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Amended Final Report of the Safety Assessment of Drometrizole as used in Cosmetics[1]

Drometrizole is used in cosmetics as an ultraviolet (UV) light absorber and stabilizer. In an earlier safety assessment, the available data were found insufficient to support the safety of this ingredient, but new data have been provided and assessed. In voluntary industry reports to the Food and Drug Administration, this ingredient is reported to be used in noncoloring hair care products, and in an industry use concentration survey, uses in nail care products at 0.07% were reported. Drometrizole has absorbance maxima at 243, 298, and 340 nm. 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. Short-term studies using rats reported liver weight increases, increases in the activities of enzymes aminopyrine *N*-demethylase, and UDP glucuronosyl transferase, but no significant effects were noted in the activities of acid hydrolases or in hepatocyte organelles. Although Drometrizole is insoluble in water and soluble in a wide range of organic solvents, a distribution and elimination study using rats indicated that some Drometrizole was absorbed, then metabolized and excreted in the urine. Drometrizole and products containing Drometrizole were nontoxic in acute oral, inhalation, and dermal studies using animals. No increase in mortality or local and/or systemic toxicity were observed in a 13-week oral toxicity study using dogs; the no observed effect level (NOEL) was 31.75 mg/kg day^{-1} for males and 34.6 mg/kg day^{-1} for females. In a 2-year feeding study using rats, a NOEL of 47 to 58 mg/kg day^{-1} was reported. Developmental studies of Drometrizole in rats and mice found no teratogenic effects and a NOEL of 1000 mg/kg day^{-1} was reported. Drometrizole was not genotoxic in Ames tests, a mouse bone marrow micronucleus test, or somatic mutation assays observing interphase nuclei and chromosomal aberrations using Chinese hamsters. There was no evidence of dominant lethal effects in studies using mice or rats. Drometrizole at a 1% concentration was minimally to moderately irritating to rabbit eyes, if followed by rinsing, but mildly to severely irritating in unrinsed eyes. A nail product containing 0.03% Drometrizole, however, was nonirritating to unrinsed rabbit eyes. A nail polish containing 1.0% Drometrizole was nonirritating to rabbit skin and Drometrizole was negative for sensitization in two Magnusson-Kligman maximization tests in guinea pigs. In clinical tests, Drometrizole at 1% was nonirritating 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. Although there are case reports in which Drometrizole was considered the sensitizing agent, clinical tests of cosmetic products containing 0.03% to 1.0% Drometrizole produced no irritation, sensitization, photosensitization, or phototoxicity in a total of 436 subjects. The Cosmetic Ingredient Review (CIR) Expert Panel assumes that Drometrizole is used in both noncoloring hair care and nail care products at low concentrations. The available safety test data do not suggest any adverse effects associated with exposure to Drometrizole. This toxicologic profile, coupled with the low concentration of use and the unlikely dermal penetration of a chemical that is insoluble in water, support the conclusion that Drometrizole can be safely used in cosmetics.

INTRODUCTION

Drometrizole is a benzotriazole derivative used as an ultraviolet (UV) light absorber and stabilizer in cosmetics (Windholz 1983; CTFA 1984a; Gottschalck and McEwen 2006).

Cosmetic Ingredient Review (CIR) previously issued a safety assessment of Drometrizole as a cosmetic ingredient with the conclusion that the available data were insufficient to support safety (Elder 1986). The additional data identified as necessary to complete the safety assessment were: (1) 90-day subchronic oral toxicity; and (2) mutagenicity testing in two systems other than the Ames assay and the mouse bone marrow micronucleus test.

Additional unpublished data have been provided and are presented, with the previously available data, in this amended safety assessment of Drometrizole.

CHEMISTRY

Drometrizole is a benzotriazole derivative that conforms to the structure shown in Figure 1 (Gottschalck and McEwen 2006).

Also called 2-(2′-hydroxy-5′-methylphenyl) benzotriazole, Drometrizole occurs as an odorless, off-white to yellow,

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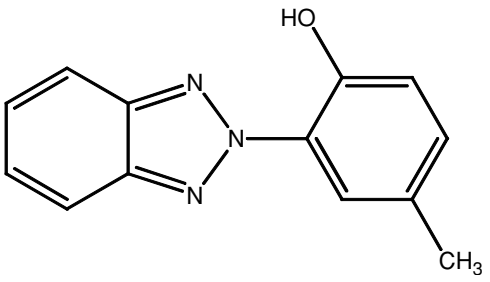

FIGURE 1
Chemical structure for Drometrizole (Gottschalck and McEwen 2006).

crystalline powder with a melting point of 131°C to 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 (Hawley 1971; Windholz 1983; Japanese Cosmetic Industry Association (JCIA) 1967; CTFA 1984a).

The physical and chemical properties of Drometrizole are presented in Table 1.

Drometrizole (in ethanol) has its maximum absorbance at wavelengths of approximately 243 ± 2, 298 ± 2, and 340 ± 2 nm; minimum absorbance occurs at wavelengths of 259 ± 2 and 214 ± 2 nm (JCIA 1967). Drometrizole exposed to light in the UV and visible range has only an insignificant luminescence (Joo 1974). Identification and assay methods are given in the Japanese Standards of Cosmetic ingredients (JCIA 1967). Gas chromatography mass spectrometry (GCMS) has been used to analyze Drometrizole (Hites 1977).

According to CTFA (1984a), 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.

Hites (1977) suggested that 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. It is also stable to conditions and chemicals used in polymerization or compounding of plastics (Windholz 1983).

TABLE 1
Physical and chemical properties of Drometrizole

Property	Value	Reference
Physical occurrence	Off-white to yellow crystalline powder	Hawley 1971, JCIA 1967, CTFA 1984a
Empirical formula	$C_{13}H_{11}N_3O$	Hawley 1971, Windholz 1983, JCIA 1967, CTFA 1984a
Molecular weight	225.23	Windholz 1983, JCIA 1967
Melting range (°C)	131–133	Windholz 1983
Boiling point (°C)	225 (10 mm Hg)	Hawley 1971, CTFA 1984a
Particle size	2.5% max retained on 200 mesh screen 7.5% max retained on 325 mesh screen	CTFA 1984a
Specific gravity	151	CTFA 1984a
Ash	1% max.	CTFA 1984a
Loss on drying	<0.5%	JCIA 1967
Residue on ignition	<0.1%	JCIA 1967
Solubility		
Acetone	Soluble	Windholz 1983, JCIA 1967, CTFA 1984a
Caprolactam solutions	Soluble	Windholz 1983
Chloroform	Soluble	CTFA 1984a
Dioctylphthalate	Soluble	Windholz 1983
Ethanol	Soluble	JCIA 1967
Ethyl acetate	Soluble	Windholz 1983, CTFA 1984a
Methyl ethyl ketone	Soluble	Hawley 1971
Methyl methacrylate	Soluble	Hawley 1971
Oleyl alcohol	Soluble	Windholz 1983
Petrolatum (hot) ketone	Soluble	Windholz 1983
Styrene	Soluble	CTFA 1984a
Toluene	Soluble	CTFA 1984a
Water	Insoluble	Hawley 1971, CTFA 1984a

USE

Cosmetic

Drometrizole is used as a UV light absorber and stabilizer in cosmetics (Windholz 1983; CTFA 1984a; Gottschalck and McEwen 2006).

In 1981, the Food and Drug Administration (FDA) compilation of voluntary industry use data reported that Drometrizole was primarily used at concentrations below 0.1% in the following product categories: bath, fragrances, coloring and noncoloring hair care, manicuring, shaving, skin care, and suntan preparations. Of this total, 77% of the 217 reported uses of Drometrizole were in nail polishes and enamels, and 11% were in noncoloring hair shampoos; and 53% were at concentrations ≤0.1%, 4% at ≥0.1–1%, and 43% at unknown concentrations (FDA 1981).

In 2005, voluntary industry reports to the FDA included two uses: one in a noncoloring shampoo and one in "other" noncoloring hair preparation (FDA 2005). The *International Cosmetic Ingredient Dictionary and Handbook* indicates that Drometrizole is used in nail polishes and enamels, but does not include noncoloring hair care as a product category in which this ingredient is used (Gottschalck and McEwen 2006).

A survey conducted by the Cosmetic, Toiletry and Fragrance Association (CTFA) indicated use in nail care products (basecoats and undercoats) at 0.07% (CTFA 2004).

Table 2 presents the available historical and recent use as a function of product category and concentration.

According to the Japan Ministry of Health, Labor and Welfare (MHLW), Drometrizole is not included on the list of ingredients that must not be combined in cosmetic products that are marketed in Japan (MHLW 2005a), or on the list of restricted ingredients for cosmetic products that are marketed in Japan (MHLW 2005b); nor is its use restricted in the European Union (European Economic Community 2005).

Noncosmetic

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 (Hawley 1971; Windholz 1983; Gabriele 1982; Dunn 1959; Komarova 1979). It is used in orthodontic adhesives and dental restorations as well as in polyurethane elastomers for

TABLE 2
Historical and current cosmetic product uses and concentrations for Drometrizole

Product category	1981 uses (Elder 1987)	2005 uses (FDA 2005)	1981 concentrations (Elder 1987) (%)	2005 concentrations (CTFA 2004) (%)
Bath				
Oils, tablets, and salts	8	—	≤0.1	—
Fragrances				
Colognes and toilet waters	1	—	≤0.1	—
Noncoloring Hair Care				
Rinses	1	—	≤0.1	—
Shampoos	24	1	≤0.1	—
Other	1	1	≤0.1	—
Hair Coloring				
Shampoos	2	—	≤0.1	—
Nail Care				
Nail basecoats and undercoats	5	—	≤0.1–1.0	0.07
Nail polishes and enamels	169	—	≤0.1–1.0	—
Nail polish and enamel remover	1	—	≤0.1	
Other manicuring preparations	2	—	>0.1–1.0	—
Shaving				
Preshave lotions (all types)	1	—	≤0.1	—
Skin Care				
Moisturizers	2	—	≤0.1	—
Other	1	—	≤0.1	—
Suntan				
Suntan gels, creams, liquids, and sprays	1	—	>0.1–1.0	—
Total uses/ranges for Drometrizole	**219**	**2**	**≤0.1–1.0**	**0.07**

maxillofacial use (Randklev 1981; Berg 1979; Schmitz 1980; Engel 1981; Chu 1978).

Drometrizole is used as a UV absorber in agricultural products for the prevention of leaf burn and apple peel spot (Motoyoshi 1975; Balazs 1981). It is also formulated as a stabilizer in insecticides (Letchworth 1972, 1976; Stubbs 1979).

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 (2003), Title 21, part 178.2010.

GENERAL BIOLOGY

Cytotoxicity/Photoprotection

Epstein et al. (1965, 1967) reported that Drometrizole had very low cytotoxicity to *Tetrahymena pyriformis*, with a median LD_{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), Drometrizole (at 159 μg/ml) doubled the irradiation time required to immobilize 90% of *T. pyriformis*.

The authors concluded that the protection afforded by Drometrizole was due to its UV light absorption.

Absorption, Distribution, Metabolism, and Excretion

The distribution and elimination of Drometrizole in the rat also was studied by Schmid et al. (1980). ^{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 reported to be negligible, i.e., 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 to 0.22 μg/g). The chemical nature of the radioactive excretion products was not identified.

ANIMAL TOXICOLOGY

Acute Oral Toxicity

The acute oral LD_{50} of Drometrizole in mice is given as 6.5 g/kg according to the Labor Hygiene and Occupational Diseases (1966), in the then Soviet Union, and >5.0 g/kg according to Epstein (1967).

Komarova and Maksimova (1979) 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. The authors considered Drometrizole to be of low toxicity.

In a series of reports by CTFA (1978a, 1979a, 1980a, 1984b), four cosmetic nail products containing Drometrizole at concentrations of 1.0% (in two of the four products), 0.30%, and 0.03% were evaluated for oral toxicity in rats. The resultant LD_{50} values 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. The authors stated that all products were considered practically nontoxic by ingestion.

The Environmental Protection Agency (EPA) reported a study in which the Drometrizole LD_{50} was >10,000 mg/kg (EPA 2004). Tif:RAlf (SPF) rats were administered Drometrizole suspended in polyethylene glycol (PEG) 400 by gavage in a single dose of 4640, 7750, or 10,000 mg/kg (five male and five female rats per dose group). Animals were observed 14 days after treatment for clinical signs of toxicity and mortality.

Within 2 h after treatment, animals had sedation, dyspnea, curved position, and ruffled fur. Two females in the 10,000 mg/kg group died within seven days. All other animals recovered within 8–10 days of treatment and no treatment related effects were observed at necropsy (EPA 2004).

Acute oral toxicity test results are presented in Table 3.

Acute Inhalation Toxicity

EPA (2004) reported an acute inhalation study using Charles River rats exposed to a Drometrizole/air mixture. Five male and five female rats were exposed for 4 h at 1420 mg/m^3. Drometrizole powder was aerosolized by passing clean, dry air through a ferris wheel dust mechanism. The size of the aerosol particles was not reported. Animals were observed for 14 days after exposure and monitored for clinical signs, toxicity, and mortality. Survivors were killed and necropsied.

No effects related to exposure were observed. No deaths occurred during the observation period and no changes were observed at necropsy. The LC_{50} (4 h) was >1420 mg/m^3(EPA 2004).

Acute Dermal Toxicity

CTFA (1978a) reported a study in which 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.

CTFA (1979b) reported a study in which 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

TABLE 3
Acute oral toxicity

Compound	Animal	LD_{50}	Comments	Reference
Drometrizole	Mice	6.5 g/kg	—	Labor Hygiene and Occupational Diseases 1966
Drometrizole	Mice	>5.0 g/kg	—	Epstein 1967
Drometrizole	Mice	5.0, 10.0 g/kg administered	Low toxicity	Komarova 1979
	Rats	5.0, 10.0 g/kg administered		
Drometrizole	Rats	>10 g/kg	—	EPA 2004
Drometrizole 1.0% in a nail polish	Rats, 5	>15.0 g/kg	Practically nontoxic	CTFA 1979a
Drometrizole 1.0% in a nail polish	Rats, 5	>15.0 g/kg	Practically nontoxic	CTFA 1980a
Drometrizole 0.30% in a nail product	Rats, 10 or more	>5.0 g/kg	Nontoxic	CTFA 1984b
Drometrizole 0.03% in a nail product	Rats, 10 or more	>5.0 g/kg	Nontoxic	CTFA 1978a

for 14 days. No deaths occurred. Necropsy was performed on day 14, with no toxic effects reported.

Short-Term Oral Toxicity

The effects of Drometrizole on rat liver were studied by Schmid et al. (1980). 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. Liver tissues were prepared for examination 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 P450. 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 *O*-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 (Schmid 1980).

Subchronic Oral Toxicity

In a study reported to the EPA (2004), four groups of male and female Beagle dogs (number of animals not reported; weights ranging from 8.1 to 12.4 kg in males and 6.4 to 10.7 kg in females; ages ranging from 31 to 34 weeks) were administered 0, 1000, 3000, or 10,000 ppm Drometrizole in food for 13 weeks.

After the 13-week period, one animal of each sex per dose group was fed the control diet for a period of 1 month to test for recovery. There were no mortalities or clinical signs of local and/or systemic toxicity observed. The 10,000 ppm group had decreased food consumption and body weight gain. No effects on ophthalmology or auditory perceptions were noted. An increase in serum alanine aminotransferase activity in the 3000 and 10,000 ppm groups was observed as well as an

increase in serum gamma-glutamyltranspeptidase activity in the 10,000 ppm group. One female of the highest dose group was observed to be emaciated. No other gross or histopathological observations, related to the treatments, were noted.

The no observed effect level (NOEL) was determined to be 1000 ppm, which was determined to correspond to doses of 31.75 mg/kg day^{-1} for males and 34.6 mg/kg day^{-1} for females (EPA 2004).

Chronic Oral Toxicity

EPA (2004) reported a 2-year feeding study using rats. Five hundred CFY rats (25 ± 1 day old) were placed into one of five treatment groups (50 of each sex in each group): control, 100 ppm (4 to 6 mg/kg bodyweight/day), 300 ppm (14 to 17 mg/kg bodyweight/day), 1000 ppm (47 to 58 mg/kg bodyweight/day), or 3000 ppm (142 to 169 mg/kg bodyweight/day).

At the 3000 ppm level, a slight decrease in weight gain was observed among males in the second year of treatment ($p < .05$) and a slight reduction in food intake was noted in females from weeks 53 to 80 of treatment ($p < .05$). Survival rates in the 3000 ppm group were marginally lower during the final 26 weeks of treatment in males, but the difference compared to the male control group was not significant. The other treatment groups had results comparable to the control groups for body weight, food consumption, and mortality.

The study reported a NOEL of 1000 ppm, which was determined to correspond to a dose range of 47 to 58 mg/kg day^{-1} (EPA 2004).

Ocular Irritation

Instillation of 500 mg Drometrizole into the eye of a rabbit produced moderate irritation after 24 h (Marhold 1972).

CTFA (1978b, 1978c) reported that 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 s 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.

The report concluded that, 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) (CTFA 1978b, 1978c).

CTFA (1980b, 1980c) reported that 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) (CTFA 1980b, 1980c).

CTFA (1984b) reported that 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.

Ocular irritation test results are summarized in Table 4.

Dermal Irritation

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 (CTFA 1978d).

Dermal Sensitization

Drometrizole was evaluated for sensitization in guinea pigs by two separate Magnusson-Kligman maximization tests (CTFA 1978e, 1978f). 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.

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.

TABLE 4
Ocular irritation

Ingredient	Test method	Results	Reference
Drometrizole	500 mg instilled into one eye	Moderately irritating after 24 h	Marhold 1972
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	CTFA 1978c
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	CTFA 1978b
Drometrizole 1.0% in a nail polish	Draize, 3 rabbits/rinsed	Score of 11, 9, 5, 1, and 0 on days 1, 2, 3, 4, and 7, respectively[a]; mildly irritating	CTFA 1980c
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	CTFA 1980b
Drometrizole 0.03% in a nail polish	Draize, 6 rabbits/unrinsed	All scores of 0[a]; nonirritating	CTFA 1984b

[a]Maximum score = 110.

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 occlusive 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 (CTFA 1978e, 1978f).

REPRODUCTIVE AND DEVELOPMENTAL TOXICITY

According to a report provided to the EPA (2004), Drometrizole was administered at doses of 150, 500, or 1000 mg/kg by oral gavage on days 6 to 15 of gestation to an unknown number of female NMRI-derived albino mice. During treatment, general condition, weight gain, food consumption, and symptomology were checked daily. Dams were killed and the fetuses were removed by cesarian section on day 18 of gestation.

A NOEL of 1000 mg/kg day^{-1} was reported. No reaction to treatment was noted in pregnant dams and the rates of implantation and embryotoxicity were not significantly affected by treatment. No teratogenic effects were noted.

The same study protocol as above was performed on female Sprague-Dawley rats. Dams were administered the Drometrizole doses via oral gavage on days 6 to 15 of gestation and were killed on day 21 of gestation. Fetuses were removed for study by cesarian section.

The NOEL was 1000 mg/kg day^{-1}. No teratogenic effects were noted in the fetuses and no reaction to the treatment doses was noted in the dams (EPA 2004).

GENOTOXICITY

Jonsen (1980) evaluated Drometrizole 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.

Hacmiya (1982) reported that an 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 doses 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 to 2.5 g/kg or three doses of 0.63 g/kg. All results were negative (Hacmiya 1982).

A series of genotoxicity tests were reported to the EPA (2004).

An Ames study was performed using *Salmonella*

tyhpimurium strains TA98, TA100, TA1535, and TA1537, with and without metabolic activation. Concentrations studied were 10, 30, 90, 270, and 810 μg/0.1 ml. Drometrizole was not mutagenic in this Ames test.

A somatic mutation assay observing interphase nuclei tested male and female Chinese hamsters (three males and three females per group). The hamsters were administered Drometrizole at doses of 500, 1000, or 2000 mg/kg by gavage daily for 2 consecutive days. Control groups were administered 128 mg/kg cyclophophamide (positive) or 20 ml/kg 0.5% carboxymethylcellulose vehicle (negative). Twenty-hour hours after the second treatment, the animals were killed and bone marrow was harvested from shafts of both femurs. Bone marrow cells (1000/animal) were scored for chromosomal anomalies.

In all test groups, the percent of cells displaying nuclei anomalies did not differ significantly from the negative control. The positive control produced significant anomalies ($p < .01$). It was concluded that Drometrizole was nonmutagenic.

In a somatic mutation assay for chromosomal aberrations, Chinese hamsters (6 females and 4 males per treatment group) were administered 500, 1000, or 2000 mg/kg Drometrizole by gavage daily for 2 consecutive days. Two hours after the administration of the second dose, the animals were injected intraperitoneally with colchicine (10 mg/kg) and then were killed 4 h later. Bone marrow from two females and two males per test group was harvested and analyzed for chromosomal aberrations.

The results were compared to the positive (10 females and 6 males treated with 64 mg/kg cyclophophamide) and negative (8 females and 6 males treated with 20 ml/kg 2% sodium carboxymethyl cellulose vehicle) control groups. The chromosome displays of the hamsters treated with Drometrizole showed no aberrations and the investigators concluded that Drometrizole was not mutagenic.

Male NMRI albino mice (20/group) in a dominant lethal assay reported to the EPA (2004) were administered a single dose of Drometrizole by gavage at a dose of 0 (control given 0.2 ml/10 g body weight aqueous carboxymethylcellulose vehicle), 1000, or 3000 mg/kg. Each male was placed in a cage with two untreated females immediately after treatment. At the end of 1 week, females were removed and replaced by another group of two females. This procedure continued for 6 consecutive weeks. Females were examined daily for successful mating (existence of vaginal plug). The first day the plug was observed was considered day 0 of gestation. Females were necropsied on day 14 of pregnancy. The number of live embryos and embryonic deaths were noted along with resorptions.

No evidence of dominant lethal effects were noted. There were no differences in mating ratio, number of implantations, or embryonic deaths between controls and treated groups (EPA 2004).

CARCINOGENICITY

In a lifetime carcinogenicity study in 400 MAGf (SPF) mice (50 males and 50 females per dose group), reported to EPA (2004), Drometrizole was administered in the diet for 24 months at dosages of 0, 5, 50, and 500 ppm (0.8, 6.5, and 64 mg/kg day^{-1} in males and 0.8, 6.7, and 62 mg/kg day^{-1} in females).

The mean body weight gain, food consumption, and food conversion as well as median survival time and mortality distribution of all treatments groups were similar to the control group.

No clinical signs of local and/or systemic toxicity were observed. A marked decrease of liver weight in the male 50 ppm group and a slight increase in adrenal weights in treated female groups were noted but attributed to the natural aging process of the animals.

Gross or microscopic changes in organs and tissues from treated animals were not different from controls. Benign and malignant tumors were observed in both control and treatment group, but were not considered to be treatment related. The study concluded that Drometrizole did not produce inflammatory, degenerative, proliferative, or neoplastic lesions.

A long term feeding rat study of Drometrizole in five hundred CFY rats (25 $\pm$ 1 days old) was also described. The rats were placed into one of five treatment groups (50 of each sex in each group): control, 100 ppm (4 to 6 mg/kg day^{-1}), 300 ppm (14 to 17 mg/kg day^{-1}), 1000 ppm (47 to 58 mg/kg day^{-1}), or 3000 ppm (142 to 169 mg/kg day^{-1}).

A slight increase in tumors were seen in female rats in the 300 and 1000 ppm groups when compared to controls, but these increases were not statistically significant. Tumor incidences in the other female groups and in all of the males were comparable to those of the controls (EPA 2004).

CLINICAL ASSESSMENT OF SAFETY

Results of clinical irritation, sensitization, and photosensitization tests are reported in Table 5.

Irritation and Sensitization

Joo (1974) applied Drometrizole daily for 8 weeks by means of an occlusive dressing to 300 patients with and without dermatosis. No irritation or eczematous reactions were observed.

CTFA (1980d) reported that a nail polish containing 0.5% Drometrizole was evaluated for irritation and sensitization by a Modified Draize-Shelanski-Jordan repeat-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.

TABLE 5
Clinical irritation, sensitization, photosensitization, and phototoxicity

Ingredient	Test	No. of subjects	Results	Reference
		Irritation		
Drometrizole 1% in peach kernel oil	SIPT[a]	100 females	No erythema or edema noted; nonirritating	CTFA 1984c
Drometrizole	Daily occlusive application for 8 weeks	300 with or without dermatosis	No irritating or eczematous reactions	Joo 1974
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	CTFA 1978g
Drometrizole 0.30% in a nail product	Controlled use study: 2× weekly for 4 weeks	53	No adverse reactions; nonirritating	CTFA 1984d
Drometrizole 0.03% in a nail product	Controlled use study—1× weekly for 4 weeks	48	No adverse reactions; nonirritating	CTFA 1984e
		Sensitization		
Drometrizole 0.5% in a nail polish	RIPT[b]: modified Draize-Shelanski-Jordan	148–59 males and 89 females	All scores of 0; nonsensitizing	CTFA 1980d
		Photosensitization		
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	Joo 1974
Drometrizole 0.03% in a nail product	Prophetic patch test with UV exposure	99	All scores of 0; nonirritating, nonsensitizing, and nonphotosensitizing	CTFA 1984f
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	CTFA 1984f
		Phototoxicity		
Drometrizole 0.1% in a suntan oil	Phototoxicity with UVA and UVB exposure	10; 2 males and 8 females	All scores of 0; nonphototoxic	CTFA 1983a
Drometrizole 0.1% in a suntan oil	Phototoxicity with UVA and UVB exposure	10; 2 males and 8 females	All scores of 0; nonphototoxic	CTFA 1983b

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

CTFA (1984c) reported that 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 min and 24 h after patch removal. No erythema or edema was noted. Drometrizole was not a primary irritant.

CTFA (1984d, 1984e) reported on the evaluation of two nail products containing 0.30% and 0.03% Drometrizole 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.

CTFA (1984 g) reported that 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.

Photosensitization and Phototoxicity

Joo (1974) reported a 3-year clinical therapeutic trial of two UV light–absorbing preparations in 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 OsramUltra Vitalux lamp or with sunlight; 445 successful applications indicated that the preparations were highly effective. Hypersensitivity reactions were observed in only two cases.

CTFA (1983a, 1983b) reported on the evaluation of two suntan oils, each containing 0.1% Drometrizole, 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 minimal erythema dose (MED) of UVB followed by 12 min 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 to 400 nm. A Schott WG345 filter was used to screen out UVB. All sites were scored at 15 min and 24 and 48 h. All scores for both suntan oils were 0. Neither product produced evidence of phototoxicity.

CTFA (1984f) reported that 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.

Case Reports

Cronin (1980) stated that 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 of 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.

Degroot (1983) patch tested a 37-year-old woman 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.

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. In voluntary industry reports to the Food and Drug Administration, this ingredient is reported to be used in noncoloring hair care products and in an industry use concentration survey, uses in nail care products 0.07% were reported.

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 protozoan by the photosensitizing agent benzo(a)pyrene.

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 produced no significant toxic effects in acute oral, inhalation, and dermal studies.

Drometrizole administered orally to rats for 14 or 28 days to determine its effects on the liver 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.

A 13-week oral toxicity study using dogs administered up to 10,000 ppm Drometrizole in food. No mortality or symptoms of local and/or systemic toxicity were observed. A NOEL was determined to be 31.75 mg/kg day^{-1} for males and 34.6 mg/kg day^{-1} for males.

In a 2-year feeding study using rats, a NOEL of 47 to 58 mg/kg day^{-1} was reported.

Reproductive and developmental toxicity studies to Drometrizole using rats and mice found no teratogenic effects and a NOEL of 1000 mg/kg day^{-1} was reported.

Drometrizole was not mutagenic in three Ames tests using *Salmonella typhimurium* both with and without metabolic activation or in a mouse bone marrow micronucleus test. Drometrizole was also found not mutagenic in somatic mutation assays observing interphase nuclei and chromosomal aberrations in Chinese hamsters. There was no evidence of dominant lethal effect or carcinogenicity in mice or rats.

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.

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% to 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

The CIR Expert Panel acknowledged that there is some question about the actual uses of Drometrizole in cosmetics. The most recent reports by industry to FDA indicated use only in hair care products. Historically, the use concentrations for hair care had been at a concentration of $<0.1\%$. A recent industry survey, however, identified use only in nail care products (at a concentration of 0.07%). The Expert Panel reasoned that both pieces of data should be presumed to be correct, and that Drometrizole is used in both hair care and nail care products at low use concentrations.

The Expert Panel noted that Drometrizole 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. Although Drometrizole has a molecular weight of 225, its solubility profile does not suggest that it would readily penetrate the skin.

The available safety test data do not suggest any adverse effects associated with exposure to Drometrizole. For example, Drometrizole was studied in a 90-day feeding study in beagle dogs, in a 2-year rat feeding study, and in reproductive and developmental toxicity studies with rats and mice, with no apparent adverse effects. Likewise, Drometrizole was not toxic in acute oral, inhalation, and dermal studies. Drometrizole was not genotoxic in both bacterial and mammalian systems and not carcinogenic in a lifetime carcinogenicity study using mice and rats.

In clinical testing, Drometrizole produced no irritation, sensitization, photosensitization, or phototoxicity.

This toxicologic profile, coupled with the low concentration of use and the unlikely dermal penetration of a chemical that is insoluble in water, support the conclusion that Drometrizole can be safely used in cosmetics.

CONCLUSION

The CIR Expert Panel concludes that Drometrizole is safe as a cosmetic ingredient in the practices of use and concentration as described in this safety assessment.

REFERENCES

Balazs, E., A. Toth, E. Bogsch, B. Stefko, I. Gebhardt, and D. Mathe. 1981. Method and composition for the prophylaxis of apple peel spot. Pat. Specif. (Aust.) Patent No. 514160 (Richter, Gedeon, Vegyeszeti Gyar Rt.).

Berg, E. P. 1979. Oligomeric methacrylic-substituted alkylsiloxanes. Ger. Offen. Patent No. 2922932 (Minnesota Mining and Mfg. Co.).

Chu, C. C., and T. E. Fischer. 1978. Evaluation of sunlight stability of polyurethane elastomers for maxillofacial use. I. *J. Biomed. Mater. Res.* 12:347–359.

Cosmetic, Toiletry and Fragrance Association (CTFA). 1978a. Submission of unpublished data. Oral intubation and dermal toxicity studies (2-38-19).[2]

CTFA. 1978b. Draize eye irritation test. Unpublished data submitted by CTFA (2-38-3).[2]

CTFA. 1978c. Draize eye irritation test Unpublished data submitted by CTFA (2-38-2).[2]

CTFA. 1978d. Primary skin irritation test in rabbits. Unpublished data submitted by CTFA (2-38-4).[2]

CTFA. 1978e. Guinea pig allergy study. Unpublished data submitted by CTFA (2-38-12).[2]

CTFA. 1978f. Guinea pig allergy study. Unpublished data submitted by CTFA (2-38-16).[2]

CTFA. 1978g. Clinical skin irritation test. Unpublished data submitted by CTFA (2-38-5).[2]

CTFA. 1979a. Acute oral toxicity test in rats. Unpublished data submitted by CTFA (2-38-1).[2]

CTFA. 1979b. Acute dermal toxicity test in guinea pigs. Unpublished data submitted by CTFA (2-38-7).[2]

CTFA. 1980a. Acute oral toxicity in rats. Unpublished data submitted by CTFA (2-38-6).[2]

CTFA. 1980b. Draize eye irritation test. Unpublished data submitted by CTFA (2-38-8).[2]

CTFA. 1980c. Draize eye irritation test. Unpublished data submitted by CTFA (2-38-9).[2]

CTFA. 1980d. Clinical Repeat Insult Patch Test. Unpublished data submitted by CTFA (2-38-10).[2]

CTFA. 1983a. Clinical phototoxicity test. Unpublished data submitted by CTFA (2-38-14).[2]

CTFA. 1983b. Clinical phototoxicity test. Unpublished data submitted by CTFA (2-38-15).[2]

CTFA. 1984a. Cosmetic ingredient chemical description. Unpublished data submitted by CTFA (2-38-13).[2]

CTFA. 1984b. Oral intubation and ocular irritation tests. Unpublished data submitted by CTFA (2-38-17).[2]

CTFA. 1984c. Clinical Single Insult Patch Test. Unpublished data submitted by CTFA (2-38-11).[2]

CTFA. 1984d. Clinical controlled use study. Unpublished data submitted by CTFA (2-38-20).[2]

CTFA. 1984e. Clinical controlled use study. Unpublished data submitted by CTFA (2-38-21).[2]

CTFA. 1984f. Prophetic patch and Repeat Insult Patch Test with UV exposure. Unpublished data submitted by CTFA (2-38-18).[2]

CTFA. 2004. Concentration of use of drometrizole in cosmetic products. Unpublished data submitted by CTFA.[2]

[2]Available for review from the Director, Cosmetic Ingredient Review, 1101 17th Street, Suite 412, Washington, DC 20036, USA.

Cronin, E. 1980. *Contact dermatitis*, 102. New York: Churchill Livingstone.

Degroot, A. C., and D. H. Liem. 1983. Contact allergy to Tinuvin P. *Contact Dermatitis* 9:324–325.

Dunn, J. R., and S. G. Fogg.1959. The protection of transparent vulcanizates against aging in sunlight. *J. Appl. Polym. Sci.* 2:367–368.

Elder, R. L. 1986. Final report on the safety assessment of drometrizole. *J. Am. Coll Toxicol.* 5:455–470.

Engel, M. R. 1981. Durable, polishable direct filling material. U.S. Patent No. 4288221. http://www.uspto.gov

Environmental Protection Agency (EPA). 2004. Robust summaries and test plans: Phenolic benzotriazoles category. High Production Volume (HPV) Challenge Program. http://www.epa.gov/chemtrk/phenbenz/c13266tc.htm (accessed September, 2005).

Epstein, S. S., I. B. Saporoschetz, and S. H. Hutner. 1967. Toxicity of antioxidants to *Tetrahymena pyriformis*. *J. Protozool.* 14:238–244.

Epstein, S. S., I. B. Saporoschetz, M. Small, W. Park, and N. Mantel. 1965. A simple bioassay for antioxidants based on protection of *Tetrahymena pyriformis* from the photodynamic toxicity of benzo(a)pyrene. *Nature* 208:655–658.

European Economic Community (EEC). 2005. EEC Cosmetics Directive 76/768/EEC, as amended through the Adapting Commission Directive 2005/42/EC (June 20, 2005), Annexes I–VII. Annex VI. List of preservatives which cosmetic products may contain. Brussels: EEC.

Food and Drug Administration (FDA). 1981. Product formulation data. *FDA database.* Washington, DC: FDA.

FDA. 2005. Frequency of use of cosmetic ingredients. *FDA database*. Washington, DC: FDA.

Gabriele, P. D., J. R. Ceib, J. S. Puclisi, and W. J. Reid. 1982. Influence of light stabilizers on maintaining surface integrity and preventing biological defacement of polymers. *J. Coatings Tech.* 54:27–30.

Gottschalck, T. E. and G. N. McEwen, Jr., eds. 2006.*International cosmetic ingredient dictionary and handbook,* 11th ed., vol. 1. Washington, DC: CTFA.

Hacmiya, N., Taketani, A., and Takizawa, Y. 1982. Mutagenicity of environmental substances. *Nippon Koshu Eisei Zasshi* 29:236–239.

Hawley, G. G. 1971. *The condensed chemical dictionary*, 8th ed. New York: Van Nostrand Reinhold.

Hites, R. A., G. A. Jungclaus, V. Lopez-Avila, and L. S. Sheldon. 1977. Potentially toxic organic compounds in industrial waste waters and river systems: Two case studies. In *American Chemical Society Symposium Series No. 94. Monitoring Toxic Substances*, ed. D. Schuetzle, 63–90. Washington, DC: American Chemical Society.

Japan Cosmetic Industry Association (JCIA). 1967. *Japanese Standards of Cosmetic Ingredients.* Tokyo, Japan: Yakuji Nippo Ltd. (Translated from the Japanese.)

Jonsen, J., N. Jacobsen, and A. Hensten- Pettersen. 1980. Bacterial mutagenesis (Ames test) as a screening method for carcinogenic substances of dental materials. *Adv. Biomater.* 1(*Eval. Biomater*):333–339.

Joo, I., and N. Simon. 1974. Benzotriazole derivatives as UV-absorbing agents. *Arch. Dermatol. Forsch.* 249:13–19.

Komarova, E. N., and N. S. Maksimova. 1979. Hygienic properties of the Soviet stabilizer Benazol.*P. Khim. Prom-st. Ser. Toksikol. Sanit. Khim. Plastmass.* 1:25–27. (Translated from the Russian.)

Labor Hygiene and Occupational Diseases. 1966. *Gigiena Truda i Professional'nye Zabolevaniia.* (Vlo' Mezhdunarodnaya Kniga,' Kuznetskii Most 18, Moscow G-200, U.S.S.R.). 10:49. (Translated from the Russian.)

Letchworth, P. E., and F. M. Pallos. 1972. Stabilized insecticidally active compounds. S. African Patent No. 71 05370. http://www.european-patent-office.org/index.en.php

Letchworth, P. E., and Pallos, F. M. 1976. Benzotriazoles as stabilizers for certain insecticidal epoxy compounds, U.S. Patent No. 3984541. http://www.uspto.gov

Marhold, J. V. 1972. *Sbornik Vysledku Toxixologick eho Vysetreni Latek A Pripravku*, Institut Pro Vychovu Vedoucicn Pracovniku Chemickeho Prumyclu, Czechoslovakia. 146. (Translated from the oridinal Czech.)

Ministry of Health, Labor and Welfare (MHLW). 2005a. MHLW Ordinance No. 331, Appendix 1. List of ingredients that cosmetics shall not contain. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045. Japan. (Translated from Japanese.)

MHLW. 2005b. MHW Ordinance No. 331, Appendices 2-4. Restricted lists. Ministry of Health, Labor and Welfare, Pharmaceutical and Medical Safety Bureau, Inspection and Guidance Division, 2-2, 1-chome, Kasumigaseki, Chiyoda-ku, Tokyo 100-8045. Japan. (Translated from Japanese.)

Motoyoshi, M., T. Ito, M. Yukutomi, Y. Tanaka, and A. Iyama. 1975. Agricultural composition for prevention of leaf burn. Japan Patent No. 75 19465. http://library.dialog.com/bluesheets/htmlaa/bl0347.html

Randklev, R. M. 1981. Orthodontic bracket adhesive and abrasive for its removal. Eur. Pat. Appl. Patent No. 37677. http://www.european-patent-office.org/index.en.php

Schmid, K., W. Schweizer, W. Staeubli, and F. Waechter. 1980. Effect of 2-(2′-hydroxy-5′-methylphenyl) benzotriazole on rat liver.*Food Cosmet. Toxicol.* 18:245–252.

Schmitz, J. R., M. Walkowiak, H. H. Schulz, B. Boemer, and C. Sueling. 1980. Cold-hardened material for dental uses. Cer. Offen. Patent No. 2913220. http://www.european-patent-office.org/index.en.php

Stubbs, V. K., F.S . Downing, and G. J. Marrs. 1979. Tickicidal pyrethroid mixtures and stabilizer. U.S. Patent No. 4171355. http://www.uspto.gov

Windholz, M., ed. 1983. *The Merck Index*. Rahway, NJ: Merck and Co.