 g/day, which was calculated assuming that 0.5 mg/cm^2 was applied twice a day to the average body surface area of a Korean male, 16,822 cm^2. Three concentrations were used to find out the maximum allowed concentration of drometrizole. The previous regulatory concentration in cosmetics was 7%. To simulate the SED to meet a safe concentration, 1% or 1.2% was proposed. Dermal absorption rate (DAp) was 9.61%, obtained from the skin absorption rate experiment conducted by the Advanced Evaluation Research Group for the Evaluation of Hazardous Chemicals. The resulting SEDs of drometrizole were 0.27228, 0.32674, and 1.90598 mg/kg bw/day, for 1, 1.2 and 7%, respectively.

SED calculations according to the concentration of drometrizole in cosmetics are presented in Table 11.

RISK CHARACTERIZATION

To evaluate the safety of drometrizole usage in cosmetics, the margin of safety (MOS) is estimated using NOAEL obtained from animal studies. When the MOS is more than 100 considering species differences of "10" and individual differences of "10", it is considered to be safe.

MOS values obtained according to the drometrizole concentration in cosmetics are presented in Table 12. MOS values were 116.6, 97.2, and 16.7 for sunscreen products containing 1.0, 1.2, and 7.0% of drometrizole, respectively. When the sunscreen product contains drometrizole below 1.0%, it is considered to be safe since MOS value would be greater than 100.

SUMMARY AND CONCLUSION

Drometrizole was not toxic in acute oral toxicity studies using mice and rats (19-26). In addition, inhalation and dermal acute toxicity studies in rats, rabbits and guinea pigs showed no significant acute toxic effects (22,26,30). Oral toxicity studies for 14 to 28 days showed a significant increase in liver weight and slight changes in hepatic enzyme activities, suggesting that drometrizole is a weak enzyme inducer for mixed-function oxidases (28). In a 13-week oral study of drometrizole in beagles, the NOAEL was determined to be 31.75 mg/kg bw/day for males and 34.6 mg/kg bw/day for females. In a 2-year oral study in rats, the NOAEL was reported to be 47 mg/kg bw/day (26).

Drometrizole was moderately irritating to the eyes of rabbits. A nail polish product containing drometrizole 1% was minimally to mildly irritating when rinsed after treating rabbit eyes. When not rinsed after treatment, it was mildly to severely irritating (29-33). The occlusive patch test of a nail polish containing 1.0% drometrizole was not

irritating when applied to rabbit skin (34).

Drometrizole was negative for sensitization in two Magnusson-Kligman maximization tests to guinea pigs (40,41). Two cases of allergic contact dermatitis arising from cosmetics usage have been reported for drometrizole. Drometrizole showed positive reactions in 1% and 5% patch tests (43,44).

Drometrizole showed no teratogenic activity in reproductive and developmental toxicity studies using rats and mice, treated for 6 to 15 days of gestation (26). Ames' tests showed that drometrizole is not mutagenic. Test results of somatic mutation assays in hamsters were negative (26,47, 48). A long-term carcinogenicity study of drometrizole in mice and rats showed no significant carcinogenic effects compared to controls (26).

Two hypersensitivity cases were observed during 445 applications in a 3-year clinical therapeutic trial using two UV-absorbing preparations containing 5% drometrizole (35). A suntan oil containing 0.1% drometrizole was nonphototoxic in 10 humans (49,50). A nail product containing 0.03% drometrizole was nonirritating, nonsensitizing and nonphotosensitizing in 147 humans (51).

For the risk assessment, the NOAEL of drometrizole was determined to be 31.75 mg/kg bw/day according to a 13-week oral toxicity study in beagles (26). The SED of drometrizole had a range between 0.27228 and 1.90598 depending on the concentration in the cosmetics. Risk characterization demonstrated that when the cosmetic product contains 1.0% of drometrizole, the MOS is over 100 and the concentration is considered safe for use in cosmetics. Based on the results of risk assessment, the MFDS revised the regulatory concentration of drometrizole from 7% to 1% in 2015. Under current revised regulations, drometrizole may be safe for use in cosmetic products and may not threaten the consumer's health. If new toxicological data are obtained in the future, the risk assessment should be carried out to update the guidelines appropriately.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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